HCC screening in patients with compensated HCV-related cirrhosis aware of their HCV-status improves survival: a modeling approach

Abbas Mourad[1,2] (abbas-mourad@hotmail.com), Sylvie Deuffic-Burban[1,2] (sylvie.burban@neuf.fr),

Nathalie Ganne-Carrié[3] (nathalie.ganne@jvr.aphp.fr), Thibaud Renaut-Vantroys[4]

(thibaudrv@hotmail.fr), Isabelle Rosa[5] (isabelle.rosa@chicreteil.fr), Anne-Marie Bouvier[6]

(Anne-Marie.Bouvier@u-bourgogne.fr), Guy Launoy[7] (guy.launoy@unicaen.fr), Stephane Cattan[4]

(stephane.cattan@chru-lille.fr), Alexandre Louvet[1,4] (alexandre.louvet@chru-lille.fr), Sébastien

Dharancy[1,4] (sebastien.dharancy@chru-lille.fr), Jean-Claude Trinchet[3]

(jean-claudetrinchet@jvr.aphp.fr), Yazdan Yazdanpanah[2,8] (yazdan.yazdanpanah@bch.aphp.fr),

Philippe Mathurin[1,4] (philippe.mathurin@chru-lille.fr**).**

[1]Inserm U995, Université Lille Nord de France, Lille, France

[2]Inserm ATIP/Avenir, U738, Université Paris Diderot, Paris, France

[3]Service d'Hépato-Gastroentérologie, Hôpital Jean Verdier, Bondy, France

[4]Service Maladies de l'Appareil digestif et de la Nutrition, Hôpital Claude Huriez, Lille, France

[5]ANGH CHANGH Study Group, Centre Hospitalier Intercommunal, Créteil, France

[6]Inserm U866, Registre des Cancers digestifs, Dijon, Burgundy, France

[7]Inserm-UCB U1086, Caen, France

[8]Service des Maladies infectieuses et tropicales, Hôpital Bichat Claude Bernard, Paris, France

Corresponding authors:

Philippe Mathurin, Service des Maladies de l'Appareil Digestif et de la Nutrition,

Pôle Médico Chirurgical, Hôpital Huriez, CHRU Lille, 1 place de Verdun, 59037 Lille Cedex, France

Tel: 33 (0)3 20 44 56 09 - Fax: 33 (0)3 20 44 55 64 - E-mail: philippe.mathurin@chru-lille.fr

Sylvie Deuffic-Burban, ATIP-AVENIR, Inserm U995, Parc Eurasanté, 152 rue du Docteur Yersin

59120 Loos, France

Tel: 33 (0)3 20 44 59 62, extension: 35128 - Fax: 33 (0)3 20 96 86 62 - E-mail: sylvie.burban@neuf.fr

Abbreviations

BCLC, Barcelona Clinic Liver Cancer

HCC, hepatocellular carcinoma

HCV, hepatitis C virus

LT, liver transplantation

LE, life expectancy

RR, relative risk

RCT, randomized controlled trial

US, ultrasonographic screening

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Abstract (271 words)

Because of the ongoing debate on the benefit of ultrasound (US) screening for HCC, we assessed the impact of screening on HCV-related compensated cirrhosis aware of their HCV status. A Markov model simulated progression from HCC diagnosis to death in 700 patients with HCV-related compensated cirrhosis aware of their HCV status to estimate life expectancy (LE) and cumulative death at 5 years. Five scenarios were compared: S1, no screening; S2, screening by currently existing practices (57% access and effectiveness leading to the diagnosis of 42% at stage BCLC-0/A); S3, S2 with increased access (97%); S4, S2 with an efficacy of screening close to that achieved in a randomized controlled trial leading to the diagnosis of 87% of patients at stage BCLC-0/A; S5, S3+S4. The analysis was corrected for lead-time bias. Currently existing practices of HCC screening increased LE by 11 months and reduced HCC mortality at 5 years by 6% compared to no screening (*P*=0.0013). Compared to current screening practices we found that: a) increasing the rate of access to screening would increase the LE by 7 months and reduced HCC mortality at 5 years by 5% (*P*= 0.045); b) optimal screening would increase the LE by 14 months and reduced HCC mortality at 5 years by 9% (*P*=0.0002); c) combination of an increased rate of access and optimal effectiveness of HCC screening would increase the LE by 31 months and decreased HCC mortality at 5 years by 20% (*P*<0.001). Conclusion: The present study shows that US screening for HCC in patients with compensated HCV-related cirrhosis aware of their HCV status improves survival and emphasizes the crucial role of screening effectiveness.

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death and represents 7% of all cancer-related deaths (1). HCC mainly develops in patients with cirrhosis. Patients with hepatitis B virus (HBV) and hepatitis C virus (HCV) have a yearly risk of HCC of approximately 2-5% (2-3). Prognosis is very poor due to late diagnosis, which often prevents curative treatment (4).

Recent EASL and AASLD guidelines (4-5) have recommended the Barcelona Clinic Liver Cancer (BCLC) classification staging system for the management of HCC (6). A therapeutic algorithm was developed based on the BCLC classification with four stages (0/A, B, C and D). Curative treatment (surgical resection, liver transplantation (LT) and radio-frequency ablation) is destined for patients with early stage HCC (BCLC-0/A). These curative treatments are the only chance of survival, with an overall three-year survival rate of approximately 80% (4, 7). Patients with intermediate stage disease (BCLC-B) can benefit from transarterial chemo-embolization, with a three-year survival rate of approximately 30% (8). Sorafenib is the only therapeutic option for patients with advanced HCC (BCLC-C) (9).

Screening of patients with cirrhosis includes tests or examinations to detect early stage cancer and increase the chance of optimal therapeutic options. Screening has been shown to effectively diagnose early stage HCC in randomized controlled trials (RCTs) (10-11), controlled and uncontrolled studies (12-15). The benefit of ultrasound (US) in the detection of early stage HCC has also been confirmed in RCTs (16-17). Screening is considered to be validated when there is strong evidence that it improves survival. Although International guidelines recommend US screening of patients with cirrhosis every 6 months by experienced personnel (4-5), experts continue to seek conclusive evidence that HCC screening improves survival (10-11, 18-20). The most effective way to evaluate the impact of HCC screening on survival would be to perform a RCT assessing the influence of screening in patients with compensated cirrhosis who are candidates for curative treatment. However, randomization is considered to be unethical by patients and clinicians, who refuse to prevent patients from receiving the benefits of screening, i.e. early stage diagnosis (21). Controlled or

4

uncontrolled cohort studies may be an alternative approach. However, besides their well known limitations, non-RCTs also have a lead-time bias (an apparent improvement in survival due to early diagnosis) although certain studies have taken this bias into account (19, 22-24). A recent cohort study questioning the impact of HCC screening on survival in patients with alcoholic cirrhosis has added to this controversy (25). However, that study had a major bias because it included patients with decompensated cirrhosis in whom curative therapies are usually not indicated.

The use of a model based approach is complementary to controlled and uncontrolled studies because it has different goals and uses an analytic methodology that accounts for events over time and across populations. Because of the methodological issues of HCC screening, modeling can be interesting to determine the impact of HCC screening on survival and to test different screening protocols with corresponding therapeutic options according to tumor stage. It can also take into account the lead-time bias. To develop a model, data on the progression of HCC, on the impact of therapeutic options on survival, on the availability of liver grafts for HCC patients and on the probability of entering into a screening program and being treated according to tumor stage, must all be robust (16, 26). Because these data are often available for HCV patients and because most patients with decompensated cirrhosis are not candidates for treatment, we focused on an HCV-related HCC population with compensated cirrhosis to optimize the accuracy of the model.

The goal of this study was to assess the influence of routine US screening for HCC in patients with compensated HCV-related cirrhosis aware of their HCV status upon survival using a model-based analysis by comparing current HCC screening practices to: a) no screening; and b) different scenarios that increase the rate of access to HCC screening and improve the effectiveness of screening.

Materials and methods

Analytic overview

A Markov model of the progression of HCC in compensated HCV-related cirrhosis was developed using TreeAge Pro suite 2009 (TreeAge Software Inc). Life expectancy (LE) and the risk of HCV-related HCC deaths from the date of diagnosis were calculated according to different rates of access to HCC screening and to the effectiveness of screening in detecting early stage HCC. All analyses were corrected for lead-time bias.

Model overview

This model describes the progression from the time of HCC diagnosis to death from HCV-related HCC in patients with monoinfection and compensated cirrhosis (Figure 1). The population was first stratified by age (<70 years old, ≥70 years old), a factor which affects therapeutic options, and then by HCV status (known or not), since awareness of HCV status influences HCC screening. HCV-related HCC patients were then staged according to the BCLC classification (0/A, B, C, D) and pre-established prognostic variables (6). Patients were treated according to BCLC stage: BCLC-0/A patients received surgical resection, LT, radio-frequency ablation and/or transarterial chemo-embolization; BCLC-B received LT, transarterial chemo-embolization and/or sorafenib; BCLC-C patients received sorafenib; and BCLC-D patients received supportive care. Liver transplantation was limited by the number of available grafts allotted to patients with HCV-related HCC in compensated cirrhosis. Some patients received supportive care because of contraindications that were or were not related to liver disease. Finally, the risk of HCV-related mortality depended on treatment and tumor stage.

Input data

Rate of HCC screening

6

Our working hypothesis was that HCC screening is related to the awareness of HCV status. Patients had to be aware of their HCV status and have been diagnosed with compensated cirrhosis to be screened for HCC. We first estimated the existing rate of screening for HCC in HCV-related cirrhosis based on data from literature (27). In that cohort (27), 28.5% of all patients with HCV-related cirrhosis (aware or not of HCV status) had access to HCC screening. Considering that 49.7% of the HCV patients were aware of their HCV-status (28), we assumed that 57% of these patients had access to HCC screening (i.e. $(49.7\% \times \text{access-rate})_{HCV\text{-}known} + (50.3\% \times 0\%)_{HCV\text{-}unknown} = 28.5\% \Rightarrow \text{access-rate}_{HCV\text{-}known} = 57\%$). The rates of currently existing practices of HCC screening correspond to the percentage of patients with cirrhosis who have access to HCC screening.

Effectiveness and efficacy of US screening according to BCLC stages (Table 1)

Patients with compensated HCV-related HCC were classified by BCLC stage and depending on whether they were entered into an HCC screening program. Distribution of patients by BCLC stage without HCC screening and according to currently existing practices of HCC screening was based on data from the CHANGH cohort in HCV patients (26), CHANGH is a prospective French cohort study performed from May 2008 to October 2009 in 98 French community hospitals and 5 Tertiary Care Hepatology Units (26). The CHANGH cohort described the epidemiological characteristics, management and survival of HCC in real-life practice in France. All inpatients and outpatients with newly diagnosed HCC were prospectively and consecutively included. The cohort included 1027 patients. One hundred and seventy eight cases of HCC were related to HCV infection (17%) and compensated cirrhosis (110 Child A, 42 Child B and 26 Child C) was present in 62%. Forty-two percent of patients who were in an HCC screening program were BCLC-0/A, 25% BCLC-B, 32% BCLC-C and 1% BCLC-D at diagnosis. In contrast, 18% of patients who had not been screened for HCC were BCLC-0/A, 13% BCLC-B, 60% BCLC-C and 9% BCLC-D at diagnosis.

We defined the effectiveness of screening (performance under real-world conditions) as its capacity to detect early HCC (BCLC-0/A). Thus, according to the CHANGH cohort the effectiveness of current US screening practices was the diagnosis of 42% of HCC in compensated HCV-related

7

cirrhosis at stage BCLC-0/A (26). The efficacy of US screening (performance under best case scenario, e.g. RCT) in the randomized CHC-2000 trial was the diagnosis of 87% of HCC in compensated HCV-related cirrhosis at BCLC-0/A (16).

Therapeutic options and survival

The possible therapeutic options according to BCLC stage and patient age were obtained from the CHANGH cohort (Table 1). Sixty three percent of patients <70 years old who were candidates for LT were within to the Milan criteria (BCLC-0/A), while 37% of patients were outside the criteria (BCLC-B). These data were similar to those from the French National Agency for Organ Sharing and Transplantation (Agence de la Biomédecine) (62% and 38%, respectively) (29). Our model included the hypothesis that some patients in the BCLC-0/A group received chemo-embolization or supportive care due to deterioration of liver function, tumor progression or other complications. Moreover, some candidates for LT were removed from the list because of tumor progression and death related to liver deterioration or other factors, and consequently received palliative treatment. LT is not considered to be a therapeutic options in patients over 70 (30) and the probability of these patients receiving therapeutic management is reduced due to a higher prevalence of co-morbidity than in younger patients (26). Overall, 36% of patients under 70 were not considered for therapeutic management, compared to 45% of patients over 70.

Survival rates after treatment for HCC in compensated HCV-related cirrhosis were estimated taking into account tumour progression and the complications of cirrhosis and based on publications in the literature (supplementary Table 2).

Procedure

Validity of the model

To determine the validity of our model, we simulated the progression from diagnosis until death of all compensated HCV-related HCC patients in France (both those aware and not aware of

8

their HCV status) who were still alive in 2001, along with new cases from 2001 to 2010 (31) (Supplementary Table 1 and supplementary material for more details).

Application

To assess the impact of HCC screening, we simulated a population of 700 HCV-related HCC patients in France corresponding to newly diagnosed patients with HCC and compensated cirrhosis in 2013 who were aware of their HCV status (41% <70 years old, 59% ≥ 70 years old) (31). We estimated LE and cumulative death at 5 years from the date of diagnosis of HCC according to five scenarios: scenario 1, no access to HCC screening; scenario 2, currently existing practices of HCC screening (26) i.e. access to screening in 57% and effectiveness of screening with 42% of patients diagnosed at BCLC-0/A; scenario 3, scenario 2 with an increase in access to screening to 97%; scenario 4, scenario 2 with an efficacy of screening corresponding to optimal HCC screening as observed in the CHC-2000 randomized trial (87% of patients diagnosed at BCLC-0/A) (16); scenario 5, scenario 3 + scenario 4.

Finally, we estimated the gain in LE and relative risk (RR) of death 5 years after the diagnosis of HCC for scenario 2 compared to scenario 1, and for scenarios 3, 4 and 5 compared to scenario 2.

Lead-time bias

Lead-time bias corresponds to improved survival due to early detection of the disease, but with no effect on disease outcome (32) (Figure 2). Survival in scenarios 2 to 5 was corrected for lead-time (see detailed methodological information in the Supplementary materials).

Statistical analysis

The Chi-square test was used to compare risk of death at 5 years in the different scenarios. A 2-tailed p-value <0.05 was considered to be statistically significant. Statistical analysis was performed with NCSS 2007 software.

Sensitivity analysis

Sensitivity analysis was performed in two steps to evaluate the impact of data uncertainty and to determine the robustness of our overall conclusions. The first step evaluated the impact of HCC screening (scenario 2 vs. scenario 1) on LE and the risk of death at 5 years by varying the model variables (see more details in Supplementary materials): effectiveness of HCC screening, rate of access to HCC screening, rate of access to treatment, survival rates after the most efficient treatment options (i.e. resection, transplantation, radiofrequency ablation and chemo-embolization) and tumor volume doubling time. Moreover, we simultaneously varied the two variables, effectiveness of screening and rate of access to screening to determine when HCC screening still improved 5-year mortality compared to scenario 1. The second step evaluated the impact of alternative scenarios (scenarios 3, 4 and 5 vs. scenario 2) on LE and risk of death at 5 years varying the most important variables (see more details in Supplementary materials).

Results

Validity of the model

We validated the predictive performance of the model for yearly HCV-related HCC deaths and yearly LT for compensated HCV-related HCC. First, the relative mean difference between estimated and observed HCV-related HCC deaths from 2002 to 2010 was 1% (range, 0-5%) (Supplementary Figure1). Second, the relative mean difference between estimated and observed numbers of LT for compensated HCV-related HCC was 6% (range, 2-10%) (Supplementary Figure2).

Life expectancy

Current HCC screening practices (scenario 2) were associated with a 9-month increase in LE compared to the absence of screening (scenario 1), (Figure 3A). Compared to currently existing practices of HCC screening practices (scenario 2): a) increasing the rate of access to HCC screening from 57% to 97% (scenario 3) increased the LE by 7 months; b) increasing the effectiveness of HCC screening from 42% to 87% (scenario 4) increased the LE by 14 months; c) improving the rate of access to HCC screening as well as its effectiveness (scenario 5) increased the LE by 31 months (Figure 3B).

HCV-related HCC mortality at 5 years

The five-year risk of HCV-related HCC death was 90.8%, 85.3%, 81.4%, 77.6% and 68.4% in scenarios 1, 2, 3, 4 and 5, respectively (Figure 4). Thus there was a 6% reduction in HCV-related HCC mortality with current HCC screening practices (scenario 2), compared to without HCC screening (scenario 1): RR = 0.95 (CI$_{95\%}$: 0.91-0.98; *P*=0.0013, Figure 4A). Once again, increasing the rate of access to HCC screening from 57% to 97% (scenario 3 vs. scenario 2) reduced mortality by 5%: RR = 0.95 (CI$_{95\%}$: 0.91-1.00; *P*= 0.045, Figure 4B). In contrast the efficacy of HCC screening, such as in clinical trial CHC 2000, significantly improved HCV-related HCC mortality (scenario 4 vs. scenario 2): RR = 0.91 (CI$_{95\%}$: 0.86-0.96; *P*=0.0002, Figure 4B). Finally, the influence of increasing access to

screening and the effectiveness of HCC screening (scenario 5 vs. scenario 2) was even greater: RR = 0.80 (CI$_{95\%}$: 0.75-0.85; P< 0.0001, Figure 4B).

<u>Sensitivity analysis</u>

Figure 5 shows the most influential variables in the model. LE and risk of death at 5 years were most sensitive to the effectiveness of HCC screening and the rate of access to HCC screening. When comparing scenario 2 to scenario 1, a) LE increased by 7 to 25 months when varying the effectiveness of screening and by 4 to 14 months when varying the rate of access to screening (11 months in baseline analysis); b) HCV-related HCC mortality was reduced by 4% to 15% when varying the effectiveness of screening (6% in baseline analysis) and by 2% to 10% when varying the rate of access to screening (6% in baseline analysis). Moreover, a 20% rate of access to screening did not significantly impact LE (+4 months) and HCV-related HCC mortality at 5-year (-2%) (P=0.18) (Figure 6). Therefore, for screening to be beneficial, the minimum rate of access to screening should be 34% with a 42%-effectiveness and the minimum effectiveness of screening should be 31% with a 57%-rate of access to screening. This interaction between the effectiveness and the rate of access to screening is illustrated in Figure 7. It shows the minimum rate of access and effectiveness of HCC screening necessary for these variables. The results of additional sensitivity analyses are shown in Supplementary material (Supplementary Figures 3 to 5).

12

Discussion

American and European guidelines on screening for HCC are a subject of debate (33-34) since some investigators consider that data from RCTs on the impact on survival are not reliable. However it is ethically impossible to perform RCTs to assess the impact of screening on survival with a design that includes an arm without screening (21). The present study uses a model that provides more facts and less speculation on the survival benefit of HCC screening at diagnosis. All of the different scenarios showed that HCC screening led to a substantial increase in LE and decreased the risk of HCV-related HCC death in patients aware of their HCV status. Scenarios that include improving the effectiveness of HCC screening were the most efficient, with the greatest increase in LE of approximately 31 months for the scenario combining the efficacy of HCC screening with an increase in access to screening. Analysis of the different variations of rates of access to screening and effectiveness of screening show the impact of their interaction on mortality from HCC at 5 years.

In France, as in other countries, screening for HCC is not standard in real clinical practice. It should be noted that screening rates vary drastically according to the type of center and hospital with higher rates of screening for HCC in tertiary-care centers (35) or primary care practices (36) than those observed in the national registration database (27, 37).

Ideally the design of studies testing the benefits of screening on survival should: 1) only include patients with compensated cirrhosis; indeed, patients with decompensated cirrhosis are often not candidates for treatment; 2) provide appropriate therapeutic options to patients, especially curative treatment for early stage disease; 3) integrate the limited availability of liver grafts; 4) take into account lead-time bias. Most studies have not fulfilled all of these prerequisites. Our study only evaluated patients with compensated cirrhosis. The proportion of HCV-related HCC patients with compensated cirrhosis in whom curative treatment was indicated increased from 14.4% in those without HCC screening to 25.0% with current HCC screening, to 40.0% with an efficacy of screening corresponding to optimal HCC screening and 58.5% when the rate of access to screening was increased and the effectiveness of screening was improved. We also attributed a limited number of

13

LT based on real-data (38). Finally, we took into account lead-time bias and also performed sensitivity analysis according to tumor growth, thus guaranteeing the reliability of results. However, these results cannot be extrapolated to other etiologies of cirrhosis, since part of the modeling data are lacking for non-HCV-related HCC.

At first glance, increasing the rate of access to screening appears to be an easy way to improve the outcome of patients with HCC. Our baseline assumption of a rate of access to screening of 57% may at first glance appear to be different from the rate of around 20% that has been reported in the general population (27, 39). However, our study was limited to HCV patients with cirrhosis who were aware of their HCV status while in the global HCV population (aware or not of their virological status), the rate of access to screening access is markedly lower because patients who are not aware of their HCV status, are, by definition, not in an HCC screening program because their liver disease is undiagnosed. Our results show that a 20% rate of access to screening was not effective. Because this rate may reflect the rate of access in the general population with cirrhosis (27, 39), these results strongly suggest that public health policies should not only increase the rate of access to screening in patients aware of their liver disease but also the percentage of patients aware of their HCV status.

The influence of HCC screening on survival has been evaluated in two RCTs (10-11). The first study was inconclusive because a large proportion of diagnosed patients did not receive appropriate treatment (10). Although the second trial showed that HCC screening was beneficial, experts have shown (34, 40) that there were methodological flaws and limitations in the study design (11). Other cost-effectiveness studies in patients with hepatitis C and cirrhosis concluded that US screening provided a benefit in survival (41-43). The main objective of that study was to identify the most cost-effective HCC screening method. Conversely, the goal of our study was to evaluate the impact of US screening on survival in real-life and to test the influence of different strategies to improve current screening practices. As suggested in a prior study (44) our study showed that the effectiveness of HCC screening was the most important variable. Indeed, compared to currently existing practices of HCC screening practices, efficacy of HCC screening increased the number of patients diagnosed with

early stage disease (87% vs. 42%) and reduced 5-year mortally by 9%. The efficacy of HCC screening described in RCTs (16-17) may be due to highly experienced operators and centers, standard quality US material, selection of patients and strict follow-up. Therefore, we strongly recommend that clinicians and policymakers target the effectiveness of US screening to improve survival in HCC patients.

As expected in a modeling approach, the present work had several limitations because of data from multiple sources and assumptions. The impact of these weaknesses seems to be limited since we focused on available and robust data from HCV patients. In addition, our study took into account lead-time bias. Moreover, we performed sensitivity analysis to assess the potential impact of uncertainties. The results of these sensitivity analyses did not modify the main conclusions of our study and confirmed the robustness of baseline assumptions.

In summary, the present study shows that US screening for HCC in compensated HCV-related cirrhosis improves survival, and emphasizes the importance of screening effectiveness. Policy makers and experts should recommend better training for US operators, standard quality US materials, better education of patients in terms of compliance, better quality follow-up and an improved multidisciplinary network to increase awareness of the benefits to survival of HCC screening in patients and for general practitioners.

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Figure legends

Figure 1. Model of HCV-related HCC progression. Patients staged by the BCLC classification at diagnosis and according to whether or not they were in a screening program for HCC. Patients were given therapeutic options according to BCLC stage. For each cycle, patients (treated or not) either remained alive and received the next cycle or died from HCV-related HCC.

Figure 2. Illustration of lead-time bias based on three screening situations: case A, no screening; case B, screening with no impact on survival; and case C, screening with an impact on survival impact. We assumed that all HCC developed at the same time, but cases B and C were diagnosed earlier than case A. Without screening, case A was diagnosed when clinical signs or symptoms had developed. Case B was diagnosed by screening before symptoms developed, but both patients (A and B) died at the same time. The longer survival time for patient B simply reflected a longer time from cancer detection to its clinical diagnosis. Patient C was diagnosed by screening at the same time as patient B but died later than patients A and B. Although there existed a true benefit in terms of survival, perceived survival was still higher than true survival.

Figure 3. Life expectancy according to five HCC screening scenarios. Months of life saved appear in light gray areas, after comparison of A) scenario 2 with scenario 1 and B) scenarios 3, 4 and 5 with scenario 2.

Figure 4. Cumulative mortality of HCV-related HCC at 5 years corrected for lead-time according to: A) scenario 2 vs. scenario 1; B) scenarios 3, 4 and 5 vs. scenario 2

Figure 5. Sensitivity analysis. This tornado diagram shows the effect of different degrees of effectiveness of HCC screening, rates of access to screening, rates of access to treatment, survival rates after resection, survival rates after transplantation, survival rates after radiofrequency ablation

21

and survival rates after chemo-embolization, as well as tumor volume doubling time, on: A) variation of life expectancy (scenario 2 vs. 1), B) relative risk of death at 5 years (scenario 2 vs. 1). The values in curly brackets are the plausible range tested in sensitivity analysis, the solid line indicates results (variation of life expectancy and relative risk of death at 5 years) with the baseline parameters, the bars show the variability on results caused by changes in the indicated variable, all other variables held constant.
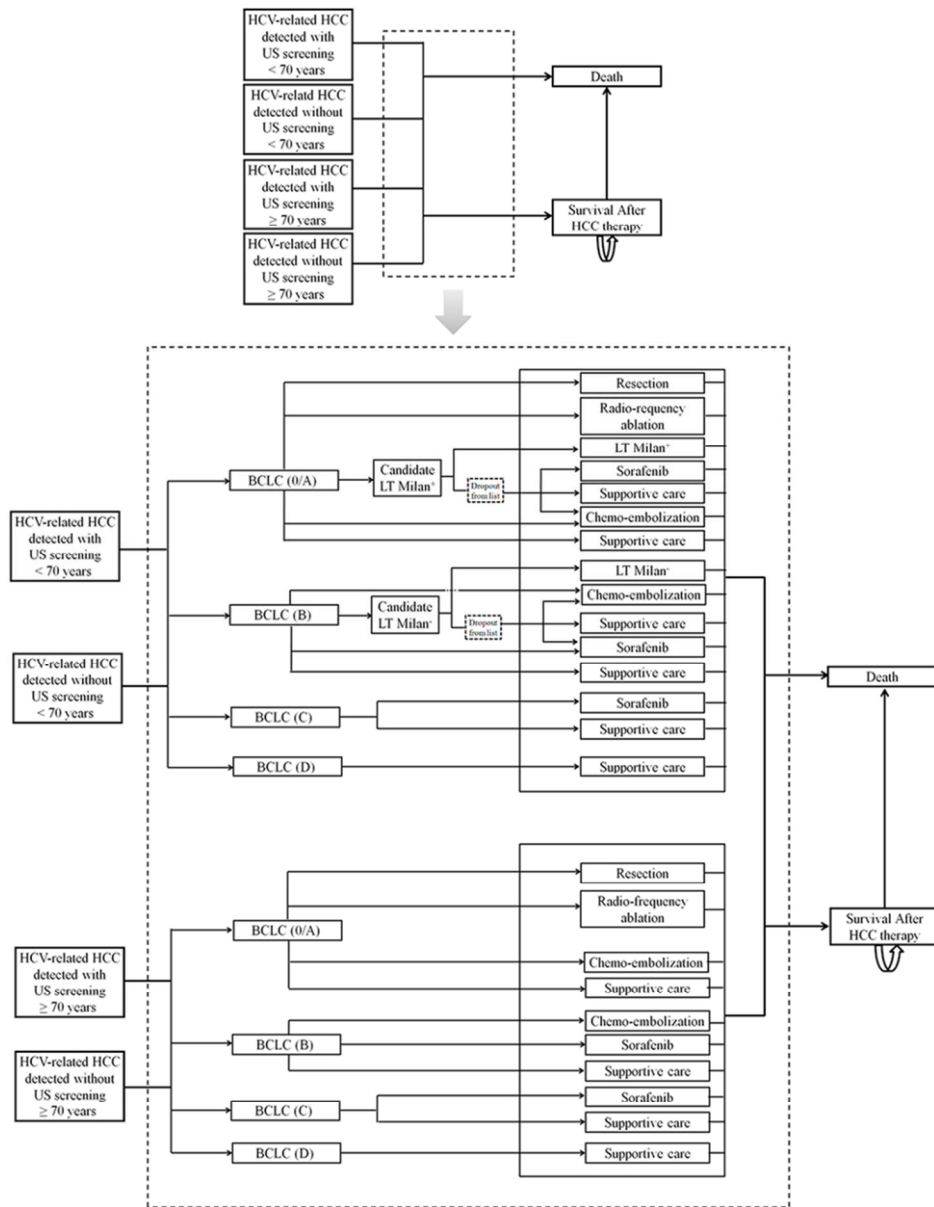
Figure 6. Sensitivity analysis corresponding to a decrease in access rate to HCC screening from 57% to 20% (39). Life expectancy corrected for lead-time according to five HCC screening scenarios: A) light gray area is the number of life months saved by scenario 2 compared to scenario 1; B) light gray areas are numbers of life months saved by scenario 3, 4 and 5 compared to scenario 2. Cumulative mortality of HCV-related HCC at 5 years corrected for lead-time according to: C) scenario 2 vs. scenario 1; D) scenarios 3, 4 and 5 vs. scenario 2

Figure 7. Zones corresponding to the benefit of HCC screening on survival (dark gray) or not (light gray) by simultaneously varying screening effectiveness and access to screening. The curve corresponds to the limit of significance between the scenarios with and without screening. For examples, at dot X with a 42%-effectiveness of screening, the minimum access rate to screening would be 34% for screening to be beneficial; at dot Y with a 57%-access to screening, the minimum effectiveness of screening would be 31% to have benefit from screening.

22

Table 1. Distribution by BCLC stage of patients who did not undergo HCC screening (26), who underwent currently existing practices of HCC screening (26), and who underwent optimal effectiveness of HCC screening (16), and distribution of therapeutic options for HCC patients according to BCLC stage.
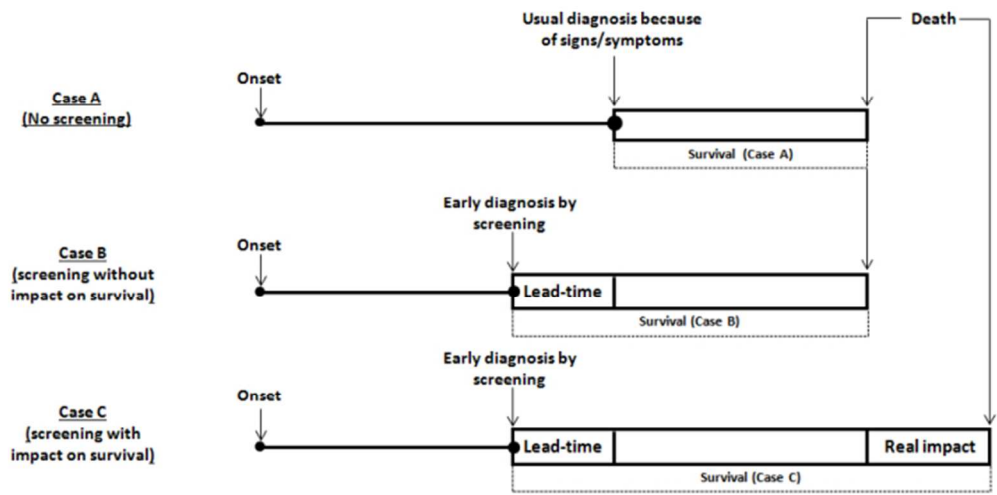
	Baseline (range)		Sources
Distribution of HCV-related HCC in BCLC stages			
Patients who did not undergo HCC screening			(26)
BCLC-0/A	18%		
BCLC-B	13%		
BCLC-C	60%		
BCLC-D	9%		
Patients who underwent current HCC screening			(26)
BCLC-0/A	42%		
BCLC-B	25%		
BCLC-C	32%		
BCLC-D	1%		
Patients who underwent optimal HCC screening			(16)
BCLC-0/A	87%		
BCLC-B	6%		
BCLC-C	7%		
BCLC-D	0%		
Therapeutic options for HCC patients	< 70 years	≥ 70 years	(26)
BCLC-0/A			
Resection	12.0%	12.0%	
Candidates for liver transplantation	39.0%	0.0%	
Radiofrequency ablation	44.0%	44.0%	
Chemo-embolization	3.0%	27.0%	
Sorafenib[*]	0.0%	0.0%	
Supportive care	2.0%	17.0%	
BCLC-B			
Candidates for liver transplantation	38.0%	0.0%	
Chemo-embolization	22.0%	40.0%	
Sorafenib[*]	20.0%	30.0%	
Supportive care	20.0%	30.0%	
BCLC –C			
Sorafenib[*]	34.0%	34.0%	
Supportive care	66.0%	66.0%	
BCLC-D			
Supportive care	100%	100%	
Drop out from list of transplantation			(45)
Milan[+]	6%		
Milan-	20%		
Treatments after drop out from list of transplantation			
Chemo-embolization	25% (20%-30%)		
Sorafenib	50% (40%-60%)		
Supportive care	25% (20%-30%)		

[*]Date of initial sorafenib marketing authorization was July 19, 2006 (46)

81x104mm (300 x 300 DPI)

60x29mm (300 x 300 DPI)

A) Life expectancy from the date of diagnosis (months)
- Scenario 1: 24 months
- Scenario 2: 35 months (+11 months)

B) Life expectancy from the date of diagnosis (months)
- Scenario 2: 35 months
- Scenario 3: 42 months (+7 months)
- Scenario 4: 49 months (+14 months)
- Scenario 5: 66 months (+31 months)

- Scenario 1= no access to HCC screening
- Scenario 2= currently existing practice of HCC screening, i.e. access to screening equal to 57% and effectiveness of screening corresponding to 42% of patients diagnosed at BCLC-0/A
- Scenario 3= scenario 2 with an increase in access to screening to 97%
- Scenario 4= scenario 2 with an efficacy of screening corresponding to optimal HCC screening as observed in the CHC-2000 randomized trial (87% of patients diagnosed in BCLC-0/A)
- Scenario 5= scenario 3 + scenario 4

75x43mm (300 x 300 DPI)

A)

RR = 0.94 (0.90-0.98)
P = 0.0013

B)

RR = 0.80 (0.75-0.85)
P < .0001

RR = 0.91 (0.86-0.96)
P = 0.0002

RR = 0.95 (0.91-1.00)
P = 0.045

Cumulative mortality at 5 years from the date of diagnosis (%)

90.8%   85.3%

Scenario 1   Scenario 2

Scenarios

Cumulative mortality at 5 years from the date of diagnosis (%)

85.3%   81.4%   77.5%   68.4%

Scenario 2   Scenario 3   Scenario 4   Scenario 5

Scenarios

- Scenario 1= no access to HCC screening
- Scenario 2= currently existing practice of HCC screening , i.e. access to screening equal to 57% and effectiveness of screening corresponding to 42% of patients diagnosed at BCLC-0/A
- Scenario 3= scenario 2 with an increase in access to screening to 97%
- Scenario 4= scenario 2 with an efficacy of screening corresponding to optimal HCC screening as observed in the CHC-2000 randomized trial (87% of patients diagnosed in BCLC-0/A)
- Scenario 5= scenario 3 + scenario 4

98x42mm (300 x 300 DPI)

A)

B)

73x116mm (300 x 300 DPI)

A) — Life expectancy from the date of diagnosis (months); Scenario 1: 24months; Scenario 2: 28months (+4 months)

B) — Life expectancy from the date of diagnosis (months); Scenario 2: 28 months; Scenario 3: 42 months (+14 months); Scenario 4: 33 months (+5 months); Scenario 5: 66 months (+38 months)

C) — Cumulative mortality at 5 years from the date of diagnosis (%); Scenario 1: 90.8%; Scenario 2: 88.6%; RR = 0.98 (0.94-1.01) P = 0.18

D) — Cumulative mortality at 5 years from the date of diagnosis (%); Scenario 2: 88.6%; Scenario 3: 81.4%; Scenario 4: 86.1%; Scenario 5: 68.4%; RR = 0.92 (0.88-0.96) P = 0.0002; RR = 0.97 (0.93-1.01) P = 0.15; RR = 0.77 (0.73-0.82) P < .0001

- Scenario 1= no access to HCC screening
- Scenario 2= currently existing practice of HCC screening , i.e. access to screening equal to 20% and effectiveness of screening corresponding to 42% of patients diagnosed at BCLC-0/A
- Scenario 3= scenario 2 with an increase in access to screening to 97%
- Scenario 4= scenario 2 with an efficacy of screening corresponding to optimal HCC screening as observed in the CHC-2000 randomized trial (87% of patients diagnosed in BCLC-0/A)
- Scenario 5= scenario 3 + scenario 4

99x74mm (300 x 300 DPI)

Survival benefit from HCC screening

No survival benefit from HCC screening

Access rate to screening (%)

Effectiveness of screening (%)

78x27mm (300 x 300 DPI)

Hepatology

Hepatology

- ● Observed death from HCV-related HCC ── Predicted death from HCV-related HCC
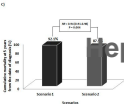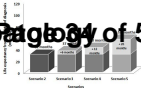
Hepatology

A)

B)

Hepatology

- Scenario 2= currently existing practice of HCC screening, i.e. access to screening equal to 57% and effectiveness of screening corresponding to 42% of patients diagnosed at BCLC-0/A
- Scenario 4= scenario 2 with an efficacy of screening corresponding to optimal HCC screening (70% of patients diagnosed in BCLC-0/A)
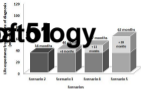- Scenario 5= scenario 3 + scenario 4

Hepatology
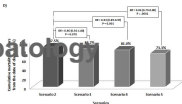
- Scenario 1= no access to HCC screening
- Scenario 2= currently existing practice of HCC screening, i.e., access to screening equal to 30% and effectiveness of screening corresponding to 40% of patients diagnosed with HCC: A/A
- Scenario 3= scenario 2 with increase in access to screening to 60%: B/A
- Scenario 4= scenario 2 with an efficacy of screening corresponding to optimal HCC screening as observed in the CHC-2000 randomised trial (80% of patients diagnosed in HCC: A/B)
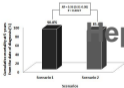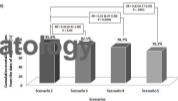- Scenario 5= scenario 4 + scenario 3

- Scenario 1: no access to HCC screening
- Scenario 2: currently existing practice of HCC screening, i.e. access to screening equal to 53% and effectiveness of screening corresponding to 63% of patients diagnosed at BCLC-0/A
- Scenario 3: access to screening equal to 53% and an increase in access to screening to 63%
- Scenario 4: an increase in access to HCC screening to optimal HCC screening as observed in the COC-2000 randomized trial (85% of patients diagnosed in BCLC-0/A)
- Scenario 5: scenario 3 + scenario 4

Supplementary material

Validity of the model

According to our assumption, 28.5% of new compensated HCV-related HCC patients (whether aware of their HCV status or not) had access to HCC screening. They were classified at diagnosis by BCLC stage based on the routine clinical data from the CHANGH cohort (1). We compared the estimates of our model with these data for two outcomes. First, we used data on mortality from HCC between 2002-2010 from CépiDC-Inserm (Epidemiological Center for Medical Causes of Death) (2), given that 23% of HCC deaths were attributed to HCV in 2001 (3), with a linear increase over time (4-5). Second, we obtained data from the Agence de la Biomédecine on LT in HCV-related HCC due to compensated and decompensated cirrhosis performed between 2007-2010: 107 in 2007, 99 in 2008, 110 in 2009 and 124 in 2010 (6). Based on these figures we determined LT for HCV-related HCC due to compensated cirrhosis. Since 52% of LT for HCC were attributed to compensated cirrhosis in 2001 (7) and 58% in 2004 (8) this proportion was 64% in 2007 and 70% in 2010 based on a linear increase over time.

Lead-time bias

In our study, patient survival according to scenarios 2 to 5 was corrected for lead-time bias using Schwartz's formula, originally proposed for calculating tumor growth (9):

$t = D_T \times 3 \times \log(d_U/d_S)/\log(2)$

Where t is the lead-time (days), D_T is the median value of tumor volume doubling time and d_S and d_U are median tumor diameters of screened and unscreened patients, respectively. We applied $D_T = 117$ days as proposed by Scheu et al, (10). To correct for lead-time bias related to currently existing practice of HCC screening compared to non-screening, we applied $d_S = 2.80$ cm and $d_U = 4.28$ cm according to median tumor diameters observed in the CHANGH cohort, respectively, in screened and

1

unscreened patients(1). Similarly, to correct for lead-time bias related to optimal practice of HCC screening compared to non-screening, we applied d_S = 2.20 cm for median tumor diameters of screened patients according to the randomized CHC-2000 (11) trial and d_U = 4.28 cm for unscreened patients (1). The calculated lead-times were 215 days (7 months) for current practice of HCC screening compared to no screening and 335 days (11 months) for optimal practice of HCC screening compared to no screening. These lead-times were subtracted from the model estimate of patient survival time from the date of HCC diagnosis.

Sensitivity analysis

In the first step comparing scenario 2 to scenario 1, we first varied effectiveness of currently existing practice of HCC screening with a lower rate at 33% as observed in Tradati et al. (12) and a higher rate at 87% as observed in CHC-2000 (11) (vs. 42% in baseline analysis). Second, we varied the access rate to HCC screening from 20% close to that observed in literature (13) to 97% (vs. 57% in baseline analysis). Third, we varied by 20% the percentage of HCC patients treated with available therapeutic options (curative and palliative) used in baseline analysis. Fourthly, we considered the case of more and less aggressive tumors by varying the median value of tumor volume doubling time D_T used to calculate the lead-time (from 60 days to 171 days as proposed by Barbra et al. (14) vs. 117 days in baseline analysis). For a median of 60 days, the calculated lead-times were thereby 112 days (i.e. 4 months vs. 7 months in baseline analysis) for currently existing practices of HCC screening compared to no screening, and 175 days (i.e. 6 months vs. 11 months in baseline analysis) for optimal practices of HCC screening compared to no screening. For a median of 171 days, the calculated lead-times were thereby 312 days (i.e. 10 months vs. 7 months in baseline analysis) for currently existing practices of HCC screening compared to no screening, and 490 days (i.e. 16 months vs. 11 months in baseline analysis) for optimal practices of HCC screening compared to no screening. Finally, we varied the survival rates at 1-year and following years after most efficient therapeutic modalities (i.e.

2

resection, transplantation, radiofrequency ablation and chemo-embolization) according to survival range observed in the literature (Supplementary Table 1).

In the second step evaluating alternative scenarios, we first considered a more attainable goal for clinicians by examining the impact of a lower optimal effectiveness of HCC screening: 70% of patients diagnosed in BCLC-0/A, as observed in Santi et al. (15) vs. 87% in baseline analysis. Second, we only considered the case of less aggressive tumors by increasing the median value of tumor volume doubling time D_T used to calculate the lead-time. Third, we considered that a higher percentage of patients might not be candidates for any treatment. We therefore examined the impact of a 20% decrease in the percentage of therapeutic options (curative and palliative) used in baseline analysis.

3

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7

Legends to supplementary figures

Supplementary Figure1. Observed and estimated annual HCV-related HCC deaths from 2002 to 2010. Dots are observed deaths from HCC attributable to HCV (2-3). Solid line shows deaths from HCC attributable to HCV estimated by the model.

Supplementary Figure2. Observed and estimated yearly numbers of LT for HCV-related HCC performed between 2007 and 2011. Dots are observed numbers of LT for HCV-related HCC (6). Solid line shows numbers of LT estimated by the model.

Supplementary Figure3. Sensitivity analysis when decreasing the effectiveness of HCC screening from 87% (11) to 70% (15): A) Life expectancy corrected for lead-time according to 3 HCC screening scenarios; light gray areas are numbers of life months saved by scenarios 4 and 5 compared to scenario 2; B) cumulative mortality of HCV-related HCC at 5 years corrected for lead-time according to scenarios 4 and 5 vs. scenario 2.

Supplementary Figure4. Sensitivity analysis when decreasing by 20% the percentage of HCC patients treated with available therapeutic options (curative and palliative). Life expectancy corrected for lead-time according to five HCC screening scenarios: A) light gray area is the number of life months saved by scenario 2 compared to scenario 1; B) light gray areas are numbers of life months saved by scenario 3, 4 and 5 compared to scenario 2. Cumulative mortality of HCV-related HCC at 5 years corrected for lead-time according to: C) scenario 2 vs. scenario 1; D) scenarios 3, 4 and 5 vs. scenario 2.

Supplementary Figure5. Sensitivity analysis varying the median value of tumor volume doubling time D_T (171 days compared to 117 days in baseline analysis) used to calculate lead-times. Life expectancy corrected for lead-time according to five HCC screening scenarios: A) light gray area is the number of life months saved by scenario 2 compared to scenario 1; B) light gray areas are numbers of life months saved by scenario 3, 4 and 5 compared to scenario 2. Cumulative mortality of HCV-related

8

HCC at 5 years corrected for lead-time according to: C) scenario 2 vs. scenario 1; D) scenarios 3, 4 and
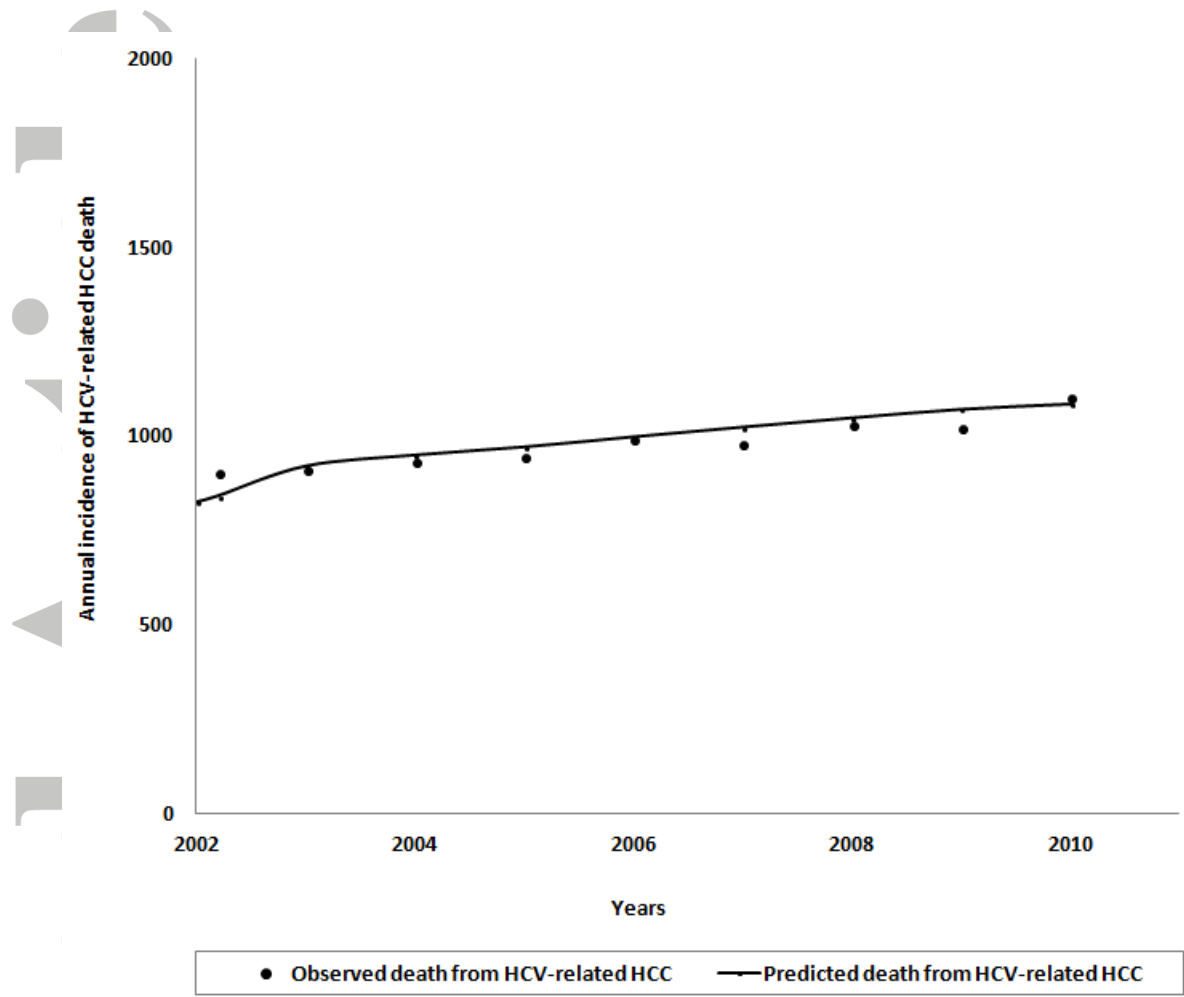
5 vs. scenario 2.

9

Supplementary Table 1. Baseline values (range) of HCC yearly survival rate and survival rate at 5 years, in compensated HCV-related cirrhosis, according to treatment.
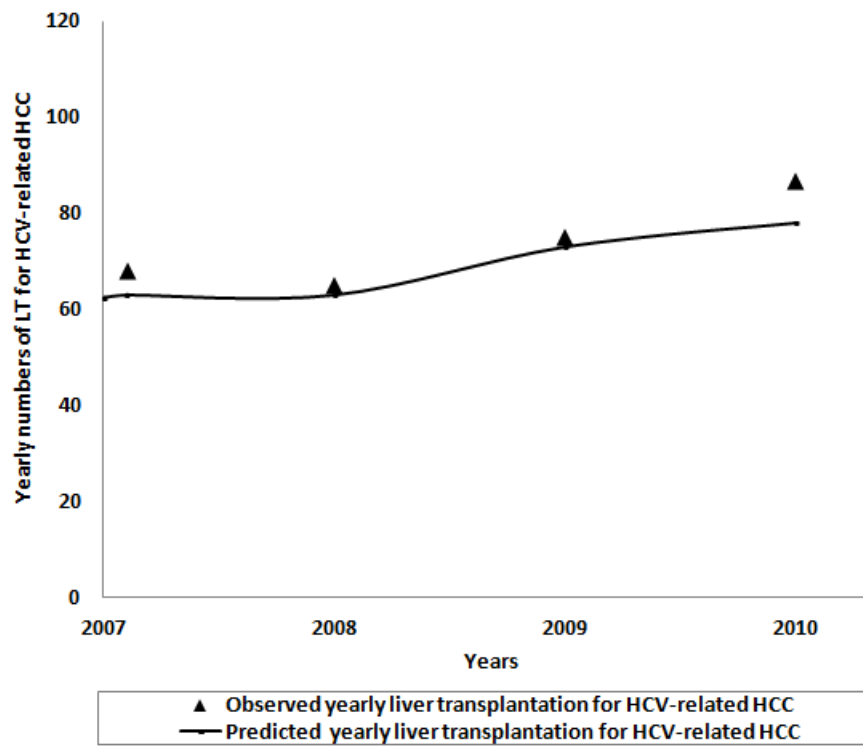
	Yearly survival			Survival rate at 5 years	Sources
	1st year	2nd year	Following years		
Curative treatments					
Resection	92% (88%-96%)		91 % (80%-95%)	63%[*]	(16-18)
Liver transplantation					(19-20)
Milan-	81% (73%-81%)		90% (82%-90%)	53%	
Milan+	88% (86%-88%)		96% (92%-96%)	75%	
Radiofrequency ablation	92% (83%-100%)		82% (78%-82%)	41%	(21-23)
Palliative treatments					
Chemo-embolization					(24-26)
BCLC-0/A	90% (90%-100%)		78% (78%-94%)	34%	
BCLC-B	82% (82%-95%)	77% (44%-77%)	46% (14% -46%)	6%	
Sorafenib					(27-30)
BCLC-B	55% (55%-70%)	51% (51%-70%)	32% (32%-70%)	0%	
BCLC-C	41% (41%-43%)	41% (0%-41%)	30% (0%-30%)	0%	
Supportive care					
BCLC-0/A	81% (81%-100%)	69% (57%-69%)	38% (38%-79%)	3%[¥]	(14, 31)
BCLC-B	63% (63%-79%)		42% (27%-42%)	1%	(31-32)
BCLC-C	29% (12%-33%)	53% (0%-53%)	0%	0%	(30-31, 33)
BCLC-D	11% (0%-11%)	0%	0%	0%	(31)

[*] $63\% = 92\% \times (91\%)^4$; [¥] $3\% = 81\% \times 69\% \times (38\%)^3$
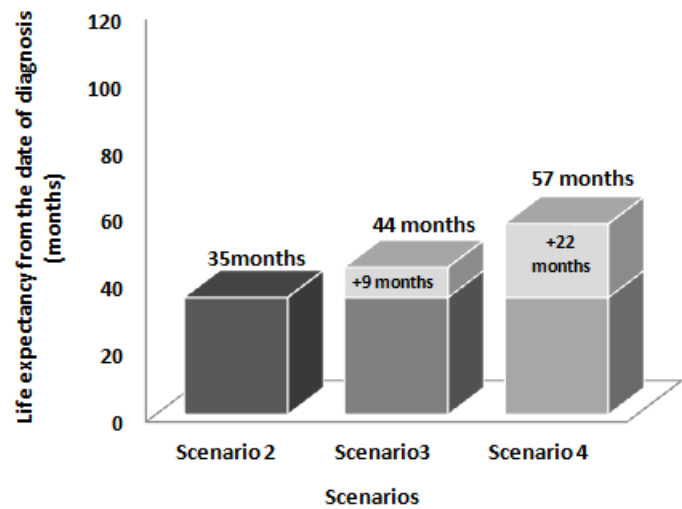
Supplementary Table 2. Newly diagnosed HCV-related HCC patients with compensated cirrhosis in France (aware of their HCV status or not), still alive in the year 2001 (prevalence) and new cases from 2001 to 2010 (incidence) as estimated by a previously published model (5).

	Aware of HCV status			Unaware of HCV status				
	< 70 years	≥ 70 years	Total	< 70 years	≥ 70 years	Total	Total	Range
Prevalence								
2001	107	137	244	185	260	445	689	(649-729)
Incidence								
2001	204	219	423	263	269	532	955	(884-1027)
2002	223	244	467	259	268	527	994	(920-1068)
2003	235	269	504	255	266	521	1025	(949-1101)
2004	246	292	538	250	264	514	1052	(975-1129)
2005	256	316	572	244	262	506	1078	(1000-1157)
2006	258	331	589	245	267	512	1101	(1022-1180)
2007	262	346	608	246	271	517	1125	(1045-1207)
2008	267	361	628	246	275	521	1149	(1067-1230)
2009	270	374	644	245	278	523	1167	(1086-1251)
2010	274	387	661	244	281	525	1186	(1102-1269)

11

Observed death from HCV-related HCC   Predicted death from HCV-related HCC

12

A)

B)

- Scenario 2= currently existing practice of HCC screening , i.e. access to screening equal to 57% and effectiveness of screening corresponding to 42% of patients diagnosed at BCLC-0/A
- Scenario 4= scenario 2 with an efficacy of screening corresponding to optimal HCC screening (70% of patients diagnosed in BCLC-0/A)
- Scenario 5= scenario 3 + scenario 4

14

A) — Life expectancy from the date of diagnosis (months), Scenario 1: 22 months; Scenario 2: 31 months (+ 9 months)

B) — Life expectancy from the date of diagnosis (months), Scenario 2: 31 months; Scenario 3: 37 months (+6 months); Scenario 4: 43 months (+ 12 months); Scenario 5: 57 months (+ 26 months)

C) — Cumulative mortality at 5 years from the date of diagnosis (%), Scenario 1: 92.1%; Scenario 2: 87.5%; RR = 0.94 (0.91-0.98) P = 0.004

D) — Cumulative mortality at 5 years from the date of diagnosis (%), Scenario 2: 87.5%; Scenario 3: 84.2%; Scenario 4: 81.0%; Scenario 5: 73.3%; RR = 0.96 (0.92-1.00) P = 0.078; RR = 0.93 (0.89-0.97) P = 0.001; RR = 0.84 (0.79-0.88) P < .0001
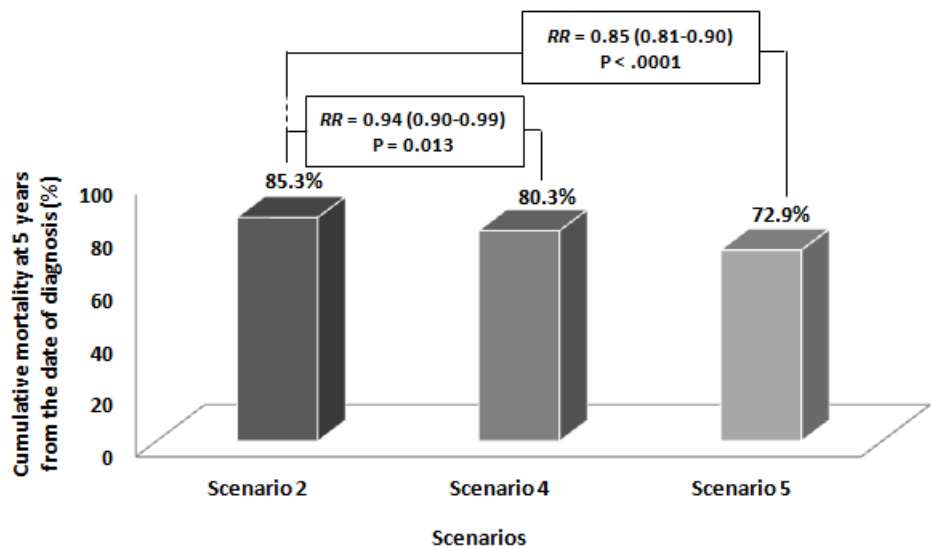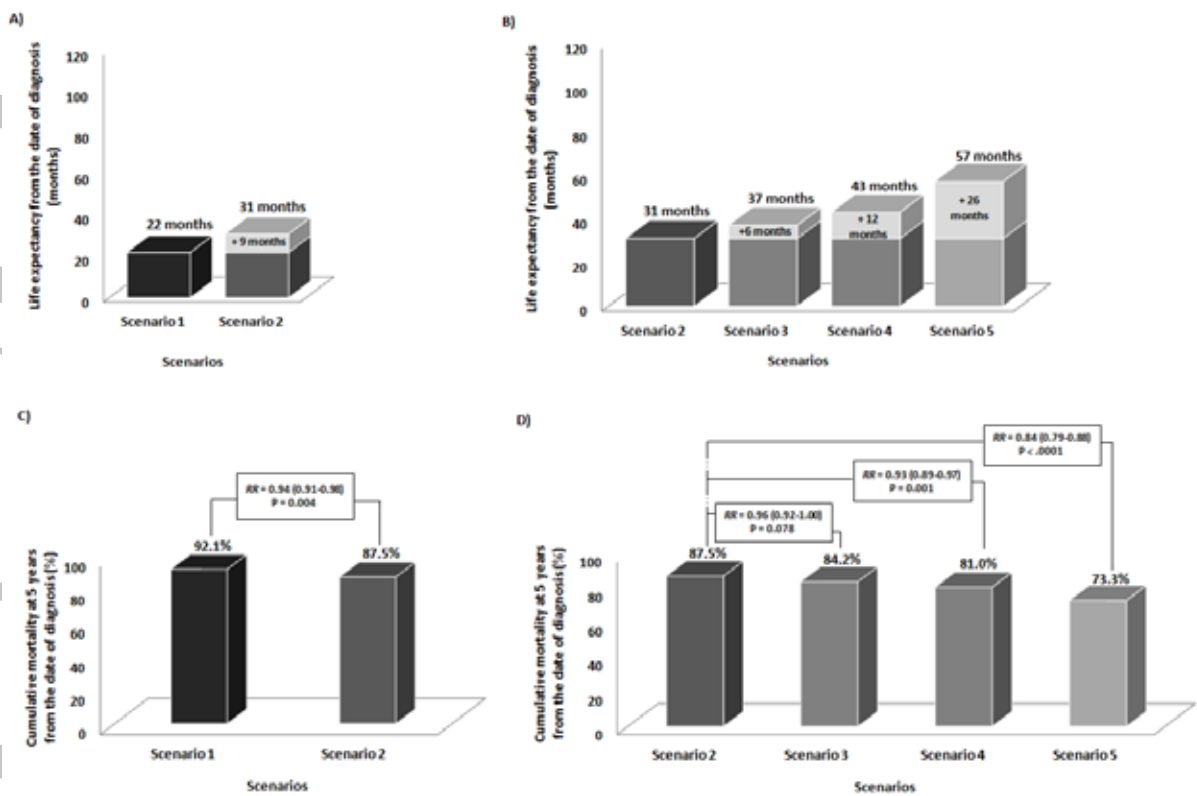
- Scenario 1= no access to HCC screening
- Scenario 2= currently existing practice of HCC screening , i.e. access to screening equal to 57% and effectiveness of screening corresponding to 42% of patients diagnosed at BCLC-0/A
- Scenario 3= scenario 2 with an increase in access to screening to 97%
- Scenario 4= scenario 2 with an efficacy of screening corresponding to optimal HCC screening as observed in the CHC-2000 randomized trial (87% of patients diagnosed in BCLC-0/A)
- Scenario 5= scenario 3 + scenario 4

15

- Scenario 1= no access to HCC screening
- Scenario 2= currently existing practice of HCC screening , i.e. access to screening equal to 57% and effectiveness of screening corresponding to 42% of patients diagnosed at BCLC-0/A
- Scenario 3= scenario 2 with an increase in access to screening to 97%
- Scenario 4= scenario 2 with an efficacy of screening corresponding to optimal HCC screening as observed in the CHC-2000 randomized trial (87% of patients diagnosed in BCLC-0/A)
- Scenario 5= scenario 3 + scenario 4

16