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THE COST-EFFECTIVENESS OF SCREENING FOR HEPATOCELLULAR CARCINOMA IN HEPATITIS C-RELATED CIRRHOSIS

by

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ABSTRACT

Background: Approximately four million individuals in the United States are infected with hepatitis C virus (HCV). The relative risk of hepatocellular carcinoma (HCC) in patients with hepatitis C-related cirrhosis is at least 7 to 10 times that of the general population. The majority of patients who develop symptoms from HCC harbour tumors that are at an advanced and rapidly fatal stage. Screening has therefore been advocated as a mean of reducing cancer-related deaths.

Objective: To determine, from a Canadian perspective, the cost-effectiveness of screening for HCC with biannual liver ultrasound (US) and alpha foetoprotein levels (AFP) in patients with well compensated hepatitis C-related cirrhosis.

Methods: Decision analysis with a Markov model was used to simulate a cohort of 3 500 patients with compensated HCV related cirrhosis who would either be screened biannually with US and AFP or be followed expectantly. Therapeutic alternatives included surgical resection and percutaneous ethanol injection (PEI). The probabilities of clinical events were extracted from a systematic review of the literature on HCC and hepatitis C in Western patients; costs were determined from a third party payer perspective, in 1997 Canadian dollars; utilities were generated from a computerized interview of members of the general public; costs and utilities were discounted at 3% per year.

Results: Screening is associated with an incremental cost-effectiveness ratio of 6 820 dollars per quality-adjusted life year ($/QALY). Screening was an economically attractive strategy over the entire range of possible values of all variables.

Conclusion: Screening for HCC with liver US and AFP in hepatitis C-related cirrhosis is a highly cost-effective strategy, even in populations with a low incidence of HCC.

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INTRODUCTION

Hepatitis C virus (HCV) is the leading cause of chronic liver disease worldwide[1]. The Centres for Disease Control estimate that about four million individuals in the United States are infected with this virus[2]. It is agreed among hepatology experts that HCV-associated liver disease has rapidly become the major problem in hepatology in the Western world, i.e. in Europe and North America, replacing alcohol and hepatitis B[3]. The overall prevalence of chronic HBV infection among the general U.S. population is 0.3% while that of chronic HCV infection is 1.4%. In the United States, blood sampling of all adult patients presenting to an inner-city emergency department during a six-week period, representing a total of 2523 patients, revealed an 18% seropositivity for HCV, 5% for HBV and 6% for HIV-1[4]. During 1980-89, an estimated 200,000 new HBV infections and 150,000 acute HCV infections have occurred annually in the United States [5,6]. Although the incidence of acute hepatitis B is greater than that of hepatitis C, the chronic carrier state is only found in 1% of hepatitis B sufferer, as opposed to 90% in hepatitis C; this explains why the prevalence of hepatitis C is greater than that of hepatitis B.

Hepatitis C virus infection leads to chronic inflammation of the liver which, in most cases, leads slowly and progressively to liver damage[7]. Patients with hepatitis C-related cirrhosis have a decreased life-expectancy. They progressively become at risk of various life-threatening complications of cirrhosis, such as ascites, peritonitis, bleeding varices, encephalopathy, and hepatocellular carcinoma (HCC). In a follow-up study of 131 patients

with chronic HCV infection who had a single blood transfusion to mark the time of exposure, Tong et al, in the United States, found that the average duration of infection was 14 +/- 11, 21 +/- 10, and 28 +/- 12 years for patients to develop chronic hepatitis, cirrhosis, and hepatocellular carcinoma respectively[7].

Case-control studies have revealed that the relative risk of HCC among occidental patients with chronic hepatitis C ranges between 7 in the USA[8] and 10 in Greece[9]. In all cohorts of HCV infected individuals, the occurrence of HCC was strongly related to the presence of cirrhosis as opposed to chronic hepatitis[7,10,11].

HCC is a leading cause of cancer-related deaths worldwide[1]. Its incidence differs greatly among countries and races. The highest incidences of HCC are found among Oriental and South African men, where age-adjusted incidence rates are of 40.0 to 90.0 and 36.0 per 100 000 respectively. In contrast, in most Northern hemispheric countries, the age-adjusted incidence is low, varying between 0.8 to 2.6 per 100 000 men in the Netherlands and Canada respectively. European countries such as Spain, France, Italy and Greece have intermediate age-adjusted incidences of 8.0 to 14.0 per 100 000 men[12]. There has been a significant rise in incidence of HCC over the past two decades in the United States, from 1.4 (95% C.I. 1.3-1.4) to 2.4 (95% C.I. 2.3-2.4) per 100 000[13]. The age-specific incidence has shifted toward younger individuals. It has been suggested that chronic viral hepatitis B and C are responsible for this observation[13,14].

Worldwide, 80 to 90% of HCC's occur in association with cirrhosis[15]. The yearly incidence rate of HCC among cirrhotics ranges from 1% to 4%[11,16,17], increasing with the duration and severity of the liver disease. Other major risk factors are aflatoxin B1

exposure, chronic hepatitis B virus infection, and male gender[15]. Cigarette smoking, family history of HCC, oral contraceptives, anabolic steroids, low vegetable intake, and exposure to thorotrast, arsenic, or vinyl chloride are also reported to be risk factors[15]. In Western Europe and North America, hepatitis C-induced cirrhosis and alcohol-induced cirrhosis account for 60 to 90% of the cases of HCC[18-21].

HCC often has a subclinical phase, lasting up to 2 years, during which it may grow as a solitary mass. The growth rate of HCC is characteristically unpredictable and its detectable preclinical phase is usually short but may vary considerably among affected individuals[22]. The tumour usually presents as a mass lesion of the liver, which may be unifocal or multifocal. Once patients with HCC become symptomatic, the tumor is often large, multifocal, or metastatic. Symptoms related to HCC often are those of decompensated cirrhosis. Other manifestations include fever of unknown origin, severe abdominal pain and acute hemoperitoneum[23]. Rarely, HCC's may trigger various paraneoplastic syndromes (hypoglycemia, hypercalcemia, polycythemia) but these have not been reported as presenting symptoms. Results of therapy in symptomatic patients with HCC is most unsatisfactory and their survival, with or without therapy, averages 2 to 7 months[24]. On the other hand, patients with small tumors hold greater chances of undergoing successful therapy.

Surgical resection is the standard therapeutic modality for HCC. However, most patients with HCC are not candidates for surgery, because either the liver contains multiple tumoral nodules which involve multiple hepatic segments, the tumor is not accessible by surgery, or the patient has significant liver-related or age-related co-

morbidity. For these reasons, orthotopic liver transplantation (OLT) offers obvious advantages over surgical resection, curing both tumor, even if multifocal, and cirrhosis at the same time[25]. Unfortunately, the limited availability of donor livers restrict considerably the use of this modality.

In 1983, Okuda et al developed a technique of ultrasound-guided intratumoral absolute ethanol injections for tumor destruction, so-called percutaneous ethanol injection (PEI)[26]. Initially used for patients with small and multiple lesions, it has since been used for most unresectable tumors, either large, multifocal or associated with advanced cirrhosis. Over the past 10 years, this therapy has gained much popularity for the treatment of HCC. Firstly, it is a safe procedure, which, as opposed to the other available therapies, can even be used in patients with significant co-morbidity, such as liver failure. As well, it is cheap and easily performed in any radiology department, rendering this therapy widely available[27]. It can also be effectively used for tumor recurrence. The use of PEI has resulted in improved survival rates of individuals with unresectable tumors[28]. The limitations of PEI are that it may not successfully treat either very large lesions (i.e. greater than 5 cm in diameter), multiple lesions (i.e. greater than 3 per liver), or diffuse infiltrative lesions. Intratumoral therapy has also been performed with acetic acid or hot saline, but ethanol is the most commonly used substance at this time. Chemotherapy with various agents has had limited success, especially if infused systemically. However, if the chemotherapy is infused selectively, i.e. directly into the hepatic artery or in conjunction with lipiodol (a liposoluble radio-contrast), some favorable results have been obtained.

Multimodal therapy, using pre operative intra-arterial therapy or combined PEI with selective intra-arterial chemotherapy may have additive benefits[29].

Survival from HCC not only depends on the stage of the tumour but also on the degree of co-existing cirrhosis[30,31]. The relative effectiveness of PEI and surgery have never been compared in a randomized controlled fashion. However, studies of each of these modalities, among similar populations, have yielded comparable survival rates. These comparative reports reveal that, in selected cases, the long-term (i.e. 3 to 5 years) survival of patients undergoing PEI is similar to that of the patients who undergo surgical resection, and may be up to 60% at 5 years[28].

Screening of high-risk patients has therefore been emerging as an approach to detect the malignancy at an earlier, resectable stage and to, hopefully, reduce the high mortality from HCC. Several diagnostic modalities can be used for tumor detection in cirrhotics. The two most common measures are serum alpha foetoprotein (AFP) levels and liver ultrasonography (US). As a single or periodic screening test, AFP has a sensitivity of 85% to 90% and a specificity of 70% to 80%[32]. Liver US performs better and has a sensitivity of 88% and a specificity of 98%[32]. The combined use of AFP and liver US may be more sensitive than either modality alone. Liver US may detect tumors as small as 2 cm in diameter and has the advantage of providing information about the resectability of the HCC but it is also operator dependent. On the other hand, even if high titre of AFP are usually associated with large tumors, a low but rising titre of AFP may be observed prior to the ultrasonographic detection of an HCC[33].

The efficacy of screening cirrhotics for HCC, using serial AFP levels, liver US, or both, has been prospectively evaluated in various parts of the world. The best results from screening have been reported from Japan, where tumors are small and often encapsulated, and where up to 70% of the screened population would have resectable tumors[34]. It is suggested that, in Oriental countries, HCC is biologically different from that of Occidental countries. Reports from France and Italy have been contradictory: some report no increased proportion of resectable tumors compared to those who present with symptoms[35], while others did detect resectable tumors at a rate comparable to the Japanese[36]. This may be explained by several factors: the varying incidence of HCC among high risk groups, which may in turn depend on the underlying liver disease (both its etiology and duration); the biology of the tumor; the frequency at which screening is performed[33]; the compliance of the screened population[35]; and the characteristics of the screening tests.

Moreover, even if screening can effectively detect resectable tumors, survival may not be affected. Firstly, if surgical resection is the only evaluated therapeutic modality, many patients would not be surgical candidates because of the advanced degree of cirrhosis and age. More importantly, therapy may not affect the high recurrence rate of the tumor, which may occur either at the resection margin or in distant parts of the cirrhotic liver[1]. However, the report of long-term (i.e. greater than 10 years) survivors among screened individuals is evidence in favor of screening, since patients detected with clinically suspected HCC's would not survive beyond 1 year of diagnosis[37]. This

observation is evidently subject to length-time bias, since screen-detected cases with a long preclinical phase may be overrepresented[38].

Despite these controversies, experts around the world now recommend screening cirrhotics for HCC. The NIH and the Italian Association for the Study of the Liver recommend using AFP level every 3 to 6 months and liver US every 6 months to 1 year[39,40].

In summary, in cirrhosis, HCC is a common, devastating illness. Several different treatments are used, as well as several different screening strategies. It remains unclear whether screening for HCC in cirrhotics is a clinically and economically sound practice.

To establish whether or not screening programs for a given cancer are justified, certain criteria should be fulfilled: 1) that the tumor is an important public health problem; 2) that it has an identifiable latent or subclinical phase; 3) that subjects with an increased likelihood of developing the tumor can be identified; 4) that the techniques that are to be used for tumor detection are effective and that their cost is acceptable; and, 5) that treating the tumor in the subclinical phase will improve survival rates[41]. In China, Japan or South Africa, where HCC is frequent among all adult ages, screening for HCC is a well accepted practice. However, since the tumor is less frequent in the Western population, the indications for HCC screening remain controversial. Physicians' and policy makers' decisions to adopt or reject this screening practice requires the knowledge of its cost-effectiveness. In calculating the cost-effectiveness of HCC screening, the impact of screening using AFP and liver US or AFP alone, as well as the impact of the choice of therapeutic modality should be considered.

Decision analysis is a technique which is particularly useful in resolving controversial healthcare issues such as the one presented here. On one hand, through its ability to synthesize data from multiple sources and to extrapolate from primary data, it can accurately determine the prognostic implications of a given intervention. On the other hand, it can also combine multiple attributes such as costs and quality of life and transform simple decision algorithms into complex economic evaluations. Decision analysis can therefore be of use at multiple levels in healthcare: from bedside decision making to health economics and policy making levels.

A Markov model is a special type of decision analysis which is particularly appropriate for modeling the progression of chronic diseases. The model allows the patient to move over time between a finite number of mutually exclusive health states, based on distinct transition probabilities. It is a particularly well-suited approach for the present problem, since a patient with well compensated cirrhosis may develop either decompensated cirrhosis, HCC, or die, with increasing, time-dependent, probabilities.

If we consider the present problem of whether to screen for HCC in patients with HCV-related cirrhosis, decision analysis offers several advantages over other methods of evaluation. Firstly, it is obvious that the costs and efforts that would be required to perform a randomized controlled trial on screening for HCC in HCV-related cirrhosis, especially in a low prevalence area such as North America, would be too great to justify such an endeavor. However, since large enough cohorts of HCV-infected patients have now been followed for several years, the transition probabilities of one HCV-related health state to another are therefore available and can be directly input into a decision analytic

model. In this sense, decision analysis can be a particularly appropriate technique for the study and the management of diseases that are either rare, multisystemic, or that are associated with long-term complications.

In summary, HCC is an important public health problem, that frequently has an identifiable subclinical phase. Populations with HCV-related cirrhosis are at high risk for HCC, and may benefit from screening followed by treatment. However, the effectiveness and costs of periodic screening for HCC among patients with HCV-related cirrhosis, considering currently available therapeutic modalities for HCC, are unknown.

Therefore, the objective of this analysis was to determine, from a Canadian third party payer perspective, the economical attractiveness of screening for HCC in patients with well-compensated HCV-related cirrhosis. Decision analysis with the Markov model offers a valid approach to this problem by allowing us to 1) synthesize the multiple sources of data on the natural history of HCV- related cirrhosis, the natural history of HCC, the effectiveness of screening for HCC, as well as the efficacy of surgical resection and PEI in the treatment of HCC; 2) link relative costs and quality of life measure to each outcome; 3) determine, from a third-party perspective, the incremental cost per quality-adjusted life year gained by patients with HCV-related cirrhosis who undergo screening for hepatocellular carcinoma; and 4) determine, by sensitivity analysis, the factors responsible for the dominance of one strategy over the other.

METHODS

1 Decision Analytic Model

1.1 Markov model

To evaluate the benefit of screening for HCC among patients with hepatitis C related cirrhosis, we developed a decision analytic model that integrates the natural histories of cirrhosis and of HCC simultaneously. HCV related cirrhosis is a state of progressive liver damage that translates into an asymptomatic early stage (Child's class A), followed by a symptomatic or "decompensated" advanced stage, sequentially referred to as Child's classes B and C. The studied population of cirrhotics is therefore heterogeneous and evolves over time from a stage of compensated cirrhosis (stage A) to decompensated cirrhosis (stages B and C), and to death. The risk of developing HCC increases with the duration of the cirrhosis, making patients with decompensated cirrhosis at greater risk than those with compensated cirrhosis.

The use of a Markov model enables our hypothetical cohort of patients with hepatitis C-related cirrhosis to move through states of health defined by clinical events. Time is represented by a series of cycles. During each cycle, patients may remain in the same health state, progress to decompensated cirrhosis and/or to HCC, die of complications of liver disease (including HCC), die of complications of investigations or therapies for HCC, or die of unrelated causes, the probability of which is related to age, gender and race. At the end of

each three-month cycle, the proportion of the population who shifts from one given state of health to another is based on probabilities extracted from the literature.

The structure of the Markov model is presented in Figure 1. At stage zero, all patients are in the compensated cirrhosis state. The decision note at the root of the tree (clear square; figure 1a) leads to either the "Screen" Markov subtree or the "No Screen" Markov subtree. Both subtrees have a similar structure and similar outcomes; only probabilities differ. The cycle length is three months. Each subtree contains 12 health states, including the "death" state. Of these 12 health states, 9 are HCC-related. In order to analyse the death outcome more thoroughly, 15 "death states" were created, each named after the specific cause of death. Of these 15 causes of deaths, 11 were HCC-related (Table 1).

Figure 1: **Markov model of screening for hepatocellular carcinoma in patients with well-compensated hepatitis C-related cirrhosis.**

A: **Decision node.**

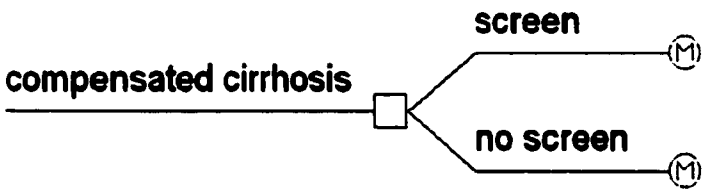


Fig. 1A: The decision node (square) represents the decision to screen of not to screen patients with compensated cirrhosis for HCC. Each group of patients ("screen" and "no screen") then go through the Markov process, represented by the round node.

B: Markov health states.

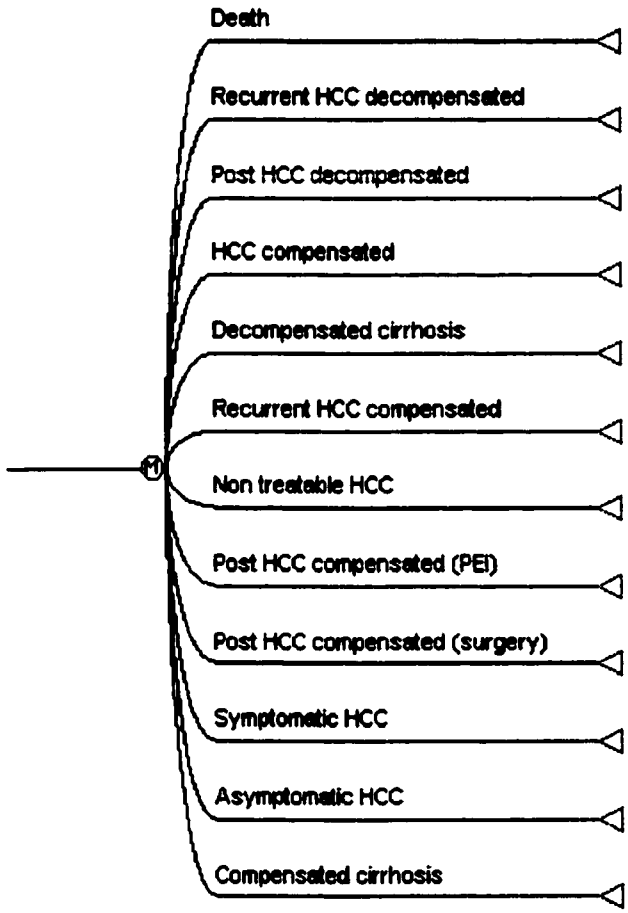


Fig. 1B: The Markov node (circle) leads to 12 different subtrees, each representing a health state. Each health state is mutually exclusive. At the first cycle, all patients enter the "compensated cirrhosis" subtree. Subsequently, the patients are redistributed among the 12 health states, according to the probabilities of events during each cycle. Death is the absorbing health state which indicates the state at which the Markov process ends.

C: Compensated cirrhosis subtree.

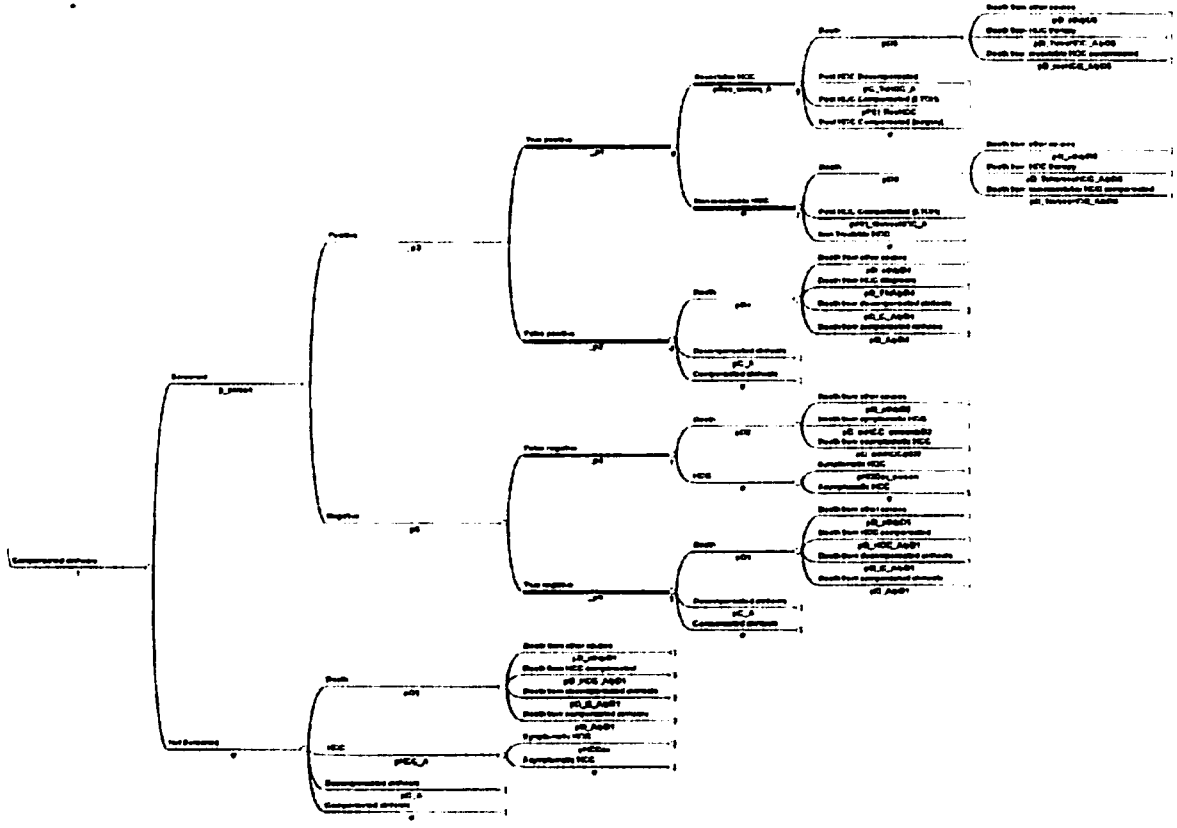


Fig. 1C: Each chance node is represented by a clear circle and each terminal node is represented by a clear triangle. In a Markov process, each terminal node indicates the health state which is entered at the start of the next cycle. The compensated cirrhosis subtree may take either one of two structures, depending on the probability of screening. The "No screen" subtree represents the natural history of compensated cirrhosis. The "Screen" subtree integrates the screening test and its characteristics, the subsequent staging and therapeutic management of the detected cases of HCC.

D: Other subtrees.

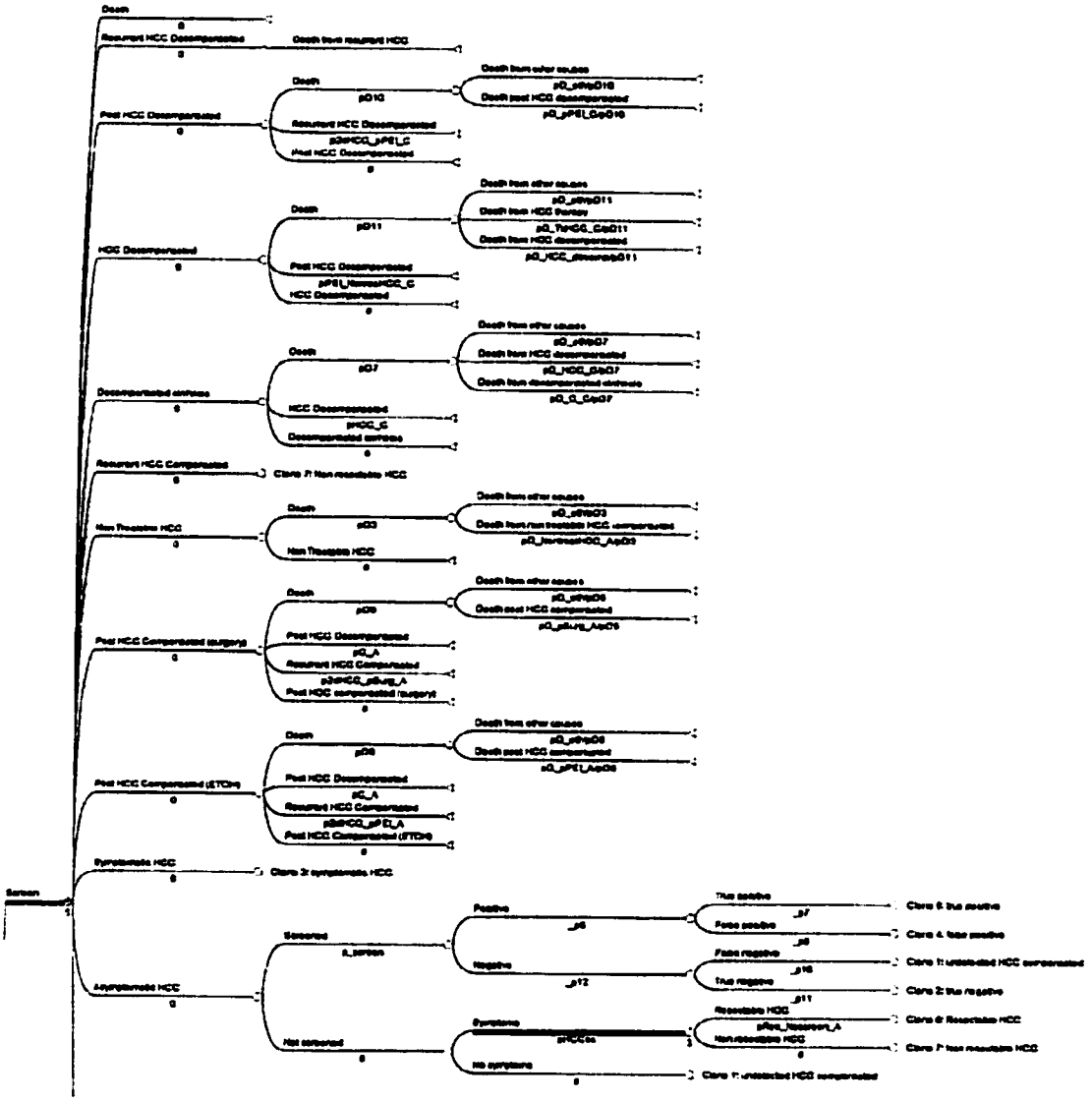


Fig. 1D: The subtrees for the 11 health states other than "compensated cirrhosis" are represented here. The "asymptomatic HCC" patients who are screened follow outcomes similar to those described in the screened subtree of the "compensated cirrhosis" health state, outcomes which are referred to as "clones", represented by the thick branches in figure 1C and 1D. Each clone is designated by a number, which is written at the chance node immediately following that thick branch. Clones are also used in the "symptomatic HCC" and "Recurrent HCC Compensated" subtrees.

Table 1: **Causes of death.**

1. Death from cause unrelated to liver disease
2. Death from compensated cirrhosis
3. Death from HCC in compensated cirrhosis
4. Death from asymptomatic HCC in compensated cirrhosis
5. Death from resectable HCC in compensated cirrhosis
6. Death from non resectable HCC in compensated cirrhosis
7. Death from symptomatic HCC in compensated cirrhosis
8. Death from non treatable HCC in compensated cirrhosis
9. Death from HCC diagnosis
10. Death from HCC therapy
11. Death post HCC in compensated cirrhosis
12. Death from recurrent HCC
13. Death from decompensated cirrhosis
14. Death from HCC in decompensated cirrhosis
15. Death post HCC in decompensated cirrhosis

1.2 Decision Analysis

At first, a Markov analysis was performed to calculate the unadjusted life expectancy and to determine how many cycles are spent in each health state in each cohort. The gain in life expectancy, in life-years, was calculated by subtracting the area under the survival curve of the non-intervention arm from that of the intervention arm. For the quality-adjusted life expectancy and the cost-effectiveness ratio, each state of health was assigned a utility (see "Data - Utilities" section, below), which, when multiplied by the proportion of the cohort belonging to that state, represents the cycle-specific incremental utility for that state. By recording the proportion of the cohort in each health state at the end of each cycle, the associated treatment costs and adjusting for the utility related to each health state, the related costs per quality-adjusted life year ($/QALY) as well as the cumulative quality-adjusted life expectancy (QALE) were calculated for each intervention arm, i.e., the arm undergoing screening and the arm not being screened. The model was run until the entire population had reached death, and the cycle-specific incremental utility is near zero. The incremental QALE was calculated by subtracting the QALE of the non-intervention arm from that of the intervention arm. Assuming that no strategy would be "dominant", i.e. both less costly and more effective than the other, the incremental cost-effectiveness ratio (ICER) was calculated as the difference in mean costs between the intervention and the no intervention arms over the difference in mean effect between the intervention and the no intervention arms, i.e.

$$\text{ICER} = \frac{(\text{mean costs})_{\text{SCREEN}} - (\text{mean costs})_{\text{NO SCREEN}}}{(\text{mean effect})_{\text{SCREEN}} - (\text{mean effect})_{\text{NO SCREEN}}}$$

where the "effect" can be measured in quality adjusted life years (QALY) or in non adjusted life years (LY) units. The intervention was compared to the next least intensive strategy.

All analyses were performed using decision analysis software (Decision Analysis by TreeAge, DATA version 3.0; TreeAge Software, Inc., Boston, MA).

1.3 Study population

The hypothetical cohort was composed of North American patients from either gender, aged 30 to 70 year old, and with well compensated, biopsy-proven, HCV related cirrhosis (Child Pugh class A). The demographics of the population are derived from the published data on prospectively screened occidental cohorts of HCV-related cirrhotics. The patients were not differentiated based on the nature of their HCV viral genotype. The patients were not suffering from concomitant HBV infection or any other cause of chronic liver disease.

1.4 Intervention

In the intervention arm (i.e., the "Screen" subtree), all subjects with compensated cirrhosis were screened for HCC with liver ultrasound (US) and alpha-foetoprotein (AFP) levels every six months (i.e., every other cycle), as recommended by the US National Institute of Health [40]. Screening stopped once either decompensated cirrhosis or HCC occurred. Those who screened positive underwent a confirmatory US guided fine needle biopsy of the mass lesion, to become either "true positives" or "false positives". "False positives" were followed like the remainder of the cohort, according to the screening

protocol. "True positives" were then staged for tumor size, location, local extension, portal vein thrombosis and distant metastasis in order to determine the resectability of the tumor. The staging procedure included an abdominal CT scan, a bone scan and a chest X ray (CXR). Underlying liver function was assessed by serum bilirubin and albumin levels as well as the presence of ascites[26]. Depending on the stage of the tumor, its uni- or multi-focality, its location within the liver, as well as the patient's age and general health status, the HCC could be resectable, non resectable but amenable to percutaneous ethanol injection (PEI) therapy, or non treatable.

In the base-case analysis, subjects who were resectable underwent surgery; those who were unresectable but amenable to PEI underwent PEI; the remaining unresectable patients were considered "non treatable"and received supportive care. Those who survived the surgical resection or the PEI therapy respectively entered the "post HCC compensated (surgery)" health state and the "post HCC compensated (PEI)" health state at the next cycle. Those who survived the intervention but who developed decompensated cirrhosis entered the "post HCC decompensated" health state. Following HCC therapy, surveillance for recurrence was performed every six months with liver US and AFP levels. With time, patients could experience recurrent HCC (and enter the "recurrent HCC compensated" health state), decompensated cirrhosis (and enter the "post HCC decompensated" health state), or death. Recurrences were confirmed by fine needle aspirate (FNA) and treated by PEI. Those with decompensated cirrhosis who developed a recurrence died during the same cycle.

The subjects who screened negative could have been "true negatives" or "false negatives". "False negatives" became "asymptomatic HCC" who would either get screened

again six months later or who became symptomatic and underwent repeated investigations before then. Following their diagnosis, they were once again staged and followed the path of the "true positives" as described above. The "true negatives" continued to be screened every six months and, as for any member of this cohort, could, with time, develop either liver failure and/or die. Subjects who developed liver failure entered the "decompensated cirrhosis" health state. From this point, no more screening was performed. These subjects could, with time, develop HCC or die. A proportion of those with HCC would be amenable to PEI therapy and enter the "Post HCC decompensated" health state.

In the "No Screen" subtree, subjects who developed HCC were tested only once they became symptomatic from the cancer, and underwent subsequent staging. From there, they could enter any of the HCC related health states, as described above.

2 Structural assumptions

For simplification, the decompensated state was reached as soon as any cirrhosis-related event occurred. Those events could be ascites, jaundice, encephalopathy, variceal bleed or hepato-renal syndrome. An unspecified infectious episode, however, was not considered as a decompensated cirrhosis related event. We assumed that death would invariably occur after any third event. An event was defined as either decompensation, occurrence of HCC, or recurrence of HCC.

We assumed that FNA of the tumor is 100% sensitive and 100% specific for HCC. Once a liver nodule was detected by US in a patient with compensated cirrhosis, FNA was

performed. However, in the "post HCC" health states, US detected nodules were assumed to be HCC's and FNA was not performed. In decompensated cirrhosis, detection of a liver nodule by US was followed by confirmatory FNA in only 50% of the case, assuming that in the other 50% of patients, a severe coagullopathy would contraindicate the intervention. These patients were assumed to have HCC.

Surgical resection and PEI were the two therapeutic modalities considered. The choice of a therapeutic modality depended on the degree of liver impairment, the size, location, number and type of tumoral involvement[26], as well as the type of analysis performed. In order to undergo a surgical resection, a patient must have had good liver function (i.e., compensated cirrhosis), no significant comorbidity, as well as a single tumor nodule located within reach of surgical approach[42,43]. PEI, on the other hand, was performed independently of the degree of liver failure and/or comorbidity. However, PEI was not performed if the tumor was greater than 5cm in diameter, or if it was diffusely infiltrating the liver parenchyma, or if greater than three tumor nodules were present[27].

Liver transplantation was not considered to be a therapeutic option because the estimation of the clinical and economic outcomes of liver transplantation were beyond the scope of this thesis.

We assumed that the probability of HCC-related symptoms is directly proportional to the size of the tumor, such that all tumors equal or greater to 6 cm in diameter would be symptomatic.

We assumed that tumor recurrence would not be resectable and that it would be treated with PEI, using the above selection criteria.

3 Data - *Likelihood of Events*

3.1 Literature search

A systematic review of the literature was performed to determine the probabilities of each state transition. Because of the previously described difference in factors of hepatocarcinogenesis between oriental and occidental countries, only the sources pertaining to the study of Western populations were retained. The content areas of interest were: the natural history of hepatitis C related cirrhosis, screening for HCC in cirrhotics, the natural history of untreated HCC, the outcomes of surgical therapy or percutaneous ethanol injection in cirrhotics with HCC. Electronic databases were searched by using the search strategy presented in Appendix 1. This search strategy was applied to the following databases: Medline 1966-May 1998, Cancerlit, Biological abstracts, Current contents and Embase. Between November 1997 and April 1999, the strategy was run on each monthly update of the Medline database by the library services at the University of Ottawa. There were no additional findings over the publications identified by Medline. Proceedings of the American and European associations for the study of liver diseases, major hepatology textbooks, as well as the reference lists of all the original research and review articles were retrieved (see Table 2 for the yield of the literature search). The search strategy was designed to retrieve most publications pertaining to HCC, its diagnosis, treatment, and natural history, as well as HCV-related cirrhosis. For this reason, the initial set of reference included more than 3000 references. However, the majority of these references were not of interest to us, for several reasons. Approximately half the initial set was composed of basic science reports; another

large proportion of studies were carried in Oriental subjects; finally, all data pertaining to HCC therapy with either chemotherapy or liver transplantation was excluded.

Table 2: Yield of the literature search.

1	Computerized databases	3300
2	Second browse through titles and abstracts, with simultaneous partitioning into subfiles:	
2.1	Risk of HCC in hepatitis C:	142
2.2	Natural history of hepatitis C:	29
2.3	Reviews on hepatitis C:	18
2.4	Natural history of HCC:	69
2.5	Reviews on HCC:	39
2.6	Screening for HCC:	29
2.7	Diagnosis and staging of HCC:	80
2.8	Hepatic resection for HCC:	77
2.9	Percutaneous ethanol injection therapy for HCC:	119
	TOTAL:	530
3	Additional references, identified through reference lists of selected articles, textbooks and syllabi of hepatology meetings:	22
4	Final selection of articles, after reviewing original publications, for data extraction:	
4.1	Natural history of hepatitis C:	16
4.2	Natural history of HCC:	20
4.3	Screening for HCC:	18
4.4	Diagnosis and staging of HCC:	22
4.5	Hepatic resection for HCC:	37
4.6	Percutaneous ethanol injection therapy for HCC:	32
	TOTAL:	**145**

3.2 Inclusion criteria

Inclusion criteria concerning the study population were as follows: North American or European, cirrhosis had to be present in at least 80% of the studied population, the

etiology of which had to be either hepatitis C or cryptogenic (for studies recruiting patients prior to the availability of hepatitis C testing) in > 60% with less than 15% of cirrhosis due to alcohol and/or hepatitis B. For the screening methodology, either ultrasound alone or ultrasound combined with AFP was considered. For the interventions, we considered surgical resection with intent of cure or percutaneous ethanol injection (PEI); percutaneous intralesional therapies other than alcohol were excluded and combined therapies (e.g. intraarterial chemotherapy prior to surgical resection) were also excluded.

3.3 Data extraction

The methods used to extract the data will be briefly summarized. It has recently been stressed that the terms probabilities and rates are often used interchangeably in the medical literature[44]. A probability is the proportion of a population at risk that makes a transition over a specified period of time, whereas a rate is an instantaneous likelihood of transition at any point in time. If these concepts are not carefully differentiated and treated appropriately, errors of up to 14% may be introduced in the calculation of transition probabilities[45]. Moreover, the calculation of a probability will differ depending on the nature of the cohort (fixed or dynamic) and the presence of drop-outs.

To address these concerns, an unbiased method was used for transforming rates into probabilities and annual probabilities into cycle-specific probabilities[45]. The following equations were used:

3.3.1 To transform rates into probabilities (also available as the "RatetoProb" medical function of the DATA analysis software):

probability = $1 - e^{(-\text{rate} * \text{time})}$

where time = (duration of probability period)/(duration of rate period)

Example: "The yearly incidence of mortality was 1.9 over the first 5 years"[11]. Probability in a 3-month cycle = $1 - e^{(-\text{rate} * \text{time})} = 1 - e^{(-1.9 * 3\text{ months}/12\text{ months})} = 1 - 0.6219 = 0.3781$

3.3.2 To transform an overall probability over the time period into a cycle-specific probability:

cycle-specific probability = $1 - (1 - tp_t)^{1/t}$

where tp_t = overall probability over the time period t

t = the number of equal time intervals (i.e. cycles)

Example: "The probability of survival after the onset of the first major complication of the disease was 50% at 5 years"[11]. Probability in a 3-month cycle = $1 - (1 - tp_t)^{1/t} = 1 - (1 - (0.5))^{(1/(4\text{ cycles/year} * 5\text{ years}))} = 1 - 0.5^{1/20} = 0.0341$

These transformations are valid as long as the rate is constant over time. To ensure that the mortality rates were constant in our cohorts, probabilities were extracted for every year of follow-up then transformed into annual rates. In situations where the rate was changing over time by more than a quarter-fold, the one-year probability was used for calculation of the cycle-specific transition probability.

Probabilities extracted from multiple sources were combined using their weighted mean average, which was considered the "best estimate" for these probabilities. The range of available values was recorded for use in sensitivity analysis as indicated. Since the Markov

model used a 3 months cycle length, annual probabilities were converted to probabilities of transition per 3 months cycle.

For coherence of the decision model, some probabilities were linked when judged appropriate. The reference group used for calculation of the relative risk (RR) was compensated cirrhosis. For example, probabilities of events occurring in decompensated cirrhosis were linked to those of compensated cirrhosis in the following manner:

Probability of event "x" in decompensated cirrhosis =

Relative risk of event "x" in decompensated cirrhosis

X Probability of event "x" in compensated cirrhosis.

The range of values of the relative risk of a linked probability was calculated as follows:

Lower limit of the relative risk of event "x" in decompensated cirrhosis =

Lower limit of probability of event "x" in decompensated cirrhosis

(divided by) Upper limit of probability of event "x" in compensated cirrhosis.

Upper limit of the relative risk of event "x" in decompensated cirrhosis =

Upper limit of probability of event "x" in decompensated cirrhosis

(divided by) Lower limit of probability of event "x" in compensated cirrhosis.

Best estimate of the relative risk of event "x" in decompensated cirrhosis =

Best estimate of probability of event "x" in decompensated cirrhosis

(divided by) Best estimate of probability of event "x" in compensated cirrhosis.

The probabilities of HCC-related deaths were linked to the baseline probability of death from HCC in the presence of underlying cirrhosis (see "Methods" Section 3.4.2.1) and the probabilities of recurrent HCC were linked to the probability of HCC in HCV-related cirrhosis using similar methodology.

3.4 Outcomes

The annual probabilities of clinical events are presented in Table 3. For each probability, the best estimate, lowest value and highest value are presented. The sources of probabilistic data as well as the pertinent assumptions for each clinical outcome will be detailed in the following paragraphs. We will first review the outcomes related to compensated and decompensated cirrhosis, followed by the outcomes of cirrhotic patients with HCC. The sources of data on the sensitivity and specificity of the screening will be reviewed at the end of this section.

Table 3: **Annual probability of events.**

A: **Natural history of HCV-related cirrhosis**

Parameter	Lower limit	Upper limit	Best estimate	References
Annual probability of decompensated cirrhosis in compensated HCV related cirrhosis	0.0381	0.0661	**0.044**	11,46
Annual probability of death in compensated HCV related cirrhosis	0.0018	0.0202	**0.009**	11,16,46
Annual probability of death in decompensated HCV related cirrhosis	0.1294	0.1674	**0.1489**	11,16,46
Annual probability of HCC in compensated HCV related cirrhosis	0.0143	0.0275	**0.0212**	11,16,46
Relative risk of HCC in decompensated cirrhosis	1	10	**2.4**	47,48

B: Natural history of cirrhotic patients with HCC

Parameter	Lower limit	Upper limit	Best estimate	References
Probability of death in cirrhotic patients with HCC				
Baseline probability of death from HCC in the presence of underlying cirrhosis	0.09	0.99	**0.52**	36,49,50,51,52,53
Annual probability of death from resectable HCC in compensated cirrhosis	0.04	0.5	**0.19**	54,28,31,55,56
Relative risk of death from resectable HCC in compensated cirrhosis	1.3	79.74	**14.56**	24,57,58,59,60,61
Annual probability of death from non resectable HCC in compensated cirrhosis	0.18	1	**0.59**	
Relative risk of death from non resectable HCC in compensated cirrhosis	5.84	159.49	**45.22**	
Annual probability of death from asymptomatic HCC in compensated cirrhosis	0.04	0.08	**0.06**	31,55
Relative risk of death from asymptomatic HCC in compensated cirrhosis	1.3	12.76	**4.6**	30,62
Annual probability of death from symptomatic HCC in compensated cirrhosis	0.5	0.72	**0.672**	
Relative risk of death from symptomatic HCC in compensated cirrhosis	16.23	114.83	**51.5**	
Annual probability of death from decompensated cirrhosis with HCC	0.25	0.95	**0.65**	28,63,31,64,61
Probability of resectability				
Probability of resectable HCC in screened compensated cirrhosis	0.06	0.87	**0.43**	33,65,52,36,66,51, 53
Probability of resectable HCC in non screened compensated cirrhosis	0.06	0.34	**0.12**	67,68,62,52,64,50, 69,70
Relative risk of resectability in non screened compensated cirrhosis	0.07	5.67	**0.28**	

C: Annual probability of events related to HCC therapy

Parameter	Lower limit	Upper limit	Best estimate	References
Probability of events related to surgical resection				
Probability of death from HCC resection in compensated cirrhosis	0.025	0.2	**0.1**	71,72,73,67
Annual probability of death post HCC resection in compensated cirrhosis	0.08	0.4	**0.24**	25,65,54,74,71,75, 76,77,78,79,80,81, 82,73,67,83,84,85, 28,86,66,56
Relative risk of death post HCC resection	1.45	21.05	**8.01**	
Annual probability of recurrent HCC post HCC resection in compensated cirrhosis	0.1	0.37	**0.23**	54,65,74,77,79,87, 73,86,83
Relative risk of HCC post resection	3.64	25.87	**10.85**	
Probability of events related to PEI therapy				
Probability of PEI therapy in non resectable HCC	0	1	**0.33**	28
Probability of decompensation from PEI therapy in compensated cirrhosis			**0.0034**	27
Probability of death from PEI therapy in compensated cirrhosis	0.0009	0.007	**0.001**	27,88,57,63,89,90, 91,86,92,93
Probability of death from PEI therapy in decompensated cirrhosis	0.0009	0.014	**0.007**	
Probability of persistent HCC post PEI therapy	0	0.23	**0.09**	63,94,90,91,86,92, 95,93
Annual probability of death post PEI therapy in compensated cirrhosis	0	0.17	**0.07**	63,89,90,94,91,86, 92,96,93
Relative risk of death post PEI therapy in compensated cirrhosis	0	8.95	**2.34**	
Annual probability of death post PEI therapy in decompensated cirrhosis	0.19	0.41	**0.31**	63,8990929693
Relative risk of death post PEI therapy in decompensated cirrhosis	3.45	21.58	**10.34**	
Annual probability of recurrent HCC post PEI therapy in compensated cirrhosis	0.15	0.36	**0.23**	63,89948693
Relative risk of HCC post PEI therapy in compensated cirrhosis	5.45	25.17	**10.85**	
Annual probability of recurrent HCC post PEI therapy in decompensated cirrhosis	0.3	0.37	**0.3**	94
Relative risk of HCC post PEI therapy in decompensated cirrhosis	10.91	25.87	**14.15**	

3.4.1 Natural history of HCV-related cirrhosis (Table 3a)

3.4.1.1 Probability of decompensated cirrhosis

There are three recently published large European cohort studies on the natural history of compensated hepatitis C-related cirrhosis[11,16,46]. These provide data on a total of 892 cirrhotics followed for a maximum of 15 years. The mean age ranged between 54 and 56 years old and 59% were male. In these studies, the annual probability of decompensated cirrhosis in HCV-related compensated cirrhosis, as defined by the onset of the first major complication of the disease and excluding HCC, varied between 0.0381 and 0.0661 (weighted mean average: 0.0440).

3.4.1.2 Probability of death from HCV-related cirrhosis

In the same studies as above, the disease-specific annual probability of death in compensated cirrhosis without the features of decompensated cirrhosis is on average of 0.0005 and the annual probability of death from all cause in HCV-related cirrhosis ranges from 0.02 to 0.002 (Weighted mean average 0.009) [11,16,46]. The annual probability of death after the onset of the first major complication of cirrhosis, varied between 0.1294 and 0.1674 (weighted mean average 0.1489)[11,16].

3.4.1.3 Probability of HCC in HCV-related cirrhosis

The probability of HCC in cirrhosis is directly related to the duration of cirrhosis[7,11,97], making the risk of HCC in decompensated cirrhotics significantly greater than that of compensated cirrhotics. Data from the large prospective cohorts

did not specifically present the incidence of HCC in compensated and decompensated cirrhosis.

The short-term screening studies on patients with compensated cirrhosis were therefore judged to reflect the incidence of HCC more accurately, since, these populations were exclusively composed of patients with compensated cirrhosis. However, the screening studies, in general, were conducted on heterogeneous groups of cirrhotics. For example, alcohol-induced cirrhosis was the major etiologic factor in French studies while most Italian and Spanish studies were done on predominantly post infectious cirrhosis (either hepatitis B or C related). Since the relative risk of HCC is believed to vary according to the factors responsible for the liver disease, we used only studies conducted on populations who were HCV positive in at least 60%. As well, we excluded studies where multiple factors were at play in a majority of HCV infected patients such as concomitant intake of greater than 80g per day of alcohol or concomitant hepatitis B infection. Unfortunately, the potential presence of co-factors is not always reported, so sensitivity analysis considered values ranging from the lowest available probability to the highest.

For decompensated cirrhosis, the probability of HCC was assumed for two reasons: 1) the annual incidence of HCC is well described for patients with compensated cirrhosis, i.e. eligible for screening, but not for patients with decompensated cirrhosis; 2) many patients dying from decompensated cirrhosis actually have undetected HCC, as revealed by its unsuspected presence in explanted livers from patients with decompensated cirrhosis[98]. Zaman prospectively followed

613 cirrhotics for five years[99]. Nineteen percent of the patients who died of decompensated cirrhosis did in fact have an associated HCC. Fattovitch reported that the 5 year probability of death from decompensated cirrhosis was 50%, with approximately 20% dying within the first year[11]. Gentilini reported that the probability of death at 1 year was also of 20%[16]. Based on Zaman's report, if we assume that 19% of these deaths are due to HCC, then the yearly incidence of HCC in decompensated cirrhosis is around 4%. This incidence is valid since it corresponds to a relative risk of HCC in decompensated cirrhosis of one to four times that of compensated cirrhosis. For sensitivity analysis, we varied this estimate from one to twenty times the risk of those with compensated cirrhosis.

3.4.2 Natural history of cirrhotic patients with HCC (Table 3b)

3.4.2.1 Probability of death from HCC

For coherence in the model, it was important to derive a baseline probability of death from HCC in the presence of underlying cirrhosis. The use of such a variable would allow linkage of the probabilities of death from HCC at various stages. To derive this baseline probability, we used the CLIP prognostic system[49]. This system uses simple clinical and laboratory data to derive prognosis in HCC with underlying cirrhosis (Appendix 2). The Cancer of the Liver Italian Program (CLIP) Investigators prospectively followed 435 consecutive cases of HCC diagnosed in 16 Italian institutions[49]. Using multivariate analysis, with Child-Pugh stage, tumor type, tumor stage, portal vein thrombosis and AFP levels as covariates, and stratifying for the

presence or absence of locoregional therapy, they derived a simple scoring system to determine survival from HCC. The scoring system was internally validated by using a split-sample technique. The use of the CLIP allowed us to derive a probability of death from HCC when diagnosed in patients with compensated cirrhosis, which was used for the calculation of the relative risk of death from HCC under all other clinical circumstances. To incorporate the CLIP system into the decision analysis model, the following assumptions were made. First, "compensated cirrhosis" and "decompensated cirrhosis" correspond to Child-Pugh stages A and C respectively. Second, a "resectable HCC" was defined as a uninodular and <50% extension (score 0), without portal vein thrombosis. Also, a "non resectable HCC" was defined as any larger tumor, without portal vein thrombosis whereas a "non treatable HCC" was defined as any size tumor with portal vein thrombosis. The probability of raised AFP levels in each of these circumstances were derived from the literature[36,50-53].

To further validate the use of this system in our model, we compared the probability of death from HCC as derived by this system to the probabilities extracted from the literature. The probability of death from HCC depends on the stage of the tumor and the underlying liver function[30,49]. It was assumed that asymptomatic tumors and unifocal tumors less than 5cm in diameter occurring in Child's class A patients were resectable, whereas large, multifocal tumors or those arising in patients with decompensated cirrhosis were non resectable.

In compensated cirrhosis, survival is greatly affected by the stage of the tumor. The probability of death from resectable HCC in compensated cirrhosis was extracted

from prospective studies[28,54,56] and from retrospective studies[31,55]. Two prospective studies also provided data on the growth rate of the tumor[31,55]. The probability of death from non resectable HCC in compensated cirrhosis was extracted from randomized and non randomized comparative studies of placebo versus experimental chemotherapy, using the outcome of the placebo group[24,28,58], or from prospective and retrospective studies of untreated patients with HCC[60,61].

The probability of death from HCC in decompensated cirrhosis was available from several comparative and non comparative studies[28,31,61,63,64].

3.4.2.2 Probability of resectable HCC in compensated cirrhosis

Bismuth, in 1993, reviewed the rates of surgical resections performed on cirrhotics with HCC over the previous 20 years[100]. He was able to show that the nature of surgical practice has evolved considerably and that most surgeries are now performed on unifocal tumors less than 5 cm in size in compensated cirrhosis. This definition was therefore used for "resectable" tumor. Patients who underwent palliative resections or liver transplantation were not considered as "resectable". It could be argued that some transplanted patients could have been resectable but, because 1) transplantation can be successfully performed in those with multifocal tumors and/or advanced cirrhosis and 2) in all series, the proportion of transplanted patients was low, excluding these patients seemed to be the least biased approach.

Studies of the efficacy of screening for HCC in the occident show that, in order to detect a greater proportion of resectable tumors than historical controls,

screening has to be performed at least biannually and that patients have to be compliant with the screening protocol. The first large screening study was performed by Colombo et al, in Italy, and revealed that only a minority of screened patients were resectable, in proportions similar to those obtained from non-screened populations[39]. However, in a large proportion of Colombo's cohort, patients were screened only annually. More promising results were obtained when screening was performed every three to six months [36,52,66]. However, others have not been as successful[35,101-103]. One French study revealed that patients' compliance to the screening protocol was poor, i.e. 64%[102], possibly as a result that most French cirrhotics are drinkers rather than post-necrotic cirrhotics. This explains why the probability of detecting a resectable tumor by screening varies over a wide range, from 0.06 to 0.87, with a weighted mean value of 0.43. In comparison, the probability of resectable tumors among patients who presented with HCC without having undergone screening varies between 0.06 to 0.34, with a weighted mean value of 0.12[30,50,52,62,67,69].

3.4.3 Probability of events related to HCC therapy (Table 3c)

3.4.3.1 Probability of events related to surgical resection

The operative mortality of HCC resection is higher in cirrhotics than in non-cirrhotics. Therefore, the data was extracted solely from surgical series in cirrhosis. All non duplicated data on the long term follow up after surgical resection of HCC in cirrhosis in Europe or America was included, which represented a total of 13 studies and 767 cirrhotics followed up to a maximum of 5 years[54,56,65,73,74,77,79,80,83,86,87,104,105].

3.4.3.2 Probability of events related to PEI therapy

3.4.3.2.1 Probability of percutaneous ethanol injection (PEI) therapy in non resectable HCC

In a retrospective study of management and survival in 391 patients with cirrhosis and HCC, Livraghi et al found that a third of patients with non resectable HCC were amendable to PEI therapy[28].

3.4.3.2.2 Probability of decompensation or death from PEI therapy

The majority of reports of PEI therapy for HCC in cirrhosis report a 0% complication rate[63,86,89,90,92]. A large Italian study has reported a very low incidence of death[57]. Di Stasi et al recently performed a multicenter survey of evaluation practices and complication rates from PEI in Italy, where the incidences of liver failure and death were very low[27].

3.4.3.2.3 Probability of persistent HCC post PEI therapy

Ultrasound or CT scan follow-up of patients post PEI sometimes reveals that the tumor nodule(s) have not been completely necrosed. Persistent nodules can be biopsied to prove that the cancerous cells have not all been destroyed. The probability of persistent HCC post PEI therapy depends on the size of the tumor nodules, the volume of ethanol injection per session, the type of needle used for injection, the number of sessions, as well as the interval between each treatment, explaining why the

reported probability of persistent HCC ranges between 0% and 25%, values which were used for sensitivity analysis.

3.4.3.2.4 Long term mortality and recurrence rate post PEI therapy

The disease-free and overall survival post-PEI therapy depends largely on the severity of the underlying cirrhosis. All usable and non duplicated data on the long term follow up of cirrhotics post PEI therapy for HCC was included, which represented a total of ten reports on a total of 1396 patients followed for up to 7 years [29,57,63,86,89,90,92,94-96]. In these studies, the annual probability of death post PEI ranges from 0 to 0.17, with a weighted mean of 0.07. This is lower than the annual probability of death post surgical resection, raising the possibility of a selection bias.

3.4.4 Characteristics of the screening test

3.4.4.1 Sensitivity and specificity of US and AFP for HCC (Table 4)

The sensitivity and specificity of AFP and ultrasound depend on several factors: the experience of the operator, the presence of underlying cirrhosis, as well as the degree of severity of the underlying cirrhosis.

The presence of cirrhosis leads to an inhomogeneous echo-pattern which renders the detection of a focal mass more difficult. Moreover, cirrhosis, by its nature, leads to the formation of regenerative nodules which, with time, may enlarge to form macro-regenerative nodules[106]. Some of these nodules may be pre-neoplastic[107]. As well, the larger and more numerous these nodules get, the more difficult it is to detect a neoplastic mass or nodule from

Table 4: **Characteristics of the screening test.**

Parameter	Lower limit	Upper limit	Best estimate	References
Sensitivity of US + AFP for HCC in compensated cirrhosis	0.83	1	**0.907**	108,109,110,111,53,36,52,51, 112,113,114,115,116,117,118
Specificity of US + AFP for HCC in compensated cirrhosis	0.87	0.98	**0.931**	108,109,110,111,53,115,117, 118
Probability of death from FNA	0	0.001	**0**	119
Probability of FNA in decompensated cirrhosis	0	1	**0.5**	

Table 4: Sensitivity and specificity of the screening test and the probability of complications from the confirmatory test. US: liver ultrasound; AFP: alpha foetoprotein; HCC: hepatocellular carcinoma; FNA: ultrasound-guided fine needle aspirate of a liver mass.

a non-neoplastic or macro-regenerative one. Therefore, the diagnostic accuracy of ultrasound, when applied to a population of individuals with early, compensated, cirrhosis, differs from that achieved on patients with long-standing, decompensated, cirrhosis. This is the reason why the results of a large scale North American study of HCC screening among chronic hepatitis B carriers[120] could not be used, since the majority of their population had no underlying cirrhosis.

The accuracy of ultrasound may also depend on the operator[121]. More experienced sonographers are more likely to render accurate results. Therefore, results from studies originating from the Orient, were the incidence of HCC is much greater and the screening practice much more widely applied than it is in North America or in Europe, would not be applicable.

The sensitivity and specificity of ultrasound and AFP level determination in compensated cirrhosis was extracted exclusively from studies of HCC detection in patients with compensated cirrhosis, using a combination of selective liver angiography and percutaneous or laparoscopic biopsy as the gold standard[36,51-53,108,110-114].

3.4.4.2 Probability of death from fine needle aspiration of the liver (FNA) (Table 4)

The largest review on the complications of percutaneous abdominal fine-needle biopsy was performed by Smith, who combined the results of published surveys from both European and North-American institutions[119].

4 Data - *Utilities*

In economic evaluations of health technologies, the cost-effectiveness ratio is commonly expressed as cost per quality adjusted life years (QALY). In order to determine the QALYs, a measure of the subjective value of each year spent in a given health state is required. A utility represents an individual's strength of preference or desirability for an outcome. Its value may be from 0 (dead) to 1 (perfect health). Utilities, or preferences, can be measured using various techniques and sources. However, the optimal source and technique to be used for preference measurement is widely debated. This is because preferences for health states represent subjective values rather than objective measures of functional capacity and there is no such thing as a "correct" preference value[122]. The degree of desirability of a given health state may hold different values, depending on the individuals who were interviewed and the technique used for its measurement.

4.1 Sources of preferences

An individuals' degree of desirability for a given health state will depend in part on whether one has experienced that health state. Preferences can be obtained from patients experiencing the health state, from their surrogate, from experienced health care workers with knowledge about the given health state, or from members of the general population. These sources obviously display great variability in the nature and degree of their experience with the health state, and the optimal choice of sample to interview is controversial: community samples may not have an accurate knowledge and understanding of the morbidity of the health state under consideration; interest groups could generate lower utility values for purposes of lobbying; patients, on the other hand, have been noted to rate their health state

with a higher value than members of the general public, possibly because human beings can successfully adapt to adversity [122,123].

The choice of the most suitable source of utility measure is based on the type of study for which utilities are being measured. Since the purpose and perspective of a cost-effectiveness analysis is to consider an intervention in the context of overall resource allocation, and to make comparisons among different types of interventions, the use of a generic source of preferences, which would be the same across various economic evaluations, is recommended[122].

Aware of the controversy about the optimal source of preferences, we elected to use a community sample for this cost-effectiveness analysis. This choice is supported by the US panel on cost-effectiveness analyses[122]. We considered the option of generating utilities from both patient and community sources, but, because of the limited number of cases of hepatocellular carcinoma, we were concerned that interviewing actual patients would not allow us to complete this study in a timely manner.

4.2 Study population

To value the quality of life of patients with compensated cirrhosis, decompensated cirrhosis, and HCC, we interviewed members of the general population to determine their preference for each of these health states.

A convenience sample of thirty-one members of the general population were recruited among companions of the patients attending the Endoscopy unit at the Ottawa Hospital, Civic Site. These members of the general public were usually spouses, relatives, or friends of

patients who were undergoing outpatient endoscopic (gastrointestinal or bronchoscopic) procedures. Inclusion criteria were: age between 30 and 65, fluent in English, no underlying liver disease, mental illness or cognitive deficit, and consenting to participate in the interview.

4.3 Creation of descriptive scenarios (Appendix 3)

The three health states were: compensated cirrhosis, decompensated cirrhosis and hepatocellular carcinoma. Hypothetical scenarios were created to describe what one would typically feel and experience if living with each of these health states. The scenarios included a short text describing the health state followed by a systematic presentation of the health related quality of life descriptors of the Health Utility Index (HUI) Mark III, in point form. The HUI Mark III is a generic, preference-weighted, health state classification system which has been validated among large North American populations and which is increasingly used for disease-specific utility generation[124]. The integration of the HUI descriptors into our scenarios leads to the creation of utilities which can potentially be compared to other HUI derived utilities from the general population or from other health states. The HUI includes 8 health related quality of life domains, each with 5 to 6 items, describing the severity of impairment in that domain (see Appendix 4). All 8 domains were systematically presented, selecting the descriptor which most appropriately reflected the degree of impairment for each given scenario. The scenarios were structured similarly, and differences between each health state were highlighted in a bold font. They were written in the second singular person and the "RightWriter" software (version 3.0) was used to ensure that any individual with a level of education equal to or greater than grade six would understand the text. Labels were carefully

avoided i.e. "compensated cirrhosis" was described as "Condition X" and "decompensated cirrhosis" and "hepatocellular carcinoma" as "Condition Y" and "Condition Z" respectively. As well, usage of terms such as "liver disease", "hepatitis C", "cirrhosis" or "cancer" was avoided so that the nature of each condition remained completely unknown to the respondent. The use of labels has been shown to introduce bias in generating utilities related to tuberculosis and cancer[123] and is discouraged by experts in the field (Torrance, personal communication November 1997; Feeny, personal communication November 1997). In order to avoid duplication of the life expectancy component of the QALY measure, no notion of prognosis and life expectancy were provided in the descriptions. Respondents were simply told that any health state would last for the rest of their lives.

The content of the scenarios was determined based on the expertise of a panel of two gastroenterologists (C.D., A.R.) and a hepatologist (L.J.S.) as well as the available literature on quality of life in hepatitis C[125-130].

4.4 Instrumentation

Preferences can be measured using a variety of techniques. For the present analysis, the standard gamble (SG) technique, was used for the following reasons: 1) it is based on the axioms of utility theory [131,132], 2) it places the respondent in a situation of uncertainty and forces him (her) to make a trade, which simulates the contexts of decision making and policy making in health care. The SG offers a choice between two alternatives: living in health state A, which is less than perfect, or taking a gamble between perfect health, with a probability p, despite a probability of immediate death ($1-p$). The probability p is varied until the

respondent is indifferent between either options. Individuals are usually risk averse, so utility scores obtained with the SG are commonly greater than those obtained with other techniques[123]. The construct validity of the SG has been criticized because not all choices in health care imply a probability of immediate death. However, in the case of cirrhosis and hepatocellular carcinoma, the probability of immediate death is realistic.

4.5 Computerized utility generating interview

It has been argued that the SG is time-consuming, that it is conceptually difficult for the respondent to understand, and that it requires well trained interviewers and carefully designed props[131]. In order to surmount these difficulties, we created a computerized interview with voice, text, and a graphic display of the standard gamble. This tool facilitated comprehension, allowed the interview to be administered in a reproducible and controlled manner while simultaneously allowing the respondent to control its pace and to review previous statements as desired. The entire questionnaire was therefore created to run on a standard multimedia Windows 95® computer. A screen image of the computerized questionnaire, illustrating the standard gamble, is presented in Appendix 5.

A consent form that explained the purpose and the nature of the interview was first read and signed (see Appendix 6). The consent served as an introduction to the process of the interview, emphasizing the hypothetical nature of the health conditions that would be described as well as the fact that there was no right or wrong answer.

Respondents' characteristics (age, sex, study number and co-morbidity index [133](Appendix 7)) were gathered. A research assistant was present throughout the interview

process, to ensure its proper conduct. The presentation began with two examples of health states, each followed by a standard gamble. We chose to present "being blind in one eye" and "being blind in both eyes". The use of such examples provided 1) a simple representation of a hypothetical health state which all respondents can relate to and 2) a means of ensuring that respondents did understand the standard gamble, since it was reasonably expected that "being blind in one eye" would yield higher utilities than "being blind in both eyes". Respondents who gave a higher utility to "being blind in both eyes" than to "being blind in one eye" were excluded.

Following these two examples, respondents were asked to do the standard gamble on each of the three health states successively. The order of presentation was the same for all respondents, i.e. in order of progressive morbidity, from compensated cirrhosis to hepatocellular carcinoma. The standard gamble exercise was presented in a converging "ping-pong" order, as recommended by Furlong et al[134].

At the end of the process, the computer program generated a printed output of the respondents' characteristics and preference values. Qualitative data collection about comments or difficulties that were expressed by respondents were also gathered.

4.6 Sample size and statistical analysis

A sample size of at least 30 respondents was selected for convenience. The sample size could not be calculated a priori, since a thorough review of the literature yielded no published data on community-based utility measures in chronic liver diseases. We assumed

that a large enough sample size was used if the null hypothesis of equal utility values among the three scenarios could be rejected. For this, we used non-parametric and parametric tests.

The normality of the utilities was assessed through the use of histograms and P-P Plots. In the P-P Plots, the cumulative proportion for a single numeric variable is plotted against the cumulative proportion expected if the sample were from a normal distribution. If the sample is indeed from a normal distribution, points will cluster around a straight line.

Parametric testing was performed with a one-factor repeated-measures analysis of variance on the effect of the scenario on the utility variable, which was conducted as follows. In this experimental design, three sequential observations were made on each subject. Each observation, i.e. the preference measure, was performed after administering a different treatment to the individual, i.e. the scenario. The order of administration of the "treatments" i.e. the scenarios, was fixed, from the mildest degree of severity (i.e. "Compensated cirrhosis"), to the worst degree of severity (i.e. "HCC"). The sources of variation of the dependent variable, i.e. the utility, were: the variation due to the treatment effect (i.e. the scenarios), the within-person variation, the between-person variation, and the uncontrolled or residual source of variation (the error). Firstly, the data was analyzed for differences obtained from each scenario:

Null hypothesis: there is no difference between the mean utilities obtained from scenario X, Y, or Z; $\mu_X = \mu_Y = \mu_Z$

Alternate hypothesis: there is at least one population mean which does not equal another population mean

Type I error: 0.05

There are several methods for testing the null hypothesis with the one-factor repeated-measures analysis of variance: the univariate approach, the multivariate approach, and the adjusted univariate approach. All of these approaches are based on the assumption that the repeated measurements come from a multivariate normal distribution. The univariate approach also rests on the variance-covariance assumptions, which can be tested with the Mauchly's test of sphericity[135]. We performed the Mauchly's test of sphericity using a p value of 0.10, since it is said not to be very powerful when the sample size is small. A non-significant Mauchly's test ensures that the variance-covariance assumptions are met and that the one-factor repeated-measures ANOVA can be calculated with the univariate approach. Once the null hypothesis of equal population means could be rejected, we performed a multiple-comparison procedure to determine which population means are different[135].

If the distribution of the response was not normal, we used the non-parametric Friedman test for 2 or more related samples to verify that a statistical difference exists between the utilities for these three health states.

The determination of the health-state specific utility value for use in the model was performed by calculating the mean utility value for each scenario. The mean utility was used as a best estimate, while the range of utility values was the lowest and upper estimates.

All statistical analyses on these utility measures were performed using the SPSS statistical software.

4.7 Disutilities

Short-term health states were accounted for by disutility values. The methodology of defining disutilities has not been well studied [136]. One approach to this problem would be to elicit them directly, using the same methodology as described above for the utilities. However, we estimated that the interview was already of about 30 to 40 minutes duration, and that elongating it would probably overburden the respondents. For simplification, we assumed that the quality of life was zero during the period of time spent in these short-term states, a technique which has been used before [137]. A disutility value therefore represented the proportion of cycle-length spent in a given short-term state. These short-term states included the following tests and procedures: screening procedure (abdominal ultrasound and AFP level), ultrasound-guided fine needle biopsy, radiological investigations performed for the staging of HCC (CT scan of abdomen, bone scan, CXR), surgical resection for HCC and PEI therapy of HCC. The other short-term states such as endoscopic procedures, paracentesis and hospitalization for complications of cirrhosis and HCC were included in the global utility measure for those long-term health states. It was assumed that the duration of outpatient procedures was between a third of a day and a full day. The average and range of number of therapeutic sessions required for PEI therapy was drawn from a recently published survey[27], while the average length of hospital stay for hepatic resection and its range were drawn from administrative hospital databases (London Health Sciences Centre and Ottawa Civic Hospital).

5 Data - *Costs*

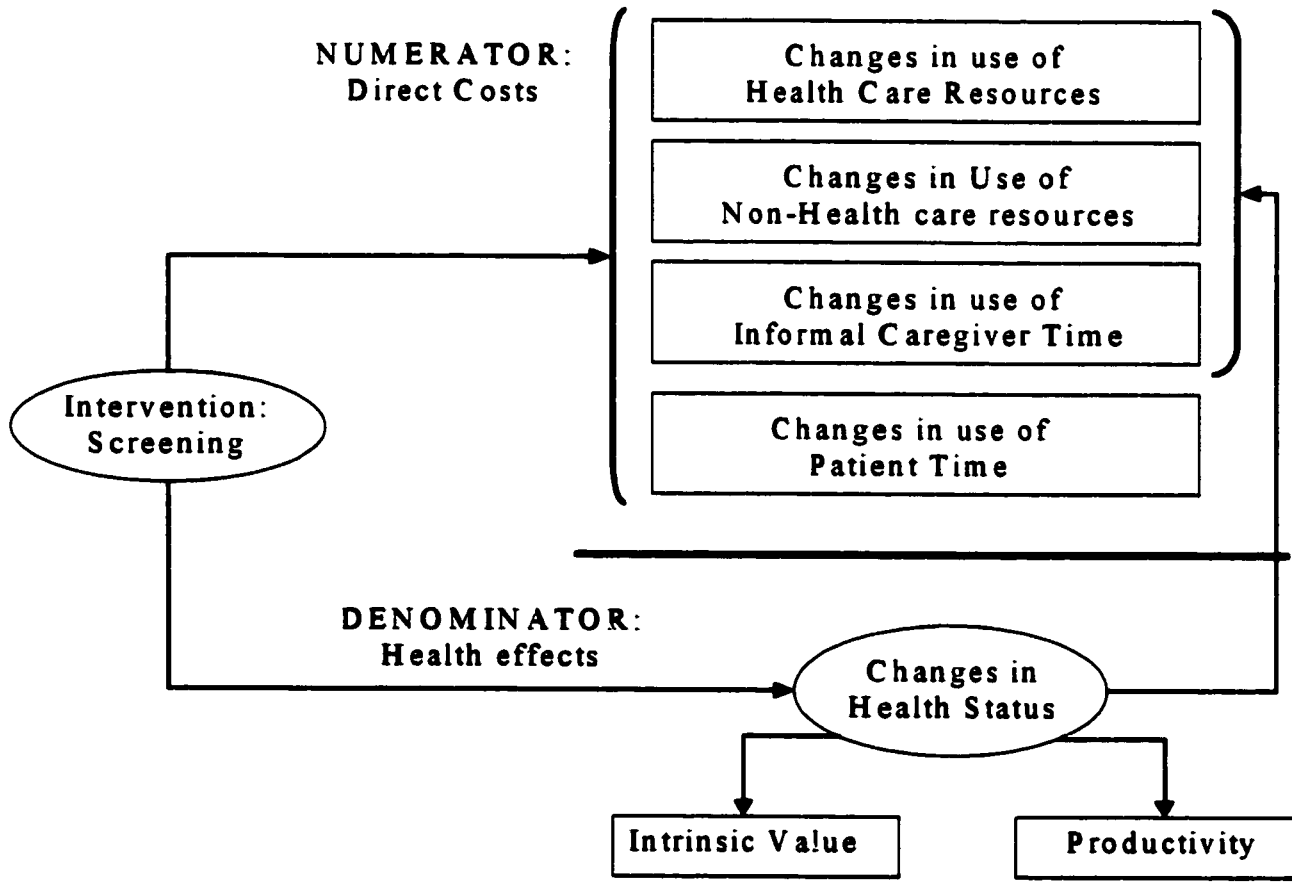
5.1 Cost-effectiveness ratio

The economic implications of a health intervention are commonly expressed as a cost-effectiveness ratio, composed of the costs in the numerator and of the health effects in the denominator. A pictorial representation of the cost-effectiveness ratio (CER) is presented in Figure 2. Our screening intervention will induce health care and social services costs, and costs that fall on the patients. The health care costs include the value of all the goods, services, and other resources that are consumed in the provision of the intervention, and in dealing with consequences linked to it (costs of tests, drugs, supplies, medical facilities, health care personnel and professionals). The social services costs are related to the costs of home care which may be provided to patients with significant morbidity, such as decompensated cirrhosis and HCC. The costs that fall on the patient and family include the direct costs related to the consumption of non-health care services (such as transportation), and the time costs. The cost of lost time can be referred to as "productivity costs" or "indirect costs", and they are the costs associated with lost or impaired ability to work or to engage in leisure activities due to morbidity and the lost economic productivity due to death[138]. They can be borne by the patient and/or by an informal caregiver[139]. The health effects, or changes in health status, are included in the denominator and translated as health related quality of life and life-expectancy[138].

Whether a given effect of a health intervention should be considered in the numerator or in the denominator, is, at times, the source of considerable debate [140,141]. The controversy resides in the fact that factors such as loss of income and of productivity may have an impact on quality of life. To avoid "double-counting" the impact of these factors, it is important to

carefully ascertain whether the measure of the health effects, i.e. the utility measure, refers to these factors. In the scenarios used to describe each health state, lost productivity and lost leisure time were specifically described.

Figure 2: **Economic consequences of health interventions: the cost-effectiveness ratio [138].**



5.2 Economic perspective

The costs to be included in the numerator depend on the perspective of the economic evaluation. In the most comprehensive perspective, the societal perspective, all significant health outcomes and costs are counted, regardless of who experiences the outcomes or costs. In other words, both the health care costs and the costs that fall on the patient and family are included. Other, more restrictive perspectives can be adopted, such as the third-party payer perspective, where the costs of non-health care resources and the time costs are usually not accounted for. Although the societal perspective is the most appropriate to determine the economic impact of health care interventions, the collection of costs data pertaining to these indirect costs is difficult outside the setting of a prospective study. In the setting of this study, indirect costs could not be accurately measured and assumptions regarding their value could suffer from a great margin of error. We therefore adopted the third-party payer perspective.

5.3 Included costs and costing methodology (Table 5)

5.3.1 Method of valuation

Physicians costs were obtained from the Ontario Health Insurance Plan (OHIP) physicians' fee schedule. The costs of outpatient procedures and bloodtests were obtained from the OHIP technical fee schedule when available or by data from the Ottawa General Hospital (OGH)'s cost model. Liver biopsy, FNA of a liver mass, PEI therapy, mesenteric angiogram and paracentesis were all assumed to include a 4 hour stay in a monitoring area such as a Medical Day Unit. Endoscopic procedures included intravenous sedation and monitoring in an endoscopy Unit. The costs of medications were obtained from the Ontario

Drug Benefit fee schedule. The costs of hospitalization for cirrhosis, HCC, hepatectomy for primary liver cancer, and chronic hepatitis C were obtained from the London Health Science Center (LHSC). This data source was selected because the London Hospital is specialized in the care of liver diseases and liver transplantation. Hospitalization costs include the costs of tests, drugs, supplies, medical facilities and health care personnel. Costs obtained from the LHSC also included the costs of major complications.

5.3.2 Prior costs

It was assumed that all patients were diagnosed with well-compensated HCV-related cirrhosis prior to their entry into either cohort. These prior costs included a consultation in internal medicine, serodiagnosis of HCV infection, blood tests for evaluation of hematological, renal and liver function, as well as an ultrasound-guided liver biopsy.

5.3.3 Costs of screening

The costs of screening included liver ultrasound and serum AFP level. The cost of ultrasound included both the radiologist's fee and the technical fee, as an estimate of the hospital's overhead costs. The cost of the AFP level measurement was derived from OHIP's technical fee.

5.3.4 Costs of diagnosis of HCC

Table 5: **Included costs and costing methodology.**

Type of cost	Components	Source of Probability Data	Method of Valuation
Prior Costs	HCV serodiagnosis Bloodtests Consultation in internal medicine US-guided liver biopsy	Expert opinion	OHIP fee schedule (physician + technical fee) OGH cost model
Costs of screening	Liver US, AFP		OHIP fee schedule (physician + technical fee)
Costs of HCC diagnosis	US-guided FNA, bloodtests CXR, CT scan, bone scan, angiogram		OHIP fee schedule (physician + technical fee) OGH cost model
Outpatient costs	Visits to physicians Medications Bloodtests Probability of complications Outpatient procedures for complications	Literature and expert opinion	OHIP fee schedule (physician + technical fee) ODB reimbursement OGH cost model
Inpatient costs	Probability of hospitalization Costs of hospitalization	Literature and expert opinion	LHSC Cost Centre OHIP fee schedule (physician fee) OCH medical records
Costs of PEI therapy	Number of session of PEI injection US-guided intralesional ethanol inection	Literature	OHIP fee schedule (physician + technical fee) OGH cost model

The costs of diagnosis of HCC included ultrasound guided FNA, bloodtests to evaluate hematological, renal and liver function, as well as the costs of a chest X-ray, CT scan

of the abdomen, mesenteric angiogram and bone scan which were used for tumor staging. Both ultrasound-guided FNA and mesenteric angiogram where assumed to include a half-day stay in a monitoring area. The cost of the FNA included professional fees (radiologist and pathologist) plus the technical fee, as a representative of hospital overhead costs. When HCC was not diagnosed at screening, the costs of liver ultrasound and AFP level were also included. In decompensated cirrhosis, staging was not performed since such patients are usually considered inoperable.

5.3.5 Outpatient costs (Table 6)

The outpatients costs included routine visits to physicians, both general practitioners and internists, the use of prescription medication, drawing of routine blood tests to assess hematological, renal and hepatic function and outpatient procedures. The frequency of visits, blood tests, and procedures which would be performed to treat complications of liver failure were derived from expert opinion which had been used in a cost-effectiveness analysis of IFN therapy in chronic hepatitis C[142]. This American data was corroborated by a local expert panel prior to incorporation into the decision analysis model. Drug therapy included diuretics (spironolactone and furosemide) for the therapy of ascites, lactulose for the therapy and prophylaxis of encephalopathy, beta blockers for the therapy and prophylaxis of portal hypertension, and antibiotics (quinolones) for the therapy and prophylaxis of spontaneous bacterial peritonitis. Outpatient procedures for complications of liver failure included paracentesis for control of ascites and gastroscopy with endoscopic treatment of gastro-esophageal varices for variceal bleeding. The costs of these outpatient interventions included

both physicians and technical fees, along with the costs of one half-day under observation in a medical day unit.

Table 6: **Costs of outpatient care.**

Health State	Intervention	Probability / Frequency
Compensated cirrhosis	GP visit	every 3 months
	Internist visit	every year
	Bloodtests	every year
Decompensated cirrhosis	GP visit	every month
	Internist visit	every 2 months
	Bloodtests	every 2 months
	Medication	all patients
	Paracentesis	every month in 50% of patients
	Endoscopic treatment of varices	every month for 6 months in 30% of patients
	Hospitalization	every year
Hepatocellular carcinoma	GP visit	every month
	Internist visit	every 3 months
	Bloodtests	every 3 months
	Medication	all patients
	Paracentesis	every month in 50% of patients
	Endoscopic treatment of varices	every month for 6 months in 50% of patients
	Hospitalization	every year

5.3.6 Inpatient costs

The inpatients costs were calculated based on the probability of hospitalization and the costs of hospitalization. The probability of hospitalization was derived from the literature. Two sources of data were used: data on the prospective follow-up of patients with decompensated cirrhosis[143], as well as estimates derived from expert opinion which had been used in a cost-effectiveness analysis of IFN therapy in chronic hepatitis C[142]. These were corroborated by a local panel of experts and, since such estimates may vary considerably[144], sensitivity analysis was performed using estimates ranging from -50% to +50% of the point estimate.

Hospitalization costs were obtained from the LHSC and supplemented by the OHIP physicians' fee schedule. Physicians' costs for hospitalizations due to decompensated cirrhosis or HCC were calculated on the following assumptions: such admissions would be triggered by the occurrence of a life-threatening complication of liver failure, such as encephalopathy, spontaneous bacterial peritonitis or variceal bleed. Physicians' services would include the daily care from an internist, including paracentesis; consultation with a gastroenterologist, who would possibly perform endoscopic therapy, and the consultation with another internist, such as an infectious disease specialist or a neurologist. Physicians' costs for hospitalizations for HCC resection would include: surgical, anesthesia fees for hepatic tumor resection, stay in intensive care, and care for post-operative liver failure. These assumptions were supported by the details of the LHSC costs data (e.g. % admissions involving the ICU and/or the endoscopy unit cost centers). The average length of stay for each type of hospitalization was derived from the LHSC's and Ottawa Hospital's databases.

5.3.7 Costs of PEI therapy

The costs of percutaneous ethanol injection therapy were derived from a published survey of practice patterns for PEI [27] which provided data on the average number of sessions required for tumor destruction. Although this survey is representative of Italian practice, we felt it would not differ from our local practice, since the number of session required for tumor destruction should be based on objective ultrasonographic criteria at follow-up of the lesion rather than individual physicians' practice patterns[145] .

5.3.8 Transition costs (Table 7)

Transition costs represented the costs incurred at the time of transition from one health state to another. For example, the transition from compensated cirrhosis to decompensated cirrhosis, symptomatic HCC, and liver related death were all assumed to lead to an admission to hospital.

Table 7: **Health state transitions and involved costs.**

Health state	Transition	Intervention	Probability /Frequency
Compensated cirrhosis	to decompensated cirrhosis	hospitalization	1
	to HCC	HCC diagnosis and staging	1
	to symptomatic. HCC	hospitalization	1
		HCC diagnosis and staging	1
	to death	hospitalization	1
Hepatocellular carcinoma	to post HCC (surgery)	hospitalization for HCC resection	1
	to post HCC (PEI)	PEI	2 to 7 times
	to death	hospitalization	1
Decompensated cirrhosis	to HCC	hospitalization	1
		US-guided FNA	0.5
	to death	hospitalization	1
Death from HCC diagnosis		hospitalization	1

5.4 Excluded costs

The costs associated with disease and death which are unrelated to the liver disease were not included. There is ongoing controversy as to whether these unrelated future costs should be included in a cost-effectiveness analysis[124]. Our decision not to include these costs resulted from two considerations: the high likelihood that these costs would be similar in both arms, therefore not affecting the cost-effectiveness ratio, as well as the practical barriers impeding the measurement of these costs. Since our patient population was already affected by cirrhosis of the liver, which is a highly morbid disease, we anticipated that costs which would occur in years of added life would largely be accounted for by the disease-related costs.

5.5 Discounting

Discounting is described as the practice of adjusting the dollar amounts to reflect the time value of money by assigning lower values to dollars paid in the future than to dollars paid in the present [124]. This practice reflects the fact that, in general, individuals and society prefer desirable consequences to occur earlier and undesirable consequences to occur later[139]. Whereas discounting of dollars spent for health care in the future is not a controversial issue, discounting for health effects has been debated extensively [146]. The sources of debate are whether we can assume, as for dollars spent, that health has less effect on quality of life in the future than the present, and, if so, whether quality of life should be discounted with the same magnitude as costs. For discounting practices, the recommendations of the US panel on cost-effectiveness analysis [146] were followed, i.e. both costs and health effects were discounted at

the same rate of 3%. The analysis was also performed with annual discounting rates of 0% and of 5%, since Canadian recommendations support a 5% discount rate.

6 Uncertainty Analysis

6.1 Sensitivity analysis

Sensitivity analysis was used to validate the assumptions of the model and to evaluate the degree of certainty of the conclusion of the decision analysis, in other words, to determine the "robustness" of the analysis. With sensitivity analysis, the incremental cost-effectiveness ratio (ICER) of the screening strategy was calculated over the range of plausible values of each variable. This was performed with probability variables, costs variables, as well as utility variables.

First, a one-way sensitivity analysis was performed, where only one variable varied over its full range while the other variables remained constant, at their best estimate value. This one-way sensitivity analysis allowed to assess how the decision was affected by the variation of one variable at a time. The results of one-way sensitivity analysis were plotted graphically, with, on the "x" axis, the values of the variable, and, on the "y" axis, the CER. The effect of the variable on the CER of one strategy can be plotted along with its effect on the alternate strategy. Some variables may have a different impact on each strategy, so that, in a graphic display of a one-way sensitivity analysis, the slopes of the CERs of each strategy would be different. Under such conditions, this variable may hold a "threshold" value. A threshold value is defined as the value of a variable at which two strategies have equal analytic

results. Arithmetically, a threshold value is therefore the value of a variable where the incremental cost-effectiveness ratio (ICER) is equal to a cutoff value for economic attractiveness. Arithmetically, this ICER is expressed as:

$$\frac{\text{Cost(intervention)} - \text{Cost(no intervention)}}{\text{Effect(intervention)} - \text{Effect(no intervention)}} = X$$

It is inferred from this explanation that, below this threshold value, the intervention would be more economically attractive than the non intervention strategy, whereas above the threshold value, it would be less economically attractive. The presence of a threshold value for a given variable signifies that this variable has an impact on the relative economic attractiveness of an intervention, and helps determine under which conditions this intervention should best be adopted. There is no consensus as to what the cutoff value of the ICER for economical attractiveness should be. For the purpose of this analysis, the indifference point was defined as the value at which screening is associated with an incremental cost-effectiveness ratio of $50,000 per quality-adjusted life year compared to no screening. This threshold incremental cost-effectiveness ratio is equal to approximately twice the average annual income[147].

To further analyse the decision model, "multi-way" sensitivity analyses (two-way or three-way, depending on the number of variables) were performed following the one-way sensitivity analyses. There, each of the variables which would hold a threshold value would be varied over their range of possible values simultaneously.

Sensitivity analysis was also used to evaluate the effect of varying specific parameters in order to 1) compare the attractiveness of PEI therapy to that of surgery; 2) determine the

effect of age at onset of screening on the incremental cost-effectiveness ratio; 3) determine how the incremental cost effectiveness ratio varies when the frequency of screening is increased or decreased.

In the base-case analysis, screening was performed every 6 months. Detected HCC's which were resectable would be treated surgically whereas the remainder would be treated with PEI. The effect of varying the frequency of screening to every 3 months and every 12 months was then calculated. For this, the incremental cost-effectiveness ratio was calculated, using the next least intensive intervention as a comparator. For example, screening every 12 months was compared to no screening, while screening every 6 months was compared to screening every 12 months. Similarly, the gain in life expectancy was calculated based on the life expectancy achieved with the next least intensive intervention.

The effect of the choice of therapeutic modality was analysed by comparing the following therapeutic strategies: 1) treating all suitable candidates with PEI, 2) treating all resectable candidates surgically, without treating the non-resectable candidates, and 3) treating all resectable candidates surgically and treating the non-resectable candidates who do not have portal vein thrombosis or metastatic disease with PEI (i.e. the base-case scenario). In this situation, we cannot determine a priori which intervention is the least intensive. Therefore, the incremental cost-effectiveness ratios were calculated from the base-case scenario.

We also performed multi-way sensitivity analyses to consider the "Best Case" and "Worse Case" scenarios, by selecting extremes values of the variables which showed an impact on the ICER in the one-way sensitivity analysis.

6.2 Monte Carlo simulation

In order to determine the confidence interval around the incremental cost-effectiveness ratio's estimate, we performed a Monte Carlo simulation. In a Monte Carlo simulation, all variables are simultaneously varied. In each individual simulation, the probability of outcome at each node is randomly sampled from the distribution of possible values of each of the variables of this node. The range of possible values of each variable is distributed according to distributions which are determined a priori. The probability of events were distributed according to a triangular distribution to allow for the uncertainty that was due to the fact that none of the input data were derived from controlled trials. The utility values were distributed according to a normal distribution. Since the costs estimates could have standard deviations which were greater than their mean estimates, we distributed those values according to a log normal distribution, which ensured that none of the cost values would be negative.

Results of a Monte Carlo simulation can be treated as parametric values and, therefore, this simulation allowed us to obtain the mean, the standard deviation (SD) and the median value for the cost, the effect, and the cost-effectiveness ratio of each strategy as well as the incremental cost-effectiveness ratio (ICER). The ICER of each simulation was calculated as follows:

$$ICER = \frac{(costs)_{SCREEN} - (costs)_{NO\ SCREEN}}{(effect)_{SCREEN} - (effect)_{NO\ SCREEN}}$$

where the effect was measured in QALYs. The mean ICER and its SD for the entire set of simulations was then computed.

In order to determine if an appropriate number of simulations was performed, results were cumulated progressively, and, with each compilation, the standard deviation and the mean ICER were recalculated. We determined that a sufficient number of simulation would have been performed once the standard deviation would remain stable and once a minimum of 2 000 simulations would have been performed (Table 8).

Table 8: Required number of Monte Carlo simulations.

Cumulative number of simulations	Mean incremental cost-effectiveness ratio ($/QALY)	Standard deviation ($/QALY)
1000	8 111	4 415
2000	8 417	4 899
2500	8 453	5 039
3500	8 422	5 116

Table 8: Effect of the number of Monte Carlo simulations on the mean value and standard deviation of the incremental cost-effectiveness ratio of screening for HCC in hepatitis C-related compensated cirrhosis.

RESULTS

1 Cost variables

Table 9 presents a summary of all cost variables. Table 10 presents the components of the inpatient physicians costs. All costs are expressed in 1997 Canadian dollars.

2 Utilities

2.1 Respondents characteristics

A total of 34 individuals were interviewed. The mean (+/-SD) age was 46 (11.2) year; 68% were female. The comorbidity index was 0 in 31 respondents and 2 in one respondent. All respondents completed the interview successfully. However, based on the assumption that coherent respondents must give a lower utility to "blind in both eyes" than to "blind in one eye", two interviews had to be excluded. The duration of the interview ranged from 20 to 35 minutes.

Table 9: **Costs estimates.**

Parameter	Lower estimate	Upper estimate	Best estimate	SD
Hospitalization costs				
Cirrhosis			$7,306.70	$7,965.24
HCC			$6,107.66	$6,609.12
Hepatic resection			$9,520.00	$2,760.54
Inpatient physician costs				
Cirrhosis	$354.85	$3,421.25	$910.49	
HCC	$354.85	$2,880.15	$964.47	
Hepatic resection	$837.15	$3,745.55	$2,365.38	
Outpatient physician and procedure costs				
Compensated cirrhosis	$13.21	$47.43	$23.71	
Decompensated cirrhosis	$75.53	$305.43	$290.78	
HCC	$75.53	$305.43	$281.11	
Screening			$77.90	
FNA			$283.60	
Staging			$427.66	
PEI	$306.80	$2,147.60	$1,027.78	
Outpatient medication costs	$22.87	$592.53	$313.80	
Outpatient bloodtests costs				
Compensated cirrhosis	$8.53	$25.59	$9.60	
Decompensated cirrhosis	$25.59	$76.77	$51.18	
HCC	$25.59	$76.77	$38.39	
Screening			$23.26	
FNA			$16.54	

Table 9: Summary of all cost estimates per three-month period. The costs of procedures include both physician fee, technical fee, and hospital overhead costs, as indicated. The cost estimates for screening, tumor staging and fine needle aspiration (FNA) represent the costs per intervention. The costs of percutaneous ethanol injection (PEI) represent the costs for each treated patient.

Table 10: Inpatient physicians costs.

Reason for admission	Length of stay (days) [mean; LE; UE]	Type of consultant	Type of procedures performed by physicians	Costs ($) [mean; LE; UE]
Cirrhosis	8; 1; 41	General internist Gastroenterologist* Other internist* Radiologist* Pathologist*	Paracentesis* Gastroscopy*	910; 355; 3 421
HCC	7; 1 ;27	General internist Gastroenterologist* Other internist* Radiologist* Pathologist*	Paracentesis* Gastroscopy*	964; 355; 2 880
Hepatic resection	13; 6; 36	General surgeon Anesthetist Intensive care* Internist*	Hepatic resection Invasive monitoring*	2 365; 837; 3 746

Table 10: Estimates of physician costs for each admission, based on the reason for admission, the number and type of physicians involved, the type of possible intervention (procedure), and the length of stay. Technical fees and hospital overhead costs are not included in these calculations (see Hospitalization costs, Table 9). Cost estimates were rounded to the dollar unit to simplify data presentation. "LE": lower estimate; "UE": upper estimate. (*) Services which were not rendered routinely, at frequencies derived from the LHSC database.

2.2 Quantitative results

The mean (+/- SD) utility values for compensated cirrhosis, decompensated cirrhosis and hepatocellular carcinoma were 0.89 (0.21), 0.60 (0.33), and 0.34 (0.31), respectively. For comparison, they were of 0.91 (0.15) and 0.69 (0.37) for "blind in one eye" and "blind in both eyes", respectively (Table 11). The median utility values for compensated cirrhosis, decompensated cirrhosis and hepatocellular carcinoma were 0.98, 0.69, and 0.305 respectively.

Table 11: Utility estimates.

Condition	Lower estimate	Upper estimate	Mean	SD
Compensated cirrhosis	0.05	1	0.89	0.208
Decompensated cirrhosis	0	1	0.6	0.332
Hepatocellular carcinoma	0	1	0.34	0.31
"Blind in one eye"	0.49	1	0.91	0.15
"Blind in both eyes"	0.01	1	0.69	0.37

No patient had inverse ordering of the other three scenarios. However, two respondents were indifferent between the "compensated cirrhosis" and the "decompensated cirrhosis" scenarios while three were indifferent between the "decompensated cirrhosis" and the "hepatocellular carcinoma" scenarios and 2 were

indifferent between all scenarios. Seven patients were indifferent between "blind in one eye" and "blind in both eyes", none of which were indifferent between the three liver disease-related scenarios.

The tests for normality showed that the utility for compensated cirrhosis was not strictly normal. The non-parametric Friedman test for two or more related samples did however show a statistically significant difference between the utilities for the three health states.

One-factor repeated-measures analysis of variance was performed with the univariate approach, as supported by the non significant p-value obtained with the Mauchly's test (Table 12a). A statistically significant p value ($p<0.001$) was obtained, and the null hypothesis stating that the mean utility of scenario X is the same as that of scenario Y and as scenario Z could be rejected (Table 12b). The multiple comparison procedure showed non-overlapping confidence intervals for all three variables, showing that the mean utility value for compensated cirrhosis was greater than that for decompensated cirrhosis which, in turn, was greater than that of HCC.

Table 12: **One-factor repeated-measures analysis of variance on the effect of the scenario on the utility variable.**

A: **Mauchly's test of sphericity.**

Measure: UTILITY

Within Subjects Effect	Mauchly's W	Approximate Chi-Square	df	p value
SCENARIO	.923	2.392	2	.302

Table 12A: Mauchly's test of sphericity was used to test the hypothesis that the variance-covariance assumptions needed for the univariate approach were met. Alpha = .10. The p value of 0.302 (> alpha) implies that the univariate approach for the repeated measures ANOVA can be used.

B: **One-factor repeated-measures ANOVA - Univariate approach.**

Source	Degrees of Freedom	Sum of squares	Mean square
Between subjects	n-1 = 31	SSBS = 4.9560	MSBS = 0.1599
Within subjects	n(k-1) = 64	SSWS = 7.6244	MSWS = 0.1191
Factor	k-1 = 2	SSF = 4.8462	MSF = 2.4231
Error	(n-1)(k-1) = 62	SSE = 2.7782	MSE = 0.0448
Total	(nk)-1 = 95	SST = 12.5803	

F = MSF / MSE = 54.0759 $p < 0.001$

Table 12B: The one-factor repeated-measures ANOVA tests the hypothesis that there is at least one of the population mean for utilities which does not equal another population mean. Alpha= 0.05. The p value = 0.001 allows us to reject the null hypothesis that the mean utility values for each of the health state scenario are all equal.

2.3 Qualitative results

Comments which were spontaneously made by respondents were collected. Several respondents spontaneously made the similar comment: "I am not a gambler". Of these, two respondents expressed a strong tendency for risk aversiveness; they rejected all gambling options, rating all health states similarly at 0.99. One of these two respondents was quite emphatic as to how difficult it was for her to picture any level of morbidity: "My fear of death as a healthy person makes it impossible for me to imagine these terrible living conditions. I wonder if my results should be used because I am so indecisive". This respondent also gave similar utilities for "blind in one eye" and "blind in both eyes" and was, in fact, excluded. Others felt prompted to justify their choices: "Being independent is the most important thing"; "My choice to gamble is based on how my illness would affect my immediate family"; "Life and death choices are not easy. It depends on so many factors, such as family. I worked with disabled people and noticed that the desire to live depends on a lot of external factors"; "For me, of all diseases one can have, being blind would be the absolute worst thing".

2.4 Disutilities

A summary of the calculation of the disutility variables used in the model is presented in Table 13.

Table 13: Disutility estimates.

Procedure	Frequency (LE ; UE ; BE)	Duration (day) (LE ; UE ; BE)	Lower estimate (LE)	Upper estimate (UE)	Best estimate (BE)	Source of data
Screening	1	0.3			0.0033	expert opinion
FNA	1	0.5			0.0056	expert opinion
Staging	1	1			0.011	expert opinion
Surgery	1	6 ; 36 ; 12.65	0.0666	0.4	0.1405	LHSH
PEI	2 ; 14 ; 6.7	0.5	0.0111	0.0778	0.0372	Di Stasi 1997

Table 13: The disutility estimates were calculated based on the length of time spent with each intervention or test. For surgery, estimates of the length of time were derived from the London Health Sciences Centre (LHSC). For percutaneous ethanol injection (PEI), the total number of sessions was derived from a practice survey on PEI therapy[27]. The final duration estimates were converted into the fraction of a three-month cycle which each intervention took. A utility of zero was given to that fraction of time.

3 Life expectancy estimation

3.1 Data validation

The use of the CLIP prognostic system to derive an estimate of the baseline probability of death from HCC in the presence of underlying cirrhosis was validated by comparing its results from those which were available in the literature (Table 14). The probability of death from resectable HCC in compensated cirrhosis, the probability of death from non resectable HCC in compensated cirrhosis, as well as the probability of death from treatable HCC in decompensated cirrhosis, could be determined from both the CLIP prognostic system and the literature. For the probability of death from resectable and non resectable HCC in compensated cirrhosis, the range of CLIP derived probabilities fall within the range of literature- derived probabilities. The range of possible values for the probability of death from treatable HCC in decompensated cirrhosis in the CLIP system is broader than that of the literature, likely because of the number of assumptions which are included in the CLIP calculation for decompensated cirrhosis. Overall, this comparison validates the use of the CLIP prognostic system for the calculation of the baseline probability of death from HCC in the presence of underlying cirrhosis. Table 14 also shows how the probabilities of death post HCC therapy as well as the probability of death from asymptomatic HCC, as extracted from the literature, compare to the calculated probabilities.

Table 14: **Validation of the use of the CLIP prognostic system[49] for estimates of the probabilities of HCC-related death.**

	CLIP PROBABILITIES			LITERATURE PROBABILITIES		
	lower estimate	upper estimate	best estimate	lower estimate	upper estimate	best estimate
Probability of death from HCC with compensated cirrhosis	0.0227	0.6952	0.17			
resectable HCC	0.0227	0.1037	0.05	0.0100	0.1600	0.05
asymptomatic HCC				0.0100	0.0200	0.0160
non resectable HCC	0.0333	0.5647	0.13	0.0500	1.0000	0.2000
non treatable HCC	0.0598	0.6952	0.27			
post HCC resection				0.0200	0.1200	0.0660
post PEI therapy				0.0000	0.0450	0.02
Probability of death from HCC with decompensated cirrhosis						
treatable HCC	0.0598	0.875	0.36	0.0700	0.5300	0.2300
non treatable HCC			0.88			
post PEI therapy				0.0500	0.1200	0.09

Table 14: The CLIP prognostic system was used to derive a baseline probability of death from HCC in the presence of underlying cirrhosis (bold), which was used to link the other HCC-related probabilities of death. Details of the CLIP scoring are provided in Appendix 2. Table 12 provides a comparison between the three-months probabilities of death from HCC derived from the CLIP score to those which were extracted from the literature.

3.2 Model validation

In order to evaluate how members of the cohorts progress through the various health states over time, the Markov analysis was performed using the probability of events alone, without considering the costs or the utilities. The results of this unadjusted survival analysis are presented in Figures 3 and 4. As expected, as time progresses, the cohort gradually leaves the compensated cirrhosis state to enter the decompensated cirrhosis and the death states. The proportion of the cohort ever entering any of the HCC related states at any given time is less than 5% (Figure 3). The median life expectancy is 10 years and 11 years for the No Screen and the Screen cohorts respectively (Figure 4). In comparison, the average life expectancy of a healthy 54 year old is 25.6 years. The shorter life expectancy of our patients is consistent with their underlying cirrhosis.

The causes of death in each cohort are presented in Figure 5. In both groups, death from HCC with decompensated cirrhosis, death from other cause and death from decompensated cirrhosis account for at least two thirds of the deaths. However, patients who are not screened are more likely to die from non resectable HCC or from HCC which has not otherwise been staged.

Figure 3: **Unadjusted Markov analysis.**

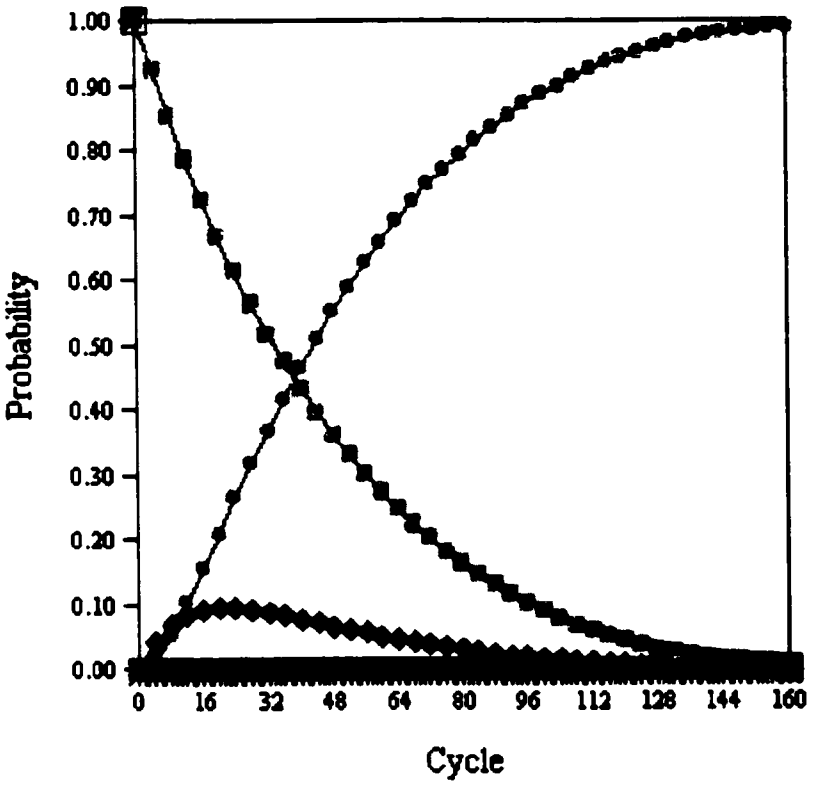


Figure 3 depicts how the cohort gradually leaves the "compensated cirrhosis" health state (squares) to enter the "death" state (circles), the "decompensated cirrhosis" health state (diamonds), as well as, to a lesser degree, the HCC-related health states (superimposed on the X axis). "Probability", on the Y axis, reflects the proportion of the cohort belonging to the health state at each 3-month cycle.

Figure 4: Life expectancy estimation.

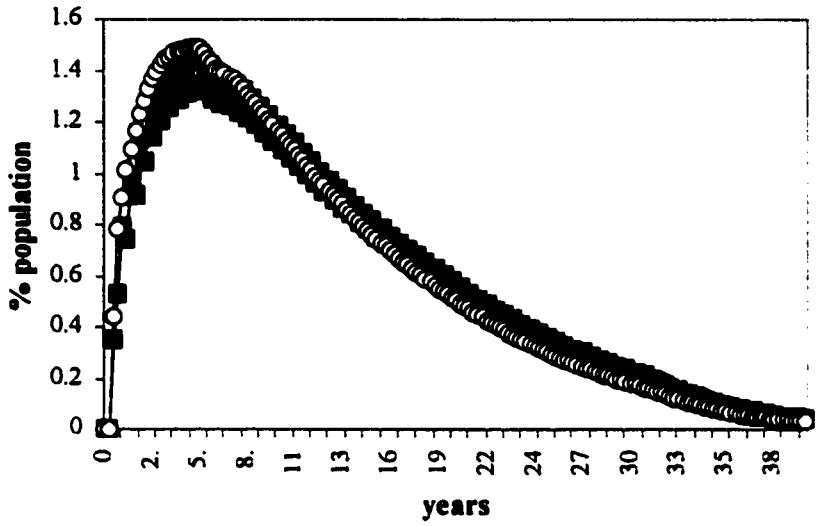


Fig. 4: Percentage of the population of patients with well compensated hepatitis C-related cirrhosis dying over time, in the "Screen" strategy (dark squares) and the "No Screen" strategy (clear circles).

Figure 5: Causes of death in each cohort.

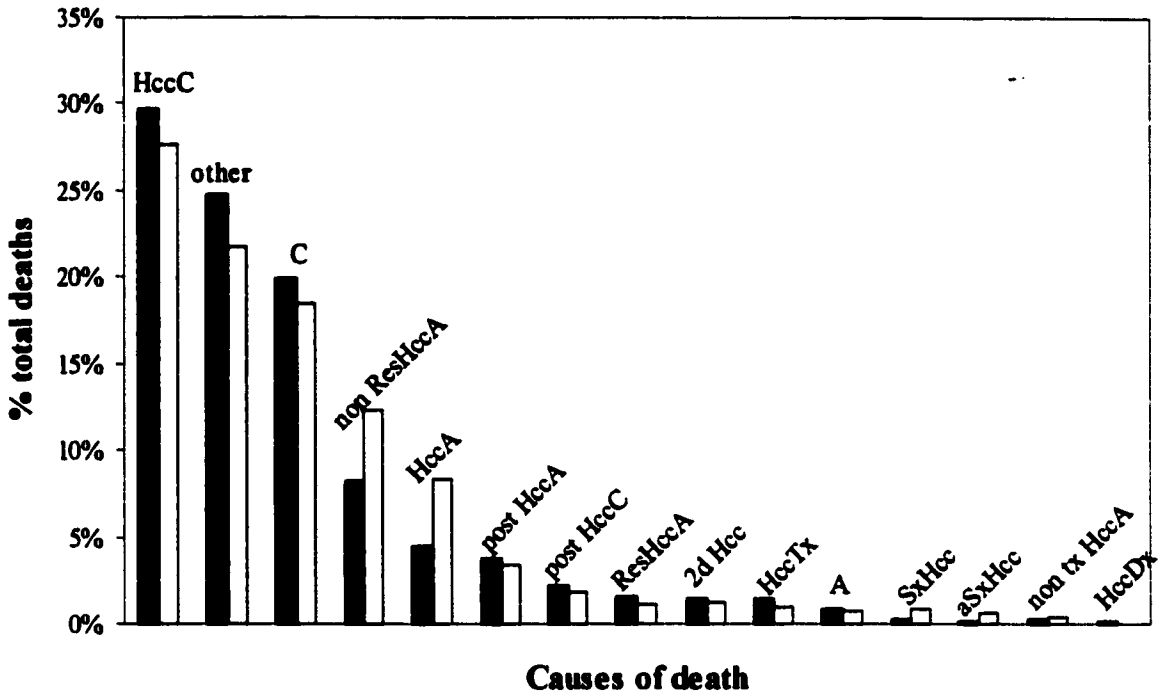


Fig. 5: Causes of death in the "Screen"(black) and "No Screen"(clear) strategies. These include: death from HCC with decompensated cirrhosis (HccC), other causes (other), decompensated cirrhosis (C), non resectable HCC with compensated cirrhosis (nonResHccA), HCC in compensated cirrhosis (HccA), post HCC in compensated cirrhosis (post HccA), post HCC in decompensated cirrhosis (post HccC), resectable HCC with compensated cirrhosis (ResHccA), recurrent HCC (2d Hcc), HCC therapy (HccTx), compensated cirrhosis (A), symptomatic HCC (SxHcc), asymptomatic HCC (aSxHcc), non treatable HCC with compensated cirrhosis (non tx HccA), or HCC diagnosis (HccDx).

3.3 Base case analysis (Table 15)

Based on the best estimate of value of each variable in the model, if screening is performed every 6 months and PEI therapy is reserved for either non resectable tumors or inoperable patients, the life expectancy of the unscreened cohort is 11.78 life-years, while that of the screened cohort is 12.71 life-years. Thus, screening was associated with a gain in life expectancy of 0.93 life-year.

3.4 Frequency of screening (Table 16)

If screening is performed every twelve months, the gain in life expectancy is 0.46 life-year compared to no screening. If screening is performed every 6 months, the gain in life expectancy is 0.47 life-year over that of the screening every 12 months whereas screening every 3 months leads to a gain in life expectancy of 1.03 life-year over that of screening every 6 months.

3.5 Choice of therapy (Table 17)

If surgical resection is the only therapeutic modality considered, only resectable HCC is treated. The total unadjusted life expectancy of the cohort is then of 11.68 and 12.64 life-years in the unscreened and screened strategies respectively. In this situation, screening leads to a gain in life expectancy of 0.96 life-years. Instead, if all cases of HCC undergo PEI therapy, regardless of the resectability, the total unadjusted life expectancy of the cohort is of 11.82 and 12.77 life-years in the "No Screen" and "Screen" strategies

respectively. If all treatable tumors are treated with PEI, screening leads to a gain in life expectancy of 0.95 life-year.

Table 15: Base case results.

	Screen	No Screen	Increment
Life Expectancy (LY)	12.71 (9.23)	11.78 (9.09)	
Gain in Life Expectancy (LY)			0.93
Effectiveness (QALY)	8.25 (2.04)	7.75 (1.94)	
Incremental Effectiveness (QALY)			0.5 (0.18)
Cost ($)	31 900 (17 174)	28 508 (16 325)	
Incremental Cost ($)			3 392 (1 068)
Cost-Effectiveness ($/QALY)	3 884	3 696	
Incremental Cost-Effectiveness ($/QALY)			6 820 (5 116)
95% C.I. ICER ($/QALY)			6 701 - 19 341

Table 15: Mean and standard deviation (SD) of the life expectancy, QALY and costs results from the base case analysis*. The SD was calculated from a total of 3500 Monte Carlo simulations.
*In the base case analysis, screening is performed every 6 months; resectable tumors are treated with surgical resection while unresectable tumors without portal vein thrombosis are treated with PEI. Costs and utilities are discounted at a 3% rate.

Table 16: **Effect of the frequency of screening.**

Strategy	Life Expectancy (LY)	Gain in Life Expectancy (LY)	Effective-ness (QALY)	Incremental Effective-ness (QALY)	Cost ($)	Incremental Cost ($)	Cost-Effective-ness ($/QALY)	Incremental Cost-Effective-ness ($/QALY)
No Screen	11.78		7.75		28 508		3 696	
Screen every 12 months	12.24	0.46	8	0.25	30 211	1 703	3 792	6 816
Screen every 6 months	12.71	0.47	8.25	0.25	31 900	1 689	3 884	6 756
Screen every 3 months	13.74	1.03	8.75	0.5	35 296	3 396	4 032	6 792

Table 17: **Effect of the choice of HCC therapy.**

Strategy	Life Expectancy (LY)	Gain in Life Expectancy (LY)	Effective-ness (QALY)	Incremental Effective-ness (QALY)	Cost ($)	Incremental Cost ($)	Cost-Effective-ness ($/QALY)	Incremental Cost-Effective-ness ($/QALY)
Surgery alone								
No Screen	11.68		7.75		28 035		3 660	
Screen	12.64	0.96	8.25	0.5	31 515	3 480	3 856	6 756
PEI alone								
No Screen	11.82		7.75		28 974		3 660	
Screen	12.77	0.95	8.25	0.5	31 705	3 331	3 836	6 488

Table 17 presents the results of the analysis if the choices of HCC therapy are alternated from A) "surgery alone", i.e. performing surgical resection on all resectable tumors and not offering any other alternative therapy to the patients with non resectable tumors or B) "PEI alone", i.e. treating all tumors with PEI, except those with associated portal vein thrombosis, which are considered non treatable.

4 Cost-effectiveness analysis

4.1 Base-case analysis (Table 15)

Screening for HCC in compensated HCV-related cirrhosis is associated with an incremental quality-adjusted survival of 0.5 QALY and an incremental cost of $3 392, which corresponds to an ICER of $6 820 per additional quality-adjusted life year. Because of this relatively low ICER, no strategy was clearly dominated by another. The 95% confidence interval of the ICER is 6 701 $/QALY to 19 341 $/QALY.

If no discounting is applied, the ICER is $6 340 per additional quality-adjusted life year while if a 5% discount rate is used, the ICER is $7 164 per additional quality-adjusted life year (Table 18). Screening is economically attractive, independently of the chosen discount rate.

4.2 Effect of the frequency of screening (Table 16)

Screening every 12 months leads to an incremental quality-adjusted survival of 0.25 QALY and an incremental cost of $1 703, which corresponds to an ICER of 6 816 $/QALY. Compared to screening every 12 months, screening every 6 months leads to a gain of 0.25 QALY at an incremental cost of $1 689, which corresponds to an ICER of 6 756 $/QALY. Screening every 3 months yields an additional 0.5 QALY, at an incremental cost of $ 3 396 and an ICER of 6 792 $/QALY.

Table 18: **Effect of discounting.**

Strategy	Effectiveness (QALY)	Incremental Effectiveness (QALY)	Cost ($)	Incremental Cost ($)	Cost-Effectiveness ($/QALY)	Incremental Cost-Effectiveness ($/QALY)
No Discounting						
No Screen	9.75		37 888		3 852	
Screen	10.5	0.75	42 808	4 919	4 036	6 340
Discounting 3%						
No Screen	7.75		28 508		3 696	
Screen	8.25	0.5	31 900	3 392	3 884	6 820
Discounting 5%						
No Screen	6.75		24 158		3 596	
Screen	7	0.5	26 904	2 746	3 792	7 164

4.3 Effect of the choice of therapy (Table 17)

The ICER of screening every 6 months if surgery is the only therapeutic modality is 6 756 $/QALY whereas it is 6 488 $/QALY if all patients with HCC are treated with PEI.

4.4 Sensitivity Analyses

4.4.1 One-way

One way sensitivity analyses were performed on every probability, utility and cost variable of the tree (Table 19). The difference between the costs and outcomes of screening for HCC in compensated HCV-related cirrhosis versus expectant management was not affected by univariate changes in the value of most variables. In the majority of cases, screening was both more costly and more effective than non screening. However, the incremental cost-effectiveness remained, in most cases, small (i.e. less than $15 000 per QALY).

4.4.1.1 Probability of events related to the natural history of HCV-related cirrhosis (Table 19 a)

The probability of decompensated cirrhosis in well-compensated HCV-related cirrhosis had a relatively marked effect on the ICER of the screening intervention, which ranged from 4 600 $/QALY at the lowest probability estimate to 13 000 $/QALY at its highest (Figure 6). This effect was best explained by the greatest gain in QALY of the screened patients at low probability for decompensated cirrhosis.

Table 19: **One-way sensitivity analyses.**

A: **Effect of the probability of events related to the natural history of HCV-related cirrhosis**

Parameter	Best probability estimate	Range tested	Is screening more effective?	Is screening more costly?	Range of ICER ($/QALY)	Threshold
Annual probability of decompensated cirrhosis in compensated HCV related cirrhosis	0.044	0.06-0.07	Yes	Yes	4 600-13 000	No
Annual probability of death in compensated HCV related cirrhosis	0.009	0.002-0.02	Yes	Yes	6 600-5 700	No
Annual probability of death in decompensated HCV related cirrhosis	0.1489	0.12-0.17	Yes	Yes	6 800	No
Annual probability of HCC in compensated HCV related cirrhosis	0.0212	0.01-0.03	Yes if p>0.011	Yes	15 600-6 700	No
Relative risk of HCC in decompensated cirrhosis	2.4	36169	Yes	Yes	8 600-6 100	No

Table 19A-F: Results of the one-way sensitivity analyses. The possible range of annual probabilities and their best estimate are presented. The range of ICER obtained is presented from the ICER value resulting from the lowest estimate of the probability tested, to the ICER value obtained from its upper estimate. When the range of ICER value obtained was less than 100 $/QALY, only a single value is provided. A threshold value was present if the ICER was equal or greater than 50 000 $/QALY.

Figure 6: **One-way sensitivity analysis on the probability of decompensated cirrhosis in compensated cirrhosis.**

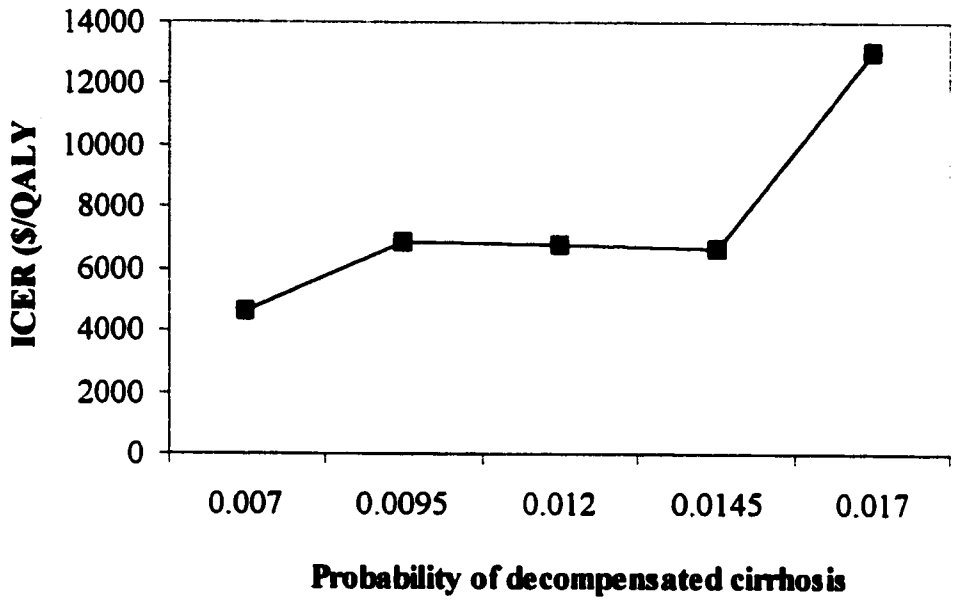


Fig. 6: Results of the one-way sensitivity analysis on the probability of decompensation in well-compensated HCV-related cirrhosis. The probabilities are expressed as three month probabilities. The best estimate for the three-month probability of decompensation variable was 0.009.

The probability of HCC in well-compensated HCV-related cirrhosis also has a relatively significant impact on the ICER of the intervention, with a range of 15 600 $/QALY to 6 700 $/QALY at the lowest and highest probability estimates respectively (Figure 7 a). In other words, the ICER of screening lessens as the probability of HCC in compensated cirrhosis increases. This result is expected, since screening interventions are likely to be most cost-effective when the disease prevalence is high. If the three-month probability of HCC in compensated HCV-related cirrhosis is exaggerated to 0.011 or greater (which corresponds to an annual probability of HCC of 0.04, the upper estimate for this variable being equal to 0.03), screening becomes less costly than the no intervention strategy (Figure 7 b).

By contrast, the probability of disease-specific mortality in cirrhosis had little impact on the ICER of the intervention.

Figure 7: **One-way sensitivity analysis on the probability of hepatocellular carcinoma in HCV-related cirrhosis.**

A: **Effect on the ICER of screening**

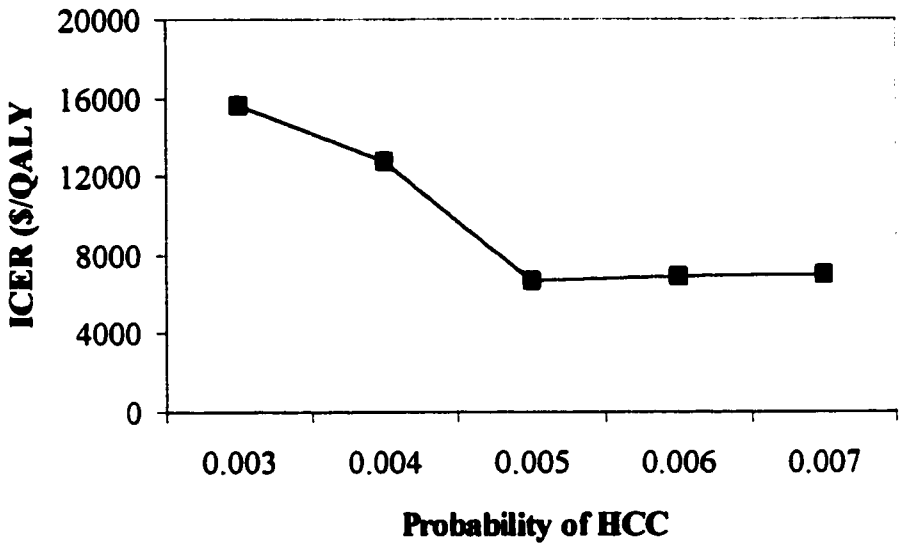


Fig. 7A: Results of the one-way sensitivity analysis on the probability of HCC in HCV-related cirrhosis. The probabilities are expressed as three month probabilities. The best estimate for the probability of HCC variable was 0.005.

Figure 7: **One-way sensitivity analysis on the probability of hepatocellular carcinoma in HCV-related cirrhosis.**

B: **Effect on the CER of each arm**

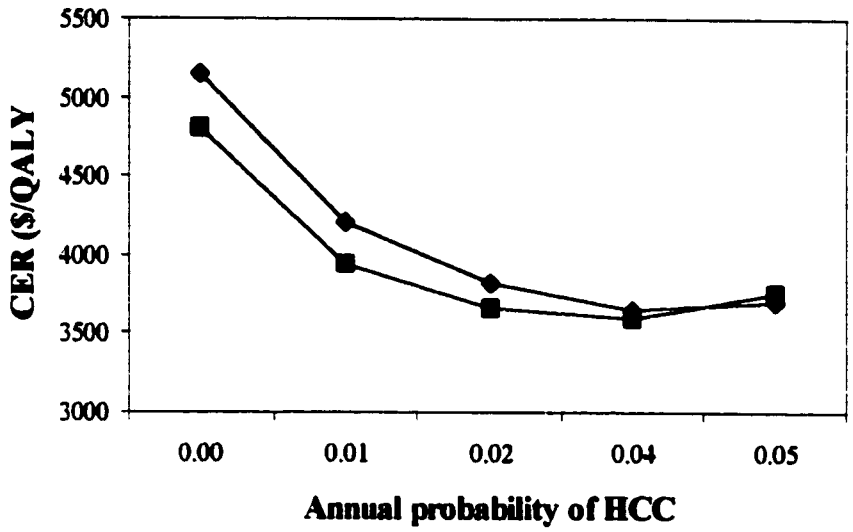


Fig 7B: Results of the one-way sensitivity analysis of the effect of varying the probability of HCC in compensated hepatitis C-related cirrhosis on the cost-effectiveness ratios, in the "No Screen" strategy (squares) and the "Screen" strategy (diamonds). The range of values has been extended beyond its possible range to show that if the annual probability of HCC is 0.04 or greater, the CER of screening becomes less than that of the expectant management (the range of possible values for the annual probability of HCC is of 0.0143 to 0.0275; best estimate equals 0.0212).

4.4.1.2 Probability of events related to the natural history of cirrhotic patients with HCC (Table 19 b)

The baseline probability of death from HCC in the presence of underlying cirrhosis had a relatively important impact on the ICER of the screening intervention, with a range of 12 700 $/QALY to 5 000 $/QALY at the lowest and highest probability estimates respectively (Figure 8). The impact of a high probability of death from HCC in cirrhosis on the ICER was due to the fact that screened patients would lose relatively less QALYs than the non screened patients. As seen in Figure 8 a, the effect of this variable on the ICER is not linear. This is explained by the fact that all the other HCC-related probabilities of death are linked to this variable.

The effect of the other HCC-related probabilities of death, such as the probabilities of death from resectable, non resectable, or symptomatic HCC on the ICER was minimal.

The probability of resectable HCC in screened and in non screened patients did not affect the QALYs in either group, but higher probabilities of resectability increased the costs. Therefore, a higher probability of resectability in non screened patients would increase the costs in that group, lessening the ICER of the intervention, while a higher probability of resectability in screened patients would increase the ICER. Overall, the impact of these variables on the ICER was minimal.

Changes in the probability of events occurring as a result of HCC therapy and the probability of recurrent HCC had little impact on the ICER of the intervention (Table 19 c).

Table 19: **One-way sensitivity analyses.**

B: **Effect of the probability of events related to the natural history of cirrhotic patients with HCC**

Parameter	Best probability estimate	Range tested	Is screening more effective?	Is screening more costly?	Range of ICER ($/QALY)	Threshold
Probability of death in cirrhotic patients with HCC						
Baseline probability of death from HCC in the presence of underlying cirrhosis	0.52	0.09-0.99	Yes	Yes	12 700-5 000	No
Annual probability of death from resectable HCC in compensated cirrhosis	0.19	0.04-0.5	Yes	Yes	6 900-6 800	No
Annual probability of death from non resectable HCC in compensated cirrhosis	0.59	0.18-1.0	Yes	Yes	6 400-6 800	No
Annual probability of death from symptomatic HCC in compensated cirrhosis	0.672	0.5-0.72	Yes	Yes	6 800	No
Annual probability of death from decompensated cirrhosis with HCC	0.65	0.25-0.95	Yes	Yes	5 700-6 800	No
Probability of resectability						
Probability of resectable HCC in screened compensated cirrhosis	0.43	0.06-0.87	Yes	Yes	6 000-7 000	No
Probability of resectable HCC in non screened compensated cirrhosis	0.12	0.06-0.34	Yes	Yes	7 400-6 800	No

Figure 8: **One-way sensitivity analysis on the baseline probability of death from HCC with underlying cirrhosis.**

A: **Effect on the ICER of screening**

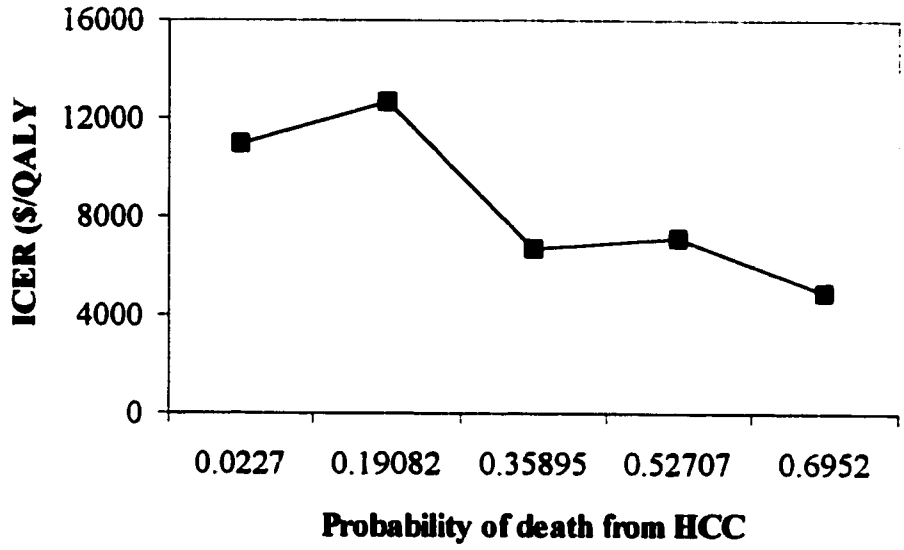


Fig 8A: Results of the one-way sensitivity analysis on the baseline probability of death from HCC with underlying cirrhosis. The probabilities are expressed as three month probabilities. The best estimate for the three-month probability of death from HCC variable was 0.17.

Figure 8: **One-way sensitivity analysis on the baseline probability of death from HCC with underlying cirrhosis.**

B: **Effect on the CER of each arm**

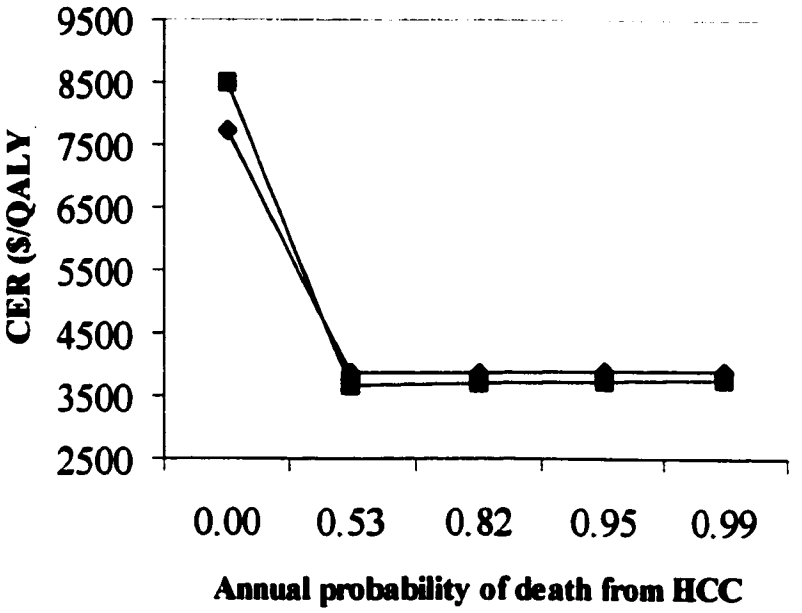


Fig 8B: Results of the one-way sensitivity analysis of the effect of varying the probability of death from HCC in the presence of underlying cirrhosis on the cost-effectiveness ratios, in the "No Screen" strategy (squares) and the "Screen" strategy (diamonds). The CER of screening is less than that of the expectant management if the probability of death from HCC is low, i.e. less than 0.45 per annum (the range of possible values for the annual probability of death from HCC in the presence of underlying cirrhosis is of 0.09 to 0.99; best estimate equals 0.52).

Table 19: **One-way sensitivity analyses.**
C: **Effect of the probability of events related to HCC therapy**

Parameter	Best probability estimate	Range tested	Is screening more effective?	Is screening more costly?	Range of ICER ($/QALY)	Threshold
Probability of events related to surgical resection						
Probability of death from HCC resection in compensated cirrhosis	0.1	0.025-0.2	Yes	Yes	6 800	No
Annual probability of death post HCC resection in compensated cirrhosis	0.24	0.08-0.4	Yes	Yes	7 000-6 800	No
Annual probability of recurrent HCC post HCC resection in compensated cirrhosis	0.23	0.1-0.37	Yes	Yes	6 700-6 800	No
Probability of events related to PEI therapy						
Probability of PEI therapy in non resectable HCC	0.33	0	Yes	Yes	7 000-6 800	No
Probability of death from PEI therapy in compensated cirrhosis	0.001	0.0009-0.007	Yes	Yes	6 800	No
Probability of death from PEI therapy in decompensated cirrhosis	0.007	0.0009-0.014	Yes	Yes	6 600	No
Probability of persistent HCC post PEI therapy	0.09	0-0.23	Yes	Yes	6 800	No
Annual probability of death post PEI therapy in compensated cirrhosis	0.07	0-0.17	Yes	Yes	6 700-6 800	No
Annual probability of death post PEI therapy in decompensated cirrhosis	0.31	0.19-0.41	Yes	Yes	6 800	No
Annual probability of recurrent HCC post PEI therapy in compensated cirrhosis	0.23	0.15-0.36	Yes	Yes	6 800	No
Annual probability of recurrent HCC post PEI therapy in decompensated cirrhosis	0.3	0.3-0.37	Yes	Yes	6 800	No

Table 19: **One-way sensitivity analyses.**

D: **Effect of the test characteristics variables**

Parameter	Best probability estimate	Range tested	Is screening more effective?	Is screening more costly?	Range of ICER ($/QALY)	Threshold
Sensitivity of ultrasound	0.91	0.83-0.99	Yes	Yes	6 700-6 900	No
Specificity of ultrasound	0.93	0.87-0.98	Yes	Yes	6 300-7 400	No
Age at onset of screening	54	30-80	Yes	Yes	5 600-8 600	No
Probability of death from FNA	0	0-0.001	Yes	Yes	6 800	No

4.4.1.3 Test characteristics variables (Table 19 d)

The impact of the sensitivity of the screening test on the CER of each arm is presented in Figure 9 a . Varying the sensitivity of the test had little impact on the ICER, which increased with the sensitivity. This is explained by the fact that the more HCC is detected, the more subsequent therapies are performed. To prove this, a one-way sensitivity analysis on the test sensitivity variable was also performed when no HCC therapies were offered, i.e. all detected HCC were considered non treatable. This time, the cost-effectiveness ratio was unaffected by the variable.

Varying the specificity of the test had a slightly greater impact on the ICER, which increased with the specificity. The impact of the specificity of the screening test on the CER of each arm is presented in Figure 9 b . The CER of screening is inversely proportional to the specificity of the test: it decreases as the proportion of false positives diminishes.

The age of the cohort was varied from 30 to 80 years (Figure 10). The gain in QALYs was greatest between the ages of 35 and 45 years. The costs decreased with life expectancy. The overall effect of age at onset of screening on the ICER was not very important. The younger the age at onset of the period of observation, the greater the cost-effectiveness ratios in both strategies (Figure 10 b).

Varying the cost of screening from its lowest to its highest value led to an increase of the ICER of the intervention, from 3 300 to 6 800 $/QALY (Table 19 e). The other cost variables had a minimal impact on the ICER (Table 19 e).

Figure 9: **One-way sensitivity analysis on the characteristics of the screening test.**

A: **Sensitivity of ultrasound for HCC**

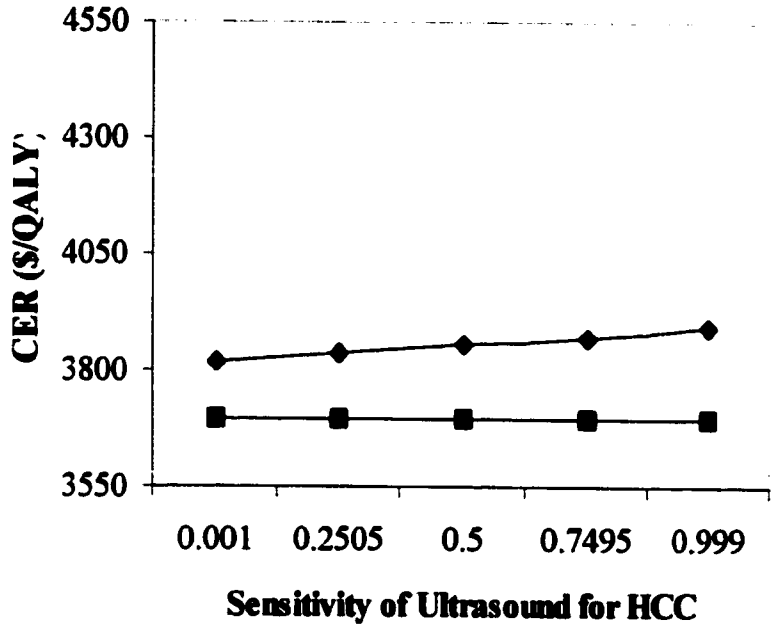


Fig 9A: Results of the one-way sensitivity analysis of the effect of varying the sensitivity of the screening test (liver ultrasound combined with AFP level) on the cost-effectiveness ratios, in the "No Screen" strategy (squares) and the "Screen" strategy (diamonds).

Figure 9: **One-way sensitivity analysis on the characteristics of the screening test.**

B: **Specificity of ultrasound for HCC**

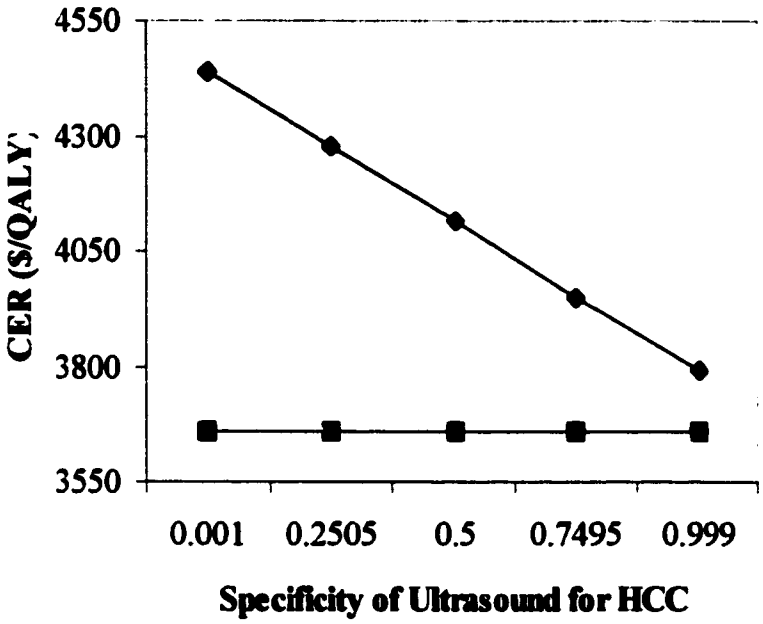


Fig 9B: Results of the one-way sensitivity analysis of the effect of varying the specificity of the screening test (liver ultrasound combined with AFP level) on the cost-effectiveness ratios, in the "No Screen" strategy (squares) and the "Screen" strategy (diamonds).

Figure 10: **One-way sensitivity analysis on the age at onset of screening.**

A: **Effect on the ICER of screening**

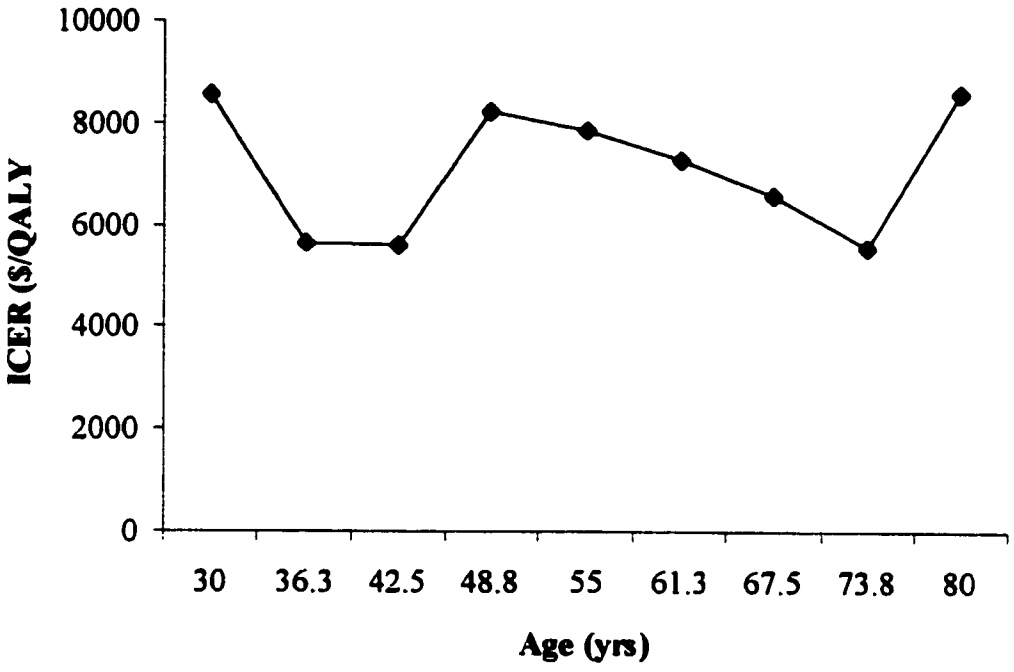


Fig. 10A: Results of the one-way sensitivity analysis of the age at onset of the cohort, which was varied from 30 to 80 years. The gain in QALYs was greatest between the ages of 35 and 45 years. The costs decreased with life expectancy, more so in the "Non screen" than in the "Screen" strategy at the extreme of life.

Figure 10: **One-way sensitivity analysis on the age at onset of screening.**

B: **Effect on the CER of each arm**

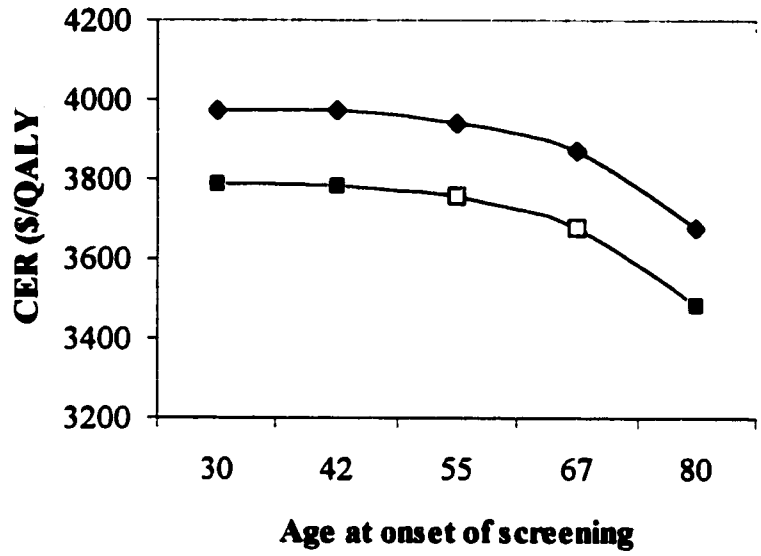


Fig. 10B: Results of the one-way sensitivity analysis of the effect of varying the age at onset of screening on the cost-effectiveness ratios, in the "No Screen" strategy (squares) and the "Screen" strategy (diamonds).

Table 19: **One-way sensitivity analyses.**

E) **Effect of the cost variables**

Parameter	Best probability estimate	Range tested	Is screening more effective?	Is screening more costly?	Range of ICER ($/QALY)	Threshold
Costs in compensated cirrhosis			Yes	Yes	6 600	No
Costs in decompensated cirrhosis			Yes	Yes	6 500-6 800	No
Costs in HCC			Yes	Yes	6 800-6 900	No
Costs of screening			Yes	Yes	3 300-6 800	No
Costs of FNA			Yes	Yes	6 100-6 800	No
Costs of PEI			Yes	Yes	6 800-6 900	No
Costs of staging			Yes	Yes	6 800	No
Costs of surgery			Yes	Yes	6 400-6 800	No
Annual probability of hospitalization in decompensated cirrhosis	0.5	0.3-1	Yes	Yes	5 300-7 200	No
Annual probability of hospitalization in HCC	1.5	36161	Yes	Yes	6 800	No

4.4.1.4 Utility and disutility variables (Table 19f)

The cost-effectiveness ratios are very sensitive to the utility of compensated cirrhosis, if this value ranges between 0 and 0.3 (Figure 11a). At these values, the ICER of screening becomes infinite because the difference in QALYs between screen and no screen equals zero (Figure 11b). However, for values of the utility of compensated cirrhosis which lie within the most likely range (i.e. greater than 0.3), the ICER is less affected. Values of the utility of decompensated cirrhosis and of HCC impacted minimally on the ICER (Figure 12). Disutility values had no impact on the ICER.

Table 19: **One-way sensitivity analyses.**

F) **Effect of the utility and disutility variables**

Parameter	Best probability estimate	Range tested	Is screening more effective?	Is screening more costly?	Range of ICER ($/QALY)	Threshold
Utility of compensated cirrhosis	0.89	0.25-0.99	Yes	Yes	4 500-13 600	No
Utility of decompensated cirrhosis	0.6	0.0-0.99	Yes	Yes	6 800	No
Utility of HCC	0.34	0.0-0.99	Yes	Yes	6 800	No
Disutility of screening	0.0033	0.0020-.0040	Yes	Yes	6 800	No
Disutility of FNA	0.0056	0.0040-.0070	Yes	Yes	6 800	No
Disutility of PEI	0.0372	0.0111-0.0778	Yes	Yes	6 800	No
Disutility of surgery	0.1405	0.0666-0.4	Yes	Yes	6 800	No
Disutility of staging	0.0055	0.0033-0.0222	Yes	Yes	6 800	No

Figure 11: One-way sensitivity analysis on the utility for compensated cirrhosis.

A: Effect on the ICER of screening

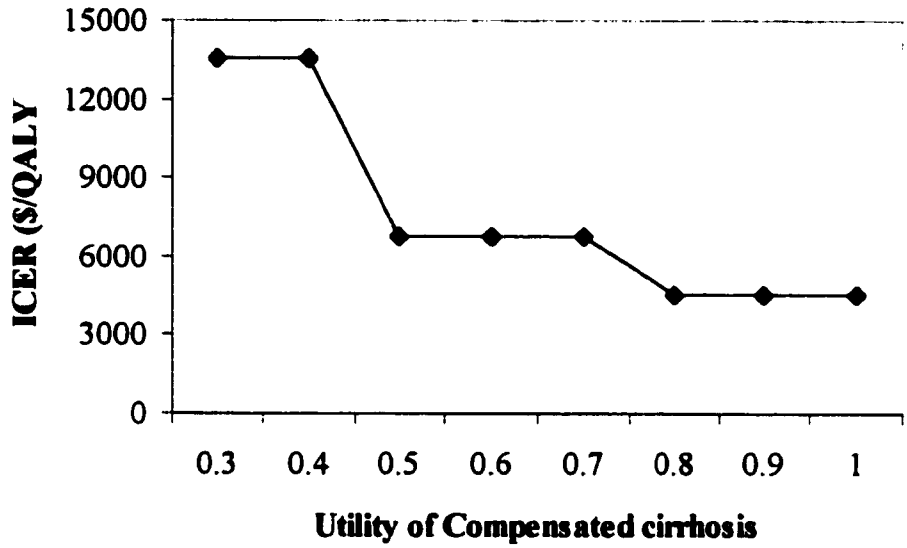


Fig. 11A: Effect of varying the utility value for compensated cirrhosis on the ICER of the intervention. At utility values less than 0.3, the ICER goes to infinite, because the difference in QALYs between screen and no screen equals zero (not shown on graph).

Figure 11: One-way sensitivity analysis on the utility for compensated cirrhosis.

B: Effect on the CER of each arm

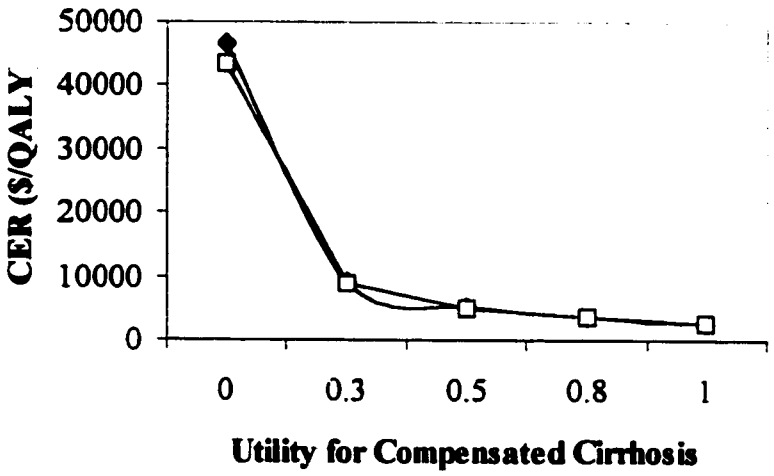


Fig. 11B: Results of the one-way sensitivity analysis of the effect of varying the utility value in compensated cirrhosis on the cost-effectiveness ratios, in the "No Screen" strategy (grey squares) and the "Screen" strategy (black diamonds).

Figure 12: One-way sensitivity analysis on the utility variables.

A: Utility for decompensated cirrhosis

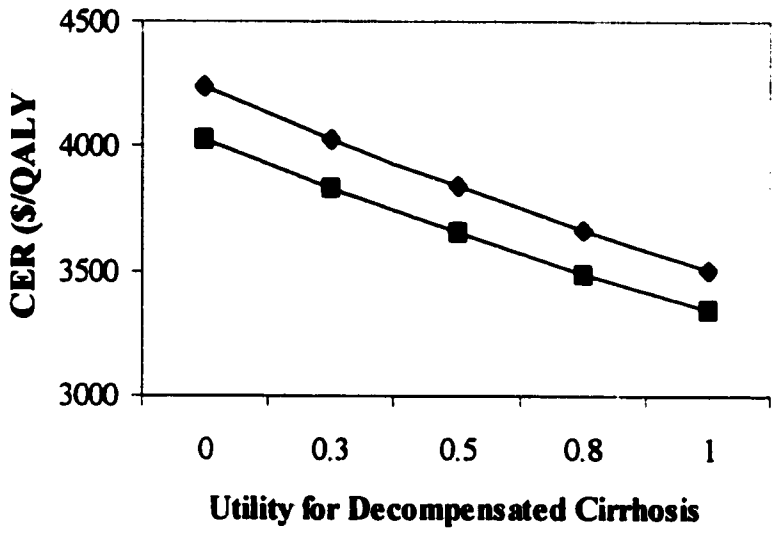


Fig. 12A: Results of the one-way sensitivity analysis of the effect of varying the utility value in decompensated cirrhosis on the cost-effectiveness ratios, in the "No Screen" strategy (squares) and the "Screen" strategy (diamonds).

Figure 12: **One-way sensitivity analysis on the utility variables.**

B: **Utility for hepatocellular carcinoma**

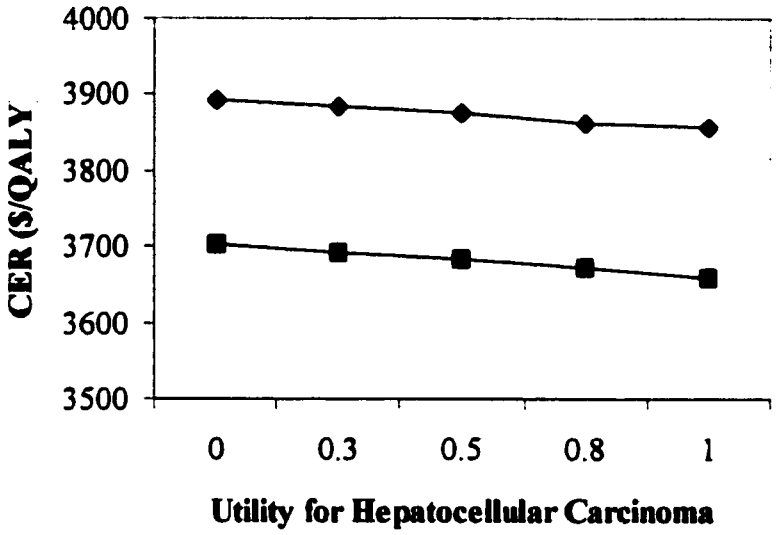


Fig. 12B: Results of the one-way sensitivity analysis of the effect of varying the utility value in hepatocellular carcinoma on the cost-effectiveness ratios, in the "No Screen" strategy (squares) and the "Screen" strategy (diamonds).

4.4.2 Two-way sensitivity analyses

One-way sensitivity analysis revealed that there were only two probability variables which affected the relative attractiveness of each strategy: the probability of HCC in compensated hepatitis C-related cirrhosis and the baseline probability of death from HCC with underlying cirrhosis (Figures 7 and 8).

These two variables were analysed simultaneously in a two-way sensitivity analysis (Figure 13). This analysis shows that, of these two probabilities, the probability of HCC in compensated cirrhosis seems to have the most impact, and that screening is most favoured when the incidence of HCC is high.

4.4.3 Best case and worse case scenarios (Table 20)

The best and worse case scenarios used the extreme values of the variables that showed an impact on the ICER in the one-way sensitivity analysis, i.e. the probability of HCC in compensated HCV-related cirrhosis, the probability of death from HCC with underlying cirrhosis, the probability of decompensated cirrhosis, the frequency of screening, the age at onset of screening, and the utility for compensated cirrhosis. As shown in Table 20, in the best case scenario, the gain in unadjusted life expectancy in the screen strategy is 6.76 LYs, the gain in quality adjusted life-years is 3.5 QALYs and the ICER is 1 429 $/LY or 2 760 $/QALY (compared to baseline values of 0.93 LYs, 0.5QALYs and 6 820 $/QALY). In the worse case scenario, the gain in life expectancy is minimal, i.e. 0.01 LY and 0 QALY, leading to an ICER of 73 300 $/LY (in this case, the ICER cannot be calculated in $/QALY because of the zero value in the denominator).

Figure 13: Two-way sensitivity analysis on the probability of HCC in compensated cirrhosis and the probability of death from HCC with underlying cirrhosis.

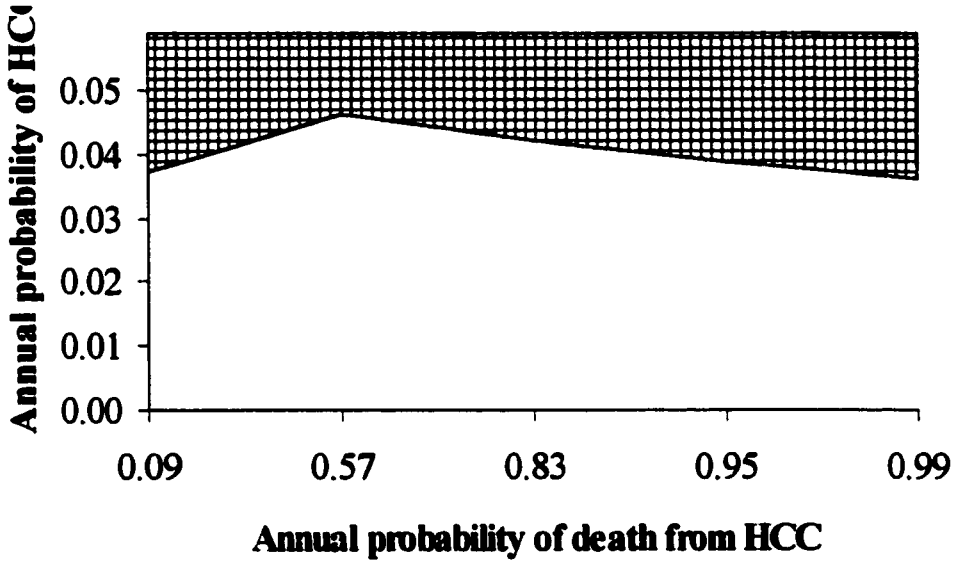


Fig. 13: Graphical representation of the results of the two-way sensitivity analysis of the effect of varying the probability of death from HCC in the presence of underlying cirrhosis and the probability of HCC in compensated cirrhosis. At any given value of the two variables, the optimal strategy is represented by a specific pattern (square grid for the "Screen" strategy and shaded area for the "No Screen" strategy). The junction line between the two areas represent the points at which the CER's of each strategy are equal.

Table 20: **Best case and worse case scenarios.**

	Best	Worse
Variable		
Annual probability of HCC	0.03	0.01
Annual probability of death from HCC	0.99	0.09
Annual probability of decompensated cirrhosis	0.04	0.07
Frequency of screening	every 3 months	every 12 months
Age at onset screening	40	80
Utility in compensated cirrhosis	0.99	0.25
Gain in life expectancy (yr)	6.76	0.01
Gain in QALYs (QALY)	3.5	0
Incremental cost ($)	9 661	733
ICER ($/LY)	1 429	73 300
ICER ($/QALY)	2 760	(Infinite)

4.5 Monte Carlo simulation

A total of 3 500 Monte Carlo simulations were performed. The mean and standard deviation of the ICER were 6 820 and 5 116 $/QALY. The 95% confidence interval of the ICER was 6 701 $/QALY to 19 341 $/QALY (Table 15). This implies that, in 95% of the time, screening for HCC in patients with well compensated hepatitis C-related cirrhosis will be associated with a cost of $19 341 per additional quality-adjusted life year or less, compared with expectant management.

DISCUSSION

It has been demonstrated that the relative risk of primary liver cancer in patients with hepatitis C related cirrhosis is 16 (95% C.I. 12-22) times that of the general population[148]. The majority of patients who develop symptoms from this cancer harbour tumors which are at an advanced and rapidly fatal stage. Therefore, screening for primary liver cancer in patients with cirrhosis has been advocated as a means of preventing cancer-related deaths. However, it is unclear how often screening should be performed and whether early detection actually prolongs survival in patients with cirrhosis[14]. As well, the cost-effectiveness of such an intervention, considering currently available therapeutic modalities for primary liver cancer, is unknown. A long-term randomized study comparing screening for hepatocellular carcinoma to expectant management in such patients might establish the benefit of this intervention, but such a study would be extremely expensive and would require decades of follow-up. Recent evidence suggests a rise in the incidence of hepatocellular carcinoma in the United States[13] and in Canada (S. El Sadani, Statistics Canada, personal communication February 1999). Because the decision to screen must be made now rather than in several decades, we turned to decision analysis to assess the cost-effectiveness of screening for hepatocellular carcinoma in patients with well compensated hepatitis C-related cirrhosis, on the basis of the best available information.

This analysis has demonstrated that screening for hepatocellular carcinoma in patients with well compensated hepatitis C-related cirrhosis is both more costly and more effective than expectant management of these patients. If screening is performed every 6

months, the incremental cost-effectiveness ratio, is $6 820/QALY when a 3% discounting rate is applied. If we account for the uncertainty around the variables' estimates, the incremental cost of this intervention may be as high as $19 341 per additional quality-adjusted life year. This compares favourably to medical interventions which are considered acceptable in Canada, such as renal transplantation with a cadaveric organ (~$10 000/QALY)[149]. In other words, screening for hepatocellular carcinoma in patients with well compensated hepatitis C-related cirrhosis should be considered relatively economically attractive.

The results of this economic evaluation are insensitive to the majority of variables used in the model. Screening becomes most economically attractive if the probability of hepatocellular carcinoma is high. Screening may therefore be more advantageous in higher risk populations, such as patients with concomitant alcohol consumption or hepatitis B virus infection[148], or, possibly, in patients who are infected with the hepatitis C viral genotype 1b[150,151]. Conversely, since recent evidence suggests a lower risk of hepatocellular carcinoma after interferon therapy[11,46,152] it may be less economically attractive to screen patients who have received this therapy, especially if they responded to it.

The effectiveness of the intervention is greatest when screening is performed every 3 months, yielding a gain in life expectancy of 1.96 life-year compared to expectant management and of 1.03 life-year compared to screening every 6 months. The incremental cost-effectiveness ratio of screening every 3 months is $6 788/QALY compared to expectant management, and $6 792/QALY, compared to screening every 6 months. These

findings are supported by the prospective studies of screening for hepatocellular carcinoma in patients with cirrhosis. For example, Colombo et al found that screening Italian patients with well compensated cirrhosis and normal alpha foetoprotein levels every 12 months failed to increase the rate of detection of small, potentially operable tumors and suggested that screening every 3 months would likely yield more resectable tumors [33].

Weinstein and Wright have recently proposed using the gains in life expectancy from medical interventions as a mean of assessing their relative effectiveness and value[153]. They have compared the gains in life expectancy obtained from a variety of medical interventions and target populations. In populations at high risk for a disease, such as ours, the gains in life expectancy for preventive interventions would vary from 0.15 month (hepatitis B virus vaccination in 12-to-50-year-olds at high risk for hepatitis) to 76 months (reduction of cholesterol to 5.2 mmol/l in female subjects with a cholesterol level of > 7.8 mmol/l). They have proposed that, in preventative interventions for populations at elevated risk of a disease, a gain in life expectancy of a year can be considered large.

The gain in life expectancy from screening for hepatocellular carcinoma every 6 months in hepatitis C-related compensated cirrhosis is 0.93 life-year, or 11.16 months. Therefore, our intervention can be considered highly effective since it is yielding a large gain in life expectancy compared to other medical interventions performed on populations at high risk of disease.

Our conclusions differ from those of a previously published cost-effectiveness analysis on screening for hepatocellular carcinoma in compensated cirrhosis[154]. Sarasin et al used a Markov model to perform a cost-effectiveness analysis of screening for

hepatocellular carcinoma in Western patients with asymptomatic cirrhosis, using biannual alpha foetoprotein and liver ultrasound, and have concluded that such an intervention would yield an incremental cost-effectiveness ratio of $48 000 to $284 000US for each additional life-year saved, which is more than the cost of many other accepted medical practices[154]. These authors also found that screening is associated with a gain in life expectancy of < 3 months. Surgical resection was the only therapeutic modality. The cost per year of life gained was calculated, without adjusting for quality of life and future costs were not included. In their analysis, the cost of screening and of treating resectable hepatocellular carcinoma relative to the overall costs of cirrhosis seem inflated by several factors. It was assumed that the probability of death from a small, asymptomatic hepatocellular carcinoma was zero, and that, in such a case, one can only die from complications of cirrhosis or of surgery. This exaggerates the probability of death in the group of patients who are found to have resectable hepatocellular carcinoma at screening since our review of the literature revealed that the three-month (cycle-specific) probability of death from a small, asymptomatic hepatocellular carcinoma ranges from 0.01 to 0.02[31,55], which represents 10 to 100% of the risk of death from hepatocellular carcinoma resection[65,80,155]. The average life expectancy of patients with Child's A cirrhosis who underwent screening ranged from 6.3 to 8.8 years, for the worse and best case scenarios respectively. The average life expectancy of our hypothetical group of well compensated hepatitis C cirrhotics who underwent screening was 18.1 years (12.71 life-years). Their estimates of the costs of the screening test, the staging, and the costs of hospitalization or death from cirrhosis, hepatocellular carcinoma, and surgical resection, were up to 2 to 3-

fold higher than ours. Their costs of cirrhosis were relatively underestimated since there was no accounting for the probability of hepatocellular carcinoma in decompensated cirrhosis, and of its subsequent therapy. Screening was relatively ineffective because their estimates of tumor resectability at the time of detection were derived from only three reports (as opposed to the 15 we found from our systematic review), and these values were much lower than our estimates.

These differences underscore how difficult it may be to compare results of economic evaluations on health interventions. Incremental cost-effectiveness ratios can only be appropriately compared if they were derived using similar methods. This measure of economic attractiveness is a composite measure which can be derived using different methodologies and assumptions. In particular, to interpret the results of any cost-effectiveness analysis, one must consider the following: economic perspective and methods of cost valuation; time horizon; method of effectiveness measure or, in the case of a cost-utility measure such as ours, of QALY measure; intervention or programme to which the intervention is being compared; and whether discounting of costs and effectiveness was applied.

The benefits of a screening intervention may only be seen in the distant future. For that reason, we used a Markov model which allowed this study to hold a time horizon of a lifetime. As well, both costs and benefits were discounted. The Markov model also allowed us to integrate the natural history of well compensated hepatitis C-related cirrhosis as well as that of treated and untreated hepatocellular carcinoma into the analysis.

Our comprehensive literature search yielded probability estimates which were largely derived from uncontrolled studies. Nevertheless, such estimates as the probabilities of death from hepatocellular carcinoma at various stages were consistent with probabilities which were calculated from a prognostic score[49]. However, aware of the potential inaccuracy of such uncontrolled data, we 1) performed multiple sensitivity analyses around the variables' estimates, 2) performed Monte Carlo simulations to evaluate the magnitude of uncertainty around the estimate of the incremental cost-effectiveness ratio of our intervention, and 3) considered alternate screening and treatment strategies.

Many of the methodological aspects of economic evaluation are the subject of ongoing controversy. We tried to adhere to the recommendations of the US Panel on Cost-effectiveness Analysis in Health Care[124]. However, our cost estimates did not include the time costs to patients and proxies ("productivity costs"), or the non health care costs. However, it has been argued that the time costs to patients is included in the quality of life adjustment[141] or that, since patient's time costs are not necessarily equivalent to a loss of productivity, productivity costs can potentially be exaggerated[140]. Therefore, although the US Panel on Cost-Effectiveness Analysis in Health Care recommends to measure both direct costs and indirect costs, this study's limitation to the direct costs may still reflect an appropriate economical context. It is also worth mentioning that some guidelines for economic valuations (e.g. Australia) argue against including the indirect costs.

Our analysis did not account for future costs which are unrelated to the disease of interest. However, the impact of neglecting future costs is probably minimal in this case: patients from both groups, even when cured from hepatocellular carcinoma, remain

cirrhotic, which represents a source of considerable morbidity. In fact, the Markov analysis shows that only 22% and 25% of patients in the "no screen" and "screen" groups respectively die from causes other than those related to cirrhosis and/or hepatocellular carcinoma. Therefore, even if our analysis did account for the costs related to these deaths, the relative cost difference between the screening intervention and not screening would not likely be affected.

This analysis accounted for two forms of therapy of hepatocellular carcinoma: surgical resection and percutaneous ethanol injection. The base case analysis considered the following therapeutic strategy: surgical resection for all resectable tumors and operable candidates, percutaneous ethanol injection for the non resectable and/or non operable candidates, and no therapy for those with portal vein thrombosis or metastatic disease. Alternate therapeutic strategies were also considered: surgical resection for suitable candidates alone versus percutaneous ethanol injection for all treatable candidates (i.e. all subjects except those with portal vein thrombosis and/or metastatic disease). Contrary to what we hypothesized, the choice of therapy between surgical resection and percutaneous ethanol injection does not significantly affect the incremental cost-effectiveness ratio of our screening strategy; they were both as costly and as effective. Screening for hepatocellular carcinoma in patients with well compensated cirrhosis must therefore be recommended, in the context of therapy with either surgical resection or percutaneous ethanol injection.

Liver transplantation is an effective therapy for hepatocellular carcinoma as well as the underlying cirrhosis[156,157] and may therefore favourably affect the cost-effectiveness

ratio of a screening intervention. In fact, the Markov analysis reveals that at least half the patients in each group die from decompensated cirrhosis, with or without hepatocellular carcinoma. This finding suggests that the most effective therapy for hepatocellular carcinoma in cirrhosis would be one that treats both cancer and cirrhosis simultaneously. Some early clinical evidence corroborates this hypothesis[158]. However, liver transplantation would also be associated with greater future costs, because of long-term immunosuppression and its complications. It is likely that, in the setting of liver transplantation, the incremental cost-effectiveness ratio of screening for hepatocellular carcinoma would be much different and our results cannot be extrapolated to a clinical context of liver transplantation.

The impact of screening with liver ultrasound alone versus liver ultrasound with alpha foetoprotein level was not specifically addressed, because the additive sensitivity of alpha foetoprotein measurement could not be quantified from the available data, and also because its low cost would not affect the incremental cost-effectiveness ratio significantly. Moreover, the availability of liver ultrasound and of blood assay for alpha foetoprotein are widespread, and neither should impede the applicability of a screening policy. The feasibility of our screening intervention may be limited by the patients' compliance to the screening protocol: prospective studies of screening cirrhotics suggest that this intervention is most effective in motivated patients, who will be compliant with the protocol[35].

In conclusion, our results would strongly support the adoption of a hepatocellular carcinoma screening policy for patients with well compensated hepatitis C-related

cirrhosis. Screening should be performed every 3 to 6 months, using liver ultrasound and alpha foetoprotein level. Patients should be selected based on their motivation to comply to the screening protocol. Based on the available literature and on the results of this economic evaluation, therapy of non metastatic hepatocellular carcinoma with percutaneous ethanol injection is a safe and effective therapeutic alternative, in particular when the surgical option is unavailable. However, the economic impact of screening for hepatocellular carcinoma in the context of liver transplantation remains undetermined.

APPENDICES

Appendix 1: Search strategy.

01 hepatitis c/
02 hepatitis c.tw.
03 hcv.tw.
04 non a non b hepatitis.tw
05 nona nonb hepatitis.tw.
06 non-a non-b hepatitis.tw.
07 nanb hepatitis.tw.
08 parenterally transmitted.tw.
09 hepatitis, viral.tw.
10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11 carcinoma, hepatocellular/
12 carcinoma, hepatocellular.tw.
13 hepatocellular cancer.tw.
14 hepatoma.tw.
15 11 or 12 or 13 or 14
16 us.fs.
17 us.xs.
18 ultrasound.tw.
19 ultraso$.tw.
20 16 or 18 or 19
21 alpha-fetoproteins/
22 fetuin$.tw.
23 foetoprotein$.tw.
24 foeto protein$.tw.
25 fetoprotein$.tw.
26 feto-protein$.tw.
27 feto protein$.tw.
28 afp.tw.
29 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30 20 and 29
31 20 or 29
32 alcohol, ethyl/ad
33 alcohol, ethyl.tw.
34 ethanol.tw.
35 32 or 33 or 34
36 tu.fs.
37 ad.fs.
38 injection$.tw.
39 intralesional.tw.
40 intratumoral.tw.
41 palliative.tw.
42 36 or 37 or 38 or 39 or 40 or 41
43 42 and 35
44 surgery/
45 su.xs.
46 su.fs.
47 hepatectomy.tw.
48 hepatectomy.sh.
49 resection.tw.
50 carcinoma, hepatocellular/su or carcinoma, hepatocellular/su
51 44 or 45 or 46 or 47 or 48 or 49 or 50
52 51 or 43
53 10 and 15
54 15 and 30
55 15 and 31
56 15 and 43
57 15 and 51
58 15 and 52
59 53 or 55 or 58
60 limit 59 to human

Appendix 2: **The CLIP scoring system[49]**

Variables	Scores		
	0	1	2
Child-Pugh stage	A	B	C
Tumor morphology	Uninodular *and* extension <50%	Multinodular *and* extension < 50%	Massive *or* extension > 50%
AFP (ng/ml)	< 400	> 400	
Portal vein thrombosis	No	Yes	

Appendix 2: The CLIP scoring system uses Child' stage, tumor morphology, the AFP level and the presence or absence of portal vein thrombosis to assign a prognostic score in patients with HCC and underlying cirrhosis. The greater the score the shorter the length of survival.

Appendix 3: **Health states scenarios.**

A: **Perfect health**

Vision: Able to see well enough to read ordinary newsprint and recognize a friend on the other side of the street, without glasses or contact lenses.

Hearing: Able to hear what is said in a group conversation with at least three other people, without a hearing aid.

Speech: Able to be understood completely when speaking with strangers or friends.

Ambulation: Able to walk around the neighborhood without difficulty, and without walking equipment.

Dexterity: Able to enjoy full use of two hands and ten fingers.

Mood: Happy and interested in life.

Cognition: Able to remember most things, think clearly and solve day to day problems.

Pain: Free of pain and discomfort.

B: Compensated cirrhosis

CONDITION "X"

Your physical appearance is unchanged.
You are **tired most of the time**.
You are able to perform your daily activities, but you find it strenuous.
You have cut down on leisure and social events because they are too tiring.
You are allowed to eat what you want but you should avoid alcohol.
You are on no medication.

Vision: You are able to see well enough to read ordinary newsprint and recognize a friend on the other side of the street, without glasses or contact lenses.

Hearing: You are able to hear what is said in a group conversation with at least three other people, without a hearing aid.

Speech: You are able to be understood **completely** when speaking with strangers or friends.

Ambulation: You are able to walk around the neighborhood **without difficulty**, and without walking equipment.

Dexterity: You have **full** use of two hands and ten fingers.

Emotion: You feel **somewhat** unhappy.

Cognition: You are able to remember most things, **think clearly** and solve day to day problems.

Pain: You are **free** of pain and discomfort.

C: Decompensated cirrhosis

CONDITION "Y"

The white of your eyes and your skin are yellow. Your abdomen and your legs are heavy and swollen with fluid but your muscles are thinned out.
You are **weak and** tired **all the time**. You are short of breath and unsteady on your feet. You stay at home most of the time.
Your speech is **sometimes** slurred. Your hands are shaky and you find it difficult to write. You cannot control your moods as well as before and you sometimes cry or become very upset for no obvious reason.
You bruise easily. You **sometimes** bleed from the nose, the rectum or from minor cuts.
You have **little** appetite but **no** nausea. You are not allowed to eat meat, or food that contains salt, or to drink alcohol.
You are on medications, including some that make you urinate frequently and some that give you loose bowel movements twice a day.

Vision: You are able to see well enough to read ordinary newsprint and recognize a friend on the other side of the street, without glasses or contact lenses.

Hearing: You are able to hear what is said in a group conversation with at least three other people, without a hearing aid.

Speech: You are able to be understood **partially** when speaking with strangers or people whom you know well.

Ambulation: You are able to walk only **short distances with walking equipment**, and you require a wheelchair to get around the neighbourhood.

Dexterity: You have **some limitations** in the use of your hands or fingers, but you do not require special tools or the help of another person.

Emotion: You are **very** unhappy.

Cognition: You are **very** forgetful, and you have great difficulty when trying to think or solve day to day problems.

Pain: You have **moderate** pain that prevents a few activities.

D: **Hepatocellular carcinoma**

CONDITION "Z"

The white of your eyes and your skin are yellow. Your abdomen and your legs are **very** heavy and swollen with fluid but your muscles are **wasting away**.
You are **very** weak and tired **all the time**. You are **very** short of breath and **very** unsteady on your feet. You spend your time either at home or in the **hospital**.
Your speech is **always** slurred. Your hands are shaky and you **cannot** write. You cannot control your moods as well as before and you sometimes cry or become very upset for no obvious reason.
You bruise easily. You often bleed from the nose, the rectum or from minor cuts.
You have **no** appetite and you are nauseated. You are not allowed to eat meat, or food that contains salt, or to drink alcohol.
You are on medications, including some that make you urinate frequently and some that give you loose bowel movements twice a day.

Vision: You are able to see well enough to read ordinary newsprint and recognize a friend on the other side of the street, without glasses or contact lenses.

Hearing: You are able to hear what is said in a group conversation with at least three other people, without a hearing aid.

Speech: You are **unable to** be understood when speaking with strangers but you are able to be understood **partially** by people who know you well.

Ambulation: You are **unable to** walk alone, even with walking equipment. You are able to walk short distances with the help of another person, and you require a wheelchair to get around the neighborhood.

Dexterity: You have **limitations** in the use of your hands or fingers, and you require the help of another person for some tasks (you are not independent even with the use of special tools).

Emotion: You are **so unhappy** that life is not worthwhile.

Cognition: You are **unable** to remember anything at all, and you are unable to think or solve day to day problems.

Pain: You have **severe** pain that prevents most activities.

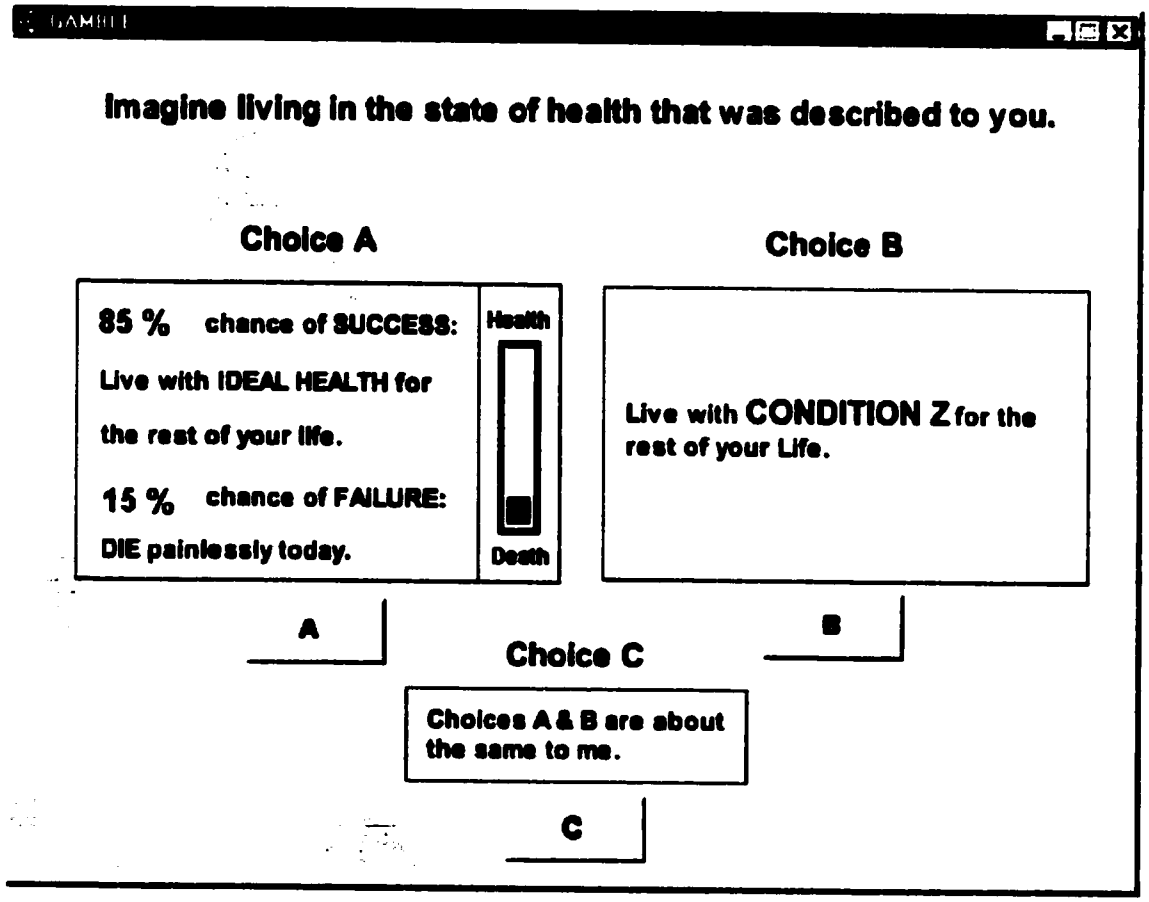
Appendix 4: **The Health Utility Index (HUI) Mark III.**

Attribute	Level	Level Description
VISION	1	Able to see well enough to read ordinary newsprint and recognize a friend on the other side of the street, without glasses or contact lenses.
	2	Able to see well enough to read ordinary newsprint and recognize a friend on the other side of the street, but with glasses.
	3	Able to see well enough to read ordinary newsprint but unable to recognize a friend on the other side of the street, even with glasses.
	4	Able to recognize a friend on the other side of the street, with or without glasses but unable to read ordinary newsprint, even with glasses.
	5	Unable to read ordinary newsprint and unable to recognize a friend on the other side of the street, even with glasses.
	6	Unable to see at all.
HEARING	1	Able to hear what is said in a group conversation with at least three other people, without a hearing aid.
	2	Able to hear what is said in a conversation with one other person in a quiet room, without a hearing aid, but requires a hearing aid to hear what is said in a group conversation with at least three other people.
	3	Able to hear what is said in a conversation with one other person in a quiet room, with a hearing aid, and able to hear what is said in a group conversation with at least three other people with a hearing aid
	4	Able to hear what is said in a conversation with one other person in a quiet room without a hearing aid, but unable to hear what is said in a group conversation with at least three other people even with a hearing aid.
	5	Able to hear what is said in a conversation with one other person in a quiet room with a hearing aid, but unable to hear what is said in a group conversation with at least three other people even with a hearing aid.
	6	Unable to hear at all.

SPEECH	1	Able to be understood completely when speaking with strangers or friends.
	2	Able to be understood partially when speaking with strangers but able to be understood completely when speaking with people who know me well.
	3	Able to be understood partially when speaking with strangers or people who know me well.
	4	Unable to be understood when speaking with strangers but able to be understood partially by people who know me well.
	5	Unable to be understood when speaking to other people (or unable to speak at all).
AMBULATION		
	1	Able to walk around the neighborhood without difficulty, and without walking equipment.
	2	Able to walk around the neighborhood with difficulty, but does not require walking equipment or the help of another person.
	3	Able to walk around the neighborhood with walking equipment, but without the help of another person.
	4	Able to walk only short distances with walking equipment, and requires a wheelchair to get around the neighborhood.
	5	Unable to walk alone, even with walking equipment Able to walk short distances with the help of another person, and requires a wheelchair to get around the neighborhood.
	6	Cannot walk at all.
DEXTERITY	1	Full use of two hands and ten fingers.
	2	Limitations in the use of hands or fingers, but does not require special tools or help of another person.
	3	Limitations in the use of hands or fingers, is independent with use of special tools (does not require the help of another person).
	4	Limitations in the use of hands or fingers, requires the help of another person for some tasks (not independent even with use of special tools).
	5	Limitations in the use of hands or fingers, requires the help of another person for most tasks (not independent even with use of special tools).
	6	Limitations in the use of hands or fingers, requires the help of another person for all tasks (not independent even with use of special tools).

EMOTION	1	Happy and interested in life.
	2	Somewhat happy.
	3	Somewhat unhappy.
	4	Very unhappy.
	5	So unhappy that life is not worthwhile.
COGNITION	1	Able to remember most things, think clearly and solve day to day problems.
	2	Able to remember most things, but have a little difficulty when trying to think and solve day to day problems.
	3	Somewhat forgetful, but able to think clearly and solve day to day problems.
	4	Somewhat forgetful, and have a little difficulty when trying to think or solve day to day problems.
	5	Very forgetful, and have great difficulty when trying to think or solve day to day problems.
	6	Unable to remember anything at all, and unable to think or solve day to day problems.
PAIN	1	Free of pain and discomfort.
	2	Mild to moderate pain that prevents no activities.
	3	Moderate pain that prevents a few activities.
	4	Moderate to severe pain that prevents some activities.
	5	Severe pain that prevents most activities.

Appendix 5: **Sample of the computerized standard gamble.**



Appendix 6: **Consent form for the computerized interview.**

PARTICIPANT'S INFORMATION AND CONSENT FORM

Assessment of Community Preferences for Three Health States

Investigator: Dr C. Dubé
Phone: 761-4691

a) THE NATURE AND PURPOSE OF THIS INTERVIEW

You are being asked to participate in an interview which will determine how members of the general population feel about three different conditions. The information obtained from this interview will be used as part of a larger study about medical practice. The interview itself is like a game, in which there are made-up situations of people with illnesses, and you are asked to make choices between different options.

Forty individuals will participate in this study at the Ottawa Civic Hospital.

The total duration of this interview is 30 minutes.

b) EXPLANATION OF THE PROCEDURE

You will be asked to read three short texts (each, less than a page long). Each of the three texts describes someone who suffers to some extent from a specific kind of disease. There is no relationship between this disease and the reason why you have come to the hospital today.

Following each description, you will be asked to imagine what it would be like if you were living with that degree of illness. You will then be asked to think about how desperately you would want to be perfectly healthy if you were suffering from that degree of illness. The way you imagine the described condition and how bad you think it would be is a very personal thing. In order to help you determine how undesirable each described condition is to you, we will use an exercise called the **standard gamble**.

The **standard gamble** is an exercise where you will be offered the opportunity to take an imaginary treatment which provides you with a chance of cure, but with a risk of immediate and painless death. By varying how much chance of cure and death you are willing to take by accepting the treatment, we will arrive at a point where you cannot decide between taking the imaginary treatment or staying in the described condition. This point will tell us indirectly how bad you think it would be to live with that degree of illness.

This is not a quiz. We simply would like you to answer the questions based on what you feel it would be like to live with those conditions. The only right answer is the one you feel is in accordance to your judgement of the situation. At any time during this interview, you can choose not to answer any question that you are not comfortable with.

c) POSSIBLE RISKS AND BENEFITS

You must remember that these descriptions and the following questions all relate to a completely made-up situation which has nothing to do with you. None of the questions will relate to you directly. Your participation in this questionnaire will not in any way make you at risk of ever suffering from these conditions.
There is no direct benefit to you. This study is part of a larger project about screening for disease.

d) CONFIDENTIALITY

The information gathered during this interview will be kept confidential. All office and hospital records related to this study may be made available to the Ottawa Civic Hospital Research Ethics Committee for audit purposes. You will not be identifiable in any publications or presentations resulting from this study. No records bearing your name will leave the Ottawa Civic Hospital.

e) CONSENT TO PARTICIPATE

I have read the above information and the content and meaning of this information has been explained to me. I have been given the opportunity to ask questions.

By signing this form, I volunteer and consent to take part in this interview.

RESPONDENT NAME	**DATE**
RESPONDENT SIGNATURE	**DATE**
WITNESS SIGNATURE	**DATE**
INVESTIGATOR SIGNATURE	**DATE**

Valid until February 18, 1999

Appendix 7: **Weighted index of comorbidity[133].**

Assigned weights for diseases	Conditions
1	Myocardial infarct Congestive heart failure Peripheral vascular disease Cerebrovascular disease Chronic pulmonary disease Connective tissue disease Mild liver disease Diabetes Ulcer disease Dementia
2	Moderate or severe renal disease Diabetes with end organ damage Hemiplegia Any tumor Leukemia Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor AIDS

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