

Université de Montréal

Cost-Utility Analysis of Imaging for Surveillance and Diagnosis of Hepatocellular Carcinoma

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Résumé

Le carcinome hépatocellulaire (CHC) est une complication sérieuse associée aux maladies hépatiques chroniques. Les lignes directrices actuelles recommandent la surveillance du CHC par échographie tous les six mois. Cependant, la surveillance par échographie peut être difficile chez certains patients, notamment ceux atteints de cirrhose ou d'obésité. Autrement, la tomodensitométrie (TDM), l'imagerie par résonance magnétique (IRM) et l'IRM abrégée ont été explorées comme techniques d'imagerie alternatives et peuvent être utilisées chez les patients qui sont susceptibles d'avoir une échographie techniquement inadéquate. L'objectif de ce mémoire est d'évaluer l'impact économique de différentes stratégies de dépistage et de diagnostic basées sur l'imagerie chez des patients à risque de CHC, tout en tenant compte d'examen techniquement inadéquats et du taux de compliance des patients au programme de dépistage.

Nous avons comparé sept stratégies de dépistage et diagnostic: stratégie A, échographie pour le dépistage et TDM pour le diagnostic; stratégie B, échographie pour le dépistage et IRM pour le diagnostic; stratégie C, échographie pour le dépistage et TDM pour une surveillance inadéquate ou positive; stratégie D, échographie pour le dépistage et IRM pour un dépistage inadéquat ou positif; stratégie E, dépistage et diagnostic par TDM suivis par une IRM en cas de dépistage inadéquat; stratégie F, dépistage et diagnostic avec IRM suivis par TDM pour un dépistage inadéquat; et

stratégie G, dépistage avec IRM abrégée suivi par TDM pour un dépistage inadéquat ou IRM pour un dépistage positif. Deux scénarios de compliance au programme de surveillance ont été évalués: optimal et conservateur. Pour chaque scénario, la stratégie la plus coût-efficace reposait sur un seuil de propension à payer de Can\$50,000 (dollars Canadiens) par année de vie ajustée en fonction de la qualité (AVAQ). Nous avons également effectué des analyses de sensibilité.

Nos résultats ont démontré que la stratégie E était la stratégie la plus coût-efficace dans le scénario de compliance optimal (Can\$13,631/AVAQ). Cependant, dans le scénario conservateur, la stratégie G constituait l'alternative la plus coût-efficace pour remplacer la pratique actuelle de surveillance par échographie (Can\$39,681/AVAQ). Les analyses de sensibilité ont confirmé l'analyse de base dans le scénario de compliance optimal. Par contre, plusieurs paramètres ont modifié le rapport de coût-efficacité dans le scénario d'observance conservateur.

En effectuant cette analyse économique, nous avons conclu qu'une approche individuelle, tenant compte des particularités cliniques des patients, est plus coût-efficace que la stratégie actuelle uniforme. Cependant, avant de mettre en place un programme de surveillance incorporant des modalités d'imagerie autres que l'échographie, les futures études devraient se concentrer sur le fardeau économique associé aux diagnostics faux positifs du CHC et sur la performance diagnostique d'examen d'IRM abrégés dans le scénario de surveillance.

Mots-clés : coût-efficacité, détection précoce, cancer du foie, imagerie du foie, modèle de Markov.

Abstract

Hepatocellular carcinoma (HCC) is a serious complication associated with chronic liver disease. Current guidelines recommended HCC surveillance using ultrasound (US) every six months. However, US surveillance can be challenging for some patients, particularly those with cirrhosis or obesity. Alternately, computed tomography (CT), magnetic resonance imaging (MRI), and abbreviated MRI have been explored as alternative imaging modalities and may be used in selected patients who are likely to have experienced inadequate US examinations. In this thesis, we aimed to assess the cost-effectiveness of imaging-based surveillance and diagnostic strategies in patients at risk of HCC while taking into account technically inadequate examinations and patients' compliance.

We compared seven surveillance and diagnostic strategies: strategy A, US for surveillance and CT for diagnosis; strategy B, US for surveillance and MRI for diagnosis; strategy C, US for surveillance and CT for inadequate or positive surveillance; strategy D, US for surveillance and MRI for inadequate or positive surveillance; strategy E, surveillance and diagnosis with CT followed by MRI for inadequate surveillance; strategy F, surveillance and diagnosis with MRI followed by CT for inadequate surveillance; and strategy G, surveillance with abbreviated MRI followed by CT for inadequate surveillance or MRI for positive surveillance. Two compliance scenarios were evaluated: optimal and conservative. For each scenario, the most cost-effective strategy was based on a willingness-to-pay threshold of

Can\$50,000 (Canadian dollars) per quality-adjusted life year (QALY). We also performed sensitivity analyses.

Our results demonstrated that strategy E was the most cost-effective strategy in scenarios with optimal patient compliance (Can\$13,631/QALY). However, in scenarios with low patient compliance, strategy G was the most cost-effective alternative to the current US-surveillance practice (Can\$39,681/QALY). Sensitivity analyses supported the base-case analysis in the optimal compliance scenario; however, several parameters altered the cost-effectiveness relationship in the conservative compliance scenario.

By performing this economic analysis, we concluded that an individual approach, considering the clinical particularities of the patients, is more cost-effective than the current “one-size-fits-all” strategy. However, before implementing a surveillance program incorporating imaging modalities other than US, future studies should address the economic burden associated with false-positive HCC diagnoses and the accuracy of abbreviated MRI examinations in a surveillance setting.

Keywords: cost-effectiveness, early detection, liver cancer, liver imaging, Markov model.

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List of Abbreviations

AASLD	American Association for the Study of Liver Diseases
AFP	Alpha-Fetoprotein
APHE	Arterial Phase Hyperenhancement
ASR	Age-Standardized Rate
BCLC	Barcelona Clinic Liver Cancer Staging
CASL	Canadian Association for the Study of the Liver
CBA	Cost-Benefit Analysis
CEA	Cost-Effective Analysis
CEUS	Contrast-Enhanced US
CI	Confidence Interval
CLIP	Cancer of the Liver Italian Program
CMA	Cost-Minimization Analysis
CT	Computed Tomography
CUA	Cost-Utility Analysis
CUPI	Chinese University Prognostic Index
DES	Discrete Event Simulation
DWI	Diffusion-Weighted Imaging
EASL	European Association for the Study of the Liver
ECA	Extracellular Contrast Agent

ER	Estrogen Receptor
GDP	Gross Domestic Product
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
HRQoL	Health-Related Quality of Life
ICER	Incremental Cost-Effectiveness Ratio
JIS	Japan Integrated Staging Score
LT	Liver Transplantation
MRI	Magnetic Resonance Imaging
NAFLD	Non-Alcoholic Fatty Liver Disease
OR	Odds Ratio
PEI	Percutaneous Ethanol Injection
PST	Performance Status Test
QALY	Quality-Adjusted Life Year
RFA	Radiofrequency Ablation
ROC	Receiver Operating Characteristic
SDI	Sociodemographic Index
TACE	Transarterial Chemoembolization
TNM	Tumor Node Metastasis
US	Ultrasound
WTP	Willingness-to-Pay

*For my parents and devoted wife, who
always believed and supported my dreams*

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1 Introduction

1.1 General Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the fourth cause of cancer-related deaths worldwide [1]. In Canada, HCC is the only malignancy for which mortality is rising, and the hepatitis C virus (HCV) infection is considered one of the most critical risk factors associated with HCC (see Etiology and Risk Factors below) [2, 3]. Although the prevalence of HCV infection reached its peak in 2003, the incidence of HCV-related HCC is expected to rise in the next decades due to the aging of the infected population and progression of liver fibrosis to cirrhosis [4, 5] (**Figure 1.1**).

In parallel, HCC-associated mortality and costs are estimated to increase, imposing a heavy human and economic burden on patients, their families, and society [4, 6]. Historically, the diagnosis of HCC has been made in advanced stages, when curative treatment options are no longer eligible, and the costs linked to care are higher [7]. The implementation of surveillance programs modified this trend by increasing the rate of early-stage tumor detection [8-10].

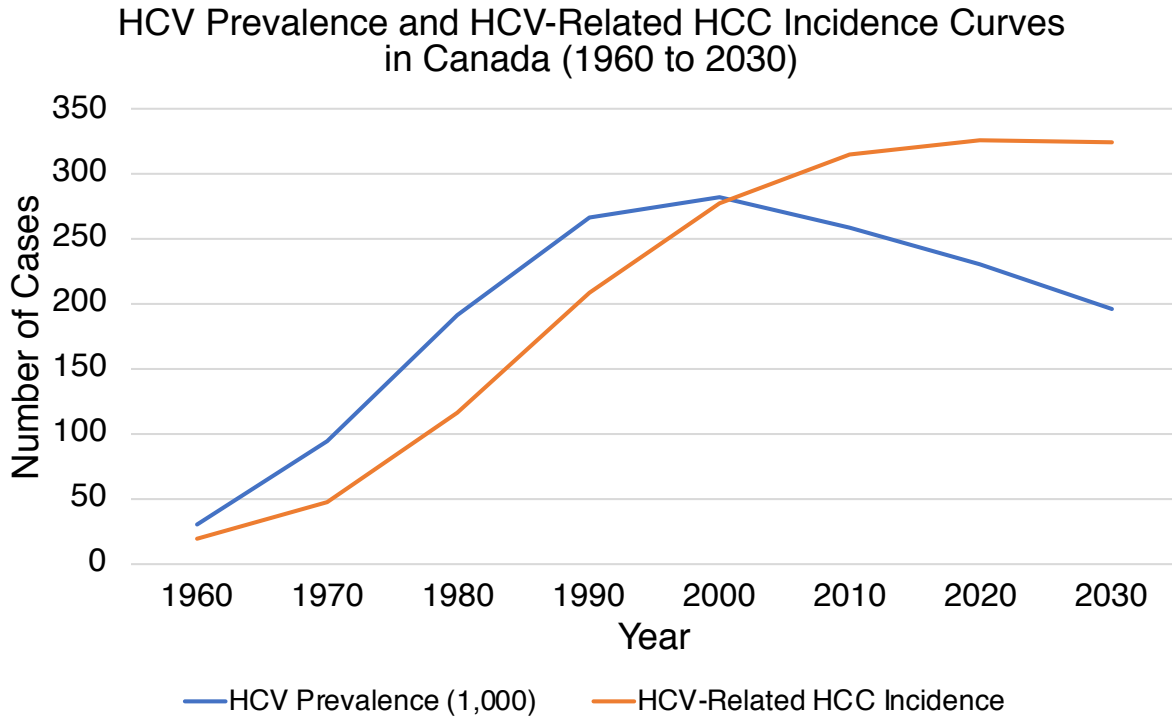


Figure 1.1 HCV prevalence and HCV-related HCC incidence curves in Canada. Data extracted from Myers et al. [4] and Remis et al. [5]. HCC = hepatocellular carcinoma, HCV = hepatitis C virus.

Due to limitations in health care system budgets, large-scale interventions, such as surveillance programs, are evaluated according to their potential cost-effectiveness before being implemented. In this scenario, economic analysis in health care proposes to identify, measure, value, and compare the costs and health outcomes of different health technologies [11]. Economic evaluations are important guides for policymakers, providing them with valuable evidence.

1.2 Reasons to Perform the Economic Analysis

There is a knowledge gap regarding the cost-effectiveness of surveillance for HCC. Current North American guidelines recommend HCC surveillance using ultrasound (US) every six months [12, 13]. However, US surveillance can be challenging in some patients, particularly those with Child-Pugh class C cirrhosis (who have advanced liver disease with innumerable nodules which may mask liver cancer) or obesity. In these patients, the US inadequacy rate can be as high as 33%, compromising surveillance effectiveness [14].

Other imaging modalities, like computed tomography (CT), magnetic resonance imaging (MRI), and abbreviated MRI, may be helpful alternatives for patients who are prone to inadequate US. However, previous economic analyses that have assessed this issue did not compare all available imaging modalities or did not take into consideration the effect of inconclusive surveillance imaging and patient compliance in their models [15-18].

1.3 Thesis Objectives

1.3.1 General Objective

To assess the cost-effectiveness of imaging-based surveillance and diagnostic strategies in patients at risk of HCC, taking into account technically inadequate examinations and patient compliance.

1.3.2 *Specific Objectives*

- To assess the cost-effectiveness of strategies relying on combinations of four imaging techniques: US, CT, MRI, and abbreviated MRI;
- To identify which is the most cost-effective strategy;
- To identify the parameters that have the greatest impact on the cost-effectiveness ratios.

1.4 Reading Guide

This master's thesis was structured so as to be accessible to different audiences, including medical students, hepatologists, general radiologists, and health economists. Medical students should read this document sequentially. Hepatologists and general radiologists, who may already be familiar with the medical aspects of HCC, may skip the Chapter 2 and begin their reading with the review of economic analysis in health care provided in Chapter 3. Health economists interested in this subject, but without a previous background in HCC, may begin their reading with the brief medical review provided in Chapter 2 and skip Chapter 3.

Chapters Description:

- Chapter 2: introduces HCC and reviews its epidemiology, natural history, surveillance, diagnosis, and management.
- Chapter 3: presents a short description of economic analysis in health care.

Chapter 1. Introduction

- Chapter 4: presents the cost-utility study performed to address the thesis objectives. The published article is presented in **Appendix 1**.
- Chapter 5: discusses the lessons learned, implications for patient care, and future directions.

2 Hepatocellular Carcinoma

HCC represents approximately 85% of all primary liver cancer [19]. HCC has a particular epidemiology, natural history, surveillance, diagnosis, and management. This chapter aims to review these key concepts.

2.1 Epidemiology

HCC is a major health problem worldwide, ranked as the sixth most common cancer and the fourth most common cause of cancer-related mortality [1]. In Canada, HCC has one of the fastest rising cancer incidences, with an increase of 2.6% to 3.6% per year [20]. Despite advances in diagnosis and management, the 5-year net survival of HCC in Canada is only about 19%, highlighting the aggressive nature of this cancer by the time of its diagnosis [21].

2.1.1 Distribution

The incidence of HCC differs widely according to geographic regions. While Northern Europe, Australia, New Zealand, and North and South America are the regions with the lowest rates, more than 80% of HCC cases occur in developing countries [1, 22] (**Figure 2.1**). However, in the last few decades, some regions traditionally classified as high-incidence areas are experiencing a decrease in the incidence rates, while several developed countries, such as the United States and

Canada, are facing an increase [2, 23]. These variations across geographic regions are explained, at least in part, due to regional differences of important risk factors (see Etiology and Risk Factors below).

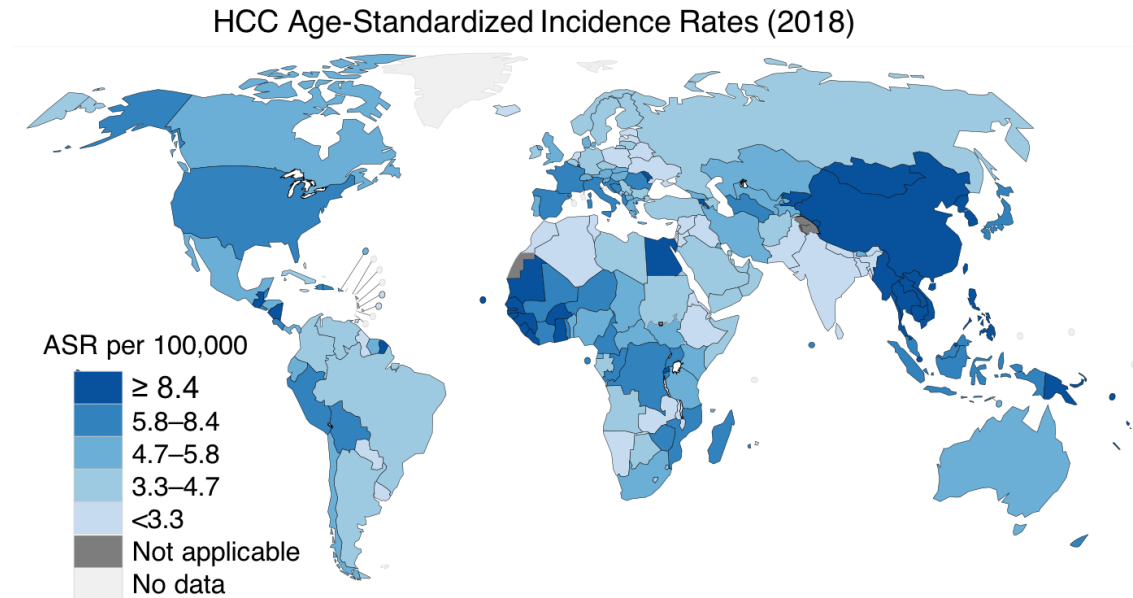


Figure 2.1 Worldwide HCC age-standardized incidence rates in 2018. Reproduced with permission from the Global Cancer Observatory [1]. ASR = age-standardized rate, HCC = hepatocellular carcinoma.

Furthermore, there is a significant incidence difference according to gender. Men are at a higher risk to develop HCC than women [1, 24]. This discrepancy is more evident in high-incidence regions, where men are affected 3.7 times more frequently than women [25]. Age also influences the HCC incidence. Since the pathogenesis of

HCC requires several decades, starting from the exposure to an etiologic agent until the diagnosis (see Natural History below), older patients are more prone to develop HCC [1, 24] (**Figure 2.2**).

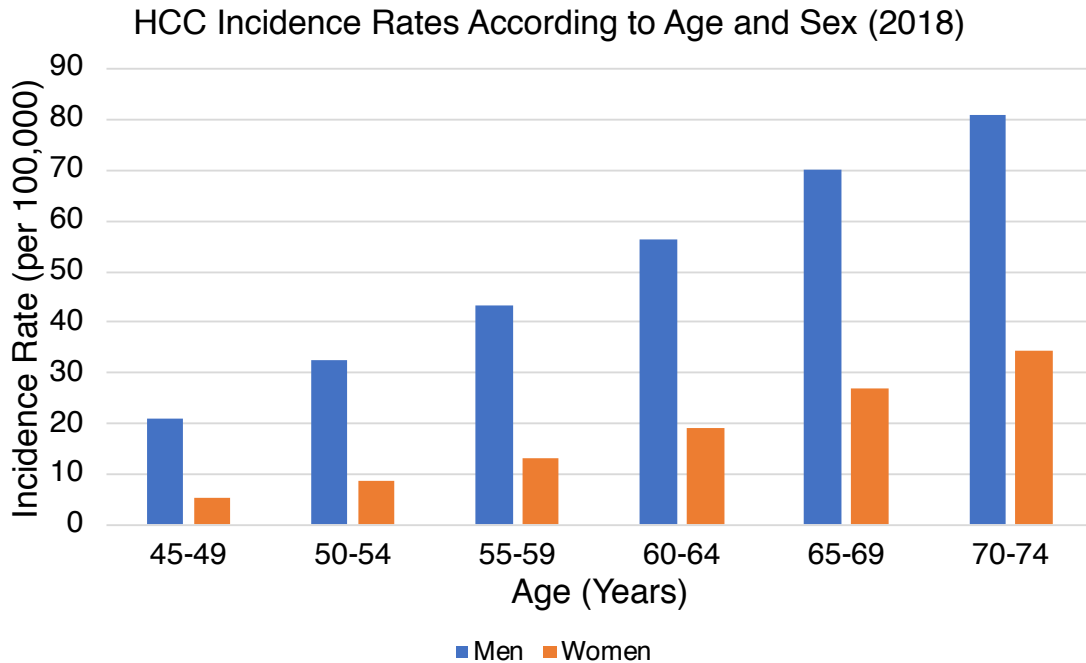


Figure 2.2 Worldwide HCC incidence rates according to age and sex in 2018. Data extracted from the Global Cancer Observatory [1]. HCC = hepatocellular carcinoma.

2.1.2 Etiology and Risk Factors

A variety of risk factors associated with HCC development have already been identified. This knowledge has enabled the recognition of etiological agents and risk groups, which are the basis for the development of prevention and surveillance strategies. The most common risk factors are hepatitis B virus (HBV) and HCV

infections, alcohol abuse, and non-alcoholic fatty liver disease (NAFLD) [26]. The importance of one risk factor over another varies according to the region studied (**Figure 2.3**). About 80% to 90% of patients who develop HCC have cirrhosis, which is the final common pathway of chronic liver aggression, regardless of the underlying etiology [27].

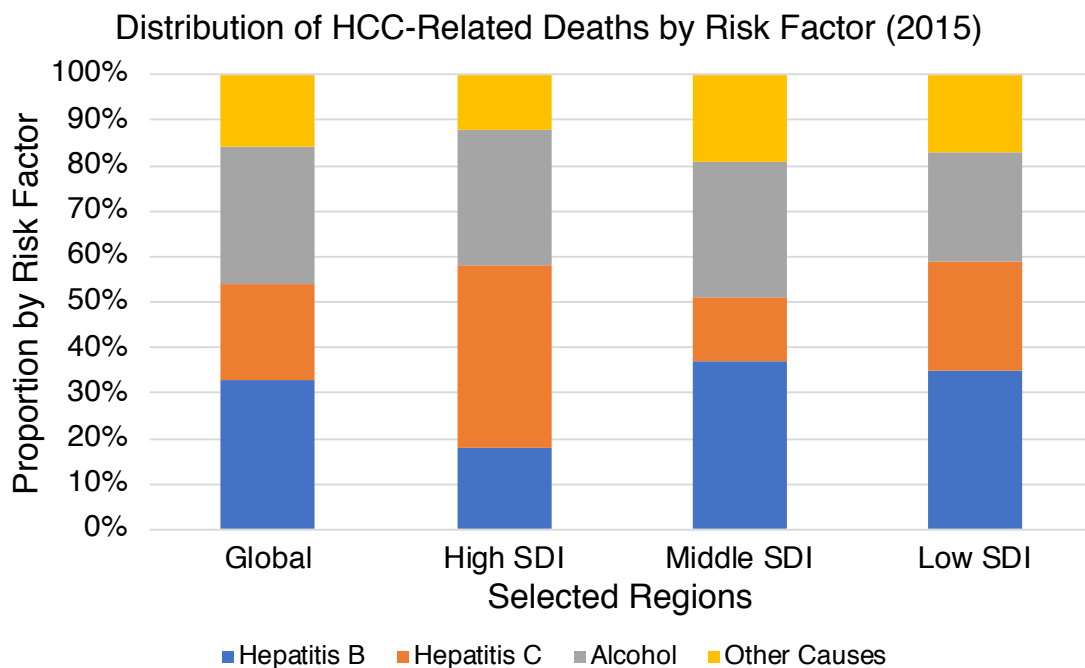


Figure 2.3 Distribution of HCC-related deaths by risk factor in selected regions. Data extracted from the Global Burden of Disease Liver Cancer Collaboration [28]. HCC = hepatocellular carcinoma, SDI = sociodemographic index.

Chapter 2. Hepatocellular Carcinoma

HBV is the leading cause of HCC development worldwide, accounting for up to 50% of all cases [22]. This risk factor is even more important in developing countries, regions where HBV infection is considered endemic and transmission generally occurs during childhood, by vertical or perinatal exposure [29, 30]. In contrast, the horizontal transmission (sexual or parenteral routes), is the most common in developed countries [29]. HBV is linked to HCC even in the absence of cirrhosis; however, patients with cirrhosis are at a higher risk [19]. The implementation of vaccination programs and the advent of successful treatment regimens have led to a decline of HBV-associated HCC incidence worldwide [31-33].

HCV is the most common risk factor for HCC in developed countries [24, 34]. In Canada, modeling data suggest that by 2035, cases of HCV-related HCC will have increased by 205%, when compared to 2013 levels; although more effective and better tolerated antivirals may change this trend [4]. Differently from chronic HBV infection, virtually all HCCs associated with chronic HCV occur in patients with advanced liver fibrosis or cirrhosis [35, 36]. The majority of HCV infections is acquired in adulthood, generally as a result of exposure to contaminated blood products or intravenous drug abuse [37]. HCV treatment is associated with a decrease in risk of developing HCC, though it is not completely eliminated [38, 39].

Alcohol abuse is the third most common cause of HCC, especially in Western countries [37, 40]. Heavy alcohol intake can lead to cirrhosis and, consequently, to HCC. However, the exact pathogenesis is not entirely understood [37]. NAFLD is an emerging cause of HCC and a well-established cause of chronic liver disease [41]. It

seems that the increased HCC risk associated with NAFLD is limited to patients with cirrhosis [42]. Other risks factors are diabetes mellitus, obesity, aflatoxin, iron overload, alpha-1-antitrypsin deficiency, acute intermittent porphyria, and gallstones [37, 43].

2.2 Natural History

Historically, HCC was diagnosed, almost invariably, in its late stages, when curative treatment options are not suitable and the progression to death occurs rapidly [44]. The implementation of surveillance strategies and advances in diagnostic techniques propitiated the detection of tumors in the early stages, leading to a better understanding of HCC's natural history. Didactically, natural history can be divided into three phases: molecular, preclinical, and clinical [45].

2.2.1 *Molecular Phase*

The molecular phase involves several sequential genomic alterations, leading to malignant transformations of the hepatocytes, biliary epithelial, or stem cells [45, 46] (**Figure 2.4**). These genomic mutations take place over the years, in a setting of continuous liver injury and regeneration, promoting proliferation and inhibiting apoptosis [45]. As a result, single or multiple dysplastic nodules are formed. Further genetic alterations arise in these nodules, leading to the full development of HCC.

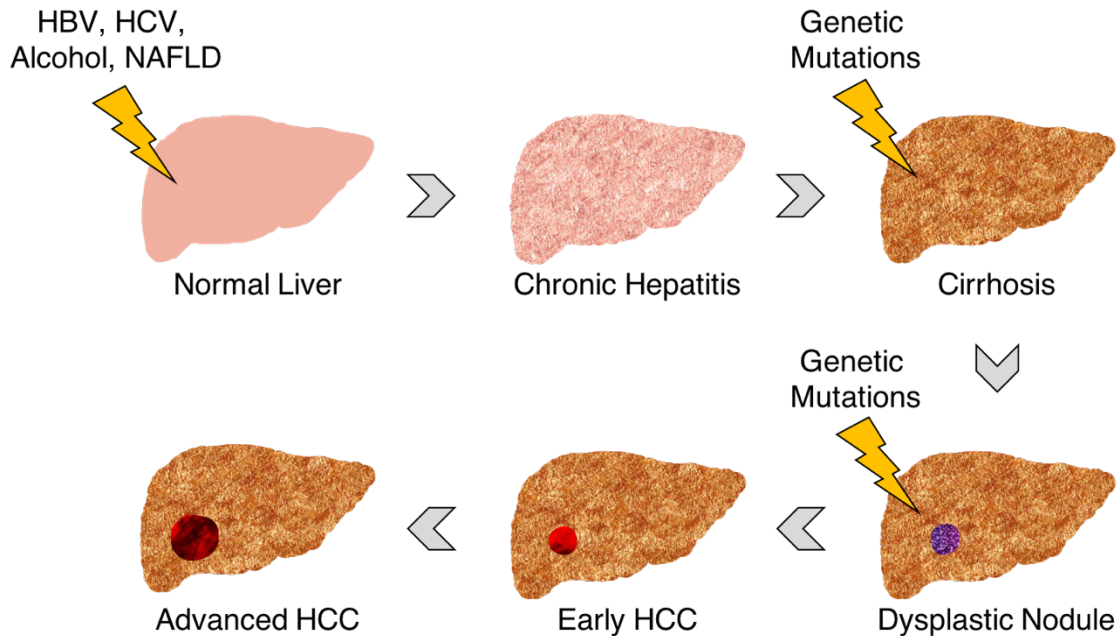


Figure 2.4 Schematic representation of HCC's natural history. HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, NAFLD = non-alcoholic fatty liver disease.

2.2.2 Preclinical Phase

The preclinical phase represents two distinct but continuous periods. In the first period (prediagnostic period), the tumor is present but still too small to be diagnosed by imaging techniques. As the tumor grows, it reaches a size threshold for imaging detection, around 1 cm to 2 cm (diagnostic period) [45]. In both periods, the tumor remains silent, characterizing the preclinical phase. Surveillance efforts are directed to identify HCC at this moment, when potentially curative therapies, such as surgical resection, ablation, or liver transplant, are still available. The 5-year survival of patients

undergoing one of these treatments ranges from 30% to 80%, versus a 5-year survival of less than 5% among those who are not eligible for treatment [15, 24, 47-52].

2.2.3 Clinical Phase

The tumor becomes symptomatic only when it reaches 4.5 cm to 8 cm [36, 45, 53]. Before that, patients may experience symptoms associated with their chronic liver disease. HCC is an important differential diagnosis among patients with compensated cirrhotic who progress to decompensation, manifested by ascites, encephalopathy, jaundice, or variceal bleeding [54]. Furthermore, the presence of upper abdominal pain, weight loss, early satiety, or palpable mass may indicate an advanced tumor [55]. The prognosis for patients at this phase is poor, with a median survival of fewer than six months after the onset of symptoms and no benefit from treatment [52, 56].

2.3 Surveillance and Diagnosis

2.3.1 Principles and Importance of Surveillance

Surveillance can be defined as the systematic use of screening tests to identify the occurrence of a given disease, within an at-risk population, while it is still subclinical [57]. The World Health Organization has created a list of criteria to determine if it is worth it or not to perform surveillance [58]; HCC surveillance meets all of these criteria: HCC has a significant impact on public health, the detection of HCC at an early stage improves outcomes, there are known groups at high risk of developing HCC, tests are

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available for surveillance, these tests can detect HCC at an early stage, the tests are cost-effective and acceptable to physicians and patients, an algorithmic approach to recall and diagnosis after the detection of findings is available, and there are effective treatments for confirmed cases of HCC [57].

The reasoning behind HCC surveillance is that patients undergoing this program are associated with early tumor detection (odds ratio [OR] 2.08, 95% confidence interval [CI] 1.80–2.37), curative treatment (OR 2.24, 95% CI 1.99–2.52), and improved survival (OR 1.90, 95% CI 1.67–2.17) [27, 59-61]. Several biases may make the interpretation of HCC surveillance outcomes difficult; these include the lead-time bias (apparent improvement in survival), the prognostic selection bias (identification of patients with slow progressive tumors who are more likely to live longer), and the overdiagnosis bias (false-positive cases). However, authors have shown that the benefits of HCC surveillance persist even after adjustment for lead-time bias [62, 63].

Several liver-study associations have published practice guidelines recommending HCC surveillance [12, 13, 64, 65] (**Table 2.1**). Despite the presence of slight differences, the overall general approach is similar. In the following topics, we will discuss the recommendations proposed by the North American guidelines [12, 13, 65].

Table 2.1 Surveillance Recommendations According to Different Associations

Organization	Target Population	Surveillance Method	Reference
AASLD	Cirrhotic patients, non-cirrhotic HBV carriers (Asian male > 40 years, Asian female > 50 years, African or North American blacks, family history of HCC)	US ± AFP every 6 months	[12]
EASL	Cirrhotic patients, non-cirrhotic HBV carriers at intermediate or high risk of HCC ^a , patients with severe liver fibrosis	US every 6 months	[64]
Canadian Consensus and CASL	Cirrhotic patients, non-cirrhotic HBV carriers (Asian male > 40 years, Asian female > 50 years, African or North American blacks, family history of HCC)	US every 6 months	[13, 65]

AASLD = American Association for the Study of Liver Diseases, CASL = Canadian Association for the Study of the Liver, EASL = European Association for the Study of the Liver, HCC = hepatocellular carcinoma.

2.3.2 At-Risk Patients

To perform surveillance, it is paramount to define subgroups that are at higher risk of developing HCC. The estimated incidence of HCC can indicate the level of risk. However, due to the lack of experimental data, economic analyses were used to determine whether or not, and at which incidence rate, it is cost-effective to perform HCC surveillance [12].

Cost-effectiveness models suggested that the incidence threshold for surveillance efficacy among cirrhotic patients ranges from 1.5% to 2% per year [17, 66, 67]. Using this value, current guidelines recommend performing surveillance in all cirrhotic patients once the diagnosis is made [12, 13, 65]. Patients with cirrhosis secondary to HBV or HCV who have cleared the infection seem to show a decrease in risk. However, since the magnitude of this decrease is difficult to evaluate, it is recommended that these patients continue surveillance [68].

Chronic HBV carriers may also benefit from surveillance if the annual HCC incidence exceeds 0.2% per year [69]. The HCC incidence in Asian patients with HBV starts to exceed 0.2% per year at around 40 years in men and 50 years in women [70-72]. Among Africans or African descendants, the incidence is increased earlier in life; as a consequence, surveillance should begin at the time of HBV diagnosis [73]. Furthermore, chronic HBV carriers with a family history of HCC are also at a higher risk and should undergo surveillance [74].

2.3.3 Surveillance Testing

An ideal surveillance method would have a positive result only if the patient has the disease and a negative result only if the patient does not have the disease [75]. Unfortunately, there is no such ideal method for HCC.

Since the primary purpose of surveillance is to detect potential disease indicators, physicians choose surveillance tests with relatively high rates of sensitivity (true positives in patients with disease), to not miss a possible disease. However, for the same method, a high sensitivity rate means a low specificity (true negative in patients without disease) rate. This relationship is demonstrated by the Receiver Operating Characteristic (ROC) curve (**Figure 2.5**). The consequence is a higher likelihood of false-positive exams, resulting in unnecessary follow-up tests and their consequences, such as physical and psychological stress and financial expenditures.

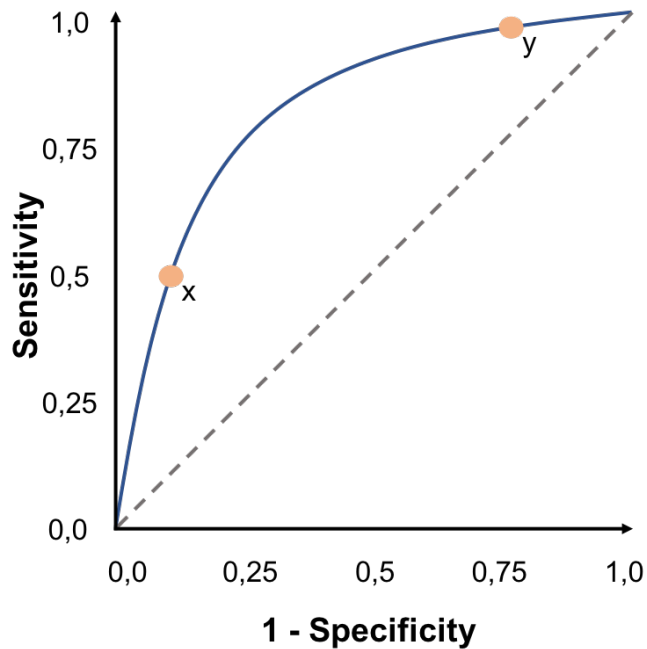


Figure 2.5 Receiver Operating Characteristic (ROC) curve. For the same test (blue curve), the higher the sensitivity (point y) the lower the specificity and the lower the sensitivity (point x) the higher the specificity.

In clinical practice, current North American guidelines recommend US every six months as the surveillance method [12, 13, 65]. US appearance of HCC is variable; furthermore, US is extremely operator dependent. In the gray-scale US, HCC typically presents as hypoechoic nodules [76] (**Figure 2.6**). However, some lesions may show increased echogenicity due to the inclusion of fatty tissue. Large lesions often put pressure on adjacent vessels and infiltrate the portal vein. They may present with hypoechoic halo suggestive of expansive growth or poorly defined margins when infiltrating the surrounding parenchyma [77].

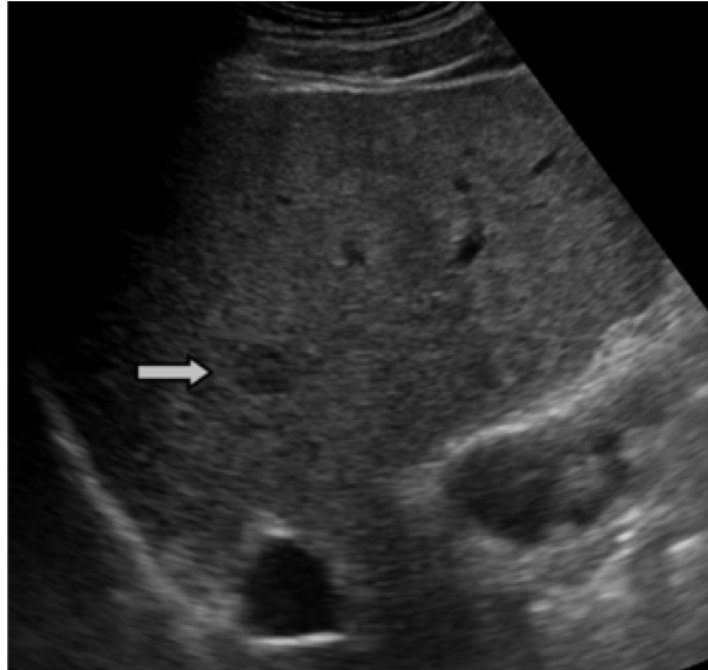


Figure 2.6 Small hypoechoic nodule in a cirrhotic liver corresponding to hepatocellular carcinoma (arrow). Reproduced with permission from Carvalho et al. [76].

A recent meta-analysis estimated an US sensitivity of 0.78 (95% CI 0.60–0.89) and specificity of 0.89 (95% CI 0.80–0.94) for detecting HCC in a surveillance setting [78]. However, up to 20% of US examinations in patients with cirrhosis are characterized as inadequate for HCC exclusion [14]. The most common reasons for inadequacy are rib shadowing and insufficient US beam penetration [14].

It is becoming evident that US limitations affect the efficacy of surveillance. Other imaging modalities, such as CT and MRI, are not recommended for routine use; nonetheless, a recent guideline recognizes these options for selected patients [12].

Furthermore, an abbreviated MRI protocol was recently proposed as an acceptable method for HCC surveillance [79-81]. This modality retains the advantages of the MRI, such as high contrast and absence of ionizing radiation, while reducing image acquisition and reading time, resulting in shorter and less expensive exams.

The use of blood biomarkers, such as alpha-fetoprotein (AFP), is considered controversial [65]. The association of AFP with US may improve overall survival [60] and maximize early tumor detection; however, it leads to a higher rate of false positives and an increase in costs [82].

2.3.4 Diagnostic Testing

A surveillance method, with few exceptions, does not aim to diagnose the illness. Thus, patients who test positive typically require further evaluation [75]. In the case of HCC, the diagnosis can be established based on noninvasive imaging, either multiphase CT or MRI, without the need for biopsy confirmation [12, 13, 65].

Figure 2.7 represents the surveillance and diagnostic algorithm recently proposed by the American Association for the Study of Liver Diseases (AASLD) [12]. According to this algorithm, patients with a positive surveillance (US demonstrating a lesion ≥ 10 mm or AFP ≥ 20 ng/ml) should undergo a diagnostic imaging modality (multiphase CT or MRI). Multiphase CT and MRI are interpreted and reported through the Liver Imaging Reporting and Data System (LI-RADS) [83]. This system is categorized in codes according to the presence or absence of well-established criteria for the diagnosis of HCC [84]. Patients whose lesion is classified as LI-RADS 1

(definitely benign) or 2 (probably benign) should return to surveillance imaging in 6 months. Those with lesion classified as LI-RADS 3 (intermediate) should repeat a diagnostic imaging immediately or in 3 to 6 months. Lesions classified as LI-RADS 4 are highly suspect, and a multidisciplinary discussion regarding the best workup is recommended. An image that is classified as LI-RADS 5 confirms the diagnosis of HCC. To be categorized as LI-RADS 5, the image should satisfy one of the following criteria [85] (**Figure 2.8** and **Figure 2.9**):

- Non-rim arterial phase hyperenhancement AND;
- If lesion 10–19 mm = nonperipheral “washout” OR threshold growth ($\geq 50\%$ size increase of a mass in ≤ 6 months) OR nonperipheral “washout” AND enhancing “capsule”;
- If lesion ≥ 20 mm = nonperipheral “washout” OR threshold growth OR enhancing “capsule”.

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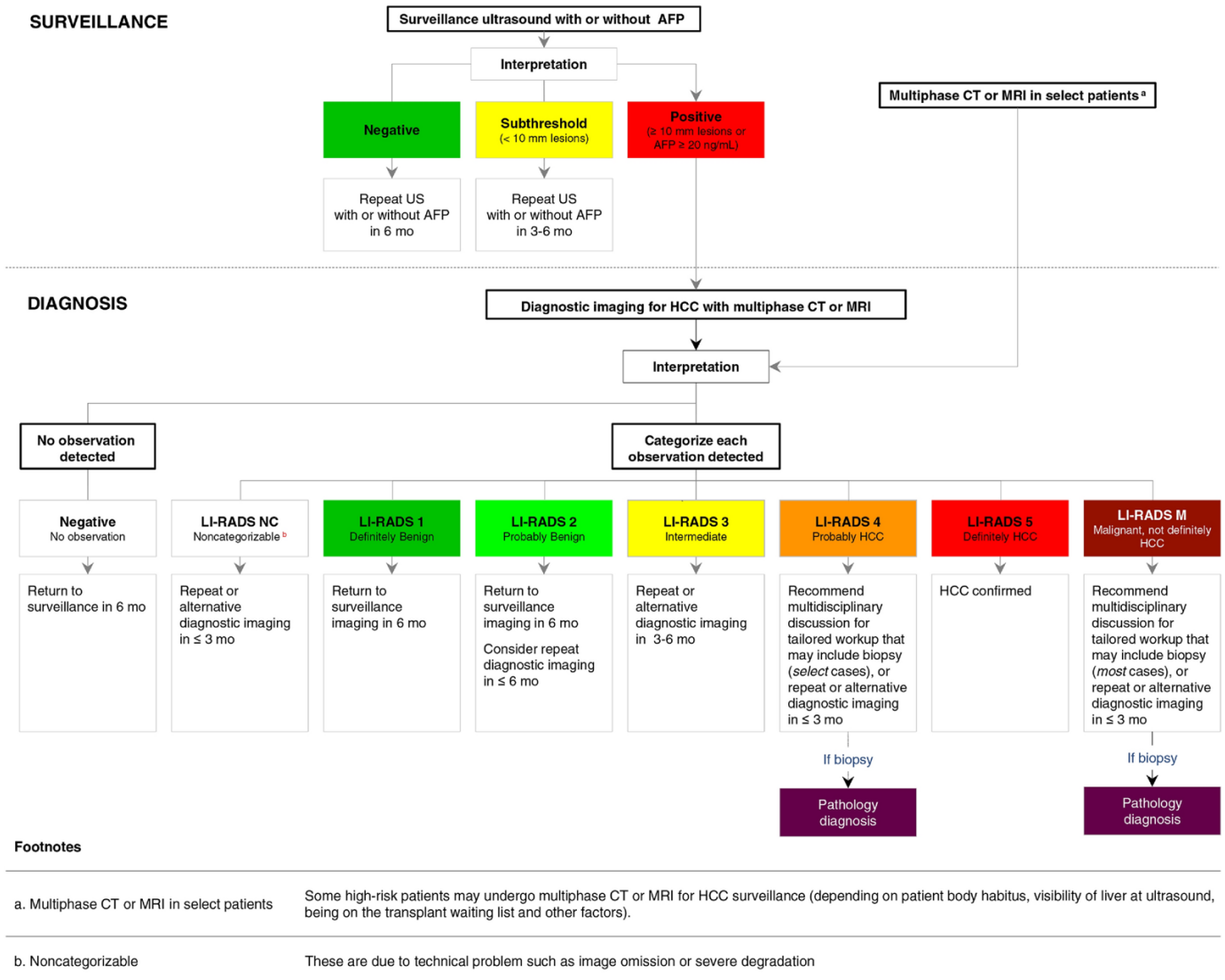


Figure 2.7 American Association for the Study of Liver Diseases (AASLD) surveillance and diagnostic algorithm. Reproduced with permission from Marrero et al. [12]. AFP = alpha-fetoprotein, CT = computed tomography, HCC = hepatocellular carcinoma, MRI = magnetic resonance imaging, US = ultrasound.

Hepatocellular Carcinoma: Major Criteria

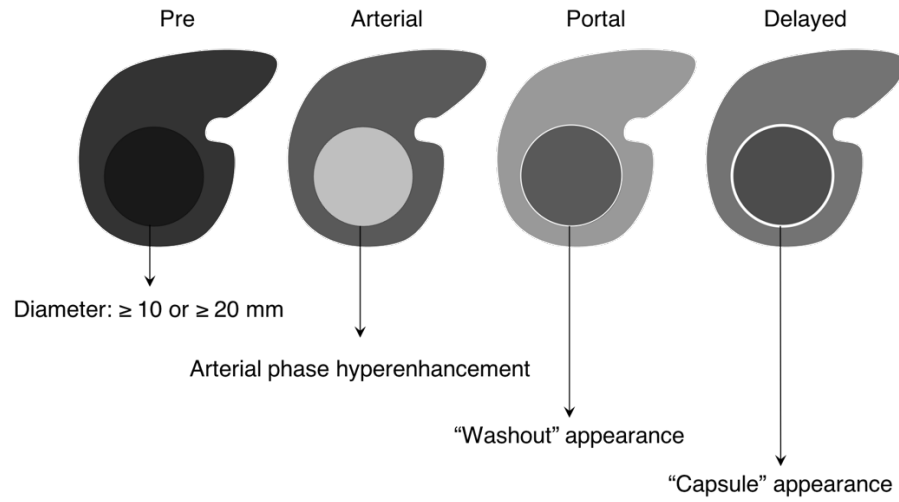


Figure 2.8 Schematic representation of LI-RADS major criteria for hepatocellular carcinoma diagnosis. Courtesy of Dr. An Tang.

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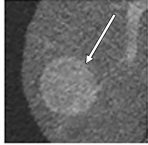
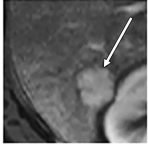



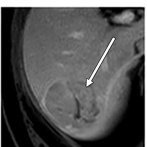
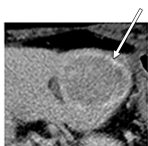



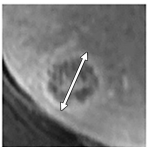
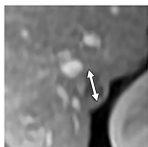
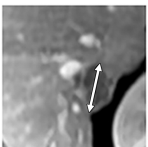
Major Feature	Definition	Examples		
		CT	MRI-ECA	MRI-Gadoxetate
Nonrim arterial phase hyperenhancement (APHE)	<p>Nonrim-like enhancement in arterial phase unequivocally greater in whole or in part than liver. Enhancing part must be higher in attenuation or intensity than liver in arterial phase.</p> <p>Comment: Nonrim APHE is required for LR-5 categorization.</p>			
Nonperipheral washout appearance ("washout")	<p>Nonperipheral visually assessed temporal reduction in enhancement in whole or in part relative to composite liver tissue from earlier to later phase resulting in hypoenhancement in the extracellular phase:</p> <ul style="list-style-type: none"> portal venous or delayed phase with ECA or gadobenate portal venous phase with gadoxetate 			
Enhancing capsule appearance ("capsule")	<p>Smooth, uniform, sharp border around most or all of an observation, unequivocally thicker or more conspicuous than fibrotic tissue around background nodules, and visible as an enhancing rim in portal venous phase, delayed phase, or transitional phase.</p>			
		Examples		
Size	<p>Largest outer-edge-to-outer-edge dimension of an observation</p> <p>Comment: Do not measure in arterial phase or DWI if margins are clearly visible on different phase or sequence (size may be overestimated in arterial phase due to summation with periobservation enhancement and is not measured reliably on DWI due to anatomic distortion).</p>			<p>Pick phase, sequence, plane in which margins are clearest</p> <p>Include "capsule" in measurement</p>
Threshold growth	<p>Size increase of a mass by $\geq 50\%$ in ≤ 6 months</p> <p>Comments:</p> <ul style="list-style-type: none"> Measure on same phase, sequence, and plane if possible. Apply threshold growth only if there is a prior CT or MRI exam. Do not assess threshold growth by comparing to prior US or CEUS exams. 			<p>50% size increase in 4 months</p>

Figure 2.9 Summary of CT and MRI diagnostic Liver Imaging Reporting and Data System major features. Reproduced with permission from Chernyak et al. [86]. APHE = arterial phase hyperenhancement, CEUS = contrast-enhanced US, DWI = diffusion-weighted imaging, ECA = extracellular contrast agent.

2.4 Management

HCC management depends upon the degree of the underlying liver dysfunction and the size of the tumor. The traditional tumor node metastasis (TNM) staging system has shown significant limitations in classifying HCC patients [87, 88]. Several new systems were proposed to address HCC staging [44, 56, 88-93] (**Table 2.2**), none of them with universal acceptance.

The Barcelona Clinic Liver Cancer Staging (BCLC) system is the most used in clinical practice and is the recommended staging system by North American guidelines [12, 13, 56, 65]. It will be described in the next sections along with the treatment options according to its classification.

Table 2.2 Hepatocellular Carcinoma Staging Systems

Classification	Type	Stages	Reference
Okuda Stage	System 3	Stage I, II, III	[44]
French	Score 3	A: 0 point B: 1–5 points C: ≥ 6 points	[93]
CLIP	Score 7	0, 1, 2, 3, 4, 5, 6	[92]
BCLC staging	Staging 5	0: Very early A: Early	[56]

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		B: Intermediate	
		C: Advanced	
		D: End-stage	
CUPI	Score 3	Low risk: score ≤ 1	[91]
		Intermediate: score 2–7	
		High: score ≥ 8	
TNM staging	System 3	Stage I, II, III	[88]
JIS	Score 4	Stage I, II, III, IV	[90]
ER	System 2	ER wild-type	[89]
		ER variant	

BCLC = Barcelona Clinic Liver Cancer Staging, CLIP = Cancer of the Liver Italian Program, CUPI = Chinese University Prognostic Index, ER = estrogen receptor, JIS = Japan Integrated Staging Score, TNM = tumor node metastasis.

2.4.1 Barcelona Clinic Liver Cancer Staging (BCLC)

The BCLC system was designed based on the results of several cohort studies and randomized controlled trials [56, 94, 95]. This system takes into account characteristics related to tumor stage (Okuda staging system, which takes into account the tumor size, the presence of ascites, and the values of albumin and bilirubin), liver functional status (Child-Pugh score, patients classified as Child-Pugh A or B have, respectively, least severe and moderately severe liver disease [compensated cirrhosis],

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while those classified as Child-Pugh C have severe liver disease [decompensated cirrhosis]), physical status (performance status test [PST], recorded from 0 [fully active] to 5 [dead]), and cancer-related symptoms to classify HCC patients into four categories: early, intermediate, advanced, and terminal (**Figure 2.10**).

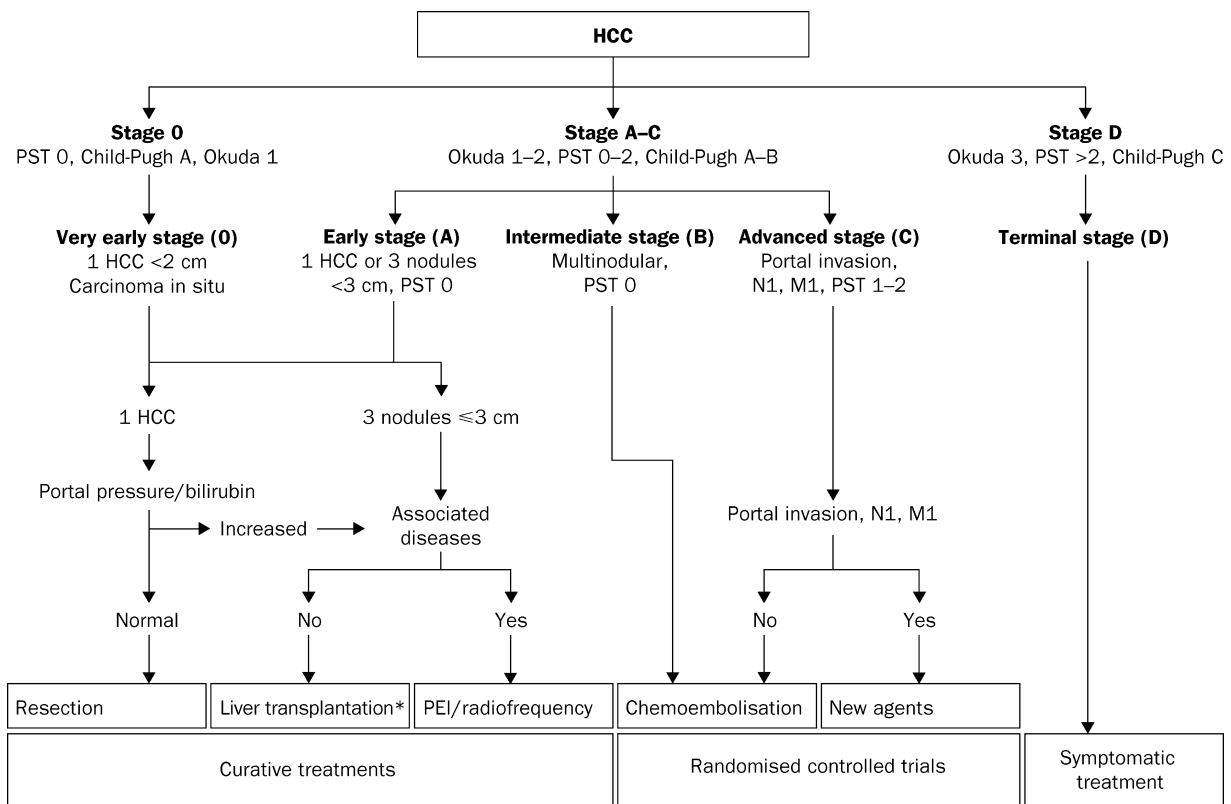


Figure 2.10 Barcelona Clinic Liver Cancer Staging (BCLC) classification and treatment schedule. Reproduced with permission from Llovet et al. [94]. *Cadaveric liver transplantation or living donor liver transplantation. HCC = hepatocellular carcinoma, PEI = percutaneous ethanol injection, PST = performance status test.

The BCLC has already been validated as the best staging system for patients with early HCC; however, some important limitations have been identified [96, 97]. The main points of disagreement are: (1) the non-inclusion of The Milano/Mazzaferro criteria for liver transplantation (LT) (patients with solitary tumor ≤ 5 cm or up to three tumors all ≤ 3 cm should be considered for LT; with the BCLC system, only some patients with three nodules ≤ 3 cm should undergo LT) [88] and (2) the non-consideration of liver resection as a treatment option for some subgroups of patients who may benefit from this approach (including some patients with early and intermediate-stage HCC) [98].

2.4.2 Early-Stage HCC (BCLC 0-A)

This category is comprised of patients who are eligible for potentially curative therapies, including liver resection, LT, and radiofrequency ablation (RFA).

Liver resection remains the optimal treatment for HCC in patients with normal liver function; however, the efficacy depends on the ability to achieve a complete resection that leaves an adequate liver remnant [37]. Furthermore, since the liver remnant may maintain precancerous disease, the recurrence is possible [99, 100].

The recurrence after LT is less frequent compared to liver resection [99, 100]. However, this advantage is counterbalanced by the long-term complications associated with transplants, such as graft rejection and immunosuppression [37]. Furthermore, the wait for a transplant can last months, even years, due to the shortage of organ donors.

During this period, the risk of tumor progression and dropout may be as high as 25% [101].

RFA is based on the use of a high-frequency alternating current transferred from the tip of an electrode into the tissue. The oscillating current induces movement of the ions within the tissue, resulting in frictional heating. When the temperature surpasses 60°C, the cells surrounding the electrode begin to die, generating necrosis. RFA is an alternative to liver resection, especially if the lesion is solitary and small [102]. It can also be used as a bridge therapy in patients waiting for LT, resulting in a decrease in the dropout rate secondary to tumor progression [103].

2.4.3 Intermediate-Stage HCC (BCLC B)

Patients at this stage are eligible for transarterial chemoembolization (TACE). This approach is based on the fact that HCC > 2 cm has a blood supply derived from the hepatic artery. The injection of a chemotherapeutic agent produces arterial embolization, resulting in ischemia and necrosis of the tumor. However, TACE is not considered a curative therapy [104, 105]. The therapy outcome depends on the initial tumor burden, tumor biology, baseline hepatic function, and the initial response [37]. Primarily, TACE therapy aims to extend overall survival and avoid dropout of patients on the waiting list for LT [104, 106].

2.4.4 Advanced-Stage HCC (BCLC C)

Patients with advanced-stage HCC should undergo systemic therapy. To date, sorafenib is the only agent that demonstrated a statistically significant, although

modest, survival benefit [107, 108]. The sorafenib molecule is a multikinase inhibitor; it acts by inhibiting the cellular proliferation and the angiogenesis.

2.4.5 End-Stage HCC (BCLC D)

These patients have a dismal prognostic, with a median survival of less than 3 to 4 months [52]. At this point, patients should receive palliative support, including management of pain, nutrition, and psychological support [109].

3 Economic Analysis in Health Care

3.1 Introduction to Economic Analysis

New health technologies or medications in health care may offer an increase in desirable outcomes when compared with the current practices. However, these options are typically more expensive when newly introduced. Economic analysis in health care aims to evaluate if the additional benefit of an intervention is compensated by the increase in cost through answering the following question: are we satisfied that the health resources should be spent in this way rather than in some other ways? [11]. Economic analysis is considered an important tool in public health, mainly because of the limitations in health care budgets and the increase in health expenditures [110] **(Figure 3.1)**.

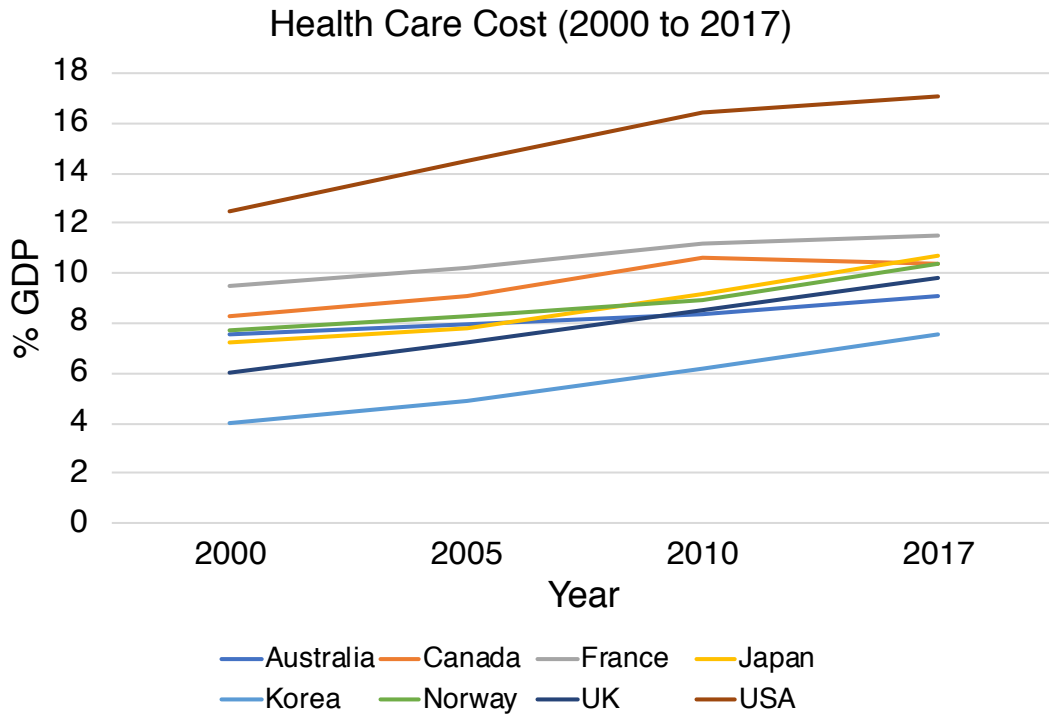


Figure 3.1 Health care cost in selected countries as a percentage of gross domestic product. Data extracted from the World Health Organization Global Health Expenditure Database [110]. GDP = gross domestic product.

Physicians could consider that letting cost influence clinical decisions or policies is unethical [111]. However, in health economics, the term “cost” has more than a simple monetary connotation. It represents the loss of potential benefits when one intervention is chosen over another, called the “opportunity cost.” For example, imagine that the directors of a hospital have Can\$1,000,000 (Canadian dollars) to spend. They could use the money to build an operating room or to buy a new MRI machine. The loss of benefits related to the surgeries that were not performed, if the directors had preferred to buy the MRI machine, or the loss of benefits associated with the imaging

diagnostics that were not performed, if the directors had preferred to build the operating room, is the opportunity cost. This concept is linked to the notion of scarcity of resources. If there is no scarcity, there is no opportunity cost.

At the patient level, economic analysis is also important. By taking into consideration the relationship between benefits and costs, physicians can ensure the best possible care for their patients while respecting the responsible allocation of public resources [112]. It is essential to underline that economic analysis should not be the only criteria for deciding which alternative to choose; patients preferences and physicians experience should also be considered [113]. However, it can be another source of information when physicians discuss management options with patients and colleagues. In the following sections, a basic description of economic analysis will be presented. The understanding of these sections will hopefully help physicians to incorporate economic concepts into their practice.

3.2 Types of Economic Analysis

3.2.1 Cost-Effectiveness Analysis (CEA)

The CEA is characterized by the measurement of gains in natural units of health, such as cures, lives saved, or decrease in blood glucose or blood pressure. The results of such analyses are given in terms cost per unit of outcome (for example, Can\$5,000 per cure). However, given that the outcomes of different technologies can be measured in different units (for example mmol/L for blood glucose or mmHg for blood pressure),

the CEA permits the comparison of two or more interventions only if the same units are used, which limits the application of this category of analysis. Further, it may be difficult for decision-makers to establish a willingness-to-pay (WTP) for such outcomes.

3.2.2 Cost-Utility Analysis (CUA)

The CUA is considered by some authors to be a subdivision of CEA [114]. The major difference between these economic analyses is that the CUA measures its health outcomes in a single generic unit, called quality-adjusted life year (QALY). The construction of this unit is based on patients' preferences according to the quality and the quantity of life [115] (see Measurement of Health below). Despite some limitations, especially regarding the subjectivity of how "quality" can be measured [116], the CUA is recommended as the most valuable economic analysis, since it allows comparisons across different conditions and interventions [117].

3.2.3 Cost-Benefit Analysis (CBA)

In the CBA analysis, costs and benefits are valued in monetary units. Differently, to the CEA and CUA, which aim to identify what is the best option to apply an existing budget, CBA answers whether or not it is worth to spending it [11]. Although popular in other fields, CBA is not commonly used in the health context due to ethical issues and difficulties related to measuring benefits in monetary terms [117].

3.2.4 Cost-Minimization Analysis (CMA)

The CMA is characterized by the comparison of interventions that are presumably identical in terms of all major clinical outcomes. The cost among the

interventions evaluated is the only difference, and the intervention with the lowest-cost is considered the preference. Generally, a CMA is realized when the analysis of treatments tested in clinical trials results in non-inferiority or equivalence. Some authors consider that the CMA is a cost analysis rather than a complete economic analysis [114].

3.3 Choosing the Population and Comparators

While developing an economic analysis, researchers should define the target population and the comparators, since the cost-effectiveness of intervention could extensively vary according to both factors. The decision problem should be guided by the choice of population and comparators, being that it is considered good practice to consider the opinions of physicians and decision-makers [117].

To address the study objectives, an economic model should reflect the entire target population. However, important heterogeneities may be present inside a large group, such as the Canadian population. In this case, the researchers should identify which differences could play an essential role in the model development (for example, differences in the natural history of the studied disease or the effectiveness of interventions), in order to incorporate different parameter values according to distinct subgroups [118, 119].

The selection of comparators is also of the highest importance. Based on the Canadian Guidelines for the Economic Evaluation of Health Technologies, the most

appropriate comparators are the standard of care (i.e. the interventions currently used in the Canadian context) and the technologies that are likely to be displaced by the intervention under investigation. Furthermore, considerations regarding the best supportive care should be made when new technologies are not fully adopted or represent uncertain value [117]. In principle, the comparators should be mutually exclusive (a patient with a given condition can only receive one intervention) [11]. They should be clearly described to allow for the identification of all relevant costs and outcomes [117].

3.4 Perspective

The perspective of an economic analysis should be related to the decision problem and consistent with both costs and outcomes. There are different possibilities of perspective (societal, public health payer, and private health payer) and costs and outcomes that are important from a given perspective may not be from another [11] (**Table 3.1**).

Because health economics is a science concerned with society's welfare, some authors argue that economic analysis should preferably evaluate technologies from the societal perspective [120, 121]. The societal perspective is also considered to be the broadest approach since it incorporates all possible costs. Nevertheless, the perspective should always be directly related to the decision problem and, if necessary, be discussed with the organism that commissioned the analysis [117].

Table 3.1 Relevant Costs According to Different Perspectives

Perspectives and Costs	Societal	Public Health	Private Health
		Payer	Payer
Health Sector	YES	YES	YES
Other Sectors	YES	YES ^a	–
Patients and Families	YES	–	–
Loss of Productivity	YES	–	YES ^b

^aThe public sector may also consider services others than the health services (broader government payer perspective). In this case, costs related to other sectors should also be considered [117].

^bDespite the Canadian guideline does not consider the loss of productivity as a relevant cost under the private health payer perspective [117], we understand that costs linked to loss of productivity due to reduced working capacity or costs to hire and train a replacement worker may be relevant to the private sector.

3.5 Time Horizon

The time horizon is also relevant in economic analysis. It depends on the decision problem and can range from a few weeks to a lifetime period, according to the natural history of the condition [117, 122]. When modeling chronic diseases or when the interventions have an impact on mortality, for example, a lifetime horizon is most appropriate [117]. In all cases, the time horizon should be long enough to capture all

significant differences between costs and outcomes of the evaluated interventions [123].

An inappropriately short time horizon can bias the results and compromise the analysis, as it may capture only a fraction of the costs and utilities associated with a given condition. For example, if one considers the cost and utility at the time “t2”, only a portion of the utility would be captured, while the cost already reached its plateau. At this point, an economic analysis could state that the intervention would not be cost-effective. Comparing the points “t2” and “t4” it is possible to observe that in the last one there is an increase in the utility value, while the cost stays almost the same, changing the cost-effectiveness relation (**Figure 3.2**).

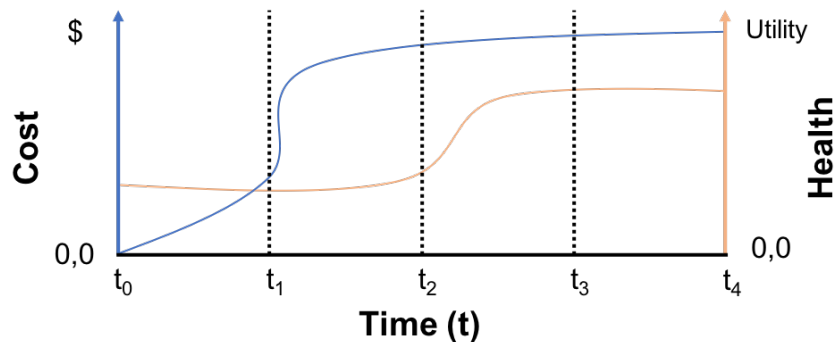


Figure 3.2 Influence of time horizon in economic analysis.

3.6 Measurement of Costs

Drummond et al. [11] classified costs as: associated with the health sector, associated with other sectors (such as education and housing), paid for by patients and families (such as transportation and feeding), and related to loss of productivity. Economic evaluations may incorporate one or more of these costs, according to their perspectives.

3.6.1 *Costs versus Time (Adjusting and Discounting)*

Even when costs have the same monetary unit, they may not be comparable because of changes in price over time. To compensate for this effect, costs should be corrected by using the concepts of adjusting and discounting.

When using costs from the past, it is necessary to adjust them to the present. This can be done by multiplying the costs by the accumulated inflation of the period. Inflation is a key concept in economic studies, it represents the increase in prices over time and, consequently, the loss of purchasing power (for example, Can\$1,000 in 2000 purchased a higher percentage of goods or services than in 2017) (**Figure 3.3**). The decrease in prices (deflation) is also possible, but less common than inflation.

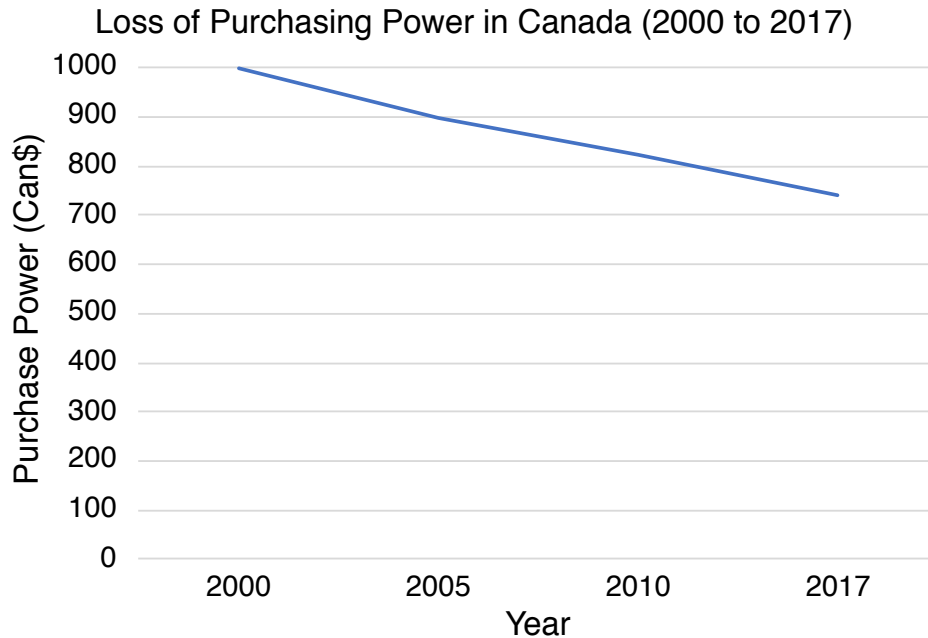


Figure 3.3 Schematic representation of loss of purchasing power in Canada. Data extracted from the Bank of Canada [124].

Similarly, economic evaluations that involve costs in the future require the application of a discount rate to reflect individuals' and society's preferences over time. Discounting makes present costs worth more than those occurring in the future. This is justified by the fact that individuals and society generally prefer to buy goods (i.e., equipment or procedures) and enjoy benefits in the present rather than wait for the future.

The principle of discounting is essential when evaluating health interventions where financial resources are consumed in the present while health benefits occur in the future [125]. The discounting rate changes according to society's preferences; in

Canada, the recommended discounting rate is 1.5% per year [117]. As well as costs, outcomes should also be discounted [117].

3.6.2 Cost Estimation

When evaluating which sources to consider, the authors of economic evaluations should always reflect the jurisdiction of interest. Where important variations exist within the jurisdiction, the author should consider them when conducting the evaluation [117].

Micro-costing is considered the most accurate method to estimate the costs of a given intervention [11]. It involves the enumeration and the costing of every input of the technology that is being evaluated [126]. Other costs used in economic analysis are usually derived from government or private sector sources, or even from previous economic analyses. However, it is always important to highlight that the selected costs depend primarily on the perspective of the study.

3.7 Measurement of Health

In economic studies, the health outcomes can be measured according to the study objective (for example, number of days free of symptoms after the use of a new bronchodilator in asthmatic patients) and the type of economic analysis. Since this thesis is based on a cost-utility analysis, the following topics will explain how to measure health outcomes in this type of analysis.

3.7.1 *The Concept of Utility*

As already mentioned, health economists created the concept of QALY to enable comparisons across a broader area of health care interventions. This outcome aims to summarize in a single measurement the impact of an intervention on the patient's quality and quantity of life. To generate QALYs, it is necessary to establish which are the health states of interest (for example, HCV infection, compensated cirrhosis, decompensated cirrhosis, and HCC) and value the preference associated with each one of these states [115].

These qualities of life weights are called utilities and represent the general population's preferences for a specific health condition. Generally, a health condition is described for a healthy group of people, which represents the society (societal point of view), and it is valued from 0 (death) to 1 (perfect health) [115]. It is important to mention that utilities may also be measured considering patients and caregivers preferences. Furthermore, differences among populations and methods may influence health state valuation [127]. In the next paragraphs, three well-established methods to directly measure utilities will be described. There are also indirect methods to measure utilities (see The Concept of Health-Related Quality of Life below).

- Time trade-off: this method estimates preferences by asking participants to imagine two distinct situations (**Figure 3.4**): perfect health (situation 1) for a shorter time (t_1) and imperfect health (situation 2) for a longer time (t_2). Then, participants have to indicate the point in which they are

indifferent between the shorter period of perfect health (t_1) and the longer period of imperfect health (t_2). The utility is calculated by dividing t_1 by t_2 [114].

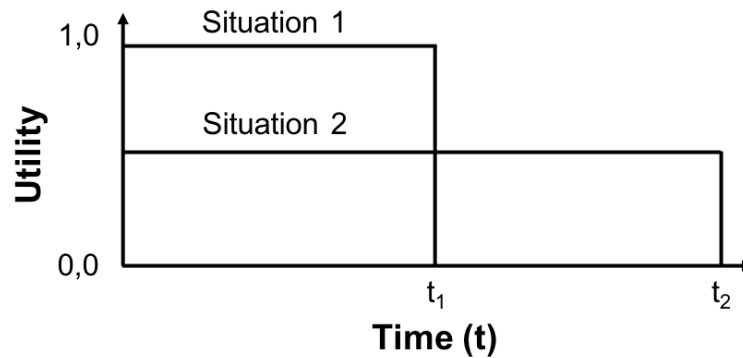


Figure 3.4 Schematic representation of the time trade-off method.

- Standard gamble: participants should choose between the certainty of remaining in an imperfect state of health chronically (situation 1) or gamble between re-establishing perfect health (probability p) or progress to death (probability $1-p$) (situation 2) [115] (**Figure 3.5**). Then, participants have to indicate the probability “ p ” in which they are indifferent between the certainty and the hazard. The chronic health state utility is equal to the value of the probability “ p .”

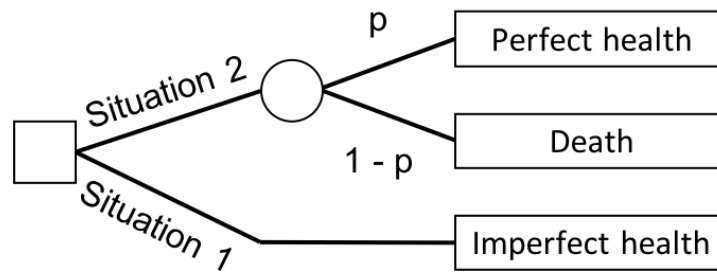


Figure 3.5 Schematic representation of the standard gamble method.

- Visual analogue scale: this method is constituted of a single line on a page with verbal and numerical descriptions at each end [128] (**Figure 3.6**). The top of the scale represents perfect health while the bottom indicates death, participants are asked to select a point between these two values according to their preferences. The visual analogue scale is the simplest method, usually used as a “warm-up” exercise before other methods [115].

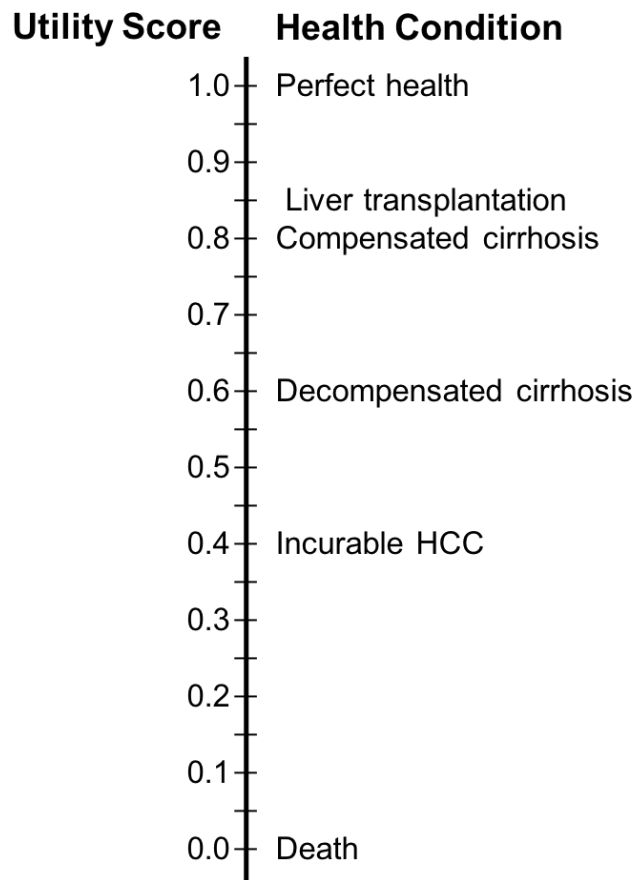


Figure 3.6 Schematic representation of visual analogue scale method.

3.7.2 The Concept of Health-Related Quality of Life (HRQoL)

Another methodology of assessing the quality of life is by applying HRQoL surveys. These instruments evaluate the patients' perspective and, usually, do not establish a general score. Instead, they produce multiple scores in different health dimensions, such as physical and social functioning, pain, and mental health [129]. Furthermore, it is possible for a given treatment to be superior in one health dimension and inferior in another. These aspects limit the application of HRQoL surveys in economic analysis [114].

To address these limitations, health economists concentrated their efforts in developing mathematical algorithms to summarize HRQoL multiple scores in one general score [130]. Given the complexity associated with directly measuring health utilities (i.e. time trade-off, standard gamble), it is recommended that researchers use utilities from an indirect method of measurement, such as the EQ-5D [117, 131].

The EQ-5D is a preference-based HRQoL instrument which evaluates the generic quality of life [132]. It is widely used in patient-reported outcome exercises, in population health studies, and in health technology assessment [131]. The EQ-5D instrument comprises five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The scores on these five dimensions can be converted to generate one summary score, varying from 0 to 1, while evaluating the different dimensions [133].

3.7.3 The Concept of Quality-Adjusted Life Year (QALY)

QALYs are calculated by multiplying the utilities (quality weights) of each health state of interest by the duration of time spent in each state. For example, a patient that lives 2 years with decompensated cirrhosis (patient A, utility equals 0.6) will have a total of 1.2 QALYs, while a patient with decompensated cirrhosis who is submitted to a LT (patient B, utility equals 0.85) lives 10 years and will have a total of 8.5 QALYs (**Figure 3.7**). In this case, the LT added 7.3 QALYs (cross-hatched area) during the patient's B life.

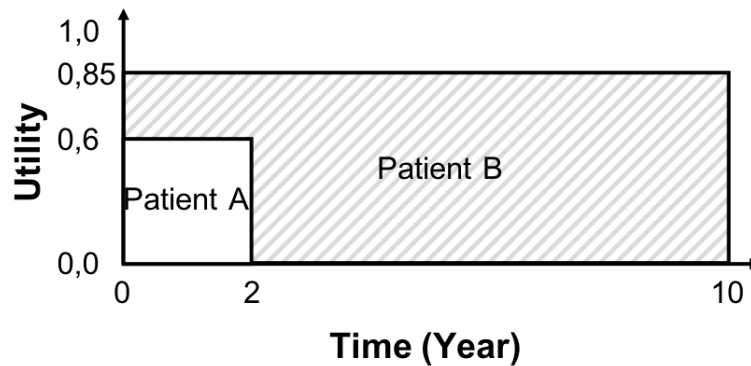


Figure 3.7 Schematic representation of quality-adjusted life year for a patient with decompensated cirrhosis (patient A) and decompensated cirrhosis submitted to a LT (patient B).

As well as costs discounting, outcomes (in this case QALYs) should also be discounted (see Measurement of Costs above). Costs and outcomes are usually discounted at a constant common rate (1.5% per year in Canada) [117].

3.8 Decision Analysis (Modeling)

The conceptualization of a model is a critical component when developing an economic analysis. Modeling can be useful by extending the results of clinical trials, extrapolating intermediate clinical endpoints to final outcomes, and comparing different health technologies [134]. Different modeling techniques are used in economic analysis, including the decision tree, Markov modeling, and the discrete event simulation.

Despite conceptual differences among the different possible modeling techniques, they should all follow a common pathway [114], which can be assisted by different types of software, like TreeAge Pro, R Statistical Software, or Microsoft Excel. In the following topics, the most common modeling techniques will be described.

3.8.1 Decision Tree

A decision tree is an analytical model in which distinct branches are used to represent potential outcomes for a cohort of patients. This model is frequently used to represent interventions that have distinct outcomes that can be measured at a specific time point [135]. The decision tree is built from left to right and starts from a root decision node, represented by a square. From this node, branches emanate to represent each competing comparator. These branches are linked to other nodes (chance nodes or end nodes). The chance nodes (circles) represent transitions between health conditions, while end nodes (triangles) represent the final outcome of interest for each competing comparator. A schematic decision tree is represented in **Figure 3.8**.

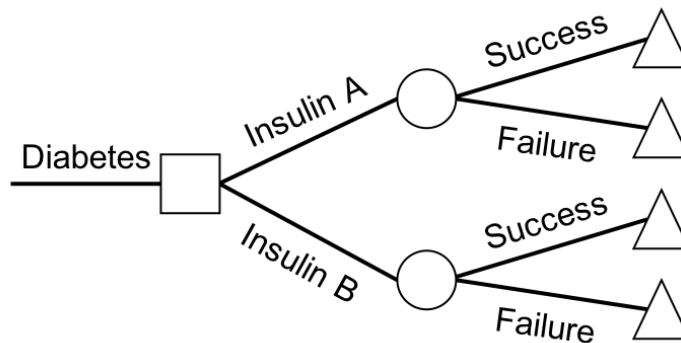


Figure 3.8 Schematic representation of a decision tree.

3.8.2 Markov Modeling

The evaluation of many diseases and conditions needs a more extended period of follow-up to reach outcomes of interest. In these situations, patients may transition from one health state to another over time [114]. For example, in an economic analysis that compares two different treatments for hypertension (initial Markov health state), it would be important to evaluate as possible outcomes the development of complications, such as myocardial infarction, heart failure, stroke (Markov health states), and death (absorbing health state) (**Figure 3.9**). In other words, the Markov modeling can simulate the natural history of a given disease or condition over time, while incorporating the interventions evaluated by the economic analysis.

Besides choosing the health states that will be incorporated into the Markov model, it is necessary to define the duration and number of cycles (the time component), and the probability of transiting from one health state to another in each cycle. The transition probabilities may be constant over time (Markov chain) or differ depending on the cycle (Markov process) [11]. The most important limitation of Markov modeling is the assumption that the transitions probabilities do not depend on health states that the patient may have experienced previously, which makes certain conditions inaccurate.

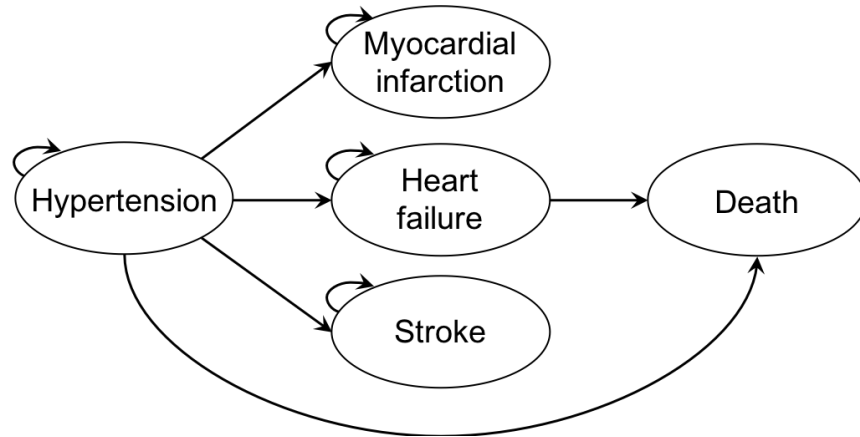


Figure 3.9 Schematic representation of a Markov model.

3.8.3 Discrete Event Simulation (DES)

In a DES, the experience of individuals is modelled over time in terms of the events that occur and the consequences of those events. To perform a DES, it is necessary to access the individual data of patients, which are not always available. [136]. Unlike Markov modeling, in which cycles have a fixed length, DES transitions between health states that may occur at varying times. DES is useful for modeling complex conditions with many possible types of events and health states or situations where the patient's history may impact on future events [137].

3.9 Calculation and Interpretation of Results

The results of economic analysis are calculated using the costs and probabilities incorporated into the model. To better explain how this calculation is made, we will

demonstrate an imaginary scenario based on the explanation made by Rascati et al. [114]. A decision tree is used as an example is demonstrated in **Figure 3.10**. Probabilities and costs used in this example are described in **Table 3.2**.

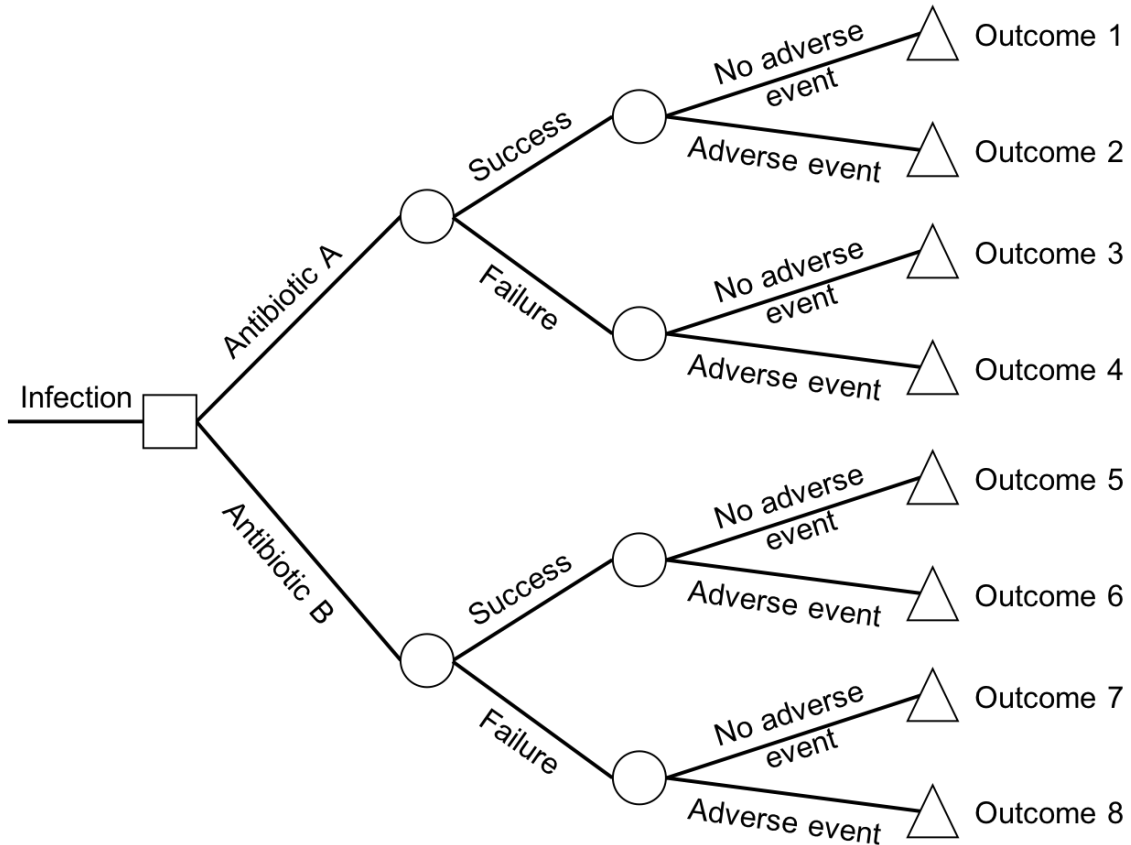


Figure 3.10 Decision tree used as an example to explain the calculations.

Table 3.2 Probabilities and Costs Used to Explain the Calculations

	Antibiotic A	Antibiotic B
Probability of success	90%	80%
Probability of failure	10%	20%
Antibiotic cost	\$600	\$500
Probability of adverse event	10%	15%
Probability of no adverse event	90%	85%
Cost of adverse event	\$1,000	\$1,000

For each branch in the decision tree, the probability of a patient with infection to have an outcome (end nodes = triangles) is calculated by multiplying the probability of success (or failure) by the probability of adverse event (or no adverse event). The cost for each branch is calculated by adding the costs from the chance nodes (circles) until the end node. In order to estimate the total cost for each therapeutic option (antibiotic A and antibiotic B), cost and probability are multiplied for each branch and then added to generate the final value for each option (**Table 3.3**).

Table 3.3 Calculation for the Example of Antibiotics

Outcome	Probability	Cost	Probability x Cost
Antibiotic A			
Outcome 1	90% x 90% = 81%	\$600	\$486
Outcome 2	90% x 10% = 9%	\$600 + \$1,000	\$144
Outcome 3	10% x 90% = 9%	\$600	\$54
Outcome 4	10% x 10% = 1%	\$600 + \$1,000	\$16
Total cost			\$700
Antibiotic B			
Outcome 5	80% x 85% = 68%	\$500	\$340
Outcome 6	80% x 15% = 12%	\$500 + \$1,000	\$180
Outcome 7	20% x 85% = 17%	\$500	\$85
Outcome 8	20% x 15% = 3%	\$500 + \$1,000	\$45
Total cost	100%		\$650

Using antibiotic A may cost from \$600 (antibiotic A without adverse event) to \$1,600 (antibiotic A with adverse event), with a mean total cost of \$700. While using antibiotic B may cost from \$500 (antibiotic B without adverse event) to \$1,500 (antibiotic B without adverse event), with a mean total cost of \$650. Note that, while antibiotic A has a higher probability of success than antibiotic B (90% versus 80%), antibiotic B is

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less costly (\$650 versus \$700). To help decision-makers, economic analysis incorporates the incremental cost-effectiveness ratio (ICER). This ratio is calculated by dividing the difference in total costs (incremental cost) by the difference in effectiveness of the interventions evaluated (incremental effect). In the example, the ICER would be calculated as follows:

$$\begin{aligned} \text{ICER} &= \Delta\text{Costs} \div \Delta\text{Outcomes} = \\ &(\$700 - \$650) \div (90\% - 80\%) = \\ &\$500 \text{ per additional success} \end{aligned}$$

If the decision-makers decided that it is worth expending \$500 more per additional success, then antibiotic A would be chosen over antibiotic B. This WTP threshold may vary depending on the intervention and the place where the analysis is being performed. Most national thresholds fall within the World Health Organization's recommended range of one-to-three times the per capita gross domestic product (GDP) [138].

While calculating the results, it is important to perform its validation. The validation process can be divided into internal and external validation [139]. Internal validation verifies the accuracy of all mathematical calculations. Preferably, it should be performed by an external researcher. In turn, external validation aims to determine whether the model estimates are coherent with external data sources, such as survival or mortality data [117].

3.10 Sensitivity Analyses

Sensitivity analyses aim to address the uncertainty of the parameters included in the model. They are concerned with the extent to which the estimated values reflect the “true values” [117]. To perform sensitivity analyses, parameter values are changed through maximum and minimum boundaries and results are calculated within this range. Deterministic and probabilistic sensitivity analyses will be described in the following topics.

3.10.1 Deterministic Sensitivity Analysis

The objective of a deterministic sensitivity analysis is to assess how results are sensitive to changes in parameter values [117]. Generally, the range of variation derives from values presented in the literature, for example, the 95% CI reported in clinical trials. The sensitivity analysis can be univariate (one-way), when each parameter varies separately, or multivariate, when two (two-way) or more parameters vary simultaneously [114]. The graphic representation (tornado diagram) of deterministic sensitivity analysis can be seen in **Figure 4.5** in the following chapter.

3.10.2 Probabilistic Sensitivity Analysis

Probabilistic (or stochastic) sensitivity analysis also aims to address uncertainty. However, differently from deterministic sensitivity analysis, which simply uses a range of values as input, this technique involves the use of distribution curves in which input parameter values are selected by random sampling. Different distributions are

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generally appropriate for different types of parameters [85]. Whenever possible, the sensitivity analysis should be performed by using this method [117]. The graphic representation (acceptability curve) of probabilistic sensitivity analysis can be seen in **Figure 4.6** in the following chapter.

4 Cost-Utility Analysis of Imaging for Surveillance and Diagnosis of Hepatocellular Carcinoma

4.1 Abstract

4.1.1 Objective

The purpose of this study is to compare imaging-based surveillance and diagnostic strategies in patients at risk for HCC while taking into account technically inadequate examinations and patient compliance.

4.1.2 Materials and Methods

A Markov model simulated seven strategies for HCC surveillance and diagnosis in cirrhotic patients: strategy A, US for surveillance and CT for diagnosis; strategy B, US for surveillance and MRI for diagnosis; strategy C, US for surveillance and CT for inadequate or positive surveillance; strategy D, US for surveillance and MRI for inadequate or positive surveillance; strategy E, surveillance and diagnosis with CT followed by MRI for inadequate surveillance; strategy F, surveillance and diagnosis with MRI followed by CT for inadequate surveillance; and strategy G, surveillance with abbreviated MRI followed by CT for inadequate surveillance or MRI for positive surveillance. Two compliance scenarios were evaluated: optimal and conservative. For

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each scenario, the most cost-effective strategy was based on a willingness-to-pay threshold of Can\$50,000 per QALY. Sensitivity analyses were performed.

4.1.3 Results

Base-case analysis revealed that strategy E was the most cost-effective when compliance was optimal (Can\$13,631/QALY), and strategy G was the most cost-effective when compliance was conservative (Can\$39,681/QALY). Sensitivity analyses supported the base-case analysis in the optimal compliance scenario, but several parameters altered the most cost-effective strategy in the conservative compliance scenario.

4.1.4 Conclusion

In an optimal compliance scenario, CT for HCC surveillance and diagnosis and MRI for inadequate CT was most cost-effective. In a conservative compliance scenario, abbreviated MRI may be an alternative to US-based surveillance.

4.2 Introduction

HCC is the sixth most common cancer and the second cause of cancer-related deaths worldwide [140]. In Canada, HCC is the only malignancy for which mortality is rising, a trend that is expected to continue through 2020 and beyond [141]. The implementation of surveillance programs targeting high-risk populations, such as cirrhotic patients, has led to the detection of HCC at earlier stages, when curative

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therapies can be applied [142]. This strategy could reduce the mortality related to HCC, as demonstrated by a large randomized controlled trial [8].

North American guidelines recommend US surveillance every 6 months in at-risk patients [12, 13]. Although US surveillance is feasible in patients with thin body habitus and without steatosis, it is challenging in obese or those with cirrhosis because of attenuation and heterogeneity of liver appearance, which limit the ability to assess the liver parenchyma [143, 144]. Furthermore, cirrhosis is often accompanied by a diffusely nodular appearance of liver parenchyma that limits the ability to detect HCC lesions [143]. Alternately, CT, MRI, and abbreviated MRI (which is limited to two or three sequences for lesion detection) have been explored as alternative imaging modalities for HCC surveillance [17, 79-81, 145, 146], and may be used in selected patients who are likely to have inadequate US examinations [12].

Costs attributable to HCC account for a substantial financial burden, are higher when HCC is diagnosed at advanced stages, and are expected to increase until the HCC incidence reaches its peak [4, 7]. Given that health care systems are limited in their financial resources, competing surveillance strategies should be analyzed for their cost-effectiveness. Cost-utility studies, which incorporate the widely applicable QALY, a measure of health outcome, should guide policymakers in their decision to implement alternative surveillance strategies. Prior cost-utility studies that assessed HCC surveillance have not taken into consideration the effect of inconclusive surveillance imaging examinations and patient compliance simultaneously. In this era of imaging-

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based surveillance and diagnosis of HCC, there is a need to investigate the cost-effectiveness of different surveillance algorithms.

Therefore, the purpose of this study was to compare imaging-based surveillance and diagnostic strategies in patients at risk for HCC, taking into account technically inadequate examinations and patient compliance.

4.3 Materials and Methods

4.3.1 Model Structure and Population

A decisional Markov model was developed using TreeAge Pro software (version 2017, TreeAge) to estimate the costs and QALYs associated with imaging-based surveillance and diagnostic strategies for HCC (**Figure 4.1**). This study was developed from a Canadian health care system perspective and followed the Canadian Guidelines for Economic Evaluation of Health Technologies [117].

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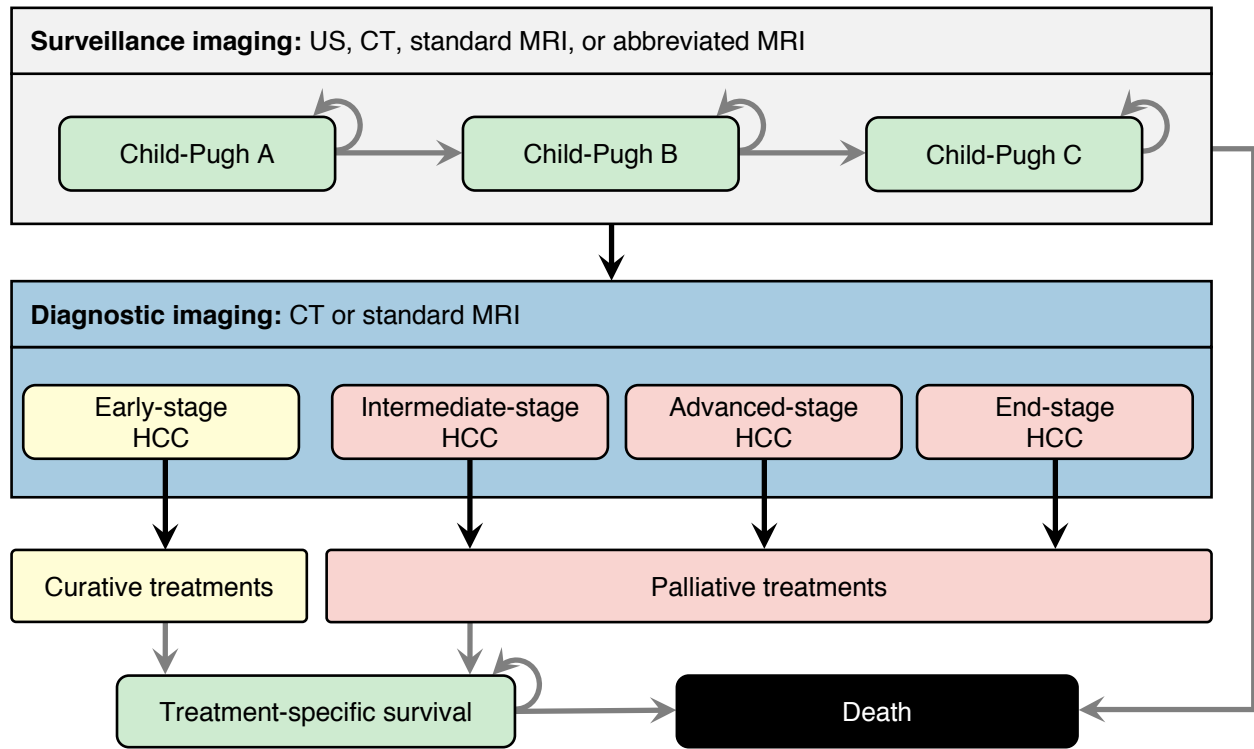


Figure 4.1 Simplified Markov model illustrating surveillance (gray box) and diagnostic imaging techniques (blue box) interposed on health states (green boxes) and temporary states (beige and pink boxes). Gray arrows indicate health state transitions, and black arrows indicate temporary state transitions (management of positive imaging results). CT = computed tomography, HCC = hepatocellular carcinoma, MRI = magnetic resonance imaging, US = ultrasound.

The simulated cohort of high-risk patients with cirrhosis underwent imaging-based surveillance every 6 months (cycle length). At baseline, patients began surveillance at the age of 50 years, the average age of cirrhosis diagnosis [147, 148].

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To reflect the full potential of surveillance, an optimal scenario was evaluated, composed of patients with compensated cirrhosis (Child-Pugh class A) at entry, with an assumed patient compliance to surveillance rate of 100%. A conservative scenario was also assessed, using the frequency of compensated cirrhosis and patient compliance to surveillance rates derived from systematic reviews [149, 150].

Imaging-based surveillance and diagnostic strategies and treatment options were superimposed onto the Markov model to reflect clinical options. At each cycle, patients could progress to decompensated cirrhosis (Child-Pugh B or C) or develop HCC or both. Patients with a positive surveillance result were submitted to a diagnostic imaging examination. Those with a positive diagnostic result were treated according to their HCC stage and Child-Pugh class (see Treatment Options subsection later). Survival after each treatment option was modeled. Patients with a negative surveillance or diagnostic result were reinvestigated in the next cycle. In the model, a new HCC could remain undetected until it was discovered by surveillance or the patient experienced symptoms; it was also possible for a patient to die with an undiagnosed HCC. Continued follow-up was made until all patients died (lifetime horizon). Both costs and outcomes were discounted at 1.5% per year [117]. Model validity was assessed comparing survival rates and diagnostic probabilities found in the model with results presented in published studies.

4.3.2 Competing Imaging Strategies

Seven surveillance and diagnostic strategies were investigated, relying on combinations of four imaging techniques: US, CT, MRI, and abbreviated MRI (**Figure**

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4.2). Strategies A and B used US-based surveillance followed by CT and MRI, respectively, for diagnosis, without additional imaging for inadequate US surveillance examinations. These strategies are recommended by current guidelines [12, 13]. Alternative strategies C and D used US-based surveillance followed by CT and MRI, respectively, for technically inadequate or positive US surveillance. These strategies follow the current recommendations of using US as the first-line surveillance modality, albeit by offering alternative imaging in case of inadequate US [12]. Replacement strategies E and F used CT and MRI, respectively, for surveillance, an approach that reflects the current practice in some North American centers. In cases of technically inadequate surveillance CT or MRI, the other imaging modality was used for confirmation. Strategy G used abbreviated MRI as surveillance followed by CT for patients with technically inadequate surveillance examinations or MRI for diagnosis of positive surveillance results. This emergent approach was recently proposed in proof-of-concept studies [79-81].

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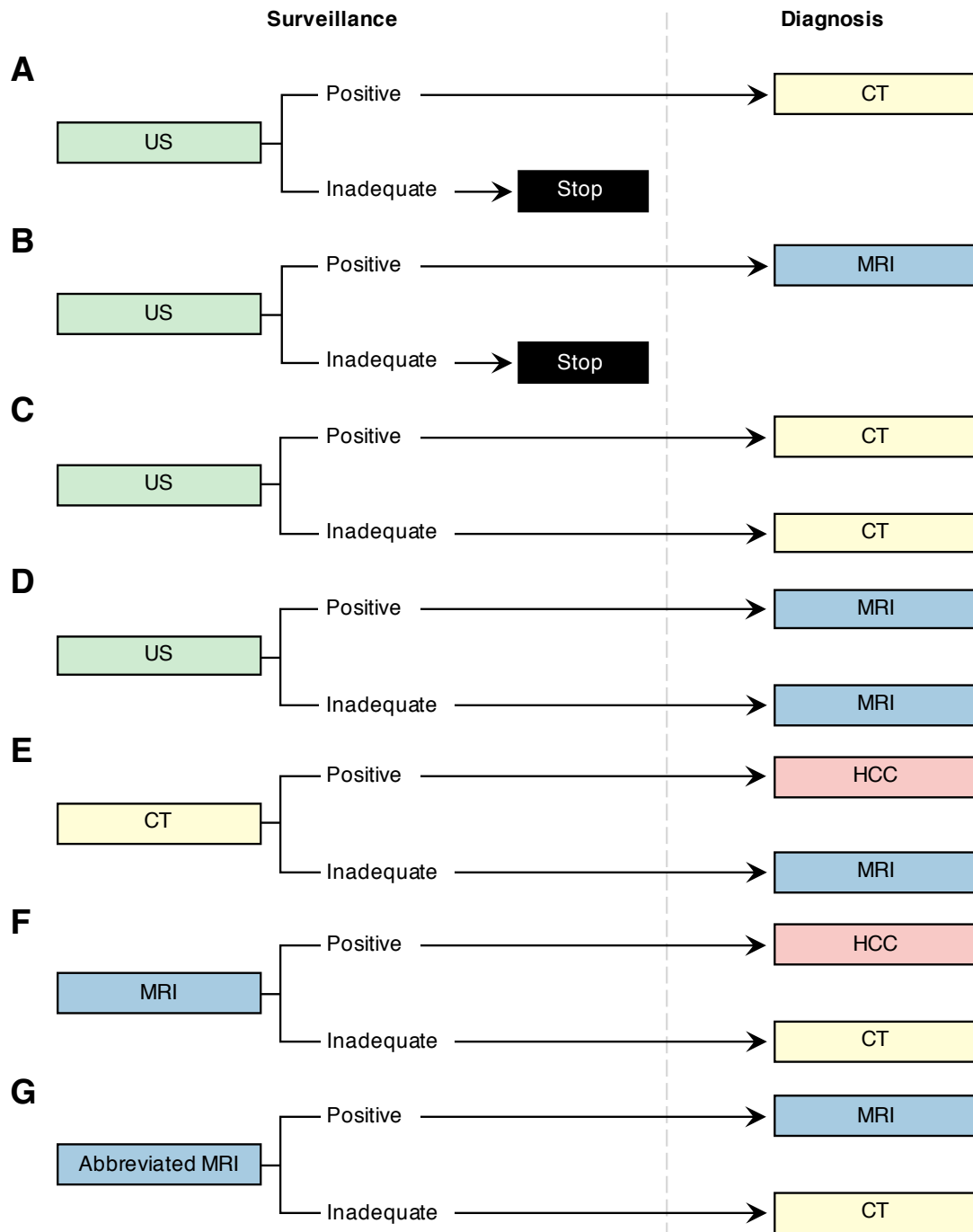


Figure 4.2 Chart of hepatocellular carcinoma (HCC) surveillance and diagnostic strategies A–G. CT = computed tomography, MRI = magnetic resonance imaging, US = ultrasound.

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4.3.3 Treatment Options

The treatments were modeled based on the Canadian consensus for the management and treatment of HCC [13] (**Figure 4.3**). Early-stage HCC could be treated with curative treatments, including liver resection, radiofrequency ablation, and LT. Intermediate-stage, advanced-stage, and end-stage HCCs received palliative treatments, such as transarterial chemoembolization, sorafenib, and symptomatic care. The relative proportion of patients eligible for each type of treatment was based on the distribution of treatments in participating North American centers of the international BRIDGE study [151].

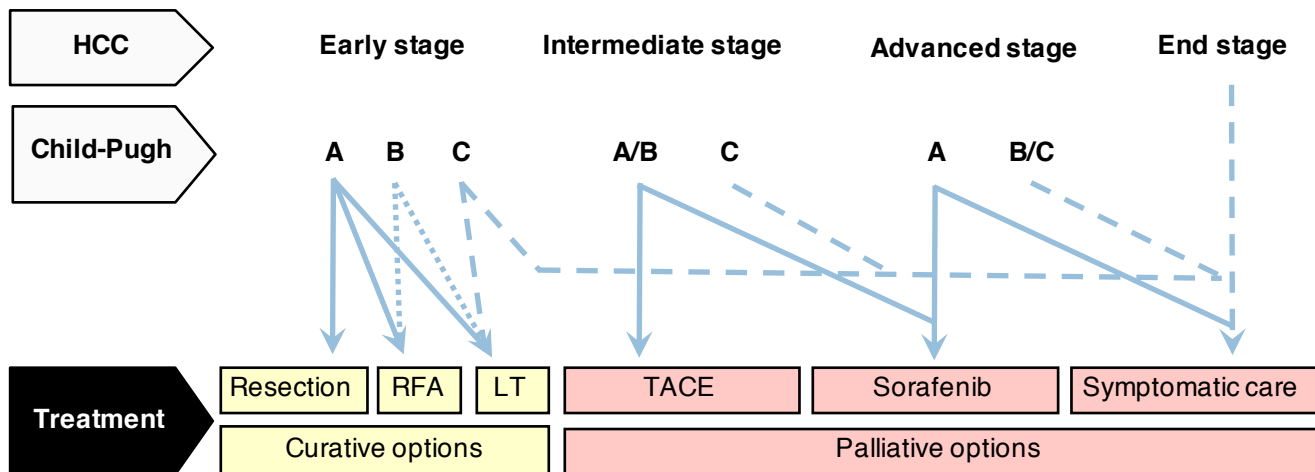


Figure 4.3 Schematic representation of treatment options according to hepatocellular carcinoma (HCC) stage and Child-Pugh class. Adapted with permission from Sherman et al. [13]. LT = liver transplantation, RFA = radiofrequency ablation, TACE = transarterial chemoembolization.

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4.3.4 Model Parameter Estimates

A literature research was performed to identify all relevant data that informed the parameters used in our model (**Table 4.1** and **Table 4.2**). Preference was given to meta-analyses, systematic reviews, and clinical trials. Transition probabilities were calculated based on the approach outlined by Miller and Homan for converting rates over time [152]. HCC incidences were based on the threshold incidence for efficacy of surveillance in cirrhotic patients (1.5%/year) [12] and incidence of HCC reported in the literature [153].

Sensitivity and specificity of US, CT, and MRI were derived from a meta-analysis which pooled estimates of diagnostic performance according to imaging modalities, setting (surveillance and nonsurveillance), and unit of analysis (per patient and per lesion) [78]. Sensitivity and specificity of abbreviated MRI were derived from proof-of-concept studies [80, 81]. The selected values for US inadequacy were derived from a retrospective study by Simmons et al. [14]. CT and MRI technical failure rates were estimated from studies that assessed frequency of contrast extravasation and claustrophobia, respectively. Contraindication to contrast due to renal dysfunction was also considered [154].

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Table 4.1 Initial Parameters and Transition Probabilities

Parameters	Base Case (Range)	References
Discount rate	1.5 (0–5)	[117]
Age at entry (y)	50 (40–60)	[147, 148]
Cirrhosis progression	5 (4–7)	[150, 155]
HCC incidence	3 (1.5–8)	[12, 153]
HCC progression	40 (20–70)	[15, 156]
Incidental or symptomatic early- and intermediate-stage HCC	30 (0–50)	[60]
Incidental or symptomatic advanced and end-stage HCC	100 (50–100)	Assumption
Optimal surveillance scenario		
Child-Pugh class A at entry	100	Assumption
Surveillance compliance	100	Assumption
Conservative surveillance scenario		
Child-Pugh class A at entry	29 (18–50)	[150]
Surveillance compliance	52 (38–66)	[149]
Mortality		
Child-Pugh class A (1 y) ^a	5	[150]
Child-Pugh class B (1 y) ^a	20	[150]

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Child-Pugh class C (1 y) ^a	55	[150]
Advanced and end-stage HCC (1 y)	76 (40–85)	[157]
Perioperative mortality of liver resection	3.9 (3.7–4.5)	[47]
Perioperative mortality of RFA	0.3 (0–1.8)	[158, 159]
Perioperative mortality of LT	4.3 (2.3–6.3)	[160]
Survival after treatment		
Liver resection (5 y)	51 (38–51)	[15, 47]
RFA (Child-Pugh class A) (5 y)	51 (32–68)	[15, 48]
RFA (Child-Pugh class B) (5 y)	31 (27–40)	[15, 48]
LT (1 y)	95 (89–97)	[49]
LT (5 y)	82 (69–86)	[49]
Sorafenib (1 y) ^a	44	[50]
TACE (1 y) ^a	62	[51]
Symptomatic care (1 y) ^a	18	[52]

Except for patient age, data are percentages. HCC = hepatocellular carcinoma, LT = liver transplantation, RFA = radiofrequency ablation, TACE = transarterial chemoembolization.

^aRange Values = -25% and 25%.

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Table 4.2 Imaging Techniques Characteristics

Parameters	Base Case (Range)	References
Surveillance US sensitivity	78 (60–89)	[78]
Surveillance US specificity	89 (80–94)	[78]
US technically inadequate rate	16 (0–39)	[14]
Surveillance CT sensitivity	84 (59–95)	[78]
Surveillance CT specificity	99 (86–100)	[78]
Diagnostic CT sensitivity	76 (72–80)	[78]
Diagnostic CT specificity	89 (84–93)	[78]
CT technically inadequate rate	0.7 (0.2–0.9)	[161-163]
Renal dysfunction frequency	5 (0–32)	[154]
Surveillance MRI sensitivity	89 (82–93)	[78]
Surveillance MRI specificity	86 (79–91)	[78]
Diagnostic MRI sensitivity	83 (80–86)	[78]
Diagnostic MRI specificity	87 (79–93)	[78]
Surveillance abbreviated MRI sensitivity	81 (71–91)	[80, 81]
Surveillance abbreviated MRI specificity	96 (90–98)	[80, 81]
MRI technically inadequate rate	1.2 (0.5–1.2)	[164, 165]

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Biopsy specificity	100 (80–100)	[15]
Biopsy sensitivity	62 (50–100)	[166]

Data are percentages. CT = computed tomography, MRI = magnetic resonance imaging, US = ultrasound.

4.3.5 Costs and Utilities

Costs incorporated into the model were preferably derived from published literature specific to the Canadian health care system (**Table 4.3**). Values that were not available from Canadian references were converted using a conversion rate of Can\$1.29 (Canadian dollars) per American dollar or Can\$1.74 per British pound. Costs of imaging modalities were microcosted from the Ontario Physicians Service [167], the Manitoba Physicians Manual [168], and the Régie de l'assurance maladie du Québec [169] (**Table 4.4**). The cost of abbreviated MRI was also microcosted (**Table 4.5**), assuming in the base case an acquisition time of 10 minutes [79, 80]. In the sensitivity analyses, the acquisition time varied from 5 to 15 minutes. All costs are of 2017 and were adjusted for inflation to 2017 when needed using the national inflation index [124].

Table 4.3 Health-Care Costs and Utilities

Parameters	Base Case (Range)	References
Costs		
(Canadian dollars, Can\$)		

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US	86 (68–261)	Table 4.4
CT	140 (105–147)	Table 4.4
MRI	419 (351–484)	Table 4.4
Abbreviated MRI	262 (158–368)	Table 4.5
Liver biopsy	995 (500–1,990)	[15]
Specialist consultation	159 (106–159)	[167]
False positive follow-up	1,800 (900–3,600)	[15]
Liver resection ^a	25,917	[170]
RFA ^a	20,260	[170]
TACE ^a	16,658	[171]
Sorafenib	54,923 (50,696– 59,149)	[172]
Symptomatic care ^a	5,000	[170]
LT (1 y)	124,204 (67,420– 180,988)	[4]
LT (long term)	25,000 (18,756– 31,260)	[173]
Utilities		
Child-Pugh class A cirrhosis	0.80 (0.64–0.96)	[174, 175]
Child-Pugh classes B and C cirrhosis	0.60 (0.48–0.72)	[174, 175]

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Early-stage HCC (Child-Pugh class A)	0.72 (0.58–0.86)	[175]
Early-stage HCC (Child-Pugh classes B and C)	0.57 (0.46–0.68)	[175]
Incurable HCC	0.40 (0.32–0.48)	[175]
After liver resection	0.70 (0.40–0.90)	[17]
After RFA ^a	0.76	[170]
After TACE	0.65 (0.52–0.77)	[176]
After sorafenib	0.76 (0.60–0.80)	[177]
After symptomatic care ^a	0.80	[170]
After LT (1 y)	0.60 (0.50–0.80)	[17, 178]
After LT (long term)	0.85 (0.70–0.90)	[17, 178]
False-positive diagnosis	-0.01 (-0.03 to 0)	[179]

CT = computed tomography, HCC = hepatocellular carcinoma, LT = liver

transplantation, MRI = magnetic resonance imaging, RFA = radiofrequency ablation,

TACE = transarterial chemoembolization, US = ultrasound.

^aRange Values = -25% and 25%.

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Table 4.4 Micro-Costing of Ultrasound, Computed Tomography, and Magnetic Resonance Imaging Examinations

Micro-costing	US	CT	MRI
One-time acquisition cost	200,000	1,700,000	2,600,000
One-time setup cost	0	0	300,000
Lifetime of machine (y) ^a	7	8	10
Number of scans/year/machine ^a	4,750	12,000	4,000
Total cost over lifetime/machine	300,884	3,918,000	10,890,000
Total no. of scans ^a	33,250	96,000	40,000
Cost per scan	9.05	40.81	272.25
Professional fees (base)	75.30	97.50	140.80
Professional fees (min)	58.30	63.10	73.50
Professional fees (max)	247.90	103.95	204.75
Total cost (base)	84.35	138.31	413.05
Total cost (min)	67.35	103.91	345.75
Total cost (max)	256.95	144.76	477.00

Except where noted otherwise, data are costs in Canadian dollars (2016 values). Data extracted from the Ontario Physicians Service [167], the Manitoba Physicians Manual [168], and the Régie de l'assurance maladie du Québec [169]. CT = computed tomography, MRI = magnetic resonance imaging, US = ultrasound.

^aAssumption.

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Table 4.5 Micro-Costing of Abbreviated Magnetic Resonance Imaging According to Acquisition Times

Micro-costing	5 minutes	10 minutes	15 minutes
One-time acquisition cost	2,600,000	2,600,000	2,600,000
One-time setup cost	300,000	300,000	300,000
Lifetime of machine (y) ^a	10	10	10
No. of scans/year/machine ^a	24,000	12,000	8,000
Total cost over lifetime/machine	19,730,000	14,426,000	12,658,000
Total scans ^a	240,000	120,000	80,000
Cost per scan	82.21	120.22	158.23
Professional fees (base)	140.80	140.80	140.80
Professional fees (mini)	73.50	73.50	73.50
Professional fees (max)	204.75	204.75	204.75
Total cost (base)	223.01	261.02	299.03
Total cost (min)	155.71	193.72	231.73
Total cost (max)	286.96	324.97	362.98

Except where noted otherwise, data are costs in Canadian dollars (2016 values). Data extracted from the Ontario Physicians Service [167], the Manitoba Physicians Manual [168], and the Régie de l'assurance maladie du Québec [169].

^aAssumption.

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A systematic review [174] and a previous cost-effectiveness study [175] provided the data for utilities associated with compensated (Child-Pugh class A) and decompensated (Child-Pugh classes B and C) cirrhosis, as well as HCC stages. Utility data for survival after each treatment option were obtained from different studies [17, 170, 176-178]. A disutility was applied to patients with a false-positive diagnosis to simulate the stress and anxiety associated with an incorrect test result. Utility values for health states are reported in **Table 4.3**.

4.3.6 Base-Case Analysis

Costs, QALYs, and ICERs were calculated for each strategy. The ICER was calculated by dividing the difference in cost by the difference in QALYs compared with the previous less costly and less effective strategy. In the Canadian health care setting, there is not a WTP threshold per se, but rather a range from Can\$20,000 to Can\$100,000 per QALY to be considered according to the context [180]. Our study considered a WTP threshold of Can\$50,000 per QALY, in accordance with previous Canadian studies that assessed the cost-effectiveness of screening interventions [181, 182]. A strategy is considered dominated when it results in a higher cost and lower QALY gain in comparison to another strategy.

4.3.7 Sensitivity Analyses

The robustness of our results was assessed in terms of deterministic and probabilistic sensitivity analyses. A one-way deterministic sensitivity analysis was performed using a range of values taken from the published literature for the majority

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of parameters. For parameters without a known interval, sensitivity analysis was performed using a range of 25% around the base-case estimates, a commonly used approach in pharmacoeconomic analyses [183]. The top five parameters with the greatest effect on ICER were selected for each scenario in the deterministic sensitivity analysis. A probabilistic analysis was performed following the methodology suggested by Briggs et al. [123].

4.4 Results

4.4.1 Base-Case Analyses

Cost-utility analysis and cost-utility curves are demonstrated in **Table 4.6** and **Figure 4.4**. In the optimal surveillance scenario (100% patients with Child-Pugh class A disease at entry and 100% compliance), strategy A (US for surveillance and CT for diagnosis) costs Can\$18,305 per person with a total utility value of 7.269 QALYs over the patient's lifetime. Strategy E (surveillance and diagnosis with CT followed by MRI for inadequate surveillance) required Can\$1,963 more per person but also delivered an incremental effectiveness of 0.144 QALYs. This option was found to be the most cost-effective strategy according to the WTP threshold of Can\$50,000/QALY, with an ICER of Can\$13,631/QALY.

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Table 4.6 Cost-Utility Analysis

Strategy	Cost (Can\$)	QALY	Incremental Cost (Can\$)	Incremental Effectiveness (QALY)	ICER (Can\$/QALY)
Optimal Scenario					
(100% Child-Pugh A patients at entry and 100% surveillance compliance)					
A. Surveillance:					
US	18,305	7.269	–	–	–
Diagnosis: CT					
E. Surveillance:					
CT					
If inadequate surveillance:	20,268	7.413	1,963	0.144	13,631
MRI					
Diagnosis: CT					
F. Surveillance:					
MRI					
If inadequate surveillance: CT	27,561	7.424	7,293	0.011	663,000
Diagnosis: MRI					
Conservative Scenario					
(29% Child-Pugh A patients at entry and 52% surveillance compliance)					

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A. Surveillance:					
US	9,286	4.300	–	–	–
Diagnosis: CT					

C. Surveillance:					
US					
If inadequate	10,400	4.332	1,114	0.032	35,108
surveillance: CT					
Diagnosis: CT					

G. Surveillance:					
abbreviated					
MRI					
If inadequate	11,273	4.354	873	0.022	39,681
surveillance: CT					
Diagnosis: MRI					

Incremental cost-effectiveness ratio (ICER) was calculated for each strategy by dividing the difference in cost (Canadian dollars, Can\$) by the difference in quality-adjusted life years (QALYs) compared with the previous less costly and less effective strategy. Dominated strategies were not included in the table. CT = computed tomography, MRI = magnetic resonance imaging, US = ultrasound.

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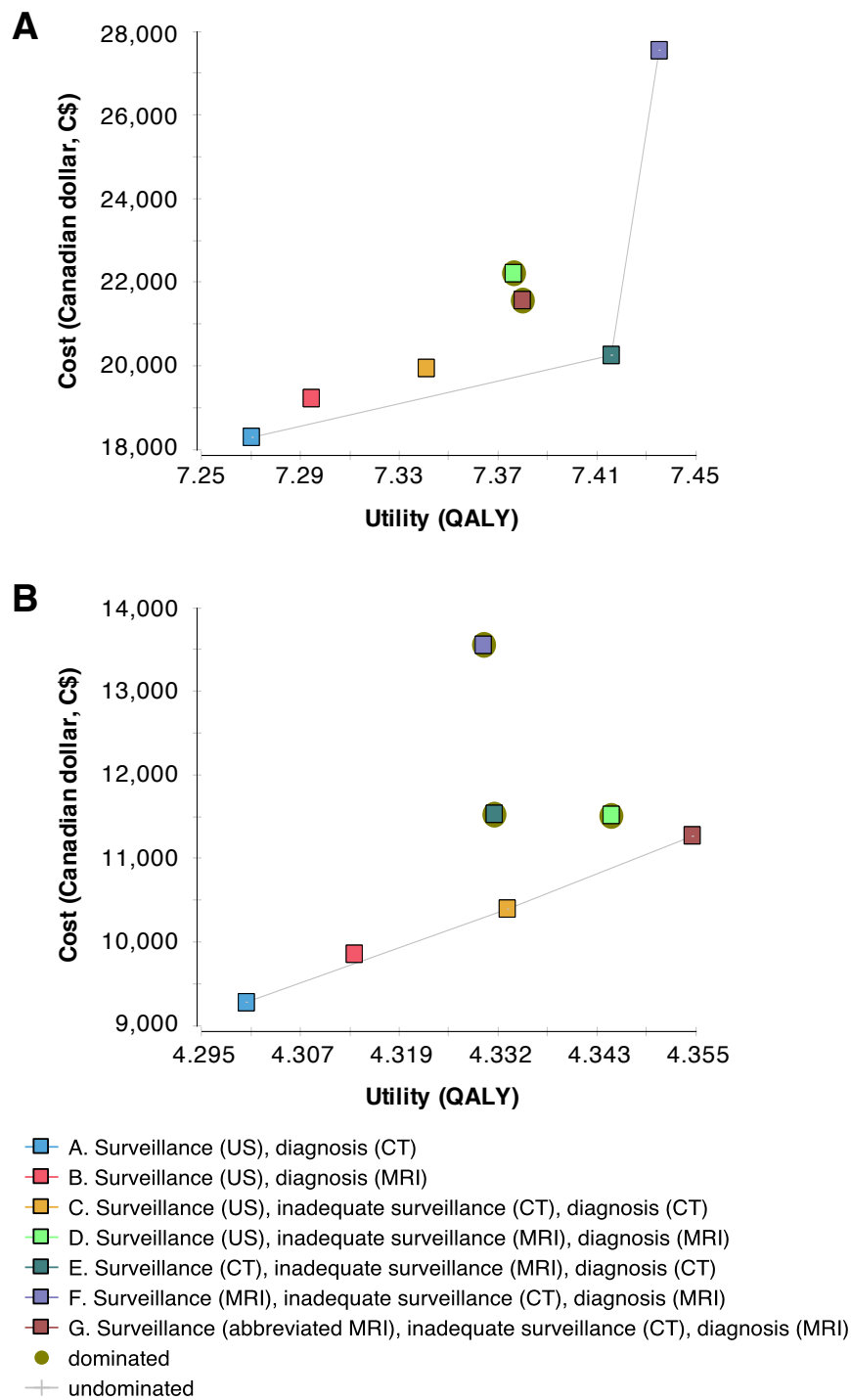


Figure 4.4 Cost-utility curves. A and B, Graphs show cost-utility curves for optimal (A) and conservative (B) surveillance scenarios. CT = computed tomography, MRI = magnetic resonance imaging, QALY = quality-adjusted life year, US = ultrasound.

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In the conservative surveillance scenario (29% patients with Child-Pugh class A disease at entry and 52% surveillance compliance), strategy A costs Can\$9,286 per person with a total utility value of 4.300 QALYs over the patient’s lifetime. Strategy C (US for surveillance and CT for inadequate or positive surveillance) required Can\$1,114 more per person but also delivered an incremental effectiveness of 0.032 QALYs, with a calculated ICER of Can\$35,108/QALY. Strategy G (surveillance with abbreviated MRI followed by CT for inadequate surveillance or MRI for positive surveillance) required Can\$873 more per person and delivered an incremental effectiveness of 0.022 QALYs when compared with strategy C. This option was found to be the most cost-effective strategy according to the WTP threshold, with an ICER of Can\$39,681/QALY.

Model validity was assessed by comparing model predictions with literature values of 1- and 2-year survival for Child-Pugh class A cirrhosis, 3-year survival for surveillance-detected and non-surveillance-detected HCCs, and probability of early-stage HCC detection among patients who underwent or did not undergo surveillance (Table 4.7).

Table 4.7 Model Validation

Parameters	Model Prediction (Strategy A ^a)	Literature Values (References)
1-year survival for Child-Pugh A cirrhosis	94%	95% [150]

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2-year survival for Child-Pugh A cirrhosis	89%	90% [150]
3-year survival for surveillance-detected HCCs	54%	51% [60]
3-year survival for symptomatic/incidental HCCs	30%	28% [60]
Early-stage HCC among patients who underwent surveillance	78%	71% [60]
Early-stage HCC among patients that did not undergo surveillance	38%	30% [60]

HCC = hepatocellular carcinoma.

^aUS for surveillance and CT for diagnosis.

4.4.2 Deterministic Sensitivity Analyses

Figure 4.5 summarizes one-way sensitivity analyses for optimal and conservative surveillance scenarios. In the optimal scenario, only the surveillance CT sensitivity could exceed the WTP threshold. If the surveillance CT sensitivity was 95%, the ICER would be Can\$11,186/QALY. At a lower limit of 59%, the ICER increased to Can\$52,321/QALY.

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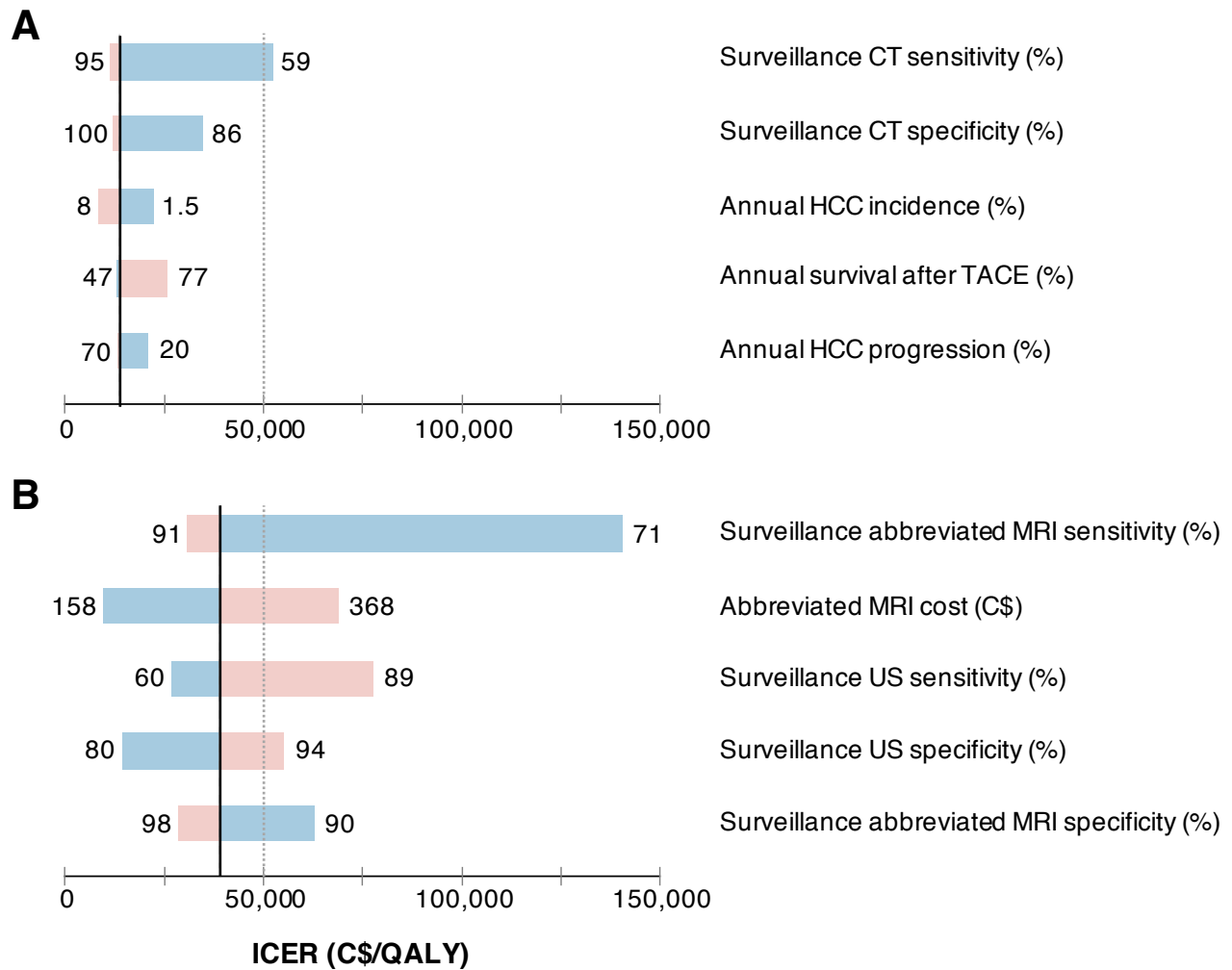


Figure 4.5 One-way sensitivity analyses. A and B, Graphs show analyses for optimal (strategy E vs strategy A; A) and conservative (strategy G vs strategy C; B) surveillance scenarios. Black lines represent expected incremental cost-effectiveness ratio (ICER) values. Dotted gray lines represent willingness-to-pay threshold. Costs are shown in Canadian dollar (Can\$). HCC = hepatocellular carcinoma, TACE = transarterial chemoembolization, ICER = incremental cost-effectiveness ratio, US = ultrasound, QALY = quality-adjusted life year.

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In the conservative scenario, all the top five parameters could exceed the WTP threshold: the sensitivity, specificity, and cost for abbreviated MRI and the sensitivity and specificity for surveillance US. The sensitivity of abbreviated MRI for surveillance varied from 71% to 91%, leading to ICER values ranging from Can\$140,556/QALY to Can\$30,435/QALY. The abbreviated MRI cost varied from Can\$158 to Can\$368, leading to ICER values ranging from Can\$9,483/QALY to Can\$68,791/QALY. This range of costs includes the values of 5-minute (Can\$158-293), 10-minute (Can\$198-331), and 15-minute (Can\$236-368) abbreviated MRI protocols. The surveillance US sensitivity varied from 60% to 89%, leading to ICER values ranging from Can\$26,704/QALY to Can\$77,489/QALY. The specificity of surveillance US varied from 80% to 94%, leading to ICER values ranging from Can\$14,261 to Can\$55,129. The specificity of abbreviated MRI for surveillance varied from 90% to 98%, leading to ICER values ranging from Can\$62,671 to Can\$28,529.

4.4.3 Probabilistic Sensitivity Analyses

Figure 4.6 summarizes the probabilistic sensitivity analyses for both optimal and conservative surveillance scenarios. This analysis evaluates the impact of uncertainty using distribution curves for each parameter instead of value ranges. In the optimal surveillance scenario, strategy E was the most likely cost-effective strategy, with a probability of 73% at the WTP threshold. In the conservative surveillance scenario, strategy G was the most likely cost-effective strategy, with a probability of 79% at the WTP threshold.

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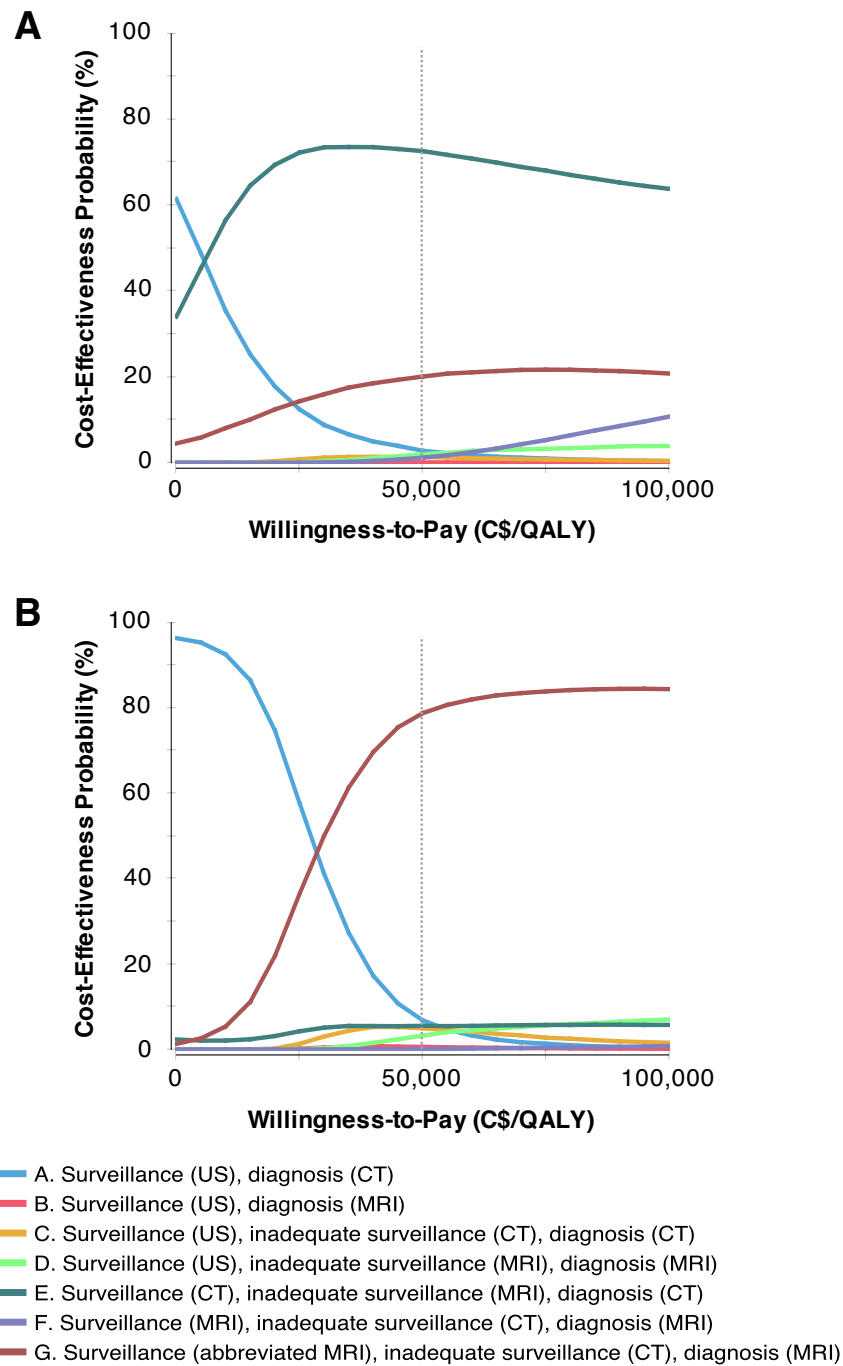


Figure 4.6 Acceptability curves after 10,000 iterations. A and B, Graphs show acceptability curves (A) and conservative (B) surveillance scenarios. Dotted gray lines represent willingness-to-pay threshold. Costs are shown in Canadian dollars (Can\$). QALY = quality-adjusted life year, US = ultrasound.

4.5 Discussion

This study complements prior cost-effectiveness studies on HCC surveillance [15-18] by comparing US, CT, MRI, and abbreviated MRI as options for HCC surveillance and by taking into account the effect of inconclusive surveillance imaging examinations and patient compliance. Our model relied on current knowledge of hepatocarcinogenesis, clinical practice guidelines for the treatment of HCC, and performance of imaging tests from a meta-analysis. The incidence, transition probabilities, costs, and utilities were based on a literature review. Furthermore, the validity of our model was supported by similarities between predicted values and data found in the literature.

To evaluate the full effect of surveillance, an optimal scenario was assessed, where all patients started surveillance when they had compensated cirrhosis (Child-Pugh class A) and the compliance to surveillance was 100%. However, because liver fibrosis and compensated cirrhosis are asymptomatic conditions, a large number of patients may be unaware of their condition [147]. Furthermore, the HCC surveillance compliance is suboptimal, with an overall rate of only 52% [149]. Thus, a conservative scenario analysis was also modeled.

As expected, all strategies in the optimal scenario delivered more QALYs than in the conservative scenario. This finding corroborates the importance of surveillance in improving health outcomes and justifies the development of programs to increase compliance. A mailed outreach program conducted by Singal et al. [184] and a clinical

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reminder program implemented by Beste et al. [185], for example, had encouraging results, but further efforts are still needed.

In the optimal surveillance scenario, the most cost-effective strategy was strategy E (surveillance and diagnosis with CT followed by MRI for inadequate surveillance). According to deterministic sensitivity analysis, strategy E exceeded the WTP threshold only if the sensitivity of surveillance CT decreased to nearly 59%. Such a low sensitivity has been reported only in the evaluation of lesions smaller than 10 mm [78], for which current guidelines do not recommend additional investigation or short-term follow-up management [12]. Hence, the results of the base-case analysis were essentially confirmed by the sensitivity analyses at the WTP threshold.

Strategies relying on a single examination for both surveillance and diagnosis (such as strategy E) are prone to higher rates of false-positive diagnoses. This is a legitimate concern, because false-positive diagnoses may expose healthy patients to psychologic stress and treatment risks and increase their health care expenditures [186, 187]. Furthermore, patients on the LT waiting list may receive additional exception points for HCC on the basis of a false-positive diagnosis. Hence, the choice of imaging-based surveillance and diagnostic strategies may have downstream effects on organ allocation [188].

In the conservative surveillance scenario, the most cost-effective strategy was G (surveillance with abbreviated MRI followed by CT for inadequate surveillance or MRI for positive surveillance). According to deterministic sensitivity analysis, strategy G exceeded the WTP threshold depending on the sensitivity and specificity of abbreviated

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MRI in a surveillance setting and the cost of the abbreviated MRI. Of note, the abbreviated MRI cost is directly related to the examination duration. An abbreviated MRI protocol could reduce the current 20- to 40-minute examination time to only 5-15 minutes [79-81]. According to our results, a 15-minute abbreviated MRI would not be cost-effective, whereas a 5- or 10-minute abbreviated MRI protocol had the potential to be cost-effective. Also, if the sensitivity and specificity of surveillance US were higher than the base-case estimates, strategy G may become less cost-effective than strategy C (US for surveillance and CT for inadequate or positive surveillance). Interestingly, the probabilistic sensitivity analysis also favored strategy G at a WTP threshold of Can\$50,000/QALY.

Abbreviated MRI protocols aim to offer a lower-cost alternative to MRI while preserving the advantages of MRI technique, such as high contrast and absence of ionizing radiation. However, to date, only retrospective simulations have assessed this emergent approach [79-81]. Further prospective or randomized studies may be required to assess the diagnostic performance of abbreviated MRI in an HCC surveillance setting before the introduction of this approach in large population-based surveillance programs.

There are limitations to our study. There is a knowledge gap in the literature concerning the costs and utilities associated with false-positive diagnoses of HCC. The cost of follow-up for a false-positive diagnosis of HCC was based on values reported by Andersson et al. [15], whereas the disutility associated with a false-positive diagnosis was based on a cost-effectiveness study of patients undergoing evaluation

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for coronary artery disease [179]. Thus, our model may overestimate the cost-effectiveness of strategies that use the same imaging modality for surveillance and diagnosis (which are prone to higher rates of false-positive diagnosis). Another limitation was that abbreviated MRI sensitivity and specificity were derived from retrospective simulations. Furthermore, some values incorporated into the model were assumed by the authors or derived from American and British sources and may not reflect the Canadian perspective. Finally, concerns regarding radiation associated with CT were not modeled. Although one may consider unacceptable the cumulative radiation burden associated with a surveillance program, we understand that the radiation exposure is less important for the population undergoing HCC surveillance due to its age and life expectancy [189].

4.6 Conclusion

In conclusion, in a scenario that assumes optimal patient compliance and takes into account inconclusive imaging examinations, CT for HCC surveillance and diagnosis and MRI for inadequate CT was most cost-effective. However, in a scenario that assumes conservative patient compliance and also takes into account inconclusive imaging examinations, abbreviated MRI may be a cost-effective alternative to the current US-surveillance practice. Before implementing a surveillance program incorporating imaging modalities other than US, future studies should address the economic burden associated with false-positive HCC diagnoses. Also, future

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prospective trials should assess the accuracy of abbreviated MRI examinations in a surveillance setting.

5 Conclusion

HCC is a significant complication associated with chronic liver disease. It is the sixth most common cancer and the fourth cause of cancer-related deaths worldwide [1]. Despite the existence of well-established surveillance recommendations [12, 13, 64], the clinical practice may be challenging. Several subgroups, such as obese patients, those with Child-Pugh B or C cirrhosis, or NAFLD-related cirrhosis, are subject to inadequate US surveillance [14]. The research in this dissertation emerged from the need to evaluate which is the most cost-effective surveillance strategy for these patients.

To reach this objective, we developed a Markov model using TreeAge Pro software. Seven strategies were compared relying on the combinations of four imaging techniques: US, CT, MRI, and abbreviated MRI. Our model was validated by comparing model predictions with literature values [60, 150].

Considering the inconclusive imaging examinations, our results demonstrated that CT for HCC surveillance and diagnosis and MRI for inadequate CT is the most cost-effective strategy in scenarios with optimal patient compliance. However, in scenarios with low patient compliance, abbreviated MRI for HCC surveillance, followed by MRI for diagnosis, or CT for inadequate abbreviated MRI, is the most cost-effective alternative to the current US-surveillance practice.

Chapter 5. Conclusion

By performing this economic analysis, we realized that an individual approach, considering the clinical particularities of the patients, is more cost-effective than the current “one-size-fits-all” strategy. New technologies have introduced us to the era of individualized medicine, particularly in the oncological field. Our findings support this perspective and are in accordance with previously published studies [18, 190, 191].

We anticipate that centers located in low-income regions may experience difficulties in implementing the new approach suggested by our work, which is based on the use of more expensive imaging modalities. However, in centers where these modalities are already available, the results presented in this research could guide physicians to adopt the best possible practice tailored to their patient's body habitus and prior history of technically inadequate examinations.

I hope that the results presented here may positively impact the lives of those who live with liver disease and help to mitigate the social and economic burden associated with HCC. Furthermore, I would like to encourage those who are interested in this subject to perform studies that address the gaps still present in the literature, such as the economic burden associated with false-positive HCC diagnoses and the accuracy of abbreviated MRI in the surveillance setting.

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Appendix

Appendix 1 Manuscript: Cost-Utility Analysis of Imaging for Surveillance and Diagnosis of Hepatocellular Carcinoma.

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Cost-Utility Analysis of Imaging for Surveillance and Diagnosis of Hepatocellular Carcinoma

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OBJECTIVE. The purpose of this study is to compare imaging-based surveillance and diagnostic strategies in patients at risk for hepatocellular carcinoma (HCC) while taking into account technically inadequate examinations and patient compliance.

MATERIALS AND METHODS. A Markov model simulated seven strategies for HCC surveillance and diagnosis in patients with cirrhosis: strategy A, ultrasound (US) for surveillance and CT for diagnosis; strategy B, US for surveillance and complete MRI for diagnosis; strategy C, US for surveillance and CT for inadequate or positive surveillance; strategy D, US for surveillance and complete MRI for inadequate or positive surveillance; strategy E, surveillance and diagnosis with CT followed by complete MRI for inadequate surveillance; strategy F, surveillance and diagnosis with complete MRI followed by CT for inadequate surveillance; and strategy G, surveillance with abbreviated MRI followed by CT for inadequate surveillance or complete MRI for positive surveillance. Two compliance scenarios were evaluated: optimal and conservative. For each scenario, the most cost-effective strategy was based on a willingness-to-pay threshold of \$50,000 (Canadian) per quality-adjusted life year (QALY). Sensitivity analyses were performed.

RESULTS. Base-case analysis revealed that strategy E was the most cost-effective when compliance was optimal (\$13,631/QALY), and strategy G was the most cost-effective when compliance was conservative (\$39,681/QALY). Sensitivity analyses supported the base-case analysis in the optimal compliance scenario, but several parameters altered the most cost-effective strategy in the conservative compliance scenario.

CONCLUSION. In an optimal compliance scenario, CT for HCC surveillance and diagnosis and complete MRI for inadequate CT was most cost-effective. In a conservative compliance scenario, abbreviated MRI may be an alternative to US-based surveillance.

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the second leading cause of cancer-related deaths worldwide [1]. In Canada, HCC is the only malignancy for which mortality is increasing, a trend that is expected to continue through 2020 and beyond [2]. The implementation of surveillance programs targeting high-risk populations, such as patients with cirrhosis, has led to the detection of HCC at earlier stages, when curative therapies can be applied [3]. This strategy could reduce the mortality related to HCC, as shown by a large randomized controlled trial [4].

North American guidelines recommend ultrasound (US) surveillance every 6 months in at-risk patients [5, 6]. Although US surveillance is feasible in patients with thin body habitus and without steatosis, it is challeng-

ing in obese patients or those with cirrhosis because of attenuation and heterogeneity of liver appearance, which limit the ability to assess the liver parenchyma [7, 8]. Furthermore, cirrhosis is often accompanied by a diffusely nodular appearance of liver parenchyma that limits the ability to detect HCC lesions [7]. Alternately, CT, MRI, and abbreviated MRI (which is limited to two or three sequences for lesion detection) have been explored as alternative imaging modalities for HCC surveillance [9–14] and may be used in selected patients who are likely to have inadequate US examinations [5].

Costs attributable to HCC account for a substantial financial burden, are higher when HCC is diagnosed at advanced stages, and are expected to increase until the HCC incidence reaches its peak [15, 16]. Given that health care systems are limited in their financial re-

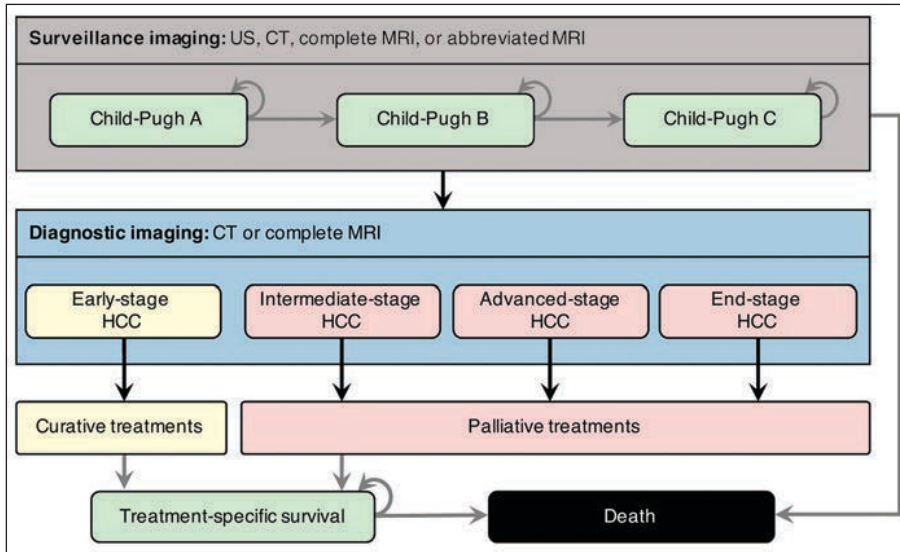


Fig. 1—Simplified Markov model illustrating surveillance (gray box) and diagnostic imaging techniques (blue box) interposed on health states (green boxes) and temporary states (beige and pink boxes). Gray arrows indicate health state transitions, and black arrows indicate temporary state transitions (management of positive imaging results). US = ultrasound, HCC = hepatocellular carcinoma.

sources, competing surveillance strategies should be analyzed for their cost-effectiveness. Cost-utility studies, which incorporate the widely applicable quality-adjusted life year (QALY), a measure of health outcome, should guide policymakers in their decision to implement alternative surveillance strategies. Prior cost-utility studies that assessed HCC surveillance have not taken into consideration the effect of inconclusive surveillance imaging examinations and patient compliance simultaneously. In this era of imaging-based surveillance and diagnosis of HCC, there is a need to investigate the cost-effectiveness of different surveillance algorithms.

Therefore, the purpose of this study was to compare imaging-based surveillance and diagnostic strategies in patients at risk for HCC, taking into account technically inadequate examinations and patient compliance.

Materials and Methods

Model Structure and Population

A decisional Markov model was developed using TreeAge Pro software (version 2017, TreeAge) to estimate the costs and QALYs associated with imaging-based surveillance and diagnostic strategies for HCC (Fig. 1). This study was developed from a Canadian health care system perspective and followed the Canadian Guideline for Economic Evaluation of Health Technologies [17].

The simulated cohort of high-risk patients with cirrhosis underwent imaging-based surveillance every 6 months (cycle length). At baseline, patients

began surveillance at the age of 50 years, which is the average age of cirrhosis diagnosis [18, 19]. To reflect the full potential of surveillance, an optimal scenario was evaluated, composed of patients with compensated cirrhosis (Child-Pugh class A) at entry, with an assumed compliance rate of 100%. A conservative scenario was also assessed, using the frequency of compensated cirrhosis and compliance to surveillance values derived from systematic reviews [20, 21].

Imaging-based surveillance and diagnostic strategies and treatment options were superim-

posed onto the Markov model to reflect clinical options. At each cycle, patients could progress to decompensated cirrhosis (Child-Pugh class B or C) or develop HCC or both. Patients with a positive surveillance result were submitted to a diagnostic imaging examination. Those with a positive diagnostic result were treated according to their HCC stage and Child-Pugh class (see the Treatment Options subsection later). Survival after each treatment option was modeled. Patients with a negative surveillance or diagnostic result were reinvestigated in the next cycle. In the model, a new HCC could remain undetected until it was discovered by surveillance or the patient experienced symptoms; it was also possible for a patient to die with an undiagnosed HCC. Continued follow-up was made until all patients died (lifetime horizon). Both costs and outcomes were discounted at 1.5% per year [17]. Model validity was assessed comparing survival rates and diagnostic probabilities found in the model with results presented in published studies.

Competing Imaging Strategies

Seven surveillance and diagnostic strategies were investigated, relying on combinations of four imaging techniques: US, CT, complete MRI, and abbreviated MRI (see Fig. S1, which can be viewed in the AJR electronic supplement to this article, available at www.ajronline.org). Strategies A and B used US-based surveillance followed by CT and complete MRI, respectively, for diagnosis, without additional imaging for inadequate US surveillance examinations. These strategies are recommended by current guidelines [5, 6]. Alternative strategies C and D used US-based surveillance followed by CT and complete

TABLE 1: Initial Parameters and Transition Probabilities

Parameter	Base Case (Range)	References
Discount rate	1.5 (0–5)	[17]
Age at entry (y)	50 (40–60)	[18, 19]
Cirrhosis progression	5 (4–7)	[21, 52]
HCC incidence	3 (1.5–8)	[5, 24]
HCC progression	40 (20–70)	[44, 53]
Incidental or symptomatic early- and intermediate-stage HCC	30 (0–50)	[54]
Incidental or symptomatic advanced and end-stage HCC	100 (50–100)	Assumption
Optimal surveillance scenario		
Child-Pugh class A at entry	100	Assumption
Surveillance compliance	100	Assumption
Conservative surveillance scenario		
Child-Pugh class A at entry	29 (18–50)	[21]
Surveillance compliance	52 (38–66)	[20]

(Table 1 continues on next page)

Cost-Utility Analysis of Imaging for HCC

TABLE 1: Initial Parameters and Transition Probabilities (continued)

Parameter	Base Case (Range)	References
Mortality		
Child-Pugh class A (1 y) ^a	5	[21]
Child-Pugh class B (1 y) ^a	20	[21]
Child-Pugh class C (1 y) ^a	55	[21]
Advanced and end-stage HCC (1 y)	76 (40–85)	[55]
Perioperative mortality of liver resection	3.9 (3.7–4.5)	[56]
Perioperative mortality of RFA	0.3 (0–1.8)	[57, 58]
Perioperative mortality of liver transplantation	4.3 (2.3–6.3)	[59]
Survival after treatment		
Liver resection (5 y)	51 (38–51)	[44, 56]
RFA (Child-Pugh class A) (5 y)	51 (32–68)	[44, 60]
RFA (Child-Pugh class B) (5 y)	31 (27–40)	[44, 60]
Liver transplantation (1 y)	95 (89–97)	[61]
Liver transplantation (5 y)	82 (69–86)	[61]
Sorafenib (1 y) ^a	44	[62]
TACE (1 y) ^a	62	[63]
Symptomatic care (1 y) ^a	18	[64]

Note—Except for patient age, data are percentages. HCC = hepatocellular carcinoma, RFA = radiofrequency ablation, TACE = transarterial chemoembolization.

^aRange values = –25% and 25%.

TABLE 2: Imaging Techniques Characteristics

Parameter	Base Case (Range)	References
Surveillance US sensitivity	78 (60–89)	[25]
Surveillance US specificity	89 (80–94)	[25]
US technically inadequate rate	16 (0–39)	[26]
Surveillance CT sensitivity	84 (59–95)	[25]
Surveillance CT specificity	99 (86–100)	[25]
Diagnostic CT sensitivity	76 (72–80)	[25]
Diagnostic CT specificity	89 (84–93)	[25]
CT technically inadequate rate	0.7 (0.2–0.9)	[65–67]
Renal dysfunction frequency	5 (0–32)	[27]
Surveillance complete MRI sensitivity	89 (82–93)	[25]
Surveillance complete MRI specificity	86 (79–91)	[25]
Diagnostic complete MRI sensitivity	83 (80–86)	[25]
Diagnostic complete MRI specificity	87 (79–93)	[25]
Surveillance abbreviated MRI sensitivity	81 (71–91)	[12, 13]
Surveillance abbreviated MRI specificity	96 (90–98)	[12, 13]
MRI technically inadequate rate	1.2 (0.5–1.2)	[68, 69]
Biopsy specificity	100 (80–100)	[44]
Biopsy sensitivity	62 (50–100)	[70]

Note—Data are percentages. US = ultrasound.

MRI, respectively, for technically inadequate or positive US surveillance. These strategies follow the current recommendations of using US as the first-line surveillance modality, albeit by offering alternative imaging in case of inadequate US [5]. Replacement strategies E and F used CT and complete MRI, respectively, for surveillance, an approach that reflects the current practice in some North American centers. In cases of technically inadequate surveillance CT or MRI, the other imaging modality was used for confirmation. Strategy G used abbreviated MRI as surveillance followed by CT for patients with technically inadequate surveillance examinations or complete MRI for diagnosis of positive surveillance results. This emergent approach was recently proposed in proof-of-concept studies [11–13].

Treatment Options

The treatments were modeled on the basis of the Canadian consensus for the management and treatment of HCC [6] (Fig. S2, which can be viewed in the *AJR* electronic supplement to this article, available at www.ajronline.org). Early-stage HCC could be treated with curative treatments, including liver resection, radiofrequency ablation, and liver transplantation. Intermediate-stage, advanced-stage, and end-stage HCCs received palliative treatments, such as transarterial chemoembolization, sorafenib, and symptomatic care. The relative proportion of patients eligible for each type of treatment was based on the distribution of treatments in participating North American centers of the international BRIDGE study [22].

Model Parameter Estimates

A literature search was performed to identify all relevant data that informed the parameters used in our model (Tables 1 and 2). Preference was given to meta-analyses, systematic reviews, and clinical trials. Transition probabilities were calculated according to the approach outlined by Miller and Homan [23] for converting rates over time. HCC incidences were based on the threshold incidence for efficacy of surveillance in patients with cirrhosis (1.5%/year) [5] and the incidence of HCC reported in the literature [24].

Sensitivity and specificity of US, CT, and complete MRI were derived from a meta-analysis that pooled estimates of diagnostic performance according to imaging modalities, setting (surveillance and nonsurveillance), and unit of analysis (per patient and per lesion) [25]. Sensitivity and specificity of abbreviated MRI were derived from proof-of-concept studies [12, 13]. The selected values for US inadequacy were derived from a ret-

TABLE 3: Health Care Costs and Utilities

Parameter	Base Case (Range)	References
Costs (Canadian dollars)		
US	86 (68–261)	Table S3
CT	140 (105–147)	Table S3
Complete MRI	419 (351–484)	Table S3
Abbreviated MRI	262 (158–368)	Table S4
Liver biopsy	995 (500–1990)	[44]
Specialist consultation	159 (106–159)	[28]
False-positive follow-up	1800 (900–3600)	[44]
Liver resection ^a	25,917	[36]
RFA ^a	20,260	[36]
TACE ^a	16,658	[71]
Sorafenib	54,923 (50,696–59,149)	[72]
Symptomatic care ^a	5000	[36]
Liver transplantation (first year)	124,204 (67,420–180,988)	[15]
Liver transplantation (long term)	25,000 (18,756–31,260)	[73]
Utilities		
Child-Pugh class A cirrhosis	0.80 (0.64–0.96)	[32, 33]
Child-Pugh classes B and C cirrhosis	0.60 (0.48–0.72)	[32, 33]
Early-stage HCC (Child-Pugh class A)	0.72 (0.58–0.86)	[33]
Early-stage HCC (Child-Pugh classes B and C)	0.57 (0.46–0.68)	[33]
Incurable HCC	0.40 (0.32–0.48)	[33]
After liver resection	0.70 (0.40–0.90)	[14]
After RFA ^a	0.76	[36]
After TACE	0.65 (0.52–0.77)	[34]
After sorafenib	0.76 (0.60–0.80)	[35]
After symptomatic care ^a	0.80	[36]
After liver transplantation (first year)	0.60 (0.50–0.80)	[14, 37]
After liver transplantation (long term)	0.85 (0.70–0.90)	[14, 37]
False-positive diagnosis	–0.01 (–0.03 to 0)	[51]

Note—US = ultrasound, RFA = radiofrequency ablation, TACE = transarterial chemoembolization, HCC = hepatocellular carcinoma.

^aRange values = –25% and 25%.

respective study by Simmons et al. [26]. CT and MRI technical failure rates were estimated from studies that assessed the frequency of contrast extravasation and claustrophobia, respectively. Contra-indication to contrast agent due to renal dysfunction was also considered [27].

Costs and Utilities

Costs incorporated into the model were preferably derived from published literature specific to the Canadian health-care system (Table 3). Values that were not available from Canadian references were converted using a conversion rate of \$1.29 Canadian per American dollar or \$1.74 Ca-

nadian dollar per British pound. Costs of imaging modalities were microcosted from the Ontario Physicians Service [28], the Manitoba Physicians Manual [29], and the Régie de l'assurance maladie du Québec [30] (Table S3, which can be viewed in the *AJR* electronic supplement to this article, available at www.ajronline.org). The cost of abbreviated MRI was also microcosted (Table S4, which can be viewed in the *AJR* electronic supplement to this article, available at www.ajronline.org), assuming in the base case an acquisition time of 10 minutes [11, 12]. In the sensitivity analyses, the acquisition time varied from 5 to 15 minutes. All costs are of 2017 and were adjusted for infla-

tion to 2017 when needed using the national inflation index [31] (all monetary values given in this article are shown in Canadian dollars).

A systematic review [32] and a previous cost-effectiveness study [33] provided the data for utilities associated with compensated (Child-Pugh class A) and decompensated (Child-Pugh classes B and C) cirrhosis, as well as HCC stages. Utility data for survival after each treatment option were obtained from different studies [14, 34–37]. A disutility was applied to patients with a false-positive diagnosis to simulate the stress and anxiety associated with an incorrect test result. Utility values for health states are reported in Table 3.

Base-Case Analysis

Costs, QALYs, and incremental cost-effectiveness ratios (ICERs) were calculated for each strategy. The ICER was calculated by dividing the difference in cost by the difference in QALYs compared with the previous less costly and less effective strategy. In the Canadian health care setting, there is not a willingness-to-pay (WTP) threshold per se, but rather a range from \$20,000 to \$100,000 per QALY to be considered according to the context [38]. Our study considered a WTP threshold of \$50,000 per QALY, in accordance with previous Canadian studies that assessed the cost-effectiveness of screening interventions [39, 40]. A strategy is considered dominated when it results in a higher cost and lower QALY gain in comparison with another strategy.

Sensitivity Analyses

The robustness of our results was assessed in terms of deterministic and probabilistic sensitivity analyses. A one-way deterministic sensitivity analysis was performed using a range of values taken from the published literature for the majority of parameters. For parameters without a known interval, sensitivity analysis was performed using a range of 25% around the base-case estimates, a commonly used approach in pharmacoeconomic analyses [41]. The top five parameters with the greatest effect on ICER were selected for each scenario in the deterministic sensitivity analysis. A probabilistic analysis was performed according to the methods suggested by Briggs et al. [42].

Results

Base-Case Analyses

Cost-utility analysis and cost-utility curves are shown in Table 4 and Figure S5 (see the *AJR* electronic supplement to this article, available at www.ajronline.org). In the op-

Cost-Utility Analysis of Imaging for HCC

TABLE 4: Cost-Utility Analysis

Strategy	Cost (Canadian Dollars)	QALY	Incremental Cost (Canadian Dollars)	Incremental Effectiveness (QALY)	ICER (Canadian Dollars/QALY)
Optimal scenario (100% of patients with Child-Pugh class A disease at entry and 100% surveillance compliance)					
A: Surveillance, US; diagnosis, CT	18,305	7.269			
E: Surveillance, CT; if inadequate surveillance, MRI; diagnosis, CT	20,268	7.413	1963	0.144	13,631
F: Surveillance, MRI; if inadequate surveillance, CT; diagnosis, MRI	27,561	7.424	7293	0.011	663,000
Conservative scenario (29% of patients with Child-Pugh class A disease at entry and 52% surveillance compliance)					
A: Surveillance, US; diagnosis, CT	9286	4.300			
C: Surveillance, US; if inadequate surveillance, CT; diagnosis, CT	10,400	4.332	1114	0.032	35,108
G: Surveillance, abbreviated MRI; if inadequate surveillance, CT; diagnosis, MRI	11,273	4.354	873	0.022	39,681

Note—Incremental cost-effectiveness ratio (ICER) was calculated for each strategy by dividing the difference in cost (Canadian dollars) by the difference in quality-adjusted life years (QALYs) compared with the previous less costly and less effective strategy. Dominated strategies were not included in the table. US = ultrasound.

Optimal surveillance scenario (100% patients with Child-Pugh class A disease at entry and 100% compliance), strategy A (US for surveillance and CT for diagnosis) costs \$18,305 per person with a total utility value of 7.269 QALYs over the patient's lifetime. Strategy E (surveillance and diagnosis with CT followed by complete MRI for inadequate surveillance) required \$1963 more per person but also delivered an incremental effectiveness of 0.144 QALYs. This option was found to be the most cost-effective strategy according to the WTP threshold of \$50,000/QALY, with an ICER of \$13,631/QALY.

In the conservative surveillance scenario (29% patients with Child-Pugh class A disease at entry and 52% surveillance compliance), strategy A costs \$9286 per person with a total utility value of 4.300 QALYs over the patient's lifetime. Strategy C (US for surveillance and CT for inadequate or positive surveillance) required \$1114 more per person but

also delivered an incremental effectiveness of 0.032 QALYs, with a calculated ICER of \$35,108/QALY. Strategy G (surveillance with abbreviated MRI followed by CT for inadequate surveillance or complete MRI for positive surveillance) required \$873 more per person and delivered an incremental effectiveness of 0.022 QALYs when compared with strategy C. This option was found to be the most cost-effective strategy according to the WTP threshold, with an ICER of \$39,681/QALY.

Model validity was assessed by comparing model predictions with literature values of 1- and 2-year survival for Child-Pugh class A cirrhosis, 3-year survival for surveillance-detected and non-surveillance-detected HCCs, and probability of early-stage HCC detection among patients who underwent or did not undergo surveillance (see Table S6, which can be viewed in the *AJR* electronic supplement to this article, available at www.ajronline.org).

Deterministic Sensitivity Analyses

Figure 2 summarizes one-way sensitivity analyses for optimal and conservative surveillance scenarios. In the optimal scenario, only the surveillance CT sensitivity could exceed the WTP threshold. If the surveillance CT sensitivity was 95%, the ICER would be \$11,186/QALY. At a lower limit of 59%, the ICER increased to \$52,321/QALY.

In the conservative scenario, all the top five parameters could exceed the WTP threshold: the sensitivity, specificity, and cost for abbreviated MRI and the sensitivity and specificity for surveillance US. The sensitivity of abbreviated MRI for surveillance varied from 71% to 91%, leading to ICER values ranging from \$140,556/QALY to \$30,435/QALY. The abbreviated MRI cost varied from \$158 to \$368, leading to ICER values ranging from \$9483/QALY to \$68,791/QALY. This range of costs includes the values of 5-minute (\$158–293), 10-minute (\$198–331), and 15-minute (\$236–

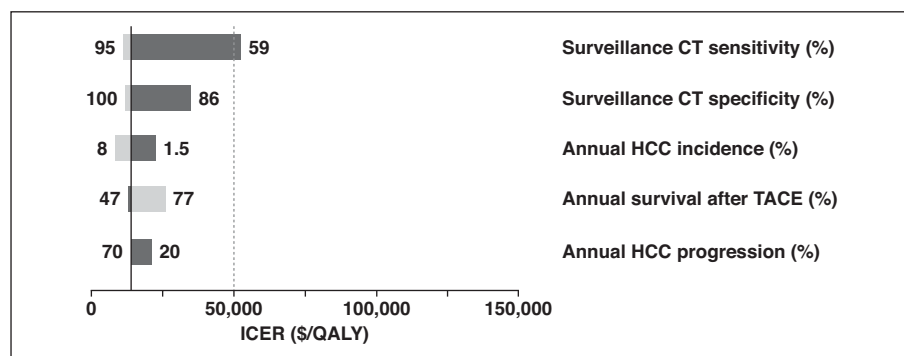


Fig. 2—One-way sensitivity analyses.

A and B, Graphs show analyses for optimal (strategy E vs strategy A; **A**) and conservative (strategy G vs strategy C; **B**) surveillance scenarios. Black lines represent expected incremental cost-effectiveness ratio (ICER) values. Dotted gray lines represent willingness-to-pay threshold. Costs are shown in Canadian dollars. HCC = hepatocellular carcinoma, TACE = transarterial chemoembolization, US = ultrasound, QALY = quality-adjusted life year.

(Fig. 2 continues on next page)

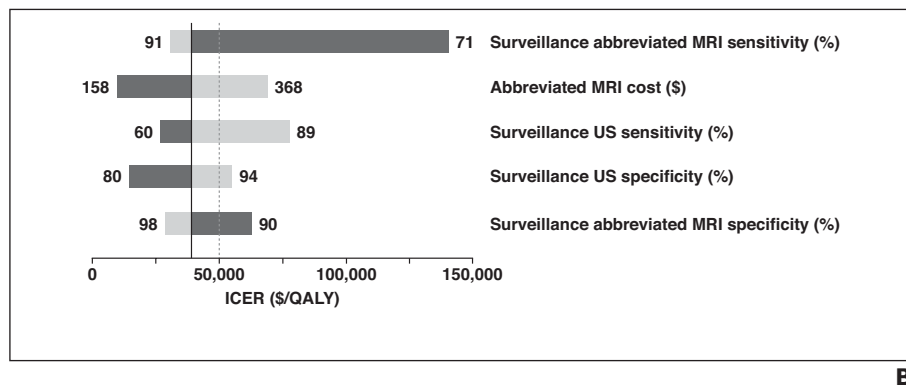


Fig. 2 (continued)—One-way sensitivity analyses. **A** and **B**, Graphs show analyses for optimal (strategy E vs strategy A; **A**) and conservative (strategy G vs strategy C; **B**) surveillance scenarios. Black lines represent expected incremental cost-effectiveness ratio (ICER) values. Dotted gray lines represent willingness-to-pay threshold. Costs are shown in Canadian dollars. HCC = hepatocellular carcinoma, TACE = transarterial chemoembolization, US = ultrasound, QALY = quality-adjusted life year.

368) abbreviated MRI protocols. The surveillance US sensitivity varied from 60% to 89%, leading to ICER values ranging from \$26,704/QALY to \$77,489/QALY. The specificity of surveillance US varied from 80% to 94%, leading to ICER values ranging from \$14,261 to \$55,129. The specificity of abbreviated MRI for surveillance varied from 90% to 98%, leading to ICER values ranging from \$62,671 to \$28,529.

Probabilistic Sensitivity Analyses

Figure 3 summarizes the probabilistic sensitivity analyses for both optimal and conservative surveillance scenarios. This analysis evaluates the effect of uncertainty using

distribution curves for each parameter instead of value ranges. In the optimal surveillance scenario, strategy E was the most likely cost-effective strategy, with a probability of 73% at the WTP threshold. In the conservative surveillance scenario, strategy G was the most likely cost-effective strategy, with a probability of 79% at the WTP threshold.

Discussion

This study complements prior cost-effectiveness studies on HCC surveillance [14, 43–45] by comparing US, CT, complete MRI, and abbreviated MRI as options for HCC surveillance and by taking into account the effect of inconclusive surveillance imaging

examinations and patient compliance. Our model relied on current knowledge of hepatocarcinogenesis, clinical practice guidelines for the treatment of HCC, and performance of imaging tests from a meta-analysis. The incidence, transition probabilities, costs, and utilities were based on a literature review. Furthermore, the validity of our model was supported by similarities between predicted values and data found in the literature.

To evaluate the full effect of surveillance, an optimal scenario was assessed, where all patients started surveillance when they had compensated cirrhosis (Child-Pugh class A) and the compliance to surveillance was 100%. However, because liver fibrosis and

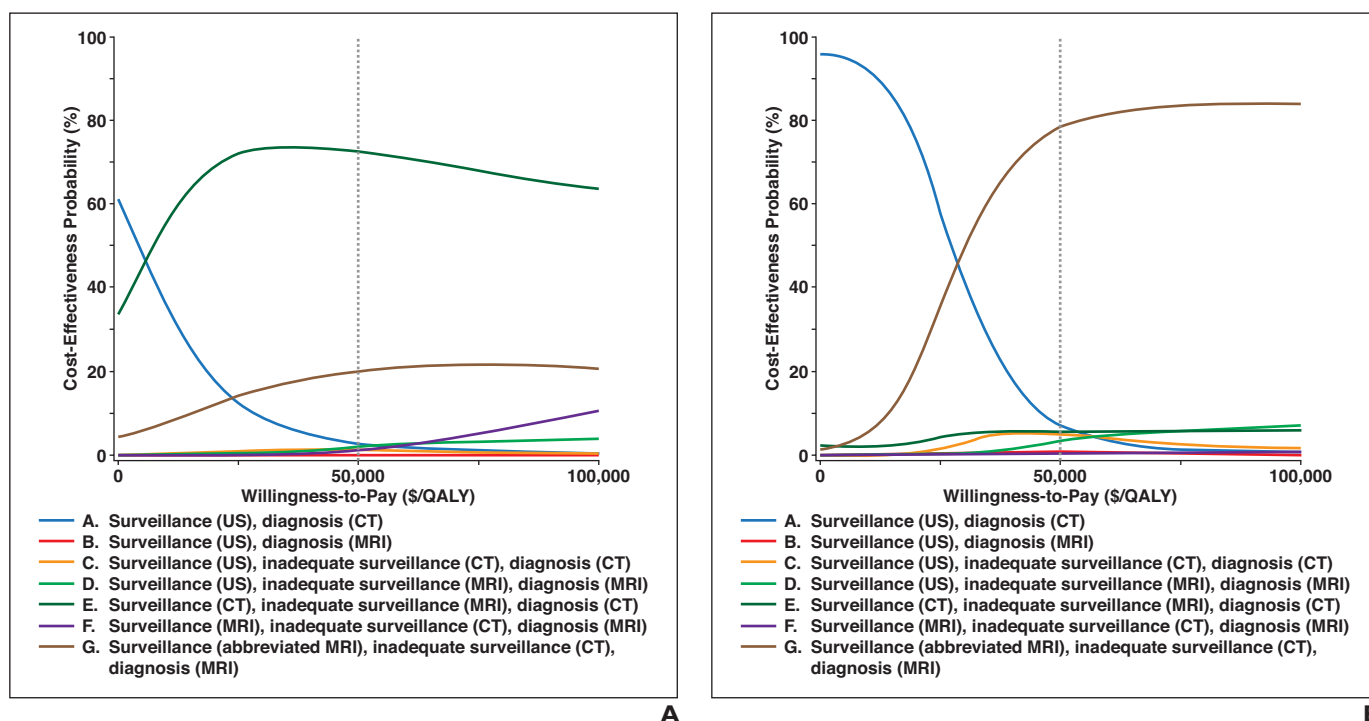


Fig. 3—Acceptability curves after 10,000 iterations. **A** and **B**, Graphs show acceptability curves for optimal (**A**) and conservative (**B**) surveillance scenarios. Dotted gray lines represent willingness-to-pay threshold. Costs are shown in Canadian dollars. QALY = quality-adjusted life year, US = ultrasound.

compensated cirrhosis are asymptomatic conditions, a large number of patients may be unaware of their condition [18]. Furthermore, the HCC surveillance compliance is suboptimal, with an overall rate of only 52% [20]. Thus, a conservative scenario analysis was also modeled.

As expected, all strategies in the optimal scenario delivered more QALYs than in the conservative scenario. This finding corroborates the importance of surveillance in improving health outcomes and justifies the development of programs to increase compliance. A mailed outreach program conducted by Singal et al. [46] and a clinical reminder program implemented by Beste et al. [47], for example, had encouraging results, but further efforts are still needed.

In the optimal surveillance scenario, the most cost-effective strategy was strategy E (surveillance and diagnosis with CT followed by complete MRI for inadequate surveillance). According to deterministic sensitivity analysis, strategy E exceeded the WTP threshold only if the sensitivity of surveillance CT decreased to nearly 59%. Such a low sensitivity has been reported only in the evaluation of lesions smaller than 10 mm [25], for which current guidelines do not recommend additional investigation or short-term follow-up management [5]. Hence, the results of the base-case analysis were essentially confirmed by the sensitivity analyses at the WTP threshold.

Strategies relying on a single examination for both surveillance and diagnosis (such as strategy E) are prone to higher rates of false-positive diagnoses. This is a legitimate concern, because false-positive diagnoses may expose healthy patients to psychologic stress and treatment risks and increase their health care expenditures [48, 49]. Furthermore, patients on the liver transplantation waiting list may receive additional exception points for HCC on the basis of a false-positive diagnosis. Hence, the choice of imaging-based surveillance and diagnostic strategies may have downstream effects on organ allocation [50].

In the conservative surveillance scenario, the most cost-effective strategy was strategy G (surveillance with abbreviated MRI followed by CT for inadequate surveillance or complete MRI for positive surveillance). According to deterministic sensitivity analysis, strategy G exceeded the WTP threshold depending on the sensitivity and specificity of abbreviated MRI in a surveillance setting and the cost of the abbreviated MRI. Of note,

the abbreviated MRI cost is directly related to the examination duration. An abbreviated MRI protocol could reduce the current 20- to 40-minute examination time to only 5–15 minutes [11–13]. According to our results, a 15-minute abbreviated MRI would not be cost-effective, whereas a 5- or 10-minute abbreviated MRI protocol had the potential to be cost-effective. Also, if the sensitivity and specificity of surveillance US were higher than the base-case estimates, strategy G may become less cost-effective than strategy C (US for surveillance and CT for inadequate or positive surveillance). Interestingly, the probabilistic sensitivity analysis also favored strategy G at a WTP threshold of \$50,000.

Abbreviated MRI protocols aim to offer a lower-cost alternative to complete MRI while preserving the advantages of MRI technique, such as high contrast and absence of ionizing radiation. However, to date, only retrospective simulations have assessed this emergent approach [11–13]. Further prospective or randomized studies may be required to assess the diagnostic performance of abbreviated MRI in an HCC surveillance setting before the introduction of this approach in large population-based surveillance programs.

There are limitations to our study. There is a knowledge gap in the literature concerning the costs and utilities associated with false-positive diagnoses of HCC. The cost of follow-up for a false-positive diagnosis of HCC was based on values reported by Andersson et al. [44], whereas the disutility associated with a false-positive diagnosis was based on a cost-effectiveness study of patients undergoing evaluation for coronary artery disease [51]. Thus, our model may overestimate the cost-effectiveness of strategies that use the same imaging modality for surveillance and diagnosis (which are prone to higher rates of false-positive diagnosis). Another limitation was that abbreviated MRI sensitivity and specificity were derived from retrospective simulations. Finally, concerns regarding radiation associated with CT were not modeled. Although it is acceptable to perform CT for diagnostic imaging, the cumulative radiation burden associated with a surveillance program may not be justifiable.

In conclusion, in a scenario that assumes optimal patient compliance and takes into account inconclusive imaging examinations, CT for HCC surveillance and diagnosis and complete MRI for inadequate CT was most cost-effective. However, in a scenario that assumes conservative patient compliance and

also takes into account inconclusive imaging examinations, abbreviated MRI may be a cost-effective alternative to the current US surveillance practice. Before implementing a surveillance program incorporating imaging modalities other than US, future studies should address the economic burden associated with false-positive HCC diagnoses. Also, future prospective trials should assess the accuracy of abbreviated MRI examinations in a surveillance setting.

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