Cost-Effectiveness Analysis of Hepatocellular Carcinoma Surveillance in Patients with Hepatitis C Related Cirrhosis after Sustained Virological Response

by

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Institute of Medical Science
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Abstract

Hepatitis-C virus related cirrhosis is associated with hepatocellular carcinoma (HCC). Antiviral therapy resulting in a sustained virological response (SVR) substantially decreases the risk for HCC. Surveillance for HCC in cirrhosis patients has been shown to be cost-effective; whether it remains so post-SVR is unknown. A Markov model was developed to evaluate the cost-effectiveness of biannual ultrasound surveillance versus no surveillance for HCC in post-SVR patients from the healthcare-payer perspective. Parameter values were obtained from the literature and expert opinion. Primary outcomes were quality-adjusted life-years (QALYs) and costs, both discounted at 5%, and the incremental cost-effectiveness ratio (ICER). Surveillance, with 0.5% annual HCC incidence, provided an additional 0.0705 QALYs leading to an ICER of $204,301/QALY. Sensitivity analyses identified HCC incidence and transition to symptomatic disease in the unscreened population as the main drivers of the analysis. With current estimates of HCC incidence post-SVR, ultrasound surveillance is unlikely to be cost-effective.
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List of Abbreviations

AFP: Alphafetoprotein
ALT: Alanine Aminotransferase
AASLD: American Association for the Study of Liver Diseases
BCLC: Barcelona Clinic Liver Cancer
BMI: Body Mass Index
CADTH: Canadian Agency for Drugs and Technologies in Health
CASL: Canadian Association for the Study of the Liver
CEA: Cost-Effectiveness Analysis
CE-US: Contrast-Enhanced Ultrasound
CHC: Chronic Hepatitis C
CIHI: Canadian Institute for Health Information
CLIP: Cancer of the Liver Italian Program
CPC: Child-Pugh Class
CPI: Consumer Price Index
CT: Computerised Tomography
DCP: Des-γ-Carboxy Prothrombin
DAA: Direct Acting Antiviral
EGF: Epidermal Growth Factor
EVR: Early Virological Response
ETR: End-of-Treatment Response
FGF: Fibroblast Growth Factor
HALT-C: Hepatitis C Antiviral Long Term Treatment Against Cirrhosis Trial
HBV: Hepatitis B Virus
HCA: Hepatocellular Adenoma
HCC: Hepatocellular Carcinoma
HCV: Hepatitis C Virus
HGF: Hepatocyte Growth Factor
HIV: Human Immunodeficiency Virus
IARC: International Agency for Research on Cancer
ICER: Incremental Cost-Effectiveness Ratio
IGF: Insulin-like Growth Factor
Chapter One: Introduction & Review of the Literature

1.1 Hepatitis C Virus Infection

1.1.1 Epidemiology

Hepatitis C virus (HCV) infection is a growing public health problem worldwide. (Pol, Vallet-Pichard, Corouge, & Mallet, 2012) Its prevalence has increased from about 2.3% (estimated 122 million infected cases) in 1990 to about 2.8% (estimated 185 million infected cases) in 2005. The mortality burden is up to 350,000 deaths per year. (Lavanchy, 2011; Sharma & Feld, 2014) It is noteworthy that most epidemiological data on HCV infection focus on chronic infection since the acute phase, being asymptomatic in many cases, is difficult to detect. (Maasoumy & Wedemeyer, 2012)

There are six recognized genotypes of HCV which differ in their geographic distributions. Genotype 1 is the most common globally, accounting for about 70% of HCV infections in the United States and 65% in Canada. (Myers, Shah, Burak, Cooper, & Feld, 2015) Genotype 3 is found in South Asia. Genotype 4 is the major type in the Middle East and Genotype 5 predominates in Central and South Africa. (Dienstag, 2012a; Pol et al., 2012) New HCV infection incidence varies in different geographical areas and is also affected by the prevalence of the infection in each area. The majority of infected individuals (nearly 70%) progress to chronic hepatitis C (CHC) following acute exposure to the virus. (Dienstag, 2012b; Sharma & Feld, 2014)

HCV transmission occurs through blood-to-blood contact. Globally, the most common route of HCV transmission remains unsterilized medical equipments; however, in wealthy countries, injection drug use is the most common mode of transmission. Central Asia and the Middle East have the highest reported prevalence of chronic HCV infection. (Sharma & Feld, 2014) Egypt has the highest prevalence globally where it is reported to be 6% to 9% in urban areas and up to 27% to 30% in rural parts of Nile delta where the infection has been traced to intramuscular or intravenous treatments for schistosomal infections under nonsterile conditions between 1920 and 1970. (Bosch, Ribes, Diaz, & Cleries, 2004; Dienstag, 2012a; Frank et al., 2000; Guadagnino et al., 1997; Sherman, 2010a) Although the prevalence is lower in Asia, due to the large population, South and East Asia are the home to the largest number of individuals with
HCV infection in the world (Mohd Hanafiah, Groeger, Flaxman, & Wiersma, 2013). Unlike other blood-borne infections, there is a low chance (nearly 5%) for HCV to be transmitted sexually or perinatally. Breast-feeding does not increase the chance of HCV transmission. Transmission to healthcare workers through accidental needle stick injury may also occur; however, the probability of infection with a single occurrence is low and poorly quantified (Pol et al., 2012).

Other at risk population groups for HCV infection are hemodialysis and hemophiliac patients and those who require organ transplantation as well as those who receive transfusions. Fortunately, introduction of third generation anti-HCV assays and automated PCR testing of donated blood for HCV RNA in blood banking practices have dramatically reduced the risk associated with transfusion of blood or blood products to one in a million. (Dienstag, 2012a; Pol et al., 2012; Selvarajah & Busch, 2012) While the risk is low in wealthy countries, improperly screened transfusions likely still account for a significant amount of HCV transmission globally. Finally, in some series, up to 30% of individuals with HCV infection have no identifiable risk factor. (Pol et al., 2012)

In Canada, modeling estimates from the Public Health Agency of Canada (PHAC) suggest that there are approximately 242,000 individuals (0.8% of the population) infected with HCV in Canada; however, well conducted seroepidemiological studies have not been performed and it is possible that the prevalence of HCV is considerably higher due to the under-sampling of high-risk populations. (PHAC, 2015; Shah, Heathcote, & Feld, 2013) There are substantial regional differences among provinces and territories in the prevalence of HCV in the country, from as low as 0.13% in Newfoundland up to 3.9% in the Yukon. (Myers, Ramji, Bilodeau, Wong, & Feld, 2012; Remis, 2007) HCV infection results in more lost-years-of-life in comparison to any other infectious diseases in Ontario and probably in Canada. (Kwong et al., 2012; Shah et al., 2013) Due to the largely asymptomatic nature of the infection, many infected individuals remain undiagnosed. PHAC estimates that 21% of Canadians with HCV remain undiagnosed, but most authorities suggest that the undiagnosed rate is considerably higher, likely above 50%, as has been reported in the US and Western Europe. (Remis, 2007)
Recent data from Canada and elsewhere suggest that though the prevalence of HCV infection may have already peaked due to the aging of the infected population, the burden of this infection in Canada is increasing. (Myers et al., 2014; Myers et al., 2012; Remis, 2007; Zou, Tepper, & El Saadany, 2000) As Myers et al. (Myers et al., 2015) have discussed, despite the decline in overall prevalence of CHC, modelling data suggest that by 2035, cases of hepatocellular carcinoma (HCC), decompensated cirrhosis and liver-related mortality will increase by 205%, 80% and 160% respectively when compared with the same levels in 2013. Figure 1.1-1 shows the above discussion schematically.

![Figure 1.1-1: Modelled incidence of hepatitis C-related sequelae in Canada (1950-2035) (Myers et al., 2015)](image)

As seen in this figure, though the prevalence of HCV infection may have already peaked due to the aging of the infected population, the burden of this infection in Canada is increasing and by 2035, cases of HCC, decompensated cirrhosis and liver-related mortality will increase by 205%, 80% and 160%, respectively when compared with the same levels in 2013.

### 1.1.2 Acute Hepatitis C

Acute HCV infection, by definition, is the initial six months after exposure; however, this phase may last longer in some individuals. (Orland, Wright, & Cooper, 2001; Sharma & Feld, 2014)
Viremia (detection of HCV RNA in plasma) is the first sign of HCV infection which may gradually increase up to detectable levels before a rapid increase and plateau level. This is followed by either spontaneous clearance of the virus in about 25% of individuals (Micallef, Kaldor, & Dore, 2006), or progression to chronic infection where HCV RNA titers will stabilize. (Sharma & Feld, 2014) Host and virus specific factors have been shown to influence the rate and time course of viral clearance. (Dienstag, 2012a; Sharma & Feld, 2014; Villano, Vlahov, Nelson, Cohn, & Thomas, 1999)

1.1.2.1 Clinical Manifestations
Some patients with acute HCV infection have nonspecific constitutional symptoms of the disease; however, most individuals are completely asymptomatic. The lack of symptoms in both the acute and chronic stages of the infection result in many individuals being diagnosed very late in the course of the disease and only after they develop symptoms of advanced liver disease, typically decades after acquiring the infection. (Maasoumy & Wedemeyer, 2012; Sharma & Feld, 2014) In the minority who become symptomatic after the incubation period, constitutional symptoms may be accompanied by jaundice, nausea, anorexia, dark urine, clay-colored stools, abdominal pain and fatigue, (Dienstag, 2012a; Maasoumy & Wedemeyer, 2012; Sharma & Feld, 2014) as well as enlarged and tender liver on clinical exam. (Dienstag, 2012a)

1.1.2.2 Outcome of Acute HCV Infection
Other than rare instances of reported acute liver failure and fulminant hepatitis (Dienstag, 2012a; Farci et al., 1996), acute HCV progresses to CHC in about 75% of adult cases in whom HCV is not spontaneously cleared. (Dienstag, 2012a; Maasoumy & Wedemeyer, 2012; Wiegand, Deterding, Cornberg, & Wedemeyer, 2008)

1.1.3 Chronic Hepatitis C
CHC is defined by the persistence of detectable levels of HCV RNA for at least six months after the initial exposure which led to viral transmission. (Maasoumy & Wedemeyer, 2012; Seeff & Hoofnagle, 2002) After establishment of CHC, spontaneous HCV clearance occurs extremely rarely, if ever. HCV causes continuous liver damage, with variable progression rates, resulting in inflammation and ultimately fibrosis and architectural reorganization of the hepatocytes which may ultimately progress to cirrhosis. Only once cirrhosis is established are infected
individuals at risk for complications of end-stage liver disease and for the development of HCC. (Dienstag, 2012b; Maasoumy & Wedemeyer, 2012)

1.1.3.1 Clinical Manifestations of Chronic Hepatitis C

Patients may complain of non-specific symptoms such as right-sided abdominal discomfort, nausea, fatigue, myalgia, arthralgia or weight loss. Jaundice and other signs of liver failure only occur once cirrhosis has developed. In addition, CHC may be associated with extra-hepatic manifestations such as essential mixed cryoglobulinemia. Symptoms relating to vasculitis such as skin rash, renal failure and neurological symptoms may develop, however many patients have mild or no specific symptoms even with detectable serum cryoglobulins. Other extra-hepatic manifestations include lichen planus, Mooren’s corneal ulcers and B cell lymphoma, all of which may be symptomatic. (Dienstag, 2012b; Maasoumy & Wedemeyer, 2012) Most infected individuals remain entirely asymptomatic until the ongoing liver damage is advanced enough to present with symptoms of decompensated cirrhosis or those of liver cancer. (Dienstag, 2012b; Shah et al., 2013; van der Meer et al., 2012)

1.1.3.2 Outcome of Chronic HCV Infection

1.1.3.2.1 Cirrhosis

In CHC and many other chronic liver diseases, chronic inflammation, liver cell injury and repair lead to the laying down of increased amounts of collagen resulting in progressive liver fibrosis. The formation of nodules of fibrotic tissue is referred to as cirrhosis. (D’Amico, Garcia-Tsao, & Pagliaro, 2006; H. Okuda, 2007) The presence of cirrhosis eventually results in complications of impaired hepatic synthetic function due to loss of functional hepatocyte mass, and portal hypertension due to impaired blood flow and increased pressure in the portal venous system (i.e., leading to decompensated liver disease). The rate of progression to cirrhosis in CHC is highly variable, depending on host, viral and environmental factors. Early follow-up studies suggest that about 20% of patients progress to cirrhosis after 20 years of infection, however many patients are infected for decades and therefore the lifetime risk of cirrhosis is considerably higher. Modeling studies suggest that 56% of CHC patients will develop cirrhosis at some point during their illness. (Maasoumy & Wedemeyer, 2012)

As the population of infected individuals ages, the prevalence of cirrhosis and its complications are predicted to rise. Davis et al estimated that among CHC patients in the United States, about
25% have cirrhosis and that this proportion will increase up to 45% by the year 2030. (Davis, Alter, El-Serag, Poynard, & Jennings, 2010). Thein and colleagues used meta-regression techniques to estimate the stage-specific rate of fibrosis progression in patients with CHC. They found that cirrhosis developed in 16% of the patients within 20 years of HCV infection but increased nearly three-fold (41%) after 30 years of HCV infection. (Thein, Yi, Dore, & Krahn, 2008) The progression rate of liver fibrosis in CHC, which is non-linear is influenced by several factors. (Thein et al., 2008) Age at the time of infection is one the most important risk factors with older age accelerating the annual progression rate of fibrosis.

Longer duration of infection is also associated with more progressive fibrosis. Concomitant hepatologic disorders, immunosuppression, HIV infection, male gender, alcohol consumption (>60 g/day) and obesity have also been identified as risk factors for progression of liver fibrosis. (Dienstag, 2012a, 2012b; Fattovich, Stroffolini, Zagni, & Donato, 2004; Freeman et al., 2001; Maasoumy & Wedemeyer, 2012) More recently, genotype 3 infection has been shown to lead to more rapidly progressive linear injury, however, the HCV RNA titre in the serum is not related to disease progression. Factors influencing fibrosis progression rate, as discussed by Maasoumy and colleagues are summarized in Figure 1.1-2. (Maasoumy & Wedemeyer, 2012)

Individuals often remain asymptomatic even in the presence of the so-called compensated cirrhosis and have a relatively favourable short to medium term prognosis. Continued injury to the liver will eventually lead to the decompensated cirrhosis, with the onset of symptoms from end-stage liver disease including ascites (fluid retention), haemorrhage from esophageal varices and hepatic encephalopathy. (D'Amico et al., 2006) The conversion from the compensated to decompensated stage occurs at an annual rate of about 5% to 7% and appearance of ascites is frequently the first sign of this transition. (D'Amico et al., 2006) Patients with CHC-related compensated cirrhosis have a 10-year survival rate of about 80% and an annual mortality rate of 2% to 6%.

The onset of the decompensation has important prognostic significance, with a median 2-year survival after the first decompensating event. (D'Amico et al., 2006; Dienstag, 2012a, 2012b) Prognostic scores have been developed to predict short term outcomes in patients with cirrhosis. The Child-Pugh score uses objective measures of liver function (albumin, bilirubin, prothrombin
time) as well as the presence of ascites and hepatic encephalopathy, while the Model for End-stage Liver Disease (MELD) score uses only the bilirubin, INR and creatinine. Both have been well validated in multiple clinical studies and the MELD score has been used to allocate organs for liver transplantation. (D'Amico et al., 2006)

1.1.3.2.2 Hepatocellular Carcinoma

Until cirrhosis develops, CHC has few health consequences in most individuals. HCC is very rare in patients without cirrhosis. However, with the onset of cirrhosis, patients are at risk for the development of HCC. This occurs in 1.4% to 4.9% annually. (Dienstag, 2012a, 2012b; Fattovich, Giustina, Degos, Diodati, et al., 1997; Lok et al., 2009; Maasoumy & Wedemeyer, 2012; Sangiovanni et al., 2006) The emerging worldwide incidence of HCC is influenced by the global prevalence of HCV so that CHC is responsible for about 25% of the overall HCC cases in the world. (Maasoumy & Wedemeyer, 2012; Y. Tanaka et al., 2006) It is important to note that

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**Figure 1.1-2: Factors influencing the progression to liver fibrosis in CHC**
(Maasoumy & Wedemeyer, 2012)-Permission has been granted.

This figure summarizes the factors influencing fibrosis progression rate. As shown, high alcohol intake, co-infection, e.g. with HBV or HIV, insulin resistance and age over 40 years are strongly associated with higher rate of fibrosis whereas the opposite is true for coffee intake, female gender and age under 30 years.

1.1.3.2.2 Hepatocellular Carcinoma

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HCC may be the first clinical complication of cirrhosis related to HCV infection, even before decompensated disease occurs (see below on Epidemiology, Natural History and Treatment of HCC). (Sangiovanni et al., 2006)

1.1.4 Treatment of CHC

1.1.4.1 Objectives
The goal of treatment for HCV infection is complete eradication of the virus. Unlike other chronic viral infections, HCV is curable. (Shah et al., 2013; van der Meer et al., 2012) Viral eradication is referred to as sustained virological response (SVR) which is defined as the undetectable serum HCV RNA, measured by a sensitive polymerase chain reaction (PCR) assay, at least 12 weeks following the end of the antiviral treatment. (Feld, 2012; Myers et al., 2015) Long-term follow-up data have shown that SVR is a durable endpoint with a less than 1% chance of late relapse. The term SVR is used rather than cure because although SVR is a virological cure, for those with established cirrhosis prior to successful therapy, liver damage remains. Although SVR prevents further progression of liver injury, HCC has been detected even years later, in patients with liver cirrhosis prior to viral clearance. (Dienstag, 2012b; Ghany, Strader, Thomas, Seeff, & American Association for the Study of Liver, 2009; Kobayashi et al., 2007; Maylin et al., 2008; Myers et al., 2012; Pearlman & Traub, 2011; Swain et al., 2010)

1.1.4.2 Antiviral Drugs
Treatment of HCV infection has evolved considerably since interferon alpha was approved for CHC treatment in 1991. The improvements continued with combination therapy with interferon and ribavirin (RBV) and the use of long-acting pegylated interferon (PEG-INF). Pegylated interferon offers better pharmacokinetics and pharmacodynamics with more stable and sustained drug concentrations over time. (Di Bisceglie & Hoofnagle, 2002; Dienstag, 2012b; Heathcote, 2004) Rates of SVR with interferon-based therapy were about 40% to 50% in genotype 1 patients whereas the rate was nearly 80% in those with genotypes 2 and 3. (Dienstag, 2012b; Myers et al., 2012; Sherman et al., 2007) However, interferon causes several adverse effects in patients including influenza-like symptoms, psychiatric side effects such as depression and mood disorders and laboratory abnormalities like bone marrow suppression, which compounds the hemolytic anemia associated with ribavirin. (Feld, 2012; Myers et al., 2012)
Until recently, combination of PEG-INF and RBV was the standard treatment but SVR rates were sub-optimal and treatment was difficult, leading to very low treatment uptake. (Myers et al., 2012) Through advances in the understanding of the viral lifecycle, direct acting antiviral agents (DAAs) which target multiple steps in the HCV replication cycle have been developed. Agents targeting the NS3/4a protease, the NS5B RNA-dependent-RNA polymerase and the non-structural 5A protein (NS5A) have been developed.

These recent improvements have quickly changed the landscape of HCV antiviral treatment. Initially, DAAs were combined with INF and RBV, (Myers et al., 2012) but more recently, interferon-free regimens combining different DAA combinations have been approved. These therapies are well-tolerated (Shah et al., 2013; Stedman, 2013) and lead to SVR rates of over 90% across all genotypes, with excellent rates of SVR reported even in those with cirrhosis prior to starting therapy. (Colombo et al., 2014; Hezode et al., 2013; Poordad et al., 2014; van der Meer, 2015) Multiple interferon-free DAA combination regimens have now been approved with well-tolerated, easy to administer oral therapies with SVR rates above 90% across the different HCV genotypes. (Afdhal et al., 2014) Remarkably, even patients with decompensated cirrhosis tolerate therapies well and SVR rates above 80% have been reported in these very advanced patients. As DAA therapies become more broadly applied, increasing numbers of patients with cirrhosis will achieve SVR. (Dore & Feld, 2015; Myers et al., 2015)

1.1.5 Favourable Effects of SVR

Antiviral treatment regimens are developing and SVR is achievable more easily than before; therefore, it becomes more and more important to evaluate the impact that SVR can have on long-term patients outcomes. (Ng & Saab, 2011) Viral clearance interrupts the inflammation and necrosis reducing new fibrosis and even reversing established fibrosis. (Di Bisceglie & Hoofnagle, 2002; Heathcote, 2004) Successful treatment of CHC resulting in SVR improves survival and lowers the risk of liver failure, HCC development and liver-related deaths, and in some cases, reverses the fibrosis (Braks et al., 2007; Maruoka et al., 2012; Shiratori et al., 2005; van der Meer, 2015; Veldt et al., 2004; Velosa, Serejo, Marinho, Nunes, & Gloria, 2011; Yu et al., 2006) enough to suggest reversal of cirrhosis. (Bruix, Sherman, & American Association for the Study of Liver, 2011; Dienstag, 2012b; Ueno, Sollano, & Farrell, 2009) Veldt and colleagues demonstrated that SVR was associated with decreased liver-related mortality and also reduced development of liver failure in a large cohort of CHC patients with advanced liver
fibrosis. (Veldt et al., 2007) In a subsequent follow-up study of the same cohort, van der Meer and colleagues (van der Meer et al., 2012) reported that SVR resulted in an approximately 3-fold decrease in all-cause mortality when compared to those who were treated but did not achieve SVR. Moreover, SVR largely prevented the risk of liver failure related to cirrhosis and reduced but did not eliminate the risk of HCC. As they have shown, SVR was associated with a reduced 10-year cumulative risk of all-cause mortality from 26% in those without SVR, down to 8.9%; it also reduced the 10-year cumulative risk of HCC development from 21.8% with no SVR down to 5.1% in those who achieved SVR; similarly the risk was reduced for liver failure from 29.9% to 2.1% and liver-related mortality (death due to liver failure, primary liver malignancy or variceal bleeding as the investigators defined) or liver transplant from 27.4% down to 1.9% respectively in patients without SVR and those with SVR. (van der Meer et al., 2012)

In another recent study, Berenguer and colleagues (Berenguer et al., 2012) showed that SVR is associated not only with reduced liver-related mortality, but also with a reduced mortality rate due to non-liver related etiologies. (Berenguer et al., 2012; van der Meer, 2015) Veldt and colleagues in another study showed that the 5-year survival of patients who achieved SVR with mild fibrosis was similar to the general population when they were matched for age and sex. (Veldt et al., 2004) In a published review, Kwon and colleagues (Kwon & Lok, 2011) similarly found that patients with SVR had a lower incidence of HCC development compared to those who have not achieved SVR. In another review, Ng and colleagues (Ng & Saab, 2011) demonstrated the same favourable effects in patients treated for CHC who achieved SVR, including reduced liver-related mortality, incidence of HCC and also hepatic decompensation. Figure 1.1-3 summarises the favourable effects of SVR. Table 1.1-1 summarises some of the studies comparing HCC incidence in sustained virological responders and non-responders used in the review performed by Ng and colleagues. (Ng & Saab, 2011) The HALT-C study also reported that the adjusted cumulative incidence of HCC after 7.5 years from beginning of the study in patients with HCV-related advanced fibrosis or cirrhosis was 1.1%, 5.5% and 8.8% among those with SVR, relapse or breakthrough and those without SVR, respectively. (T. R. Morgan et al., 2010) Collectively, there is now a large body of evidence supporting the conclusion that SVR reduces the risk of HCC. Several published meta-analyses (Camma, Giunta, Andreone, & Craxi, 2001; Miyake, Iwasaki, & Yamamoto, 2010; Papatheodoridis,
Papadimitropoulos, & Hadziyannis, 2001; A. G. Singal, Volk, Jensen, Di Bisceglie, & Schoenfeld, 2010; A. K. Singal et al., 2010) on this subject have shown that SVR decreases the incidence of HCC and liver-related mortality and morbidity in patients with HCV-related cirrhosis. SVR has also been shown to be associated with improvements in health-related quality of life in patients with both early and advanced cirrhosis. (van der Meer et al., 2014) In the long run, these data show that there is solid evidence for the effect of SVR on altering the natural history of the disease. (Pereira & Feld, 2013)

Figure 1.1-3: Survival outcomes in CHC patients with advanced hepatic fibrosis ± SVR. (van der Meer et al., 2012)-Permission has been granted. "Copyright © 2012 American Medical Association. All rights reserved."

As is evident from the graphs above, SVR was associated with a reduced 10-year cumulative risk of all-cause mortality from 26% in those without SVR, down to 8.9%; it also reduced the 10-year cumulative risk of HCC development from 21.8% with no SVR down to 5.1% in those who achieved SVR; similarly the risk was reduced for liver failure from 29.9% to 2.1% and liver-related mortality or liver transplant from 27.4% down to 1.9%, respectively in patients without SVR and those with SVR.
Notably, all studies have shown that in patients with cirrhosis prior to treatment, even achievement of SVR does not eliminate the risk of future HCC. As such, current guidelines recommend continued surveillance for HCC in patients who achieve SVR after the development of cirrhosis. (Aleman et al., 2013; Bruix et al., 2011; Dienstag, 2012b; George et al., 2009; Hirakawa et al., 2008; Kwon & Lok, 2011; T. R. Morgan et al., 2010) Whether surveillance in this group is cost-effective or not remains to be determined, (Kwon & Lok, 2011) which is the topic of this thesis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year/Country/Patient #</th>
<th>Antiviral Agent</th>
<th>Mean Follow-Up (Yr)</th>
<th>SVR (%)</th>
<th>SVR group</th>
<th>HCC Occurrence (SVR group)</th>
<th>Non-SVR group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arase et al (Arase et al., 2007)</td>
<td>2007/Japan/500</td>
<td>469 IFN; 31 IFN/RBV</td>
<td>7.4</td>
<td>140/500 (28%)</td>
<td>13/140 (9.3%)</td>
<td>58/360 (16.1%)</td>
<td></td>
</tr>
<tr>
<td>Coverdale et al (Coverdale et al., 2004)</td>
<td>2004/Australia/343</td>
<td>IFN</td>
<td>6.81</td>
<td>50/343 (14.6%)</td>
<td>1/50 (2%)</td>
<td>23/293 (7.8%)</td>
<td></td>
</tr>
<tr>
<td>Tanaka et al (Tanaka et al., 2000)</td>
<td>2000/Japan/594</td>
<td>IFN</td>
<td>4.8</td>
<td>175/594 (29.5%)</td>
<td>3/175 (1.7%)</td>
<td>30/419 (7.2%)</td>
<td></td>
</tr>
<tr>
<td>Kobayashi et al (Kobayashi et al., 2007)</td>
<td>2007/Japan/1,124</td>
<td>1039 IFN; 85 IFN/RBV</td>
<td>5.5</td>
<td>373/1124 (33.2%)</td>
<td>13/373 (3.5%)</td>
<td>61/751 (8.1%)</td>
<td></td>
</tr>
<tr>
<td>Hung et al (Hung et al., 2006)</td>
<td>2006/Taiwan/132</td>
<td>IFN/RBV</td>
<td>3.1</td>
<td>73/132 (55%)</td>
<td>5/73 (6.8%)</td>
<td>11/59 (18.6%)</td>
<td></td>
</tr>
<tr>
<td>Bruno et al (Bruno et al., 2007)</td>
<td>2007/Italy/920</td>
<td>IFN</td>
<td>8</td>
<td>124/920 (13.5%)</td>
<td>7/124 (5.6%)</td>
<td>122/759 (16.1%)</td>
<td></td>
</tr>
<tr>
<td>Hirakawa et al (Hirakawa et al., 2008)</td>
<td>2008/Japan/1,193</td>
<td>1032 IFN; 161 IFN/RBV</td>
<td>8.3</td>
<td>1193/1193 (100%)</td>
<td>9/1193 (0.75%)</td>
<td>/-</td>
<td></td>
</tr>
<tr>
<td>Mallet et al (Mallet et al., 2008)</td>
<td>2008/France/96</td>
<td>61 IFN; 34 IFN/RBV; 1 PEG-IFN/RBV</td>
<td>9.8</td>
<td>39/96 (40.6%)</td>
<td>3/39 (8.6%)</td>
<td>14/57 (24.6%)</td>
<td></td>
</tr>
<tr>
<td>Cardoso et al (Cardoso et al., 2010)</td>
<td>2010/France/307</td>
<td>33 IFN±RBV; 22 PEG-IFN; 252 PEG-IFN/RBV</td>
<td>3.5</td>
<td>103/307 (33%)</td>
<td>6/103 (5.8%)</td>
<td>40/204 (19.6%)</td>
<td></td>
</tr>
</tbody>
</table>

IFN: Interferon; PEG-IFN: Pegylated Interferon; RBV: Ribavirin
Permission has been granted.

This table summarizes some of the studies comparing HCC incidence in sustained virological responders and non-responders. In each study, the treatment used, mean follow-up period and response rate for sustained virological response and finally, the occurrence of HCC in each group are compared.
1.2 Hepatocellular Carcinoma

1.2.1 Epidemiology

Hepatocellular carcinoma (HCC), as the most frequent primary liver malignancy, is one of the most common malignancies in the world. (Carr, 2012) It is the fifth most common cancer worldwide (5.6% of all human cancers) and the third most common cause of cancer death. (Bosch et al., 2004; GLOBOCAN) HCC usually occurs in the context of chronic liver diseases with associated cirrhosis. There are over half a million new cases diagnosed annually in the world and approximately the same number die from the disease, showing the dismal prognosis of this cancer. (GLOBOCAN; Mittal & El-Serag, 2013; Nordenstedt, White, & El-Serag, 2010) Death from HCC, in some regions, is only just behind the mortality from lung cancer. (Bosch et al., 2004; Paradis, 2013; Sherman, 2010b) HCC incidence is higher in males than in females worldwide with a male to female ratio of approximately 4:1. (Bosch et al., 2004; Carr, 2012; Nordenstedt et al., 2010; Sherman, 2010b)

As the most serious complication of cirrhosis, HCC incidence shows a growing worldwide trend mainly due to increased prevalence of various risk factors important in chronic liver diseases, such as infection with hepatitis B virus (HBV) and HCV. Moreover, fatty liver diseases associated with metabolic syndrome are playing a notable role and are gaining importance due to the increase in the prevalence of obesity and the metabolic syndrome in the world. (El-Serag, 2007; Nordenstedt et al., 2010; Paradis, 2013)

Nonetheless, trends in the incidence of HCC are clearly related to a cohort effect. As the cohort of HCV-infected people who were infected between World War-II and the 1970s in Europe as well as those infected during 1960s and 1970s in North America grow older, the incidence of HCV-related-HCC increases. (Sherman, 2010a, 2010b; Umemura, Ichijo, Yoshizawa, Tanaka, & Kiyosawa, 2009) These two decades were a time when intravenous drug use, needle sharing, transfusion of unscreened blood and blood products and unsafe sexual practices were more common, all increasing the risk of HCV transmission. Altogether, the incidence rate of HCC has doubled in the United States, mainly due to CHC; however, hepatitis B has also contributed to this increase. (El-Serag & Mason, 1999; Sherman, 2010b) The rate of HCC is also influenced by migration as immigration to Europe and North America from areas where hepatitis B and C are endemic has contributed to HCC incidence in these areas. However, the children of immigrants
have a lower incidence of HCC in comparison to their parents which suggests that despite genetic factors, environmental factors are also important. (King & Locke, 1980; McCredie, Williams, & Coates, 1999; Rosenblatt, Weiss, & Schwartz, 1996; Sherman, 2010a, 2010b)

The incidence of HCC shows considerable geographic variation which correlates well with the prevalence of the major etiologic factors, particularly chronic viral hepatitis. (El-Serag, 2012; Sherman, 2010a) For example, in South East Asia, the most common underlying cause is HBV infection whereas in Japan and also in Southern Europe, the culprit is CHC. Overall, the highest incidence of HCC is seen in Asia where it accounts for about 76% of all cases in the world. (Bosch et al., 2004; Sherman, 2010b) It is important to recognize that the incidence of HBV-related HCC is likely to remain steady in the United States, whereas that of HCV-related cirrhosis and HCC has been progressively increasing; this trend is expected to continue for a few several decades. (El-Serag, 2012) The rapid improvement in HCV therapies may potentially alter these trends by increasing SVR rates and thus decreasing progression to cirrhosis as well as HCC in those with established cirrhosis.

1.2.2 Risk Factors for HCC

1.2.2.1 Hepatitis B and Hepatitis C Viruses

The most common risk factors for HCC are infection with HBV and HCV. (Bosch et al., 2004; Sherman, 2010b) Altogether, 75% to 80% of primary liver malignancies are the result of persistent viral infections with HBV (50%-55%) or HCV (25%-30%). Cirrhosis is promoted by these infections with the progression rate also influenced by the etiology of cirrhosis, geographical distribution (like the high incidence of HCC in Japan as a result of HCV epidemic 20-30 years ahead of 1960s to 1970s of North America), ethnicity (higher in Africans) and also stage of fibrosis. (El-Serag, 2012; Fattovich et al., 2004; Nordenstedt et al., 2010) The risk of tumor development is highest among HCV infected patients with cirrhosis, reaching a rate of 1% to 4% per year, though rates as high as 8% are also reported in some areas such as Japan. (Beasley, Hwang, Lin, & Chien, 1981; El-Serag, 2012; Fattovich, Giustina, Degos, Tremolada, et al., 1997; Mittal & El-Serag, 2013; Sherman, 2010c)

As cirrhosis and the related hepatic structural changes progress, the risk of HCC development also increases. (Paradis, 2013) HCC has also been reported in HCV patients without cirrhosis,
but only in those with intermediate to advanced hepatic fibrosis as was also shown in the Hepatitis C Antiviral Long Term Treatment Against Cirrhosis (HALT-C) trial where 8% of patients with advanced fibrosis but without liver cirrhosis, developed HCC. (Lok et al., 2011; Mittal & El-Serag, 2013) However, the liver structure is hardly ever normal in these cases and may show signs of regressed cirrhosis. (Bosetti et al., 2008; Colombo et al., 1991; Paradis, 2013; Sherman, 2010b) HBV and HCV co-infection also increases the risk of HCC development in comparison to mono-infection status. (Goedert, 2005; Sherman, 2010b)

1.2.2.2 Demographic and Lifestyle Factors

Men are at increased risk for HCC development even after adjusting for confounders like viral hepatitis and alcohol consumption. (El-Serag, 2012; Yuan et al., 1995) Among those who are infected with HCV or HBV, only a small percentage will develop HCC. This suggests that host genetics may be among significant influential factors in the development of HCC. (Guo, Wei, & Shen, 2010; Mittal & El-Serag, 2013; Sherman, 2010c)

Chronic heavy alcohol use (>60gr/day) is a co-factor in the process of liver fibrosis and progression towards cirrhosis, which increases the risk for HCC development. Simultaneous HCV infection increases this risk by 2-fold and it is even more increased if there is co-infection with human immunodeficiency virus (HIV). (Benhamou et al., 1999; Donato et al., 2002; Heathcote, 2004; Trichopoulos et al., 2011) Tobacco consumption also influences the risk for HCC development and the International Agency for Research on Cancer (IARC) has included HCC among those cancers which are causally associated with tobacco smoking. (Trichopoulos et al., 2011)

1.2.2.3 Emerging and Miscellaneous Factors

Diabetes mellitus, obesity (especially in the presence of HCV infection) (Calle, Rodriguez, Walker-Thurmond, & Thun, 2003; Nordenstedt et al., 2010) and insulin resistance syndrome are gaining attention regarding their association with primary liver cancer. (Bosch et al., 2004; Carr, 2012; El-Serag, 2012; El-Serag, Tran, & Everhart, 2004; Llagiou et al., 2000; Sherman, 2010c) Non-alcoholic fatty liver disease (NAFLD) also increases the risk for HCC development, though this influence is limited to patients with cirrhosis. (Mittal & El-Serag, 2013; Sherman, 2010c, 2011) Other risk factors for HCC include co-infection with HIV, increasing age, (Fattovich et al., 1991; Mittal & El-Serag, 2013; Sherman, 2010a) and dietary aflatoxin exposure. (El-Serag,
The association between increasing coffee consumption and low liver enzymes, reduced risk of cirrhosis and reduced risk of HCC has been shown in several epidemiological studies. High levels of caffeine consumption were associated with lower stages of fibrosis in patients with CHC. (El-Serag, 2012; Mittal & El-Serag, 2013; Modi et al., 2010) This HCC development risk reduction has also been shown in studies evaluating coffee drinkers in Europe and Japan highlighting that the relative risk of HCC among heavy coffee drinkers (defines as ≥3 cups/day) was 0.45 (95% CI 0.38-0.53) as compared to those who do not drink coffee. Even low or moderate coffee consumption (1-2 cups a day) was associated with a reduced risk of HCC with a relative risk of 0.70 (95% CI 0.57-0.85). (Bravi et al., 2007; Mittal & El-Serag, 2013) It is still unclear how coffee exerts this possible protective effect, but one theory is related to effects on insulin levels and reduction in the risk for diabetes mellitus which itself is a known risk factor for HCC development. (El-Serag, 2012; Huxley et al., 2009; Mittal & El-Serag, 2013; Veldt et al., 2008; S. H. Yeh & Chen, 2010)

**Table 1.2-1: Risk Factors for Hepatocellular Carcinoma**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic / Lifestyle Factors</strong></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Higher with increasing age</td>
</tr>
<tr>
<td>Sex</td>
<td>Higher in males</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Higher in Blacks</td>
</tr>
<tr>
<td>Tobacco (current or previous consumption)</td>
<td>Current or previous use</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Heavy &amp; long-term use</td>
</tr>
<tr>
<td>Obesity</td>
<td>Especially with HCV infection</td>
</tr>
<tr>
<td><strong>Co-Morbidities</strong></td>
<td></td>
</tr>
<tr>
<td>Chronic Liver Disease</td>
<td>-</td>
</tr>
<tr>
<td>Chronic HBV infection</td>
<td>Higher in co-infection with HIV</td>
</tr>
<tr>
<td>Chronic HCV infection</td>
<td>Higher in co-infection with HIV</td>
</tr>
<tr>
<td>NAFLD and alcoholic liver disease</td>
<td>In the presence of liver cirrhosis</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>-</td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td></td>
</tr>
<tr>
<td>Aflatoxin</td>
<td>Dietary exposure</td>
</tr>
<tr>
<td>Estrogens &amp; Progestogens</td>
<td>e.g. in Oral Contraceptive Pills</td>
</tr>
</tbody>
</table>

HIV: Human Immunodeficiency Virus; NAFLD: Non-Alcoholic Fatty Liver Disease

The table above summarizes the risk factors for HCC as further discussed in the text. Older males with black ethnicity who drink alcohol heavily and are overweight and at the same time have co-morbidities/co-infections are at higher risk for HCC development.
1.2.3 Pathophysiology and Pathogenesis

Most HCCs develop in the context of chronic liver disease as one of its main complications, but some may occur even in normal liver. (Craig, Peters, Edmondson, & Omata, 1980; Paradis, 2013) HCV increases the risk of HCC formation through inducing hepatic inflammation and more importantly, fibrosis; it also promotes malignant transformation of those cells infected by the virus. (Lemon & McGivern, 2012; Mittal & El-Serag, 2013)

1.2.3.1 Molecular Pathways of Pathogenesis

A phase-III randomized controlled trial study (SHARP) by Llovet and colleagues (Llovet, Ricci, et al., 2008) in 2008 showed that sorafenib, an inhibitor of tyrosine kinases, increased survival in patients who had advanced HCC. This study, through provision of evidence about the effectiveness of molecular targeted therapies in HCC, underlined the significance of understanding the molecular mechanisms in the pathogenesis of this tumor. (Sia & Villanueva, 2011)

Multiple signaling pathways have been shown to be altered in HCC. (Sia & Villanueva, 2011) The hepatocarcinogenesis is closely linked to the progression of cirrhosis. There are multiple molecular mechanisms responsible for the elevated risk for HCC in this stage. The cell-intrinsic and cell-extrinsic modifications lead to the activation of the cell cycle and apoptosis checkpoints and also chromosomal instability through telomere dysfunction. Changes in the microenvironment (factors inside the liver) and macroenvironment (systemic acting factors created due to functional impairment of a cirrhotic liver) may in turn stimulate proliferation of hepatocytes and ultimately selection of genetically altered premalignant and malignant cell clones. (El-Serag & Rudolph, 2007)

1.2.4 Clinical Manifestations

1.2.4.1 Signs and Symptoms of HCC

If active surveillance procedures diagnose an HCC early in its course, aside from the symptoms related to the underlying chronic liver disease, patients are generally asymptomatic. (Yang & Roberts, 2010) Eventually, with continued growth, HCC will become symptomatic, generally when it leads to signs and symptoms of liver failure. There may be some non-specific complaints including right upper abdominal or epigastric pain or even pleuritic chest pain due to subcapsular masses, early satiety, malaise, and also weight loss. (Sherman, 2014; Tinkle &
Haas-Kogan, 2012) Although quite uncommon in HCC patients, acute onset of severe abdominal pain and distension, hypotension and an abrupt decrease in hematocrit as a consequence of tumor rupture and intraperitoneal bleeding, may also be the presenting features. (Rossetto et al., 2010; Tinkle & Haas-Kogan, 2012; Yang & Roberts, 2010)

Physical examination often shows hepatomegaly as the most common sign in symptomatic patients. Furthermore, signs of cirrhosis with portal hypertension such as jaundice, gynecomastia, spider angiomas, ascites and palmar erythema may be present. Portal hypertension may also lead to splenomegaly. Hepatocellular carcinoma has a vascular nature, therefore, a bruit may be heard over the affected liver. (Carr, 2012)

Other presentations include fever of unknown origin and hyperviscosity syndrome due to paraneoplastic syndromes leading to erythropoiesis. In patients with compensated cirrhosis, clinical suspicion for HCC should be raised by the onset of ascites, jaundice, encephalopathy or variceal bleeding as HCC may impair liver function through replacement of functioning liver tissue or invading the portal vein leading to rapid increase in portal pressure and possible deterioration of liver function. (Carr, 2012; Yang & Roberts, 2010)

1.2.4.2 Paraneoplastic Syndromes and Metastasis

There are some paraneoplastic syndromes associated with HCC which are mainly biochemical abnormalities without clinical outcomes. These are uncommon, but may lead to hypoglycemia, hypercholesterolemia, hypercalcemia, erythrocytosis, increased thyroxin-binding globulin, watery diarrhea, changes in secondary sex characteristics (such as gynecomastia, precocious puberty and testicular atrophy), and also cutaneous manifestations. (Carr, 2012; Kassianides & Kew, 1987; Tinkle & Haas-Kogan, 2012; Yang & Roberts, 2010) Metastasis from HCC, though not a very common entity, usually targets lungs, adrenal glands, regional lymph nodes and bone. Although bone metastasis is reported in about 20% of patient necropsies, it causes bone pain only rarely in about 3% to 12% of patients. (Carr, 2012; Katyal et al., 2000; Tinkle & Haas-Kogan, 2012)
1.2.5 Diagnosis of HCC

1.2.5.1 History Taking and Physical / Laboratory Examination

As an important step in evaluating any medical complaint, history taking is of utmost importance since it can elucidate critical information about predisposing factors such as hepatitis or jaundice, any instances of blood transfusion or intravenous drug use. This thorough history may establish risk factors and/or signs and symptoms of chronic liver disease which may raise the suspicion of HCC. These will prompt for implementation of diagnostic procedures such as imaging, laboratory tests and/or histology as explained below. General performance and psychological evaluation may also provide some clues to the nature of the complaint. (Carr, 2012) Obviously, history taking should be followed by physical examination to look for signs and symptoms of the underlying disease and to assess the liver for any masses, nodularity and tenderness as well as splenomegaly. (Carr, 2012)

1.2.5.2 Diagnostic Tests

Generally, the tests used in HCC diagnosis are radiologic or liver biopsy and the choice between them is highly dependent on the clinical context. Guidelines such as the diagnostic algorithm in the American Association for the Study of Liver Diseases (AASLD) guidelines recommend a series of diagnostic tests based on the size, location and imaging characteristics of the tumor. (Bruix et al., 2011) No matter which diagnostic test is used, a dynamic imaging technique such as CT scan or an MRI would be required to evaluate the extent of the disease and blood flow characteristics. (Sherman, 2010b) HCC may also be diagnosed incidentally in patients who have abdominal imaging performed for other reasons.

1.2.5.2.1 Radiology

Anatomically, the liver has both arterial and portal venous blood supply whereas HCC receives only arterial supply. This allows better characterization using dynamic contrast-enhanced studies such as CT scan, MRI or contrast enhanced ultrasound. During the arterial phase of the intervention, contrast accumulates in the arterially supplied tumor but is not visible in the rest of the liver, which receives the majority of its blood supply from the portal vein. On the other hand, during the venous phase, the contrast material enters the portal circulation and now the portal venous blood which carries the contrast enters the liver parenchyma. On the contrary, the tumor is now receiving the arterial blood which does not contain the contrast material; therefore, the liver tissue appears brighter than the tumor and this creates the so-called washout of contrast
material, an appearance which is highly specific for HCC diagnosis. (Bruix et al., 2011; Iannaccone et al., 2005; Nicolau et al., 2006; Sherman, 2010b) These radiologic features (arterial hypervascularity and venous washout) are quite specific for HCC such that only a single radiologic study showing these typical characteristics is necessary for diagnosis and liver biopsy is reserved only for instances where radiologic appearances are not typical such as early HCC cases.

Recently, it has been shown that sequential imaging can decrease the need to perform biopsy for diagnosis. Sequential studies have enhanced the sensitivity of imaging studies to about 74% to 89%, though the specificity drops from 100% to 97% when they are compared to the situation where two typical studies are required. (Khalili et al., 2011; Sangiovanni et al., 2010; Sherman, 2010b) Magnetic Resonance Imaging, especially with the aid of newer contrast agents, can provide detailed information in this context. (Carr, 2012) Furthermore, CT scan also can take benefit from contrast agents such as Ethiodol® (Lipiodol®), which is an ethiozided oil emulsion of iodine and ethyl esters of fatty acids and is retained by liver tumors. Moreover, the changes in the tumor vascularity which are consequences of molecularly targeted therapies have paved the road for newer imaging techniques including contrast-enhanced ultrasound and dynamic MRI. (Carr, 2012)

In the context of liver cirrhosis, early recognition of HCC seems somewhat challenging with ultrasound examination. Although different characteristics involved in hepatocarcinogenesis such as low and high grade dysplastic nodules may share similar features, (R. Lencioni, Piscaglia, & Bolondi, 2008) ultrasound is an acceptable screening tool with a specificity of about 97% and sensitivity of about 60%. (Colli et al., 2006) This will be further elaborated in the later section on surveillance methods. Contrast-enhanced ultrasound (CE-US) is a fairly new technique which uses stabilized microbubbles containing air or other gases as contrast agent. CE-US provides the possibility of reliable detection of the arterial neoangiogenesis which is linked to malignant transformation. However, though a safe technique with a very low incidence of major side effects (estimated to be 0.0086%), studies to date have not shown that CE-US increases the sensitivity of ultrasound to detect small HCC nodules. Moreover, CE-US may provide false positive HCC detection in the context of cholangiocarcinoma. Therefore, at present there is no indication to use CE-US in surveillance for HCC in hope of increasing the
tumor detection rate. (Albrecht et al., 2004; Bruix et al., 2011; R. Lencioni et al., 2008; Piscaglia & Bolondi, 2006)

1.2.5.2.2 Biomarkers

Alphafetoprotein (AFP) has been used for diagnosis of HCC for a long time. (Bruix et al., 2011; Carr, 2012) However, AFP is not sufficiently sensitive or specific to be used in surveillance for HCC and has been removed from the most recent AASLD guidelines. Moreover, recent studies have called its use even as a diagnostic assay into question since it seems less specific for this purpose than was once thought. AFP can increase in some instances other than HCC, particularly in patients with active hepatitis. Hepatic inflammation will raise AFP levels in the absence of a tumor and therefore patients with active HCV or HBV infection often have repeated investigations to follow rising or fluctuating AFP levels driven by inflammation rather than a tumor. In addition, small tumors often make little or no AFP and therefore it is unlikely to identify tumors in a curable stage beyond what can be done with imaging technology. (Adachi et al., 2003; Bruix et al., 2011; Y. Sato, Sekine, & Ohwada, 1994)

Other biomarker assays such as des-γ-carboxy prothrombin (DCP) and glypican-3, are in development in combination but it is not clear that they will be adequately sensitive or specific for this purpose. (Carr, 2012) Based on the challenges with AFP, current guidelines recommend that the diagnosis of HCC rely on radiological features and on pathologic evaluation. (Bruix et al., 2011)

1.2.5.2.3 Molecular Markers of HCC Risk

So far, there are no definite molecular markers recognized for HCC risk. Nevertheless, some microarray studies have discovered genes that are differently expressed in dysplastic nodules versus early HCC, though it is not clear whether this information is clearly associated with altered risk of HCC. (Lee et al., 2004; Llovet et al., 2006; Paradis, 2013; Sherman, 2010c) Notably, in some other microarray studies, a panel of genes have been detected in the normal liver surrounding HCC which predict the development of late recurrence of HCC beyond two years after resection. This suggests that RNA analysis of liver biopsy material may distinguish those patients prone to late recurrence of the tumor and therefore makes them candidates for liver transplantation rather than tumor resection. (Carr, 2012; Sherman, 2008, 2010c)
1.2.5.2.4 Liver Biopsy and Pathologic Diagnosis

Pathological diagnosis of HCC requires both macroscopic and microscopic information. (Paradis, 2013)

1.2.5.2.4.1 Gross Macroscopic features of Hepatocellular Carcinoma

These nodules can be single or multiple and their size can range from less than 1cm in diameter to over 30cm. They are characteristically soft masses with heterogeneous macroscopic appearance, polychromic with foci of necrosis or hemorrhage. (K. Okuda, Peters, & Simson, 1984; Paradis, 2013)

1.2.5.2.4.2 Microscopy of Hepatocellular Carcinoma

HCC is usually a hypervascular tumor with diverse cellular differentiation ranging from well to poorly differentiated based on their structural and cytologic features. (Paradis, 2013) Histological proof for the presence of HCC can be obtained by an image-guided core liver biopsy of a mass. (Carr, 2012) Core biopsies can usually provide enough tissue for evaluating architecture which provides clues to differentiate adenocarcinoma from HCC. Morphological changes such as high-grade dysplastic nodules may occur in pre-malignant lesions as clear indications of HCC risk. (Sherman, 2010b) On the other hand, there may be morphological changes such as the low-grade dysplastic nodules which are present more frequently in livers with HCC. It is not yet clear whether these are risk factors for tumor development. (Carr, 2012; Sherman, 2010c)

Dysplastic nodules which occur in 25% of explanted cirrhotic livers, often together with an HCC, are identifiable clusters of hepatocytes with irregular but distinct margins. (Hytiroglou et al., 1995; Sherman, 2010c) Among dysplastic nodules, those which are high-grade manifest cellular atypia which may make it difficult to distinguish them from carcinoma. These nodules are thought to be precursor lesions for cancer since the cells inside these nodules exhibit small cell dysplasia with characteristics which may be a true precursor for HCC. (Paradis, 2013) Dysplastic nodules are commonly detected by ultrasound as these are larger than the background cirrhotic nodules. Benign lesions are rarely larger than 20mm and as the size of the nodule increases, there is a greater chance that it represents a high-grade or malignant nodule. However, not all these dysplastic nodules progress to HCC and their regression has also been reported. (Borzio et al., 1995; Sherman, 2010c; Ueda, Terada, Nakanuma, & Matsui, 1992)
The main histopathologic features of well-differentiated HCC lesions are the widened cell plates, increased cell density, increased nuclear-cytoplasm ratio, frequent mitotic figures and the absence of portal tracts. (Paradis, 2013; Sherman, 2010b) As a premalignant nodule moves towards a full-blown malignancy, an arterial blood supply grows in and the malignant cells invade portal tracts. At the same time, this invasion destroys the biliary drainage and venous supply; this may explain why the lesion may be less vascular than the surrounding liver tissue early in the transition period as venous supply is destroyed and arterioles are not fully developed yet. (Sherman, 2010b)

A distinction has lately been made between "very early" HCC and "early" HCC. Very early HCC, also known as vaguely nodular HCC, is typically hypovascular and has ill-defined margins. (Paradis, 2013; "Pathologic diagnosis of early hepatocellular carcinoma: a report of the international consensus group for hepatocellular neoplasia," 2009) On the contrary, "small HCC" has well-defined margins on ultrasound and exhibits the typical features of HCC as already mentioned on histologic examination. Despite their small size, they usually show microvascular invasion. (Kojiro, 2004; Sherman, 2010b) In this context, a positive biopsy result is useful, but a negative one by no means can be taken as conclusive. A single negative result on biopsy is not enough to exclude the diagnosis of HCC. (Sherman, 2014) Therefore, patients with lesions < 2cm and a negative biopsy result should be under close follow-up. (Sherman, 2010b) If the results are negative on a biopsy that has been evaluated by expert pathologist, imaging follow-up at 3-6 month intervals is warranted until the nodule either disappears, enlarges or is diagnosed as HCC due to radiologic characteristic features. Only if the mass enlarges without manifesting HCC specific radiologic features, is it recommended to repeat the biopsy. (Bruix et al., 2011) All of these uncertainties in diagnosis are important in asymptomatic patients since those who present with symptoms usually have fairly large lesions with typical radiologic features which make them easier to diagnose with confidence. (Sherman, 2010b)

Following liver biopsy for HCC, bleeding risk is increased in comparison to other tumors due to the hypervascular nature of this tumor and the fact that patients with HCC often have thrombocytopenia and decreased reserves of liver related clotting factors. The bleeding risk is even further increased in the presence of complications such as ascites. Another concern in
needle biopsy from the liver is needle track seeding, though it is probably uncommon with small lesions. (Bruix et al., 2011; Carr, 2012; Sherman, 2010b)

1.2.5.2.4.3 Grading and Pathological Prognostic Factors

Edmondson and Steiner system has been used as grading system for many years which, based on histological differentiation, divides HCCs into four grades. Grade I is the best differentiated consisting of small tumor cells arranged in thin trabeculae. It goes all the way to grade IV where cells are much less differentiated with hyperchromatic nuclei and loss of trabecular pattern. (Edmondson & Steiner, 1954; Paradis, 2013)

Unfortunately, since tumor grading provides little prognostic data, it is not a strong independent interpreter of the clinical course of the tumor. (Chuong, Livstone, & Barwick, 1982; Lai, Wu, Lam, & Todd, 1979; Paradis, 2013) In this regards, tumor stage (defined as the number and size of the nodules, state of vascular invasion as a predictor of tumor recurrence, survival, and metastasis), liver function (presented by Child-Pugh’s classification, portal pressure and plasma markers such as albumin and bilirubin) and finally, general health condition of the patient, can be used as major prognostic factors for HCC. (Nathan, Schulick, Choti, & Pawlik, 2009; Paradis, 2013; Pawlik et al., 2005)

1.2.5.3 Blood Tests Demonstrating HCC Risk

Immunohistochemistry studies may be used as additional steps in routine practice of HCC diagnosis to look for markers such as albumin, fibrinogen, AFP and α-1-antitrypsin. (Paradis, 2013; Shafizadeh, Ferrell, & Kakar, 2008; Wang et al., 2006) Obviously, since HCC occurs in patients with cirrhosis with higher risk of tumor development with advancing fibrosis, therefore, markers of advanced liver disease such as thrombocytopenia, ascites and biochemical evidence of liver failure, are logically associated with elevated risk of HCC development. The most studied item among these is thrombocytopenia which can be used as a risk factor to predict HCC development. (Fattovich et al., 1995; Lu et al., 2006; Maan et al., 2014; Mancebo et al., 2013; Sherman, 2010c)

1.2.6 Recommended Guidelines for HCC Surveillance

The American Association for the Study of Liver Disease (AASLD) has suggested a diagnostic algorithm for diagnosis of suspected HCC in its guideline update which takes all the above-mentioned points into account. (Bruix & Sherman, 2005; Bruix et al., 2011; Manno et al., 2004;
Lesions less than 1cm in diameter detected on ultrasonography, particularly in a cirrhotic liver, have a low likelihood of being HCC, however, the possibility remains high that a small hepatic nodule may transit towards a malignant nodule over time. (Iwasaki et al., 1998; R. Lencioni et al., 2008; Sherman, 2010b) Therefore, these nodules need to be followed-up on a regular basis with ultrasound, though the interval between examinations should be shorter than what it is for surveillance (for example 3-4 months), so that their growth pattern can be captured and proper action taken if this pattern is suggestive of malignant transformation. It is not known yet how long this more rigorous surveillance should continue, however, it should be performed for at least 18 to 24 months, bearing in mind that small HCC may be slow growing. If these detected nodules do not grow in a period of more than 1 to 2 years of follow-up, they can be counted as not malignant nodules since lack of growth over an extended period of time is the only indicator that a lesion is benign. Otherwise, they have to be investigated with more imaging studies according to their size. (Bruix et al., 2011; Sherman, 2010b)

When lesions are more than 1cm in diameter, they are more likely to be HCC. (Bruix & Sherman, 2005; Sherman, 2010b) In patients with chronic liver disease and cirrhosis, HCC can be diagnosed radiologically without the need for biopsy, if typical imaging features are present on a contrast-enhanced study such as dynamic CT scan or MRI. (Bruix et al., 2011; Forns et al., 2002; Kojiro, 2004; Levy, Greig, Gallinger, Langer, & Sherman, 2001; Mueller, Hussain, Carlos, Nghiem, & Francis, 2003; Sherman, 2010b)

Lesions which show typical characteristics on either CT scan or MRI, may be treated as HCC since the positive predictive value of clinical and radiologic findings are more than 95%. (Bruix & Sherman, 2005; Bruix et al., 2011; Sherman, 2010b) On the other hand, if the radiologic appearances are not typical for HCC and also do not suggest hemangioma, then either the second radiologic study (CT scan or MRI) could be added to confirm the diagnosis if results are characteristic for the tumor, or a liver biopsy can be performed after the first test with the atypical results. (Bruix & Sherman, 2005; Bruix et al., 2011; Sherman, 2010b) The above discussion is summarized in the diagram in Figure 1.2-1.
The algorithm for diagnosis of suspected HCC, suggested by the American Association for the Study of Liver Disease is shown above. Based on this algorithm, lesions < 1 cm in diameter need to be followed-up with ultrasound on a regular basis though with shorter intervals than is usually done for surveillance, so that if their growth pattern is suggestive of malignant transformation, proper action can be taken. If these detected nodules do not grow in a period of more than 1 to 2 years, they can be counted as not malignant nodules due to their lack of growth over an extended period of time. When detected lesions are > 1cm in diameter, they are more likely to be HCC are need to be evaluated radiologically without the need for biopsy, to see if they show the typical imaging features on a contrast-enhanced study such as dynamic CT scan or MRI, in which case, they may be treated as HCC. However, if the radiologic appearances are not typical for HCC and also do not suggest hemangioma, then either the second radiologic study (CT scan or MRI) could be added to confirm the diagnosis if results are characteristic for the tumor, or a liver biopsy can be performed after the first test with the atypical results.
1.2.7 Treatment

A patient with HCC requires care and support from a multidisciplinary team including hepatologists to assess liver function impairment before, after and during the proper treatment. Unlike many tumors, which are not affected by the function of the underlying organ, HCC survival depends heavily on the liver function because of the occurrence in a cirrhotic liver. In addition to hepatologists, surgeons, oncologists and interventional radiologists should meet to review cases and discuss management. (Bruix et al., 2011) The treatment modalities for HCC have improved substantially in the last few decades and the options have grown from surgical resection in selected patients as the only available method, to a vast array of choices such as orthotopic liver transplantation, loco-regional procedures like radiofrequency ablation (RFA), transarterial chemoembolization (TACE) techniques for those who are not candidates for surgery, and lately, sorafenib, a systemic medical treatment for those who are unlikely to benefit from any of the mentioned procedures. (Bruix & Llovet, 2009; Colombo & Sangiovanni, 2011; Llovet, Di Bisceglie, et al., 2008) A profound understanding of the natural history of HCC accompanied by the development of clinically based staging systems which help stratify patients according to the stage of their tumor and also the underlying hepatic morbidity, have made it possible to somewhat predict life expectancies and to guide proper treatment. (Bruix & Llovet, 2009; Colombo & Sangiovanni, 2011; Forner, Reig, de Lope, & Bruix, 2010)

1.2.7.1 Staging Systems

Development of a proper staging system for HCC is more challenging than for some other tumor-types. The prognosis of HCC is highly dependent on function of the underlying organ, which is not a common issue with malignancies in other organs. For example, cirrhosis limits the possible surgical therapy and furthermore, restricts chemotherapy. During the 1990s, various staging systems for HCC have been suggested which confirm the reality that none were ideal. (Colombo & Sangiovanni, 2011; Sherman, 2011)

An anatomically based staging system, like the TNM system, which takes the size of the tumor, number of affected regional lymph nodes and tumor metastasis into account, is not capable of capturing all the major prognostic factors since it does not include liver function status and requires some information which is available only after resection is done which makes this system not suitable for those who do not undergo a surgery. (Kudo, Chung, & Osaki, 2003;
Likewise, Child Pugh score (which is practically measurement of albumin, bilirubin and prothrombin time) cannot be appropriate for HCC staging since it considers only factors related to underlying liver function rather than those related to tumor spread and size. (Kudo et al., 2003)

As another example, the Model for End-Stage Liver Disease scoring system (MELD) was used in the United States. This scoring system was designed to be used in patients with chronic liver disease to predict survival without transplantation; actually it is used for prioritizing organ allocation for liver transplantation candidates. (Ioannou, Perkins, & Carithers, 2008; Sherman, 2011) Other staging systems include the Okuda classification which takes radiologic tumor size and liver function into account and Cancer of the Liver Italian Program (CLIP) score which includes the severity of liver disease (through calculating Child-Turcotte-Pugh score) and tumor characteristics, such as morphology and spread extent as well as serum AFP levels and presence of portal vein thrombosis. Each has its own advantages and disadvantages. (El-Serag, Marrero, Rudolph, & Reddy, 2008; Kudo et al., 2003; Yang & Roberts, 2010) Okuda classification, as mentioned, includes both liver function and tumor related parameters (size of the tumor, albumin and bilirubin and presence of ascites as liver function factors); however, it does not include important tumor related parameters such as whether it is unifocal versus multifocal or diffuse, with or without vascular invasion and also whether the tumor is less than 2cm in diameter or not. These are actually important prognostic factors when tumors are detected in their early phase which may happen with surveillance programs currently implemented. (Kudo et al., 2003)

As Tournoux-Facon and colleagues (Tournoux-Facon et al., 2011) have discussed, the two scores which are used commonly, i.e. the CLIP and the Barcelona Clinic Liver Cancer (BCLC), which will be discussed in detail below, have been validated as practical tools which can support decision-making procedures. (Levy & Sherman, 2002) Levy and Sherman (Levy & Sherman, 2002) found that the CLIP score offered greater value in discriminating prognosis when compared to the Okuda system. However, the CLIP system has some limitations when used for HCCs which are diagnosed in the early stages of the disease since the definition of tumor morphology in the best prognostic group (single nodule with an extent < 50% of the liver which can still be a fairly large tumor) is too general and well beyond a small nodule without vascular
invasion detected in a screening programs. Therefore, it is probably not appropriate for HCC patients in whom diagnosis is possible in the early phase of HCC through surveillance programs. (Kudo et al., 2003) Finally, Llovet and colleagues (Llovet & Bruix, 2000) pointed out that since CLIP provides almost every treatment options for all the subgroups in this scoring system, it cannot be an aid for deciding on treatment allocation.

1.2.7.1.1 The BCLC Staging System

Barcelona Clinic Liver Cancer (BCLC) is another staging system which stratifies patients according to the stage of the tumor and also the underlying liver disease. (Colombo & Sangiovanni, 2011; Sherman, 2011) Although there are several staging systems available, the BCLC is becoming the most commonly used and is approved by AASLD as a backbone for its guideline in clinical practice. (Bruix et al., 2011; Colombo & Sangiovanni, 2011; Sherman, 2011; Sherman et al., 2011)

The BCLC system has different advantages, such as being the only system which incorporates tumor stage, liver functional status (through Child-Pugh Score) and health status of the patient (through measurement of Eastern Cooperative Oncology Group, ECOG, performance) (Sherman et al., 2011) as is shown in Table 1.2-2.

<table>
<thead>
<tr>
<th>BCLC Stage</th>
<th>Performance Status</th>
<th>Tumor Volume, Number and Invasiveness</th>
<th>Child-Pugh Class/Expected Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Early</td>
<td>0</td>
<td>Single &lt;5Cm or 3 nodules &lt;3Cm each</td>
<td>A &amp; B/50-75% at 5 year</td>
</tr>
<tr>
<td>B: Intermediate</td>
<td>0</td>
<td>Large / Multinodular</td>
<td>A &amp; B/16 months</td>
</tr>
<tr>
<td>C: Advanced</td>
<td>1-2</td>
<td>Vascular Invasion and/or Extrahepatic spread</td>
<td>A &amp; B/6 months</td>
</tr>
<tr>
<td>D: End-Stage</td>
<td>3-4</td>
<td>Any of the above</td>
<td>C/&lt;3 months</td>
</tr>
</tbody>
</table>

As is shown in the table above, the Barcelona Cancer of the Liver Clinic staging system categorizes HCC based on the performance status of the patient, the tumor characteristics including volume, number and invasiveness of the nodule or nodules and also Child-Pugh Class. This leads to four stages which can be directed to their assigned treatment options.

It is also the only system which provides an allocation of treatment in addition to prognostic classification and its performance has been validated in several independent studies. (Llovet,
For example, patients in BCLC stage A can receive surgical resection, transplantation or ablation as treatment options accordingly. This staging system is schematically shown in Figure 1.2-2.

**Figure 1.2-2: The BCLC Staging System for HCC**
Adapted from (Bruix et al., 2011) - Permission has been granted.

BCLC staging, shown in the figure above, is a system which provides an allocation of treatment in addition to prognostic classification. For example, patients in BCLC stage A, based on the number and size of the nodules and the presence or absence of portal hypertension, can receive surgical resection, transplantation or ablation as treatment options accordingly. However, in stage B, the treatment option is limited to TACE and the available option for stage C will be Sorafenib. When the stage moves towards D, the only therapeutic option available will be symptomatic treatment and the best standard of care.

However, BCLC system has some disadvantages too. Among these drawbacks is that it does not deal specifically with treatment failure, rather, the patients move between different stages as their disease progresses. (Sherman et al., 2011) On the other hand, the BCLC system cannot...
further differentiate among patients in a single stage and there still exists the need for further research to modify the system so that it can include subcategories in the hope of increasing its utility. (El-Serag et al., 2008; Huitzil-Melendez et al., 2010; Sherman, 2011) Finally, it includes factors which require subjective evaluation (patients’ performance status); these may sometimes be difficult to be analysed retrospectively. (Kudo et al., 2003)

1.2.7.1.1.1 The BCLC Stages 0 and A

The BCLC system incorporates variables associated with tumor stage, liver function as well as physical competency of the patient and cancer-related symptoms. Very early HCC presents a single nodule of less than 2cm, confined to the liver and is currently quite difficult to diagnose confidently prior to treatment. (Bruix et al., 2011) These patients are asymptomatic and the tumor also does not manifest any vascular invasion. These patients can be candidates for surgical resection or RFA which probably offer similar 5-year survival rates. The choice of treatment option is dictated by the tumor location, presence of co-morbidities and degree of portal hypertension.

Early stage in the classification system denotes patients with preserved liver function and a single HCC nodule which is less than 5cm in size or up to three nodules which are each ≤ 3cm in diameter (Milan Criteria). (Forner et al., 2010) As an essential concept in treating early stage HCC, it is important to use liver-sparing therapies, such as local ablation/injection strategies and also surgical resection to save as much liver parenchyma as possible, and to focus on treatment of both the tumor and the cirrhosis. (Carr, 2012) These patients have surgical resection, liver transplantation or ablation on their treatment option menu and if selected carefully, patients with compensated cirrhosis and a tumor of ≤ 2cm in diameter, take equal advantage of all radical therapies in terms of survival (>70% at 5 years), however, with different costs and risks of intervention-related mortality. (Colombo & Sangiovanni, 2011; El-Serag et al., 2008; Kojiro & Roskams, 2005)

1.2.7.1.1.2 The BCLC Stage B

Patients who do not manifest tumor-related symptoms or vascular invasion but have compensated cirrhosis and cannot be classified in either very early or early stages, will be grouped in the BCLC intermediate stage. TACE results in 20% to 25% improvement in the two year survival when compared to conservative treatments. (El-Serag, 2011; El-Serag et al., 2008)
1.2.7.1.3 The BCLC Stage C
Patients in the advanced or the BCLC stage C have mild cancer-related symptoms and/or vascular invasion or extrahepatic spread of the tumor. Among well selected patients in this stage, TACE may increase survival. (El-Serag, 2011; El-Serag et al., 2008) These patients have shorter life expectancy, a one year survival of 50% and are candidates for sorafenib therapy. (Bruix et al., 2011)

1.2.7.1.4 The BCLC Stage D
Patients in this terminal stage, regrettably, have a one year survival of less than 10% or an average predicted survival of less than 3 months. The available treatment options do not offer any benefit to these patients and thus symptomatic palliative care is advised. (Colombo & Sangiovanni, 2011; El-Serag, 2011; El-Serag et al., 2008)

1.2.7.2 Therapeutic Options
There are some therapeutic options which are known to provide high rates of complete response. These potentially curative treatments include surgical resection, liver transplantation and percutaneous ablation. (Bruix et al., 2011; Forner et al., 2010; Llovet, Di Bisceglie, et al., 2008) Among other treatment options which are non-curative, transarterial chemoembolization and sorafenib have been shown to influence survival in a positive format. (Bruix et al., 2011; Cheng et al., 2009; Llovet, Ricci, et al., 2008)

1.2.7.2.1 Surgical Resection
Surgical resection (partial hepatectomy) is the treatment modality of choice for HCC in the very early stage in patients without cirrhosis since the remaining liver tissue has well-preserved hepatic function. (El-Serag et al., 2008) However, in those with cirrhosis, the best results are obtained from HCC surgical resection when the tumor is small (< 3cm in diameter), portal hypertension is absent, and the total bilirubin level is normal (≤ 1 mg/dL). Portal hypertension is defined as lack of esophageal varices, splenomegaly and the associated thrombocytopenia (defined as platelet count < 100,000/mm³) and the need for diuretics for controlling ascites, or as a hepatic venous pressure gradient >10mmHg. (Cabrera & Nelson, 2010; El-Serag, 2011; Llovet, Fuster, & Bruix, 1999; Llovet, Schwartz, & Mazzaferro, 2005) It has been shown that in the presence of portal hypertension or high serum bilirubin, surgical resection is not cost-effective due to the high risk of irreversible post-operative clinical decompensation and also
reduced survival where the 5-year survival has been reported to be less than 30% in patients with elevated bilirubin and portal hypertension, therefore, not only it is not cost-effective, but also not effective and imposes a high risk of surgery. (Bruix et al., 1996; Colombo & Sangiovanni, 2011; El-Serag et al., 2008)

The risk highlights the importance of careful patient evaluation and selection for ablative therapy to minimize the risk of post-operational liver decompensation which happens more in right lobe resection in comparison with the left lobe. (Bruix et al., 2011) The minimum required size for liver remnant after resection is reported as 25% in a liver with normal function and 50% in a cirrhotic liver. (Cabrera & Nelson, 2010) Resection is reserved for single tumors or multiple tumors restricted to one lobe of the liver. The size of the tumor alone, should not be a criteria to prevent surgical resection since some less aggressive tumors present as a single large lesion without microvascular invasion. (Bruix et al., 2011; Yang & Roberts, 2010) The 5-year risk of recurrence of HCC after resection is as high as 70% since the underlying chronic liver disease continues to put the patient at risk for the development of new HCC, both through intrahepatic metastases and de novo tumor formation. Tumor size and number as well as microvascular invasion act as a strong predictor for tumor recurrence, so does a narrow margin on resection. (El-Serag, 2011; Okada et al., 1994; Shi et al., 2007) Tumor invasion into the main, right portal vein is considered as a contraindication to surgical resection, mainly due to the very high rate of post-surgical recurrence rate for HCC. (Sherman et al., 2011)

Unfortunately, no known adjuvant therapy is currently available that is capable of decreasing the risk of tumor recurrence after resection. (Yang & Roberts, 2010) Interferon therapy after surgical resection has been shown to reduce the risk of HCC recurrence. (Breitenstein et al., 2009) Nevertheless, since it is not yet clear whether this is related to viral suppression or eradication effect of this medication or it is an independent response. In most patients, intrahepatic dissemination from the primary lesion results in multifocal recurrence which makes them poor candidates for repeat surgery. It has been suggested that these patients may take benefit from salvage liver transplantation, but unfortunately, this is not yet supported with clinical outcome analyses. (Bruix et al., 2011; Poon, Fan, Lo, Liu, & Wong, 2002) In the long run, improvements in surgical techniques which take benefit from intra-operative ultrasound to improve tumor localization and staging, together with enhancement of patient selection have
shown that in highly experienced facilities, mortality rate of surgical resection can be less than 3% and also the 5-year survival rates may be as high as 70%. (Cabrera & Nelson, 2010)

1.2.7.2.2 Orthotopic Liver Transplantation

Orthotopic liver transplantation (OLT) is the therapeutic option with the lowest risk of tumor recurrence in selected patients with HCC who also have cirrhosis since it also has an influence on the chronic underlying liver disease as the major culprit for HCC development. Therefore, it acts on both the tumor and also the underlying liver disease. This makes liver transplantation the most definitive treatment for HCC. (Yang & Roberts, 2010)

The best candidates can be selected from the BCLC stages 0 or A. However, limited available organs in the proper time frame for patients in need has led to imposing strict criteria to limit OLT only to those patient who are likely to have excellent results and the highest probable post-transplant survival. (El-Serag, 2011) Those patients with HCC who are within Milan criteria for OLT (a single nodule < 5cm in diameter or up to three nodules each ≤ 3cm in diameter) who receive this treatment have a 5-year survival rate of 75% and a recurrence-free survival rate of about 92%. (Mazzaferro et al., 1996)

The current selection criteria for listing patients in OLT wait-list which are also more restrictive, were developed when imaging techniques had not improved as they are now; however, there are not enough supporting information to define new limits for selection criteria. Moreover, other than clinical information, there are some ethical issues in this context, such as alterations of post-transplant life expectancy with changes of the listing and de-listing policies. (Bruix et al., 2011) However, the expansion of the listing criteria is a decision to be made by individual transplant centres based on their wait-time, drop-out while on waiting list, and the extent of the effect of failed transplantation on their whole programs. (Sherman et al., 2011)

The OLT waiting-list time varies a lot between programs, but if it is already long enough, the patient’s HCC may become larger or they may develop major OLT contraindications, such as vascular invasion or extrahepatic spread. This de-listing rate may grow as high as 25% if the waiting time is more than 12 months. (Llovet, Fuster, et al., 1999; Yao, Bass, et al., 2002) It is possible to keep HCC patients within the listing criteria during their waiting time for OLT, using TACE or RFA as bridging therapies, which is routinely done, though not supported by strong
clinical evidence and it is not yet clear whether this intervention increases post-transplantation survival. (Cabrera & Nelson, 2010; Carr, 2012; Heckman et al., 2008) Downstaging is the process of reducing the size and/or number of HCC lesions which are beyond the OLT listing criteria based on imaging results, so that they can be included within this criteria. (El-Serag et al., 2008) Reducing the size of a tumor alone is unlikely to affect its biological characteristics and downstaging is therefore not currently recommended outside of experimental protocols. (Toso, Mentha, Kneteman, & Majno, 2010)

United Network for Organ Sharing (UNOS) has adopted Milan criteria, that is one HCC ≤ 5cm or up to three lesions ≤ 3cm in diameter, as the required feature of the tumor to be a transplantation candidate. This approach has had an associated 5-year survival rate of more than 70% and tumor recurrence rate of less than 15%. (Cabrera & Nelson, 2010; Mazzaferro et al., 1996) On the other hand, the primary criteria that UNOS uses to prioritize the organ allocation for livers available to transplant those with the highest short-term mortality risk are the MELD criteria. (Bruix et al., 2011; El-Serag, 2011) Attempts have been made to expand the listing criteria for transplantation in HCC patients. Among these, criteria developed at the University of San Francisco (UCSF) go beyond Milan to include a single HCC of < 6.5cm in diameter or up to three lesions each < 4.5cm with a total combined measured diameter of less than 8cm. Several studies with medium quality have reported similar survival rates in comparison with those eligible for Milan criteria; however, limited available organs have resulted in UNOS to resist adopting this method. (El-Serag, 2011)

1.2.7.2.2.1 Living Donor Orthotopic Liver Transplantation

Among the measures implemented to reduce the dropout rate on the OLT waiting list, increasing the number of available livers seems to be the most effective one. A number of strategies such as using the livers extracted from amyloidosis patients, livers with viral infection with minimal damage, split liver transplantation, to name a few, have been tried but the best approach has been the development of living donor programs. However, living-donor liver transplantation is a highly complex procedure and requires expert surgeons to ensure the best outcomes in terms of morbidity and mortality, for both the donors and the recipients. Complications related to this intervention may develop in 20% to 40% of the donors and although uncommon, there is a mortality risk of 0.3% to 0.5% among donors. (Bruix et al., 2011; Trotter, Wachs, Everson, & Kam, 2002) Living donor liver transplantation, with a waiting list time of more than 7 months,
is suggested to be a cost-effective intervention when taking into account the monthly dropout 
risk on waiting list of 4%, the expected 5-year survival of the recipients of about 70% and also 
the mortality risk for the donor of 0.3% to 0.5%. (Sarasin et al., 2001)

1.2.7.2.3 Percutaneous Ablation

Patients with early-stage HCC who cannot be treated with surgical resection or transplantation, 
may benefit from local ablation therapies for their small lesions. Tumor cells can be destroyed 
by the injection of chemical substances (acetic acid, boiling saline, ethanol) or through 
temperature modification (cryotherapy, laser, radiofrequency, microwave).

The most widely used methods in this context are percutaneous ethanol injection (PEI) and 
radiofrequency ablation (RFA). (Bruix et al., 2011; El-Serag et al., 2008; Sandhu, Tharayil, Lai, 
& Roberts, 2008) Although PEI is still an important therapeutic tool, at present, RFA should be 
the first option for local ablation. Efficacy of this therapeutic method is assessed by dynamic CT 
scan one month after the intervention. (Bruix et al., 2001) Tumor necrosis is confirmed if there 
is no contrast uptake within the lesion, though this is not an entirely reliable finding. Post-
therapy monitoring in this modality is done with a radiologic contrast technique such as CT scan 
or MRI. Although the ideal monitoring interval is not known, a 3-4 month interval is a common 
starting point for the first two years of recurrence-free survival and then the intervals will be less 
frequent thereafter. (Bruix et al., 2011) The recurrence rate in this method is similar to surgical 
resection and happens due to the presence of "microscopic satellites" which have not been 
included in the treatment process. Local ablation is a safe and effective treatment option which 
can be used both for patients who are not candidates for surgery and also as a bridge to liver 
transplantation. (Bruix et al., 2011)

1.2.7.2.3.1 Radiofrequency Ablation

This is currently the preferred treatment option for early stage HCC in a patient who is not a 
candidate for surgical resection. This intervention uses special electrodes which are positioned 
accurately, under ultrasound guidance, into the tumor to more efficiently treat the tumor through 
thermal coagulative necrosis which affects the tumor and a small margin of normal hepatic 
tissue. Although RFA requires less treatment sessions in comparison with PEI, their efficacies 
are similar for tumors < 2 cm in diameter; however, RFA is more efficacious than PEI for 
tumors > 2 cm. (Bruix et al., 2011; S. M. Lin, Lin, Lin, Hsu, & Chen, 2004; Sandhu et al., 2008)
Moreover, it has been suggested that the survival is better after RFA than after PEI. (Cho, Kim, Kim, Rhim, & Han, 2009)

The main disadvantage of RFA is its higher cost and also higher rate (up to 10%) of pleural effusion and peritoneal bleeding as the procedure-related complications. Mortality due to the procedure ranges from 0% to 0.3%. (Livraghi et al., 2003; Sandhu et al., 2008) If the lesion is located near a large vessel, the level of lethal heating required to effectively induce tumor coagulation and necrosis, decreases, the so called "heat sink" effect which lowers the efficacy of RFA in completely treating these tumors. (Cabrera & Nelson, 2010; Sherman et al., 2011)

Altogether, RFA can be delivered in an outpatient set up and is an ideal therapy for patients with a single HCC nodule < 2.5cm, though it can also be used for lesions up to 4cm which are not candidates for either surgical resection or transplantation. (Sherman et al., 2011) Local recurrence rates for RFA have been reported from 8% to 14% at 2-3 years whereas they have been 22% to 34% for PEI. On the other hand, overall survival rates have been 100% and 98% for one and two years respectively in patients who have received RFA in comparison with 96% and 88% in cases treated with PEI. (R. A. Lencioni et al., 2003) Dong and colleagues (Dong, Zhang, Wang, & Liu, 2014) in their meta-analysis suggested that for treating small HCCs, RFA was associated with a longer overall survival when compared to PEI.

There are a number of studies that have evaluated and compared surgical resection with non-surgical ablation methods such as RFA. In one study, Lei and colleagues (Lei, Wang, Yan, Wen, & Li, 2014) suggest that RFA is an effective and at the same time, safe therapeutic option and even the preferred method for patients with small HCCs. Dong and colleagues, (Dong et al., 2014) through performing a meta-analysis concluded that surgical resection is superior compared to non-surgical methods for ablation when treating small HCCs and RFA is the most efficacious treatment modality among non-surgical ablation methods. They showed that the 5-year overall survival and also the 3-year disease free survival rate was significantly higher with surgical resection when compared with non-surgical ablation methods. Huang and colleagues (Huang et al., 2010) also showed similar results in their RCT done to compare surgical resection and RFA and showed that surgical resection resulted in higher 3 and 5 year disease free survivals.
Dong and colleagues (Dong et al., 2014) also concluded from their meta-analysis that the local recurrence rate of HCC was lower after surgical resection when compared to RFA which as they discussed, may be due to the narrower safety margin in RFA than that of surgical resection and the inability of RFA to detect sites of microscopic HCC which are taken out during resection of the whole affected section of the liver. On the other hand, they showed a higher incidence of adverse events after surgical resection compared to what happens after RFA which as they pointed, can be explained by the characteristics of these treatment methods.

1.2.7.2.4 Percutaneous Ethanol Injection

PEI is injection of 95% (absolute) ethanol into the tumor to destroy the lesion. However, it is not selective for malignant cells and similar to other ablative techniques, damages the normal cells in the vicinity of the tumor too. (Carr, 2012) The extent of necrosis achieved by PEI is determined by the size of the tumor. (El-Serag et al., 2008; Sandhu et al., 2008) Ethanol injection requires multiple treatment episodes on separate sessions to achieve complete necrosis in large tumors (those >3cm in diameter). The success rate for PEI is 70% to 80% of single HCC ≤ 3cm and nearly 100% in lesions less than 2cm in diameter. (Choi et al., 2001) When comparing the recurrence-free survival rates between RFA and PEI, results of 86% and 64% for RFA and 77% and 43% for PEI, respectively at one and two years, have been reported. (El-Serag et al., 2008)

1.2.7.2.5 Non-Curative Treatments

The ultimate goal of therapy in patients who cannot take benefit from curative therapies is to increase their life expectancy and also improve their quality of life. According to the current literature, transarterial chemoembolization (TACE) and sorafenib are among the options that have been proven to be useful in this context. (Bruix et al., 2011)

1.2.7.2.5.1 Transarterial Embolization and Chemoembolization

Patients with intermediate-stage tumor who are not neither candidates for surgical resection nor for percutaneous ablation and who do not have extrahepatic tumor spread, can be treated with locoregional therapies such as transarterial chemoembolization (TACE) and transarterial radioembolization (TARE). (Bruix et al., 2011; El-Serag et al., 2008; Sandhu et al., 2008) HCC is highly vascular with neo-angiogenic activity during its development. Therefore, as the tumor
grows, its blood supply changes from the early status of mainly venous, i.e. from the portal vein, to become progressively arterialized so that the tumor receives more than 95% of its blood supply from the hepatic artery. (Bruix et al., 2011; Sandhu et al., 2008) This specific characteristic, not only acts as the basis for radiologic diagnosis of the tumor, but also is the mainstay supporting arterial obstruction as an effective mode of therapy for the tumor.

Acute arterial blockade leads to ischemic tumor necrosis. The hepatic artery is obstructed during an angiographic intervention known as transarterial or transcatheter embolization. When this procedure is accompanied by prior delivery of chemotherapeutic agents such as doxorubicin or cisplatin, usually mixed with lipidol for delivery, the procedure is known as transarterial chemoembolization (TACE). Fortunately, due to the dual blood supply in the liver, TACE exerts minimal harmful effects on normal liver cells since only about 20% to 30% of the blood supply of the normal hepatic parenchyma is from the hepatic artery and the remaining comes from the portal veins whereas tumor cells rely on the hepatic artery for 95% to 100% of their required blood supply. (Sandhu et al., 2008) There are more novel methods of TACE which use drug-eluting beads to both reduce blood flow and also convey controlled and sustained amounts of required medications; this may reduce the procedure-related side effects. (Tinkle & Haas-Kogan, 2012) TACE cannot be used when there is lack of portal blood flow to the liver, for example in the setting of portal vein thrombosis or portosystemic anastomoses. Furthermore, patients with advanced liver disease are not good candidates for TACE since they have an increased risk of liver failure and death from the procedure itself. (Bruix et al., 2011) In selected patients, all in all, treatment associated mortality is < 5% and the median survival has been reported to be 34 months with a 5-year overall survival of 26%. (El-Serag et al., 2008; Llovet & Bruix, 2003)

The side effects of TACE which may occur in about 10% of treated patients, (El-Serag et al., 2008) include but are not limited to contrast allergy, side effects of intra-arterial chemotherapy which are similar to those during systemic administrations, renal failure due to contrast or chemotherapy, self-limited so-called post-embolization syndrome (due to acute ischemia of the HCC, appearing in about 50% of cases and manifested as fever, right upper quadrant pain and moderate degree of ileus) and infectious complications such as cholecystitis or hepatic abscess in a minority of cases. (Bruix et al., 2011; Sandhu et al., 2008) Overall, TACE is recommended
as first line treatment among non-curative options for BCLC stage-B patients, i.e. those who are not candidates for surgical resection with large/multifocal HCC lesions who do not have vascular invasion or extrahepatic spread of the tumor. (Bruix et al., 2011; Sherman et al., 2011) Furthermore, TACE can be an option in those who are candidates for RFA but the procedure cannot be performed in them due to the tumor location (e.g. proximity to a blood vessel or biliary tree) or concurrent medical morbidity. In addition, it is the first-line treatment modality for tumor downstaging to make those tumors which exceed the criteria eligible to be treated with transplantation. (El-Serag et al., 2008; Yao et al., 2005)

1.2.7.2.5.2 Transarterial Radioembolization
Transarterial radioembolization has been shown to be effective in patients with intermediate to advance stage HCC. (Bruix et al., 2011; El-Serag et al., 2008; Sandhu et al., 2008; Vente et al., 2009) This method involves delivery of radiolabeled particles to the highly vascularised HCC through the hepatic artery. This will offer the opportunity to spare the normal liver parenchyma which is mainly supplied by the portal vein. These radiolabeled particles are Yttrium 90-impregnated glass or resin-based microspheres which act as a source of beta radiation. (Vente et al., 2009) The glass microspheres are highly specific since they do not block the vasculature and therefore will not lead to tumor lysis syndrome seen in TACE, consequently, TARE can be used in HCC with portal vein thrombosis where TACE is contraindicated. (Sandhu et al., 2008; K. Sato et al., 2006) A potential complication in this method is inadvertent delivery of radiolabeled material to non-target locations in the body which can be prevented by careful procedure implementation. (Cabrera & Nelson, 2010) Due to lack of available data to demonstrate its effect on survival, TARE cannot be recommended as a standard treatment modality for advanced HCC outside of clinical trials. (Bruix et al., 2011)

1.2.7.2.6 Systemic Therapies
Systemic treatments such as chemotherapy, hormonal therapy and immunotherapy have been tried for advanced HCC, though with limited success. (Sandhu et al., 2008)

1.2.7.2.6.1 Cytotoxic Chemotherapy
HCC is considered extremely resistant to chemotherapy and standard systemic chemotherapy is not recommended to treat this malignancy; this may partially be due to the high uptake of the medication in portal venous blood which misses the tumor and may lead to systemic toxicity. Underlying portal hypertension and associated pancytopenia together with low levels of baseline
liver function leave these patients with poor tolerance to the chemotherapeutic agents. (Sandhu et al., 2008; Sherman et al., 2011; Yang & Roberts, 2010) Therefore, selective intra-arterial or systemic chemotherapy is not recommended as a standard of care for treating HCC. (Bruix et al., 2011)

1.2.7.2.6.2 Hormonal Therapy
Presence of estrogen and androgen receptors in HCC together with the higher incidence of the tumor among males have shaped the idea of hormonal therapy with anti-androgens or anti-estrogens in some early trials (Castells et al., 1995) which have later been proven to have no survival benefits. Therefore, tamoxifen, octreotide or anti-androgens are not recommended for HCC treatment. (Bruix et al., 2011; Sandhu et al., 2008)

1.2.7.2.6.3 Targeted Molecular Therapy
There is a new trend of investigations focused on elucidating the pathogenesis of HCC with the purpose of developing agents which target the major pathways in progression of the tumor. Targeted agents may offer opportunities in systemic pharmaceutical therapy of HCC. (Sandhu et al., 2008) During hepatic carcinogenesis, growth signaling pathways include the receptor tyrosine kinase signaling pathways and their downstream Raf kinase, among others. Sorafenib is an oral multikinase inhibitor which blocks both tumor cell proliferation and also angiogenesis through inhibiting c-Raf, B-Raf, Raf-1 as well as VEGF growth factor receptor tyrosine kinase signaling. (Liu et al., 2006; Sherman et al., 2011) Llovet and colleagues, (Llovet, Ricci, et al., 2008) in a multicenter, randomized placebo-controlled trial called Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) implemented with 602 patients with advanced HCC without any prior systemic therapy, showed that overall survival was 10.7 months in the sorafenib group compared to 7.9 months in the control group. This was a 37% increase in overall survival, translating to 2 to 3-month increase in life. (El-Serag, 2011) This significant difference led to the approval of sorafenib as the first agent for treating advanced HCC and indicated as the standard of care for systemic therapy in BCLC-C patients. (Sherman et al., 2011; Yang & Roberts, 2010) The SHARP study was conducted mainly in America and Europe. Cheng and colleagues, (Cheng et al., 2009) conducted a similar study with 226 patients in Asia. The difference in overall survival in these two studies stems from the differences in the study populations in terms of their previous treatment history and HCC etiologies. (Bruix et al., 2011; Colombo et al., 2013)
Sorafenib was reasonably well tolerated in both studies but is associated with a number of often dose-limiting side effects including diarrhea, weight loss, fatigue, and hand-foot skin reaction, particularly at the 800mg dose. Sorafenib is the first line recommended treatment option for patients who are not suitable candidates for surgical resection, transplantation, TACE or ablation but have maintained liver function. (Bruix et al., 2011)

1.2.8 Prognosis

On the contrary to other solid tumors, the prognosis of HCC relies not only on the tumor stage at presentation, but also on the level of liver function and patients’ performance status. (Bruix et al., 2011; Cabrera & Nelson, 2010; Sherman et al., 2011) Multiple independent prognostic factors have been recognized. Tumor status, in terms of number and size of the nodules and presence or absence of macrovascular invasion and extrahepatic spread is one of these factors. Moreover, liver function status, recognized by serum albumin and bilirubin levels, presence or absence of portal hypertension and Child-Pugh class is another prognostic factor. Furthermore, physical status of the patient, shown by Eastern Cooperative Oncology Group (ECOG) classification and presence of symptoms is also taken as a prognostic factor in this context. These are important contributors to the outcome which are related to the tumor burden and also the severity, not the etiology, of the liver impairment. (Cabrera & Nelson, 2010)

Unfortunately, HCC is still associated with a dismal prognosis. This stems from delayed diagnosis as a result of lack of observable symptoms in early stage tumor, aggressive tumor behavior which shows a great tendency for angioinvasion and also the clinical status of the patients who are usually suffering from concomitant hepatic decompensation. If diagnosed late, when it is clinically symptomatic, regrettably, the outcome is poor unless therapeutic interventions can modify the situation. (Sherman, 2014) Therapeutic options are limited for advanced cases. (El-Serag et al., 2006; Nordenstedt et al., 2010) This has resulted in the near identical incidence and mortality rates globally for HCC. (Bosch et al., 2004; Carr, 2012; El-Serag, 2012; Paradis, 2013) Tumor pathological analysis adds additional prognostic information (e.g. size and growth patterns) as well as microscopic features (development grade and vascular invasion). (Paradis, 2013)
1.2.9 Prevention
There are many reports from Europe, Japan and North America that show an increasing trend in the incidence of HCC. This trend is believed to be a result of chronic HCV infection which also had increased in these regions some decades ago. (Deuffic, Poynard, Buffat, & Valleron, 1998; El-Serag, Davila, Petersen, & McGlynn, 2003; Heathcote, 2004; K. Okuda, Fujimoto, Hanai, & Urano, 1987) Dismal prognosis of HCC if not diagnosed and treated in time, which is a time-consuming and resource intensive step in itself, and also the fact that some of the etiologic factors for HCC are preventable exposures, highlights the importance of preventive measures and focusing on modifiable risk factors. (Heathcote, 2004)

Bearing in mind that chronic liver disease due to HBV or HCV infections accounts for the majority of HCC occurrences, treatment of hepatitis infections, fortunately possible with novel treatments for HCV developed in recent years which in most cases result in SVR, independent of the presence or absence of cirrhosis, results in a substantial decrease in the risk of HCC development. (Bosch et al., 2004; Mittal & El-Serag, 2013; Sherman, 2010c) Moreover, measures such as screening products for blood transfusion and also vaccination for hepatitis when available, may have favorable effects in this regards. It is unknown however whether the benefit on HCC incidence will be seen in patients with more advanced cirrhosis who achieve SVR. Patients with advanced cirrhosis were not candidates for interferon-based therapy and as such, there are currently no data on the risk of HCC after curative antiviral therapy in patients with decompensated cirrhosis.

1.3 Surveillance for HCC
Surveillance for HCC, by definition, is the repeated performance of diagnostic tests on people who have a defined risk of developing HCC. The main objective of this surveillance is to reduce the related mortality. (Colombo, 2007; Sherman, 2010b) Unfortunately, without surveillance programs, HCC presents quite late in its course with the start of symptoms due to liver failure (as a result of massive replacement of the liver tissue with malignant cells), obstructive jaundice (due to bile duct infiltration) or constitutional symptoms. (Sherman, 2010b) Surveillance programs for HCC offer the advantage of identifying smaller HCCs, the so-called stage migration which denotes detecting tumors in their earlier stages, or even before true malignant transformation with discovery of dysplastic nodules. Although identification of small lesions creates diagnostic challenges for distinguishing malignant and benign masses, timely detection
of the tumor will potentially increase the number of curative therapeutic options available. (Bruix et al., 2011)

Surveillance includes identification of the target population, those who are at risk for the cancer under question, availability of an appropriate surveillance test(s) with appropriate intervals, proper recall and management policies to confirm and determine whether the abnormal result identified is malignant or not. (Sherman, 2010b, 2014) Randomized controlled trials will usually provide the most reliable results to test a research hypothesis. However, for logistic and ethical reasons, among some other factors, this format of study is not always feasible and practical. (Fletcher, Fletcher, & Fletcher, 2014) As such, we identified only one published randomized controlled trial from China which evaluated surveillance for HCC and has shown that biannual surveillance with AFP and ultrasound reduced the HCC mortality by 37% in comparison with the control arm who had no surveillance intervention. (Mittal & El-Serag, 2013; B. H. Zhang, Yang, & Tang, 2004) Although this trial had numerous methodological flaws, including a low adherence rate with screening and limited therapeutic options, it is unlikely that other randomized controlled trials will be performed.

However, the same benefits were seen in observational cohort and case control studies, taking into account their unavoidable limitations, for HCC surveillance. (Mittal & El-Serag, 2013; Sherman, 2007; Trevisani et al., 2002) It is likely impossible to perform a randomized controlled trial to evaluate the survival benefits of HCC surveillance because of the perceived benefits and seemingly limited potential harm of surveillance. (Sherman, 2014) The most impressive prospective data in this regards is from the study by Yeh YP. and colleagues (Y. P. Yeh et al., 2014) performed in Taiwan where they showed a reduction in mortality in the screened group compared to the unscreened high-risk patients and also the general population; accordingly, they recommended surveillance. They invited 11,114 Taiwanese subjects from 45 to 69 years of age, who were born before the nationwide anti-HBV vaccination, and therefore not protected by this early vaccination program. In the first stage, they defined a risk score to find the group who were at risk for HCC and invited them for abdominal ultrasound mass screening. These high risk groups were further divided to two subgroups: those positive for HBsAg or anti-HCV antibody and those at high risk according to the risk scores but negative for these two criteria. The attendance rate for screening test was reported to be 80.6% and the
detected lesions were confirmed by biopsy or dynamic imaging, as per AASLD practice guidelines. Abdominal ultrasound screening resulted in a 31% reduction in mortality due to HCC. They further highlighted the necessity of screening for HCC in those who are at high risk for development of HCC. (Y. P. Yeh et al., 2014) However, this may not be easily generalizable since the study is from a high incidence region. (Sherman, 2014)

HCC has a prolonged subclinical growth period which provides the possibility for the patients to be eligible for better treatment options on condition that their tumors are diagnosed early in the sub-clinical state of the disease. These anticipated benefits have prompted some professional societies, such as the American Association for the studies of Liver Diseases (AASLD) to recommend surveillance for patients at high risk of developing HCC, including patients with HCV-related cirrhosis. (Bruix et al., 2011; Mittal & El-Serag, 2013; Sherman, 2014)

1.3.1 Adherence to Surveillance
There are potentially life-saving therapeutic interventions available for cirrhosis and HCC which are capable of reducing the related morbidity and mortality if applied in a timely manner. Unfortunately, not all HCC patients are candidates for curative treatment modalities since their tumor may be at an already advanced stage when diagnosed. Furthermore, some of these therapeutic modalities like liver transplantation are resource intensive and not widely available for all eligible patients. (Kanwal et al., 2011) Therefore, surveillance programs can be of great help in this regards to detect eligible patients for these treatment options in a timely manner with an earlier-stage HCC while these therapies are still effective. (Davila et al., 2011)

Unfortunately, the extent of implementing HCC surveillance guidelines in routine clinical practice is unclear (Davila et al., 2010) and there are studies that evaluated the adherence to surveillance programs as poor due to challenges for both the provider and the patient. (Davila et al., 2011; Davila et al., 2010; Kanwal et al., 2011; Kanwal et al., 2010; Singh, Targownik, Ward, Minuk, & Bernstein, 2007) Davila and colleagues (Davila et al., 2011) conducted a retrospective cohort study on a large number of HCV-infected patients who developed HCC and showed that regular surveillance occurred only in 12% and inconsistent surveillance in 58.5% of patients eligible for the surveillance program and 29.5% of them received no surveillance. They also showed that the trend of receiving surveillance for HCC declined in the following 2 to 3 years of program start. In another study, Davila and colleagues (Davila et al., 2010) showed that
among patients eligible for surveillance for HCC, those with a higher socio-economic status and higher education were more likely to receive regular surveillance. Moreover, those patients who were seen by gastroenterologist/hepatologist or physicians within an academic organization had a 4.5 and 2.8 fold higher chance of receiving regular surveillance compared to those who were seen only by a primary care physician.

Altogether, there are several factors, patient or physician related, which contribute to the above observations such as presence of co-morbid conditions, which may reduce the probability of being eligible for a curative treatment option, alcohol use and access to healthcare services, to name a few, which influence the rate of receiving surveillance for HCC. (Davila et al., 2011) Noting that two important and major international guidelines (European Association for the Study of the Liver and the American Association for the Study of Liver Diseases) have recommended and supported surveillance for HCC in patients with HCV-related cirrhosis, it is possible that the adherence to this surveillance program increases with time, as was also discussed in the study by Davila and colleagues, mentioned above. (Davila et al., 2010) Finally, as will be further discussed in the methodology section, in order to further evaluate the effect of adherence to the surveillance program on the outcomes, it has been incorporated into the model in the current study.

1.3.2 Surveillance Methods

1.3.2.1 Serologic Tests

Among serological tests, AFP has been more extensively studied. (Trevisani et al., 2001) AFP alone, with a cut-off point of 20ng/ml has a sensitivity of 60% which is not high enough to support it as a sole means of surveillance or for HCC diagnosis. (Bruix et al., 2011; Deuffic et al., 1998; El-Serag & Mason, 1999) Increasing the cut-off point to for example, 200ng/ml drops the sensitivity to 20%; reducing the cut-off point leads to more HCCs diagnosed but at the cost of a progressive increase in the rate of the false-positive diagnosis rate. Furthermore, serum AFP is not elevated in about 50% of small HCCs and only about 80% of large HCCs are associated with elevated serum AFP levels. (Di Bisceglie et al., 2005; El-Serag, Kanwal, Davila, Kramer, & Richardson, 2014; Richardson et al., 2012; Sherman, 2014) Recently, as part of the HALT-C study, AFP was confirmed to lack the required efficacy as a surveillance test. (Bruix et al., 2011; Lok et al., 2010) In the long run, AFP is still not considered an adequate HCC screening test due
Des-γ-Carboxy Prothrombin (DCP) is also another option among serologic tests which has mainly been evaluated as a diagnostic test in available studies. There are also reports that evaluated DCP as a marker for portal vein invasion by the tumor. Studies to date have not supported its use. (Sherman, 2014) This, together with its insufficient accuracy suggest that DCP is not a good surveillance tool, a fact that has also been confirmed in the HALT-C study. (Bruix et al., 2011; Koike et al., 2001; Lok et al., 2010) There are other serologic tests suggested for this purpose such as the ratio of glycosylated AFP (L3 fraction) to total serum AFP, glypican 3 and various fucosylated glycoproteins; however, these have not yet been adequately investigated and their potential to be used as serologic surveillance tests is not known. (Sherman, 2010b)

1.3.2.2 Pathologic Testing
Liver biopsy and its role in HCC diagnosis was elaborately discussed in the previous section on diagnosis of HCC. However, as a screening test, unfortunately, in addition to its unacceptability by patients in comparison to radiologic imaging techniques for regular testing, is not entirely reliable in evaluating a small nodular lesion in a liver with cirrhosis. In this setting, as discussed by Lencioni and colleagues, (R. Lencioni et al., 2008) a positive biopsy result which is assessed by an expert pathologist, is helpful whereas a negative result cannot rule out malignancy. Moreover, it carries a low but not negligible risk of complications and morbidities including tumor seeding along the needle track. (R. Lencioni et al., 2008) These explanations and also favourable performance of US as a screening test as discussed above, are the reason why biopsy is not included in the current proposed evaluative model.

1.3.2.3 Radiologic Tests
CT scan and MRI are more specific for imaging the liver when compared to ultrasonography; however, they are both much more expensive than ultrasonography and CT scan is also associated with radiation exposure. Therefore, these are usually used in diagnosis and staging of HCC rather than in its surveillance programs. (Mittal & El-Serag, 2013) There are two distinctive vascular abnormalities in HCC, hypervascularity of the tumor mass itself
(neovascularisation or abnormal tumor-feeding arterial vessels) and thrombosis of portal veins by tumor invasion. These characteristics have made ultrasound (US) an acceptable screening tool for HCC. However, in order to accurately diagnose tumor size and presence as well as extent of portal vein invasion, a helical/triphasic CT scan should support the primary findings. (Carr, 2012) The radiation risk and the performance characteristics of CT scan when it is used as a surveillance test, is not known. (Bruix et al., 2011) Substituting abdominal US with contrast CT scan did not offer any advantage in an RCT performed in the United States where CT scan turned out to be significantly more costly due to the expenses of evaluating false positive diagnoses. (Pocha et al., 2013) Obviously, this substitution will also limit the population’s access to HCC surveillance facilities. (Sherman & Colombo, 2014)

There are different values in different studies reported for sensitivity and specificity of US when used as a surveillance tool. The sensitivity of US as a surveillance test for the detection of small HCCs is highly operator dependent and is also affected by patients and tumor characteristics. (Sherman, 2014) In a systematic review performed by Colli and colleagues, US had a specificity of about 97% and sensitivity of about 60% in this application. (Colli et al., 2006) On the other hand, combined use of serologic and radiologic tests, such as AFP and US may help increase the tumor detection, but at the same time increases the false positive diagnoses and also cost per tumor diagnosed. (B. Zhang & Yang, 1999) Altogether, abdominal US is accepted across the world as the standard modality for HCC surveillance. (Sherman & Colombo, 2014) It is recommended to be used alone by both the American and European societies for the studies of liver diseases. (Bruix et al., 2011; European Association for the Study of the, 2011)

1.3.3 Surveillance Interval

The surveillance interval is determined using the tumor growth rates rather than the degree of tumor development risk. As was also discussed by Andersson and colleagues, (Andersson et al., 2008) HCC grows with a doubling time of about 117 to 195 days, (Barbara et al., 1992; Ebara et al., 1986; Sheu et al., 1985) suggesting this would be a reasonable surveillance interval. (Sherman & Colombo, 2014) Unfortunately, the ideal interval for performing surveillance for HCC is not known though there are several studies comparing different intervals with each other. (Sherman, 2010b) One RCT in patients with cirrhosis with HCV infection or alcoholic liver disease, showed that screening patients for HCC with three versus six-month intervals, not only did not offer any survival benefits, but also increased the difficulty of detecting smaller
(<1cm) and at the same time hard to diagnose liver nodules. These were in addition to the higher false positive detections and higher cost for higher number of investigations to evaluate them. (Sherman, 2014; Trinchet et al., 2011)

On the other hand, the superiority of surveillance with a six-month interval compared to a twelve-month interval, such as early detection through surveillance, has been shown by many observational studies. (Sherman & Colombo, 2014) As Kim Do and colleagues (Kim do et al., 2011) discussed, a prospective study in Korea with a large number of patients under study demonstrated a better survival for biannual compared to annual surveillance. (Han et al., 2013) Altogether, according to current guidelines, surveillance should be based on ultrasound examination with screening intervals of six months regardless of the HCC development risk level being high or low. (Bruix et al., 2011; O. S. Lin, Keeffe, Sanders, & Owens, 2004; Mittal & El-Serag, 2013; Sherman, 2014; Sherman et al., 2011; A. Singal et al., 2009)

1.3.4 Management of an Abnormal Screening Test

Following detection of a nodule with a screening test, the diagnosis should be confirmed; therefore, a recall policy is the approach used for an abnormal screening test result. An abnormal test result in this context is any nodule which was not detected in the previous screening procedure or a nodule which enlarges between two screening procedures, even if considered benign previously. (Bruix et al., 2011) This diagnosis interpretation becomes more challenging in a nodular cirrhotic liver where ultrasound may not be able to distinguish early HCC nodules in the inherent nodular context of the cirrhosis. Contrast imaging techniques and/or ultrasound-guided thin needle liver biopsy are the standard methods in this regard. (Bruix et al., 2011; Sherman & Colombo, 2014) Diagnosis of HCC by imaging techniques is based upon the pathognomonic radiologic characteristics of the tumor which have been extensively discussed in the section on HCC diagnosis.

1.3.4.1 Sequential vs. Coincidental Testing

In its latest update, the AASLD algorithm suggests sequential testing for HCC detection. (Bruix et al., 2011) In an attempt to evaluate the benefits offered by this testing format, Manini and colleagues (Manini et al., 2014) recently performed a multicenter validation study with one single contrast imaging modality to begin with and then CT scan or MRI, and demonstrated 88% diagnosis of 1-2cm tumors and 90% of those larger than 2cm. Moreover, the need for
performing fine needle biopsy for 1-2cm nodules was reduced by 17% with this method in comparison with the one suggested in 2005 AASLD guideline.

This idea is further supported by the study performed by Khalili and colleagues (Khalili et al., 2011) who tried to determine the optimal imaging or combination of imaging diagnostic tests for 1-2cm nodules detected during HCC surveillance, in terms of performance and resource utilization. They examined multiple test formats either coincidental (tests done at the same time) or sequential, one after the other, and found that coincidental testing was resource intensive since it practically doubles the number of tests required. Moreover, with two coincident positive radiologic tests, the sensitivity for diagnosing a malignant tumor is expected to drop off but the specificity increases, which translates into more follow-up tests and more confirmatory biopsies. (Khalili et al., 2011)

Sequential imaging with high specificity tests is capable of improving sensitivity of the examination without reducing the specificity. As Khalili and colleagues (Khalili et al., 2011) have discussed, with coincidental imaging requiring both to be positive, combining CT scan, MRI and CE-US, the sensitivities and specificities fluctuated within the range of 29% to 41% and 99% to 100% respectively, while with sequential testing requiring only one scan to be positive and without any difference in the order of the imaging modalities, fluctuations were between 74% to 89% for sensitivities and 91% to 99% for specificities. They have concluded that for maximizing the sensitivity, performing the imaging tests in sequence is the preferred examination modality.

1.3.5 Cost-Effectiveness and Surveillance

Policy-makers and those who pay for the healthcare services are usually faced with questions when it comes to decisions and recommendations about interventions or medications, especially if expensive. The answers to these types of questions are most strongly influenced by the estimation of benefits by decision-makers and also the value of the alternative choices of actions and recommendations. In order to find an acceptable answer, economic or efficacy evaluation should be performed. During these evaluations, questions such as the following may arise:

- Is this health intervention, service or program worth doing compared with other options possible with the same amount of resources?
- Is it advisable to use available resources in this option rather than other possible ways?
Although economic evaluation assists decision-makers by providing them with important information, it should be preceded with three other types of evaluations, each of them addressing a different type of question. As Drummond and colleagues (Drummond, 2005) have discussed, for a particular interventions or service, these may include:

- "Can it work?"; the idea here is whether the health procedure, program or service in question does more good than harm to those who will be fully adherent to the recommendations. Practically, efficacy is evaluated in this step.

- "Does it work?"; this evaluates whether the health procedure, program or service in question does more good than harm to those to whom it is provided or offered. Inherent to this evaluation is consideration of the acceptability and usefulness of the procedure, program or service for the target population. Practically, effectiveness is evaluated here.

- "Is it available?"; this practically evaluates whether the health procedure, program or service is available for those who will benefit from or require it.

Available resources such as time, facilities, equipment, people and knowledge are scarce and systematic analyses are required to identify relevant alternatives and to minimize the possibility of excluding an important option from consideration. Moreover, without measurement and comparison of the resources used and the output of programs or interventions, there will not be enough information available to base judgement on the value of the intervention for the resources consumed. Resources consumed constitute more than just the money spent and may also include the so-called "opportunity cost" (Drummond, 2005) which is the value of obtainable benefits in other options which have been lost or forgone by spending the resources for the program, health service or intervention under evaluation.

Bearing all the above-mentioned discussion in mind, it is clear that economic evaluation deals with "costs" consumed for a program or intervention and the achieved "consequences". Meanwhile, making choices is an inbuilt step in this evaluation to face the scarcity of resources. Therefore, as Drummond and colleagues (Drummond, 2005) have discussed, economic evaluation is the "comparative analysis of alternative courses of action in terms of both their costs and consequences". Economic evaluation includes methods such as cost analysis, cost-effectiveness analysis, cost-utility analysis and cost-benefit analysis which are briefly explained below.
1) Cost analysis is simply evaluation of the costs of a procedure or program in monetary units without concern about the consequences or measuring them.

2) Cost-effectiveness analysis measures costs in monetary units but it also identifies the consequences of the program or procedure in the forms of an effect of interest common to both alternatives under investigation in the most appropriate units such as "years of life gained" or "cases correctly diagnosed" or "disability-days saved" and express the results of the evaluation in the form of a cost-effectiveness ratio.

3) Cost-utility analysis also measures costs in monetary units. It identifies the consequences in the form of single or multiple effects of interest which may not be common to both alternatives, but these consequences are adjusted by a health preference weight called utility. In this way, the quality of life-years gained, rather than just the number, can be measured and compared. Therefore, most commonly, the measure for consequences in this type of study is quality-adjusted life-year (QALY). However, some authors like Gold and colleagues (Gold, 1996) prefer not to separate cost-effectiveness and cost-utility studies since they are so similar.

Health state utilities are used to measure quality of life and are usually assessed in relation to two extremes, referred to as anchor states. These so-called anchors are commonly death with an assigned value of "0" and full health with the assigned value of "1". (Chong, 2003; Naglie, Krahn, Naimark, Redelmeier, & Detsky, 1997) Utilities have the advantage of being useful in decision analyses and cost-effectiveness studies (Chong, 2003) where their most frequent outcome, i.e. QALYs, are calculated through multiplying the time spent in a particular health state by the utility of that given state. On the other hand, as also discussed by Younossi and colleagues, (Younossi, Boparai, McCormick, Price, & Guyatt, 2001) anchoring utilities to death and full health states is quite significant since it offers the opportunity of measuring decreases in health related quality of life and the reductions in life-span, both in the same unit.

4) Cost-benefit analyses measure the costs and consequences of programs or interventions under investigation both in monetary units. However, it suffers from the fact that the range of benefits valued in monetary terms is somewhat limited. (Drummond, 2005)
As Mentioned above, cost-effectiveness analysis (CEA) is a method of finding out whether an intervention will enhance outcomes in terms of changes in costs and health benefits, when compared with one or more alternative interventions or with no intervention at all. (Sherman & Colombo, 2014) This type of analysis provides an accepted approach to evaluate alternatives and whether a health or medical service provides reasonable value for the cost in the decision-makers’ or society point of view. (Drummond, 2005; Neumann, 2009) Surveillance programs should be effective and cost-effective if they are to gain wide acceptance. Accordingly, for HCC surveillance programs, studies have focused on identifying risk factors influencing HCC development in order to identify the at-risk population who would benefit from screening and also when they need the surveillance in the course of their disease. This becomes much more important given that the prevalence of cirrhosis, HCV infection, and HCC has increased at least in some areas in the world and will continue increasing for a few more decades. (Davis et al., 2010; Kanwal et al., 2011; Sherman, 2010a, 2010c)

The level of risk for HCC development is the mainstay for deciding whether a patient is a good candidate for a surveillance program or not; this in turn relies on the incidence of the tumor in the specific patient population. Decision analysis helps delineate the required cut-off points for these programs. Traditionally, if an intervention costs less than $50,000/year of quality-adjusted life gained, it is considered cost-effective, though these levels were set many years ago and may be less applicable currently. (Bruix et al., 2011; Laupacis, Feeny, Detsky, & Tugwell, 1992) The approach to these thresholds for cost-effectiveness will be thoroughly discussed in the methods section later on.

According to AASLD, surveillance for HCC is suggested to be cost-effective if the expected annual HCC risk surpasses 1.5% in HCV infected patients; however, it may not apply to many HCC situations such as in post-SVR patients. The difference in the cut-off for HBV with other etiologies for HCC is due to the higher frequency of HCC development in a non-cirrhotic liver in hepatitis B, which allows for implementing effective therapies. (Bruix et al., 2011; Sherman, 2010b, 2011)

1.3.6 Previous CEA Studies on Surveillance for HCC

Efficacy and cost of surveillance programs for HCC have been the subject of some cost-effectiveness analyses. (Andersson et al., 2008; Arguedas, Chen, Eloubeidi, & Fallon, 2003;
Cucchetti et al., 2012; Kang, Lee, Yap, & Lun, 1992; O. S. Lin et al., 2004; Naugler & Sonnenberg, 2010; Nouso et al., 2008; Patel, Terrault, Yao, Bass, & Ladabaum, 2005; Saab et al., 2003; Sarasin, Giostra, & Hadengue, 1996; Shih, Crowley, & Sheu, 2010; Thompson Coon et al., 2008) All of these studies have concluded that screening is effective and cost-effective, in the population groups under study, since they have all found that it decreases mortality related to HCC, though they have used different protocols and found different effect sizes, with ICERs comparable with the common cost-effectiveness threshold of $50,000/QALY. (Sherman & Colombo, 2014) These studies share some similar features but differ in terms of the population under study, screening intervals, methods and the cost structure they have implemented. A noteworthy point here is that none of them describes a treatment model which is currently in practice in North America. (Sherman & Colombo, 2014) A challenging fact is that these studies have not incorporated liver transplantation or sorafenib in their therapy portfolios and have assumed the adherence to their evaluated surveillance program to be 100% instead of incorporating it as a variable in their models. Moreover, the underlying liver disease which creates a competing mortality risk in different populations is another issue hindering comparisons across studies. Despite the level of variation among these studies in terms of design and management, all of them show that screening in their settings is effective and cost-effective, at least in certain scenarios. (Sherman & Colombo, 2014) Some of the main characteristics of these studies as summarized in Table 1.3-1, will be further discussed below.

Lin and colleagues (O. S. Lin et al., 2004) compared three strategies and concluded that surveillance with AFP plus US was the most cost-effective choice. However, surveillance was limited to Child Pugh A patients only, with screening adherence assumed to be 100%; all patients who had undergone surgical resection were only eligible for palliative treatment regardless of the size or location of the tumor. Furthermore, values used for sensitivity of AFP and US (0.54 and 0.93, respectively) are unlikely to be true for tumors of small size. (Sherman & Colombo, 2014) Thompson Coon and colleagues (Thompson Coon et al., 2008) have concluded that AFP alone is the most cost-effective strategy among those reviewed. Ultrasound together with AFP will add to the efficacy and at the same time to the cost of the surveillance program. The HCC development rate was assumed to be the same in compensated and decompensated cirrhosis and 65% of HCCs < 2cm were assumed to have AFP levels > 20ng/ml; both are unlikely assumptions. (Sherman & Colombo, 2014)
Table 1.3-1: Main characteristics of some CEA studies (Sherman & Colombo, 2014)

<table>
<thead>
<tr>
<th>Author</th>
<th>Population Studied</th>
<th>Intervention</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kang &amp; Colleagues</td>
<td>Cirrhosis, not otherwise defined</td>
<td>No surveillance</td>
<td></td>
</tr>
<tr>
<td>(Kang et al., 1992)</td>
<td></td>
<td>AFP</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>US</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>AFP &amp; US</td>
<td></td>
</tr>
<tr>
<td>Sarasin &amp; Colleagues</td>
<td>Cirrhosis, CP class A</td>
<td>No Surveillance</td>
<td>$22,575</td>
</tr>
<tr>
<td>(Sarasin et al., 1996)</td>
<td></td>
<td>AFP &amp; US</td>
<td>$14,675</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US</td>
<td>$101,143</td>
</tr>
<tr>
<td>Arguedas &amp; Colleagues</td>
<td>Cirrhosis, CP class A, 50 year old</td>
<td>US &amp; AFP</td>
<td></td>
</tr>
<tr>
<td>(Arguedas et al., 2003)</td>
<td></td>
<td>CT scan &amp; AFP</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>MRI &amp; AFP</td>
<td></td>
</tr>
<tr>
<td>Saab &amp; Colleagues</td>
<td>Cirrhosis, awaiting OLT</td>
<td>AFP</td>
<td>Comparator $60,000</td>
</tr>
<tr>
<td>(Saab et al., 2003)</td>
<td></td>
<td>AFP &amp; US</td>
<td>$74,000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US</td>
<td>$101,000</td>
</tr>
<tr>
<td>Lin &amp; Colleagues</td>
<td>Cirrhosis, HCV related, 40 yrs old</td>
<td>AFP &amp; US, Q6M</td>
<td>$73,789</td>
</tr>
<tr>
<td>(O. S. Lin et al., 2004)</td>
<td></td>
<td>AFP &amp; US, Q12M</td>
<td>$23,400</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AFP, Q6M &amp; US, Q12M</td>
<td>$73,789</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CT Scan &amp; AFP</td>
<td>Not Cost Effective</td>
</tr>
<tr>
<td>Patel &amp; Colleague</td>
<td>Cirrhosis, HCV related, Age 40-70 years</td>
<td>No Surveillance</td>
<td>&lt;$51,000 depending on living donor</td>
</tr>
<tr>
<td>(Patel et al., 2005)</td>
<td></td>
<td>AFP &amp; US, Q6M</td>
<td>vs. Cadaveric liver transplantation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CT scan</td>
<td>or resection</td>
</tr>
<tr>
<td>Nouso &amp; Colleagues</td>
<td>Cirrhosis, CP class A, Age 40, in different countries</td>
<td>No Surveillance</td>
<td>No OLT $29,000</td>
</tr>
<tr>
<td>(Nouso et al., 2008)</td>
<td></td>
<td>US, Q6M</td>
<td>OLT &gt; $50,000</td>
</tr>
<tr>
<td>Andersson &amp; Colleagues</td>
<td>Cirrhosis, &gt; 50 yrs old</td>
<td>No Surveillance</td>
<td>Every 6 months-$30,700</td>
</tr>
<tr>
<td>(Andersson et al., 2008)</td>
<td></td>
<td>US, Q6&amp;12M</td>
<td>Every 12 months-$21,200</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CT scan, Q6&amp;12M</td>
<td>Adding AFP-$73,500</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MRI, Q12M</td>
<td>CT scan &amp; MRI &gt; $300,000</td>
</tr>
<tr>
<td>Thompson Coon &amp; Colleagues</td>
<td>Cirrhosis, compensated, due to HBV,HCV &amp; ALD</td>
<td>AFP &amp; US, Q6 &amp; 12M</td>
<td>£10,000-£24,000 depending on the</td>
</tr>
<tr>
<td>(Thompson Coon et al., 2008)</td>
<td>Analyzed separately &amp; combined</td>
<td>US, Q6 &amp; 12M</td>
<td>disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AFP, Q6 &amp; 12M</td>
<td></td>
</tr>
<tr>
<td>Shih &amp; Colleagues</td>
<td>High risk HBV / HCV (Not Defined)</td>
<td>AFP &amp; US (at varying intervals)</td>
<td>~$15,000</td>
</tr>
</tbody>
</table>

QALY: Quality Adjusted Life Year; Rx: Treatment; Q6M: every 6 months; ALD: Alcoholic Liver Disease; Permission has been granted. "© Georg Thieme Verlag KG"

There are some studies available in the literature which have evaluated the cost effectiveness of surveillance for HCC in pre-SVR population. This table reviews some of those studies and compares their main characteristics together. Among these characteristics are the population under study and the surveillance methods. However, no single model can be totally complete and each and every of them have their own pros and cons which have been described in the text.

Patel and colleagues (Patel et al., 2005) have also offered surveillance only to potential OLT and surgical resection candidates; they have not used utility values for all health sates. Furthermore, they have assumed the specificity of CT Scan to be 100% as a confirmatory test and therefore, they practically do not have any false positive cases in their screening, which is quite important given the morbidity and costs associated with investigating and /or treating false positive results.
One of the strengths of the analysis performed by Andersson and colleagues (Andersson et al., 2008) was that their disease model closely approximates the current practice model. They have concluded that, among the strategies they have reviewed, biannual ultrasound is the most cost-effective approach. (Sherman & Colombo, 2014) Among the very few studies which have mentioned false positive diagnoses, Arguedas and colleagues (Arguedas et al., 2003) have explained how they dealt with these cases. They followed false positive diagnoses with three-monthly triphasic CT scan or MRI for six months and if negative, they resumed the regular surveillance according to the selected strategy. However, this study has not reported any results about this population and their impact on their final outcome. Kang and colleagues (Kang et al., 1992) have also mentioned false positive diagnoses in their study but without any further information. Lastly, Shih and colleagues (Shih et al., 2010) have assumed sensitivity and specificity of their screening tests to be 100% which resulted in total absence of false positive diagnoses in the surveillance program which may have notable effects in underestimating cost and utilities.

In the long run, no single decision analysis model, including the ones discussed above, can be comprehensive and complete enough to meet each and every requirement as a result of inherent short-comings of this research method. Some lack the complete portfolio of available treatments, some do not include all patients in the program, some suffer from short follow-up periods and the last but not the least, some have multiple assumptions which may affect robustness of the studies. Moreover, none of them have evaluated and looked into the post-SVR setting. A model should reflect current practice. In North America, any disease history describing HCC treatment should reflect the BCLC treatment algorithm and take the effect of the underlying liver function into account. (Sherman & Colombo, 2014) The current model is designed to accurately reflect disease history and to address short-comings noted for cost-effectiveness analyses published to date.
2 Chapter Two: Rationale, Hypothesis and Objective

2.1 Rationale

HCC is one of the most common malignancies in the world and accounts for the third most common cause of cancer death. (Carr, 2012) There are over half a million new cases of HCC diagnosed annually in the world and approximately the same number die of the tumor, showing the dismal prognosis of this cancer. (GLOBOCAN; Mittal & El-Serag, 2013; Nordenstedt et al., 2010) Therefore, HCC has a substantial effect on the mortality and morbidity in the affected population in terms of management costs and financial problems stemming from therapeutic and diagnostic interventions as well as from lost opportunities while managing morbidities. This will be a huge burden on national health budgets which are already restricted in many areas in the world. Fortunately, HCC has turned from an almost always lethal tumor in the last decade into a malignancy that can be prevented and can be cured with available treatment options if detected early; (Bruix et al., 2011) therefore, it warrants an active intervention in the form of surveillance programs to be detected when it is still eligible for curative therapeutic options.

Patients are more involved in the decisions made for their illnesses today; this together with the decrease in available resources on the contrary to the growth in worldwide population, make it critical for physicians as well as policy makers to think also about the cost of services they offer. (Elwyn, Edwards, Eccles, & Rovner, 2001; Sepucha & Mulley, 2009) Therefore, as population outgrows the available resources, physicians ought to care not only about the best available health services for their patients, but also for the costs of those services. (Sepucha & Mulley, 2009) This, together with the rapid improvements in the efficacy of antiviral therapies in curing HCV infection and evolving expertise in HCC management, highlight the importance of reconsidering HCC surveillance protocols in post-SVR cirrhosis patients.

Economic evaluation of interventions and decisions in service provision has become an essential part of modern healthcare systems. This has resulted in an increasing demand for cost-effectiveness analysis evidence to back up efficient and wise decisions in health economic management. (Lens & Dawes, 2002; Raftery, 1998) Unfortunately, as shown by many economic evaluations, no published analyses in healthcare are free from flaws and methodological
imperfections (Lens & Dawes, 2002) and the results may not be comparable among different countries with different economic and population attributes.

On the other hand, due to logistic and ethical concerns, randomized controlled trials (RCTs) may not be a good format of study to evaluate cost-effectiveness of a surveillance program for a lethal tumor such as HCC. Retrospective studies also may suffer from confounding factors and biases such as lead time and over-diagnosis, as discussed by Lin O.S. and colleagues (O. S. Lin et al., 2004) According to the current knowledge of the literature, there have been two RCTs of HCC surveillance, both performed in China. As also reviewed by Sherman and colleagues, (Sherman, 2010b) the first study by Chen and colleagues, (Chen et al., 2003) followed up 5581 chronic hepatitis B carriers about 6 years for liver cancer with biannual AFP testing. The second study was performed by Zhang and colleagues, (B. H. Zhang et al., 2004) where they followed about 18,800 high risk patients with HBV infection or a history of the same infection, for about 5 years with biannual AFP and ultrasound screening to evaluate HCC mortality. The first one failed since many of their patients, though detected with early cancer, did not receive the recommended treatment. The second study found a 37% reduction in HCC-related mortality, however, they had sub-optimal adherence to screening in their population (58.2%) and also did not incorporate liver transplantation in their treatment options, therefore, there are some limitations in generalizing this study to other etiologies of HCC.

In the absence of RCTs, decision analysis modeling seems to be a reasonable method in these situations to evaluate such a research question. (Patel et al., 2005) Decision analysis is appropriate when there is some uncertainty about the clinical strategy under investigation and a meaningful trade-off between the strategies. (Detsky, Naglie, Krahm, Naimark, & Redelmeier, 1997) There are several cost-effectiveness analysis studies in the literature (Andersson et al., 2008; Arguedas et al., 2003; Kang et al., 1992; O. S. Lin et al., 2004; Nouso et al., 2008; Patel et al., 2005; Saab et al., 2003; Sarasin et al., 1996; Shih et al., 2010; Thompson Coon et al., 2008) which have analysed HCC surveillance programs, though each has its own pros and cons in terms of short time horizon, not including all possible treatment options and not incorporating adherence to the screening tests in their models, to name a few. Furthermore, none, according to the current knowledge, have used post-SVR patients in their evaluations.
Although the current Markov model will not be exempted from the inherent flaws of the technique as described above, it was designed with an aim to make it as complete and detailed as the inherent short-comings of this technique and also the presently available data allow, in hopes of simulating real-life situations as much as possible. An elaborated discussion on design of this model can be found in the methodology section.

2.2 Hypothesis

The hypothesis introduced here is surveillance for HCC is cost-effective in patients with hepatitis C related cirrhosis who have achieved SVR.

2.3 Objective

To determine the cost-effectiveness of biannual ultrasound HCC surveillance in patients with HCV-related cirrhosis who have achieved SVR, versus no surveillance, from the healthcare payer perspective.
3 Chapter Three: Methods

3.1 Approach to the research question

As discussed in the section on rationale for this study, decision analysis modeling is an appropriate choice to implement the study. Decision analysis includes a collection of analytical tools that though distinct from economic evaluation methods such as cost-effectiveness and cost-utility analyses mentioned above, is complementary to them. As discussed by Briggs and colleagues, (A. Briggs, Claxton, K., Schulpher, M., 2006) decision analysis defined as a systematic approach to decision making in uncertain situations, has been used in health care evaluations in terms of informing clinical decisions at different levels ranging from individuals to populations.

In order to perform an economic evaluation with this method, decision analytic models are designed using mathematical structures representing clinical reality at an adequate level of detail. This approach makes it possible to estimate the defined consequences of a particular decision in a healthcare system that would flow from a number of alternative options under investigation. (A. Briggs, Claxton, K., Schulpher, M., 2006; Caro, Briggs, Siebert, Kuntz, & Force, 2012)

Based on the data used in a model, the likelihood of each and every consequence is evaluated and interpreted in terms of probabilities. Each of these consequences then have a cost and an outcome attributed to them. (A. Briggs, Claxton, K., Schulpher, M., 2006) Decision analysis models can also help, in the context of uncertainty of the available evidence, to define the probability that a given decision would be the correct one to make. (A. Briggs, Claxton, K., Schulpher, M., 2006) Decision analysis models, on one hand, have to be sufficiently complex to include all essential and important events and values related to the question to possess the required face validity, but at the same time, sufficiently simple to be understandable as a communication tool. (Caro et al., 2012; Detsky, Naglie, Krahn, Naimark, et al., 1997; Roberts et al., 2012)

Therefore, the desire to make the model as complete as possible to include all key issues to fully describe the risk-benefit trade-off for the topic should be balanced with availability of the
required data to support the detailed structure, though it should not be driven by this data availability. (Detsky, Naglie, Krahn, Naimark, et al., 1997) On the other hand, it is essential to have a thorough picture of the problem incorporated into the model; therefore, the initial discussion for the problem and design of the model, should broadly cover as many features of the problem and its outcomes as possible, for which data may be limited or even not available. Although conducting sensitivity analyses on the model results can help evaluating the effect of these missing data on final outcomes, but a delicate balance is a must here to have a complete and robust model. (Roberts et al., 2012)

When designing a decision analysis model, an important consideration would be whether the model should characterise the "average" patient from a population who share the same characteristics or should consider individual patients and as well as incorporating the variability between patients. However, most decision models designed for economic evaluations focus on the average patient experience. (A. Briggs, Claxton, K., Schulpher, M.,, 2006) These are referred to as cohort models with "Decision tree" and "Markov models" being the two most common forms.

Decision trees are probably the simplest form of decision analysis models whereas Markov models are capable of handling the added complexity of modelling options and alternatives including multiple possible consequences. These models are structured around mutually exclusive health/disease states which represent the possible consequences for the alternative under investigation. This has offered Markov models the required flexibility to be used in evaluations such as screening programs. (A. Briggs, Claxton, K., Schulpher, M.,, 2006; Sanders et al., 2005) Calculation of the expected costs and outcomes for cohort models involve taking into account how long patients would stay and spend time in a given health/disease state. (A. Briggs, Claxton, K., Schulpher, M.,, 2006)

3.2 Conceptualization of the model

The process of conceptualization in decision analysis can be divided into two major components. One is developing the research question and understanding the problem to guide its representation in a model. The second is conceptualization of the model itself, which is the process of matching the characteristics of a particular model type to meet the needs of the
3.2.1 Model Population

The target population in this study is a closed cohort (Roberts et al., 2012; Rutter, Zaslavsky, & Feuer, 2011) of 50 year-old Canadian patients with compensated cirrhosis (Child-Pugh class A) stemming from CHC who have been cured of their HCV infection and have achieved sustained virological response (SVR). Myers and colleagues (Myers et al., 2014) discussed the prevalence of hepatitis C viremic cases in Canada and mentioned that the highest number of these cases were in the 40 to 54-year age group. They also demonstrated in an analysis that more than 70% of the HCV infected population in Canada was born between 1944 and 1978. This range, as discussed by Shah and colleagues, (Shah et al., 2013) captures about 77% of HCV infected individuals in Canada and roughly represents the range recommended by the Canadian Liver Foundation for HCV infection screening. ("Canadian Liver Foundation-Hepatitis C Testing," 2012) Sensitivity analysis evaluates the effect of changing the surveillance start age within the age range of 40-60 years.

3.2.2 Comparator Strategies

This study will evaluate the cost-effectiveness of surveillance for HCC in the target population introduced above, through comparing the strategy of "Screening all" patients with "Screening none". The screening modality is biannual abdominal ultrasound; the adherence to the surveillance program has been assumed to be 95%. However, adherence to surveillance is incorporated into the model structure, thereby allowing sensitivity analyses to evaluate the effect of different values of this variable on final results.

3.2.3 Health Outcomes

In order to measure and value the health outcomes in the model, the results are expressed as quality-adjusted life-years (QALYs), which is a standardized outcome measure to enable comparability in cost-effectiveness analyses of healthcare interventions. (Caro et al., 2012; Laupacis et al., 1992)

3.2.4 Study Perspective

The "perspective" in a cost-effectiveness analysis reflects the audience for the model. (Caro et al., 2012) This model uses the "healthcare payer" perspective, which includes only costs...
required for providing medical services and interventions modeled and does not include indirect costs such as productivity loss. (Neumann, 2009; Roberts et al., 2012)

3.2.5 Discount Rate

Discounting indicates the rate a society sets for time preference, which denotes the preference of receiving a benefit earlier or to incur a cost later. (Roberts et al., 2012) Accordingly, based on the recommendation by the Canadian Agency for Drugs and Technologies in Health (CADTH), (CADTH, 2006) a 5% annual discount rate for costs and health effects was used in this analysis. However, for sensitivity analysis, a rate of 0% will be used to evaluate the impact of discounting and then a rate of 3% will be used for the purpose of comparison with published studies in other jurisdictions which have used a 3% annual rate. (CADTH, 2006)

3.2.6 Time Horizon

Time horizon shows how far into the future outcomes will be projected and modelled and is therefore determined by the scope of the problem under investigation. (Roberts et al., 2012) The time horizon should be sufficiently large so that all health effects, harms (if any) and all costs relevant to the problem and decision under investigation can be captured. (Caro et al., 2012; Drummond, 2005; Siebert et al., 2012; Siegel, Weinstein, Russell, & Gold, 1996) Here again, the same issue of accuracy versus simplicity arises as the data for longer time periods may not be available (Detsky, Naglie, Krahn, Naimark, et al., 1997) whereas the extended time horizon may create problems when calculating utility values which are not usually constant over time, making computing even more complex. (D. Naimark, Krahn, Naglie, Redelmeier, & Detsky, 1997; Sonnenberg & Beck, 1993)

However, since HCC surveillance affects mortality through timely diagnosis of HCC thereby affecting therapies that can be used, the time horizon should be lifetime to capture QALYs gained from delayed death; (Siebert et al., 2012) therefore, a "Life-time" time horizon was used for this model in order to be as comprehensive as possible in capturing related events.

3.2.7 Willingness-To-Pay Threshold

Conventionally, $50,000 per quality-adjusted life-year (QALY) is used as a decision rule to reflect society’s willingness-to-pay (WTP) for health benefits, and as a guide in interpreting cost-effectiveness analyses. (Braithwaite, Meltzer, King, Leslie, & Roberts, 2008) This value of
$50,000/QALY decision rule has not been updated since it first emerged in 1982, (Ubel, Hirth, Chernew, & Fendrick, 2003) and may not be consistent with the current spending behaviour for health sectors in some countries including the USA, where Braithwaite and colleagues conducted a study to evaluate this threshold (Braithwaite et al., 2008). They showed that the plausible range for a cost-effectiveness decision rule would be $109,000 to $297,000 / QALY.

Conversely, Neumann and colleagues, (Neumann, Cohen, & Weinstein, 2014) note that researchers still continue to cite this traditional threshold regularly, although many have been referencing $100,000/QALY. Practically, the best approach is that the threshold should depend on the budget available to a decision maker in a particular jurisdiction who can evaluate the costs and benefits of alternative uses attributable to that budget.

To be consistent with the literature (more than 35% of cost-effectiveness analyses in the literature used the $50,000/QALY threshold) (Neumann, Sandberg, Bell, Stone, & Chapman, 2000) the $50,000 per QALY threshold was used to assess cost-effectiveness. The effect of this threshold on cost-effectiveness was further investigated in the sensitivity analysis section which will follow.

### 3.2.8 Assumptions

There are some data required in any decision analysis model that may be absent in the literature or suffer from a high level of uncertainty. The absence of published data brings up the need to make several assumptions. Measures have been taken to minimise the number of assumptions and incorporate the points into the structure of the model as much as possible to be available for sensitivity analyses. This will not only help preventing biases in this step, but will also assist to decide on the value of the missing information for future research planning. The following assumptions were made in this study:

- The model is a Markov chain; no entry to the model is allowed after cycles start.
- It is assumed that the populations entering this model are free from any specific pre-existing medical conditions and co-morbidities that disqualify them from receiving any therapeutic options available in the model.
- Adherence to the surveillance tests, values for utilities, transition probabilities, tumor incidence, incidence rates for complications related to the therapeutic interventions, mortality rates and natural history of cirrhosis and/or HCC, may change with patients’
age. (Asahina et al., 2010; Cottone et al., 1994; Van der Meer, 2013b) Nevertheless, these values are assumed to be constant over time in this study. However, the model structure has the ability of incorporating these changes on availability of reliable data on the temporal pattern of these values.

- Patients who are not adherent to the surveillance program will be treated exactly the same as those in the "Screen none" arm.
- All HCCs in the "Screen all" arm will be diagnosed within eighteen months (3 events of screening) after development of the tumor.
- Orthotopic liver transplantation in the model is only from deceased donors and is not done if the patient is over 70 years old.
- Patients on the liver transplant waiting-list will receive their organ or leave the list in one year (due to death, bridging therapy complications or the so called de-listing criteria)
- Post-OLT recurrence of HCC is assumed to be rapidly fatal; therefore, these patients will transit to "palliative treatment" or "sorafenib treatment" health states.
- HCCs are diagnosed radiologically by sequential US, CT scan and MRI, without biopsy.
- Tumor diagnosis is only through screening in the "Screen all" arm and through HCC-related symptoms in the "Screen none" group.
- Specificity of abdominal CT scan is assumed to be 100% in following up patients after surgical resection or RFA.
- No patient dies because of non-HCC related hepatic failure in the model population.

3.3 Model Design

In order to design a functional and efficient decision analysis model, there are some fundamental recommendations that should be followed. These recommendations imply that a decision tree should have balance in terms of including risk and benefits in all competing strategies under investigation and at the same time symmetry in representing all health states affecting the outcome, in all branches.

Furthermore, in order to prevent problems during conducting sensitivity analyses, each chance node ought to be followed by only two branches without any embedded decision node, and attention should be paid to linking probabilities in related branches thorough defining common variables. (Detsky, Naglie, Krahn, Redelmeier, & Naimark, 1997; Inadomi, 2004) Bearing all
these in mind, the model was developed using a decision node to introduce the two competing strategies of "Screen all" versus "Screen none" of the patients as is shown in Figure 3.3-1.

![Figure 3.3-1: Competing strategies in the model](image)

**Figure 3.3-1: Competing strategies in the model**
The model starts with a decision node which has two branches for "Screen All" and "Screen None" patients. As will be discussed later, each of these branches will lead to their specific health states.

### 3.3.1 Health State Transitions
The disease under investigation in this model has a series of processes and health states incorporated in its natural history with long-term implications; therefore, state transition modeling or Markov cohort simulation process which is derived from matrix algebra, is an appropriate choice here. (Caro et al., 2012; D. Naimark et al., 1997; Siebert et al., 2012)

Therefore, a Markov state-transition model using TreeAge Pro® 2014 (TreeAge Software, Williamstown, MA) was employed to represent the strategies under investigation. In this technique, the disease progression is modelled in a series of health states and the movement, or so-called transition of the cohort of patients among those states. (D. Naimark et al., 1997) The health states which define the clinical scenario in this study and the allowed transitions among them are schematically shown in the so-called "bubble diagrams" (D. Naimark et al., 1997; Siebert et al., 2012) in Figure 3.3-2 for "Screen All" strategy and Figure 3.3-3 for "Screen None" strategy.

Based on these simplified diagrams, several health states for both strategies are structured as a set of "mutually exclusive" options, denoting the possibility for any individual to be only in one health state during each cycle, and "collectively exhaustive" signifying the mandatory presence of every individual in the initial cohort in a health state during each cycle. (D. Naimark et al.,
These health states have been defined to capture the prominent features of HCC in the model population and also the treatments under consideration.

Since this is a Markov model, the memory issue (Markovian property or the fact that in such models transition probabilities do not depend on the history, neither on previous states nor the time in the current state), (Siebert et al., 2012) was handled through increasing the number of health states which include history. (Caro et al., 2012; Siebert et al., 2012) However, the delicate step here is to create the model with sufficient complexity to cope with the question under consideration.

Figure 3.3-2: "Screen All" strategy

Schematic "bubble diagram" summarising Markov health states. In each cycle, patients remain in the same health state, transit to the following state or die (due to HCC or related/unrelated causes). In "Screen All" strategy, all patients who are adherent to the screening undergo the screening test in their first cycle and then will be distributed accordingly to their next health states; however, those who are not adherent to the screening, will be diagnosed based on their HCC-related symptoms. Finally, patients diagnosed with HCC will be distributed according to the BCLC staging system to their proper health states to receive their treatment modality and then followed-up accordingly. In each and every state, patients may die due to HCC-related or HCC-unrelated causes.
investigation and preserve the face validity of the model and at the same time prevent the so-called "state explosion" (Siebert et al., 2012) with difficult-to-manage numbers of health states. (Caro et al., 2012)

As already discussed, the time horizon here is lifetime and for calculation purposes, life expectancy was set to be 110 years, based on the death probabilities taken from Canada life tables (Canada, 2009-2011) which shows that more than 99.9% of the model population would have died by the age of 110 years old, which is enough tracking time to be considered as lifetime time horizon as also discussed by Siebert and colleagues. (Siebert et al., 2012) This time horizon is divided into a series of equally spaced periods or cycles at the end of which the cohort members are relocated across the due health states. These movements are dictated by transition probabilities based on the natural history of HCC in the model population. The transition

Figure 3.3-3: "Screen None" strategy
Schematic "bubble diagram" summarising Markov health states. In each cycle, patients remain in the same health state, transit to the following state or die (due to HCC or related/unrelated causes). In this strategy, patients are diagnosed based on the HCC-related symptoms. Finally, patients diagnosed with HCC will be distributed according to the BCLC staging system, to their proper health states to receive their treatment modality and then followed-up accordingly. In each and every state, patients may die due to HCC-related or HCC-unrelated cause.
probabilities and also rates used in the model are all converted to per-cycle probabilities to match the cycle length (in this case, one month). This conversion is based on the calculation discussed in many studies in the field such as the one by Naimark and colleagues, (D. Naimark et al., 1997) however, in this model, this has been fulfilled thorough proper formulas and syntaxes made to be calculated by the modeling software in use.

The duration of cycle length is arbitrary and depends on the clinical problem and the nature of the disease under investigation and computational efficiency. (D. Naimark et al., 1997; Siebert et al., 2012) However, it should be short enough, especially if the likelihood of events is high, (Roberts et al., 2012) to properly represent the frequency of interventions and clinical events. (Inadomi, 2004; D. Naimark et al., 1997; Siebert et al., 2012) Therefore, a one month cycle length was used to model events such as diagnosis and treatment commencement to provide the best approximation of those occasions.

This movement through health states continues until the entire cohort population has moved to the absorbing state or the so-called "sink state" (Inadomi, 2004) which in the current model, corresponds with the separate death states for HCC-related and HCC-unrelated causes, at which point the model stops running. If costs and health-related quality of life (utilities) are assigned to these health states, one can calculate cost-effectiveness of surveillance and report the "Incremental Cost-Effectiveness Ratio" (ICER). ICER is the ratio between changes in costs and changes in effects of two competing strategies under investigation and can be calculated as:

\[
ICER = \frac{Cost_2 - Cost_1}{Effect_2 - Effect_1}
\]

where the difference of costs in strategies one and two is divided by the difference of effects of these two strategies and expressed in dollars/QALYs. (Sonnenberg & Beck, 1993)

All members of this cohort start in the first health state in both strategies. In the "Screen all" arm, those who are adherent to surveillance, undergo screening and based on the result will undergo further confirmatory imaging tests according to the current guidelines and recommendations outlined above; if diagnosis with an HCC is confirmed, they will move to the diagnosis health state where they will be distributed towards the appropriate treatment option for their status.
This procedure will be further discussed in the section on recall policy hereunder. Figure 3.3-4 schematically summarizes the abovementioned process.

Figure 3.3-4: Schematic presentation of 1st screening health state in "Screen All" strategy
As illustrated, in this health state patients have the probability of death due to causes related or not related to HCC. Among the living patients, those who are adherent to screening will undergo ultrasound as the screening test and then according to the AASLD guideline, they are evaluated until confirmed to have HCC or free from HCC. If they are diagnosed with an HCC, they will move to the proper health state to receive their treatment and if not, they go back to their own health state and wait until the next screening cycle. Those who are not adherent, may still develop HCC, but are diagnosed when they become symptomatic and then follow their path to their treatment and follow-up accordingly.

Subsequently, among surveillance-adherent patients, those who are not diagnosed and are either HCC positive or HCC negative, will move to their appropriate subsequent screening health state. Tunnel states and tunnel cross-overs, among TreeAge Pro® state bindings, were used here and later in post-intervention follow-up states, to keep track of the wait-time for patients in each health state, such as screening states where the test is done every six months, i.e. six cycles in the model, as schematically illustrated in Figure 3.3-5. In these screening states, HCC positive cases will be diagnosed in later screening cycles and those who are negative, according to the values and probabilities, have the chance of developing a tumor and moving towards the HCC positive states and undergo screening and finally diagnosis according to the model. There are
also a group of the cohort who undergo screening tests and never develop any HCC and will leave the model by death due to HCC-unrelated causes. It is uncommon in this population of patients for extrahepatic metastasis to be present without a primary lesion in the liver which could be diagnosed much earlier. (Katyal et al., 2000) Therefore, metastatic disease is not included in this model.

Figure 3.3-5: Schematic presentation of subsequent screening health state-Screen All strategy

In the subsequent screening health state, as illustrated, those who remain alive will undergo screening every 6 months and if they do not develop HCC will remain in this same situation; however, if they develop HCC, they will undergo diagnosis procedure and then directed to their appropriate treatment health state.

On the other hand, those who are not adherent to the surveillance program in the "Screen all" arm and also everybody in the "Screen none" arm will undergo diagnostic tests and move toward the diagnosis health state if results are positive, only when they develop symptoms related to and suggestive of HCC.

3.3.2 Recall Policy

Patients who are diagnosed with HCC, either through a screening test and the due confirmation in the "Screen all" arm or those who are diagnosed due to developing HCC-related symptoms in the "Screen none" arm, will move towards the "diagnosis" health state in their corresponding strategy where they will be considered for their appropriate treatment. In order to be as
comprehensive as possible in evaluating health outcomes, the treatment options in this model include orthotopic liver transplantation, surgical resection, radiofrequency ablation, sorafenib treatment and palliative care. As discussed thoroughly in the introduction section for HCC treatment, patients are allocated to their appropriate therapeutic option based on the state of their cirrhosis, stage of their tumor and size and number of their tumors, according to the Barcelona Clinic Liver Cancer (BCLC) staging system and Milan criteria. This diagnosis health state is schematically illustrated in Figure 3.3-6. The next step is undergoing the allocated treatment modality accordingly.

After liver transplantation, compared with younger recipients, older patients have a diminished long-term survival. (Collins et al., 2000; Herrero et al., 2003; Murray & Carithers, 2005) Although there is no absolute age cut-off, it is uncommon for patients to be transplanted beyond the age of 70 years in the University of Toronto transplant program ("Toronto Liver Transplant

![Figure 3.3-6: Diagnosis health state](image)

In the HCC diagnosis health state, those who remain alive will be distributed to their proper treatment options. This will be based on the BCLC staging system which other than the number and size of the detected nodules, will take co-morbidities such as presence or absence of portal hypertension into account. Therefore, OLT, RFA, surgical resection and finally, sorafenib and palliative care candidates will be directed to their proper health state from here.

After liver transplantation, compared with younger recipients, older patients have a diminished long-term survival. (Collins et al., 2000; Herrero et al., 2003; Murray & Carithers, 2005) Although there is no absolute age cut-off, it is uncommon for patients to be transplanted beyond the age of 70 years in the University of Toronto transplant program ("Toronto Liver Transplant
Database;" 2014) and as such, in this model, patients reaching 70 years of age are no longer eligible for orthotopic liver transplantation, but are eligible for other treatments.

Patients who are OLT candidates, i.e. patients with single nodule less than 2cm with portal hypertension and those with single nodule more than 2cm which is not resectable, on condition that they are within the mentioned OLT age limit, will move to the "OLT Wait-list" health state to stay in queue for organ availability, (Roberts et al., 2012) which by assumption, will take one year.

During this health state which is schematically illustrated in Figure 3.3-7, they will either receive an organ and move to the post-OLT state as described later, or will leave the state either because of death (HCC-related or HCC-unrelated causes) or unsuccessful bridging treatment while awaiting transplantation. According to the AASLD guideline, preoperative treatment, i.e. bridging treatment, should be considered when the wait-time is more than 6 months, as is the case for this model. (Bruix et al., 2011)

The post-OLT health state is divided into three separate states. During the first three months, the cost and utility of the procedure and its complications will be captured and patients will undergo abdominal CT scan to screen for HCC relapse. As stated in the assumptions, post-OLT relapse is treated either by sorafenib or palliative therapy, owing to its poor prognosis. The second section of the post-OLT health state is the remaining nine months of the first post-OLT year during which the cost of maintenance of transplant is very high. Subsequently, they will be evaluated only if they become symptomatic suggestive of tumor relapse. Similarly, for those who receive surgical resection or RFA as their primary treatment, the cost of the procedure, any complications in terms of hospitalization period and service fees provided are captured and then patients are followed by quarterly abdominal CT scans during the first post-intervention year to assess for residual HCC or relapses.

After the initial year, they return to biannual abdominal ultrasound for ongoing surveillance for late relapse or recurrent primary HCC. Recurrent HCC is managed by liver transplantation.
3.3.3 Half-Cycle Correction

Transition between health states is an inherent part of the Markov state-transition method and also applies to the current model. In TreeAge Pro®, transitions can occur at the beginning or at the end of each cycle; therefore, it will result in over- or under-estimation, respectively, of the costs and QALYs in comparison to the results if these transitions were modeled to occur randomly throughout each cycle. (D. M. Naimark, Kabboul, & Krahn, 2013) Since TreeAge Pro® counts the state membership at the beginning of each cycle, the over-estimation is roughly equal to half of one cycle’s worth of the incremental cost or utility. (D. M. Naimark, Bott, & Krahn, 2008) In an example of monthly cycles, the number of life-months (whether quality adjusted or not) is over-estimated when the membership, during calculations is counted at the
beginning of each cycle compared with the situation where the transition would occur randomly throughout the cycle.

In order to correct this bias, the standard half-cycle correction method is used in formula syntaxes used in TreeAge Pro® as is explained. (D. M. Naimark et al., 2013; Siebert et al., 2012) Imagine a health state labelled "Well" which has utility and cost values assigned to it. In this software, three parameters can be specified for each of these values in each state. The "initial" values correspond to the values assigned to the health state at the beginning of the Markov process (i.e. cycle zero). The "incremental" values correspond to the health states while the process is running and the "final" values which correspond to the values to be assigned to any members of the cohort who remain in the particular health state when the Markov process ends. In the standard half-cycle correction method in this software, the initial values will be half of their incremental values meaning 0.5×uWell and 0.5×cWell and then the complete incremental values (uWell and cWell) while they stay in the Well state and at the end, as the final reward, half of their incremental values meaning 0.5×uWell and 0.5×cWell are again assigned to those who remain in the state after completion of the due transition, hence, the over-estimation will be corrected. (D. M. Naimark et al., 2008; D. M. Naimark et al., 2013; Siebert et al., 2012)

### 3.3.4 Bias in Surveillance Studies

Naimark and colleagues, (D. M. Naimark et al., 2013) called it a bias when they discussed the over-estimation of cumulative costs and utilities in Markov models where state membership was calculated at the beginning of a cycle. This is present in the current study since TreeAge Pro® software calculates costs in the same way. However, this so-called bias, as explained before, was corrected through implementation of the standard half-cycle correction method in the analyses and formulae.

Cost-effectiveness analysis studies, mainly those funded by industry, tend to be biased by the so-called sponsorship bias in reporting favourable ratios, (Bell et al., 2006) to which, publication bias will also contribute. Compliance bias is an integrated part of surveillance programs where patients can have different rates of adherence to the program. In such a situation, some part of the favourable outcomes of screening may be attributed to higher vigilance to self-health in those who are adherent to the procedure, rather than surveillance itself. (Fletcher et al., 2014) Jembere and colleagues, (Jembere et al., 2012) showed that there is a 10% HCC survival
advantage in people with higher socioeconomic status in Ontario, which as the authors hypothesize, may be explained by the fact that these people look for treatment earlier in the course of their disease, a trend which may also apply for adherent people. However, in the current study, it is assumed that patients are free from any specific co-morbidities and characteristics affecting our specific outcome of tumor development. Furthermore, the effect of adherence to the surveillance procedure and uncertainty surrounding it is reviewed in the sensitivity analysis discussed in the section on results.

An inherent challenge of decision analysis models is the trade-off between complexity of the model and availability of the required data. Among methods to deal with this issue is the use of expert-elicited data, which is potentially a source of biases, even if unintentional. (Karnon et al., 2012) The value and strength of the data vary according to the complexity of the parameters and the experience of the expert. In the current model, some parameter values were obtained through expert opinion. To minimize the potential bias, expert estimates were validated whenever possible by asking for further values from the same expert for parameters that can be compared with available published data, asking other experts and also through conducting sensitivity analyses on these parameters with wider ranges to evaluate their impact on the final outcome of the model.

Surveillance studies all have the potential for lead-time and length-time biases. (Duffy et al., 2008) Lead-time implies more survival time but is actually more disease time due to earlier detection of a tumor with a screening test that does not change the occurrence of the outcome. In other words, the individual is diagnosed at an earlier point in time and therefore even if they die at the same time as they would have died without surveillance, they will appear to have lived longer than if the tumor had been diagnosed closer to the time of their death when it became symptomatic. (Cucchetti et al., 2014; Fletcher et al., 2014) Cucchetti and colleagues, (Cucchetti et al., 2014) estimated the lead-time in a 10-year surveillance program for HCC in patients with Child-Pugh A and B cirrhosis and demonstrated that the survival benefit from surveillance in relation to lead-time, was dependent on the follow-up length after detecting HCC, the treatment applied and the tumor doubling time. They also discussed that lead-time bias will increase as the sensitivity of screening tests such as ultrasound increases (due to ongoing technical advances) since tumors of smaller size will be detected. In the long run, though only randomized
controlled trials can correct this bias, (Cucchetti et al., 2014) attempts were made to minimize and override the confounding effect of this bias in the current model through adapting the longest possible time horizon and incorporating as many potentially curative treatment options as possible into the model.

Length-time bias in surveillance studies stems from a longer pre-symptomatic period in slowly growing tumors; therefore, they are more likely to be detected by the screening test and thereby confer an artificial survival advantage to surveillance. (Cucchetti et al., 2014; Duffy et al., 2008; Fletcher et al., 2014) The uniform group of patients in terms of their underlying disease and co-morbidities and therefore probable similarities in the nature of their hepatocarcinogenesis may help decrease but likely does not eliminate this bias.

3.3.5 Data Input
Although data are an essential ingredient for a model, it is recommended to first design a model as simple or complex as is required in relation to the question under investigation and then try to find the relevant data for the model. (Roberts et al., 2012) While there is no use in designing a model lacking information on many required inputs, one advantage to this approach is that it will lead to looking for and finding pieces of information that might otherwise be easily overlooked. (Caro et al., 2012) Bearing this in mind, in order to find the most appropriate input for the model, an extensive literature search through MEDLINE and the Cochrane database in English language was performed from 1985 until 2014 including published papers and reports on HCV infection, cirrhosis, HCC and its surveillance programs and also cost-effectiveness and natural history studies in the field. Whenever not available in the literature, expert opinion was sought for the required information. Most of the main parameter values required to structure the model were introduced in the section on conceptualization of the model and the rest, including costs, utilities and probabilities are explained in the following section. Mortality rates in the model include the age specific mortality rate for the general population which was taken from the Canada Life Tables, (Canada, 2009-2011) and the excess mortality is for HCC-related causes which will be explained in the section on probabilities.

3.3.5.1 Cost Values
Cost values and estimates were taken from Canadian sources such as the Ontario Health Insurance Plan Schedule of Benefits ("OHIP Schedule of Benefits for Physician Services,") for
physician services and the pharmacy in the Princess Margaret Hospital for end-user prices of medications such as sorafenib as well as Canadian published data. Costs were all inflated to and reported in 2014 Canadian dollars, using the Consumer Price Index (CPI) (Bank of Canada) available from the Bank of Canada and also from Statistics Canada. Relevant costs from sources outside of Canada were transformed into Canadian dollars using Purchase Power Parity (World Bank) conversion rates, available from The World Bank, before being inflated into 2014 Canadian dollars. Table 3.3-1 summarises the cost parameter values used in the model.

Table 3.3-1: Cost values used in the model with their low and high ranges (CAN $)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Parameter Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual cost of compensated cirrhosis management</td>
<td>1,413</td>
<td>(Saab, Hunt, Stone, McClune, &amp; Tong, 2010)</td>
</tr>
<tr>
<td>Annual cost of decompensated cirrhosis management</td>
<td>18,252</td>
<td>(Saab et al., 2010)</td>
</tr>
<tr>
<td>Annual cost of OLT management after the 1st post-OLT year</td>
<td>32,621</td>
<td>(Saab et al., 2010)</td>
</tr>
<tr>
<td>Annual cost of follow-up while on OLT waiting list</td>
<td>19,591</td>
<td>(Majno, Sarasin, Mentha, &amp; Hadengue, 2000)</td>
</tr>
<tr>
<td>Annual cost of OLT management during the 1st post-OLT year</td>
<td>186,793</td>
<td>(Saab et al., 2010)</td>
</tr>
<tr>
<td>Annual cost of palliative treatment for incurable HCC</td>
<td>68,525</td>
<td>(Arguedas et al., 2003)</td>
</tr>
<tr>
<td>Annual cost of Sorafenib treatment for incurable HCC*</td>
<td>78,428</td>
<td>(&quot;Zangneh HF Personal Enquirey from Princess Margaret Hospital, Toronto (August 2014)&quot;,)</td>
</tr>
<tr>
<td>Per-visit cost of gastroenterologist or oncologist consultation</td>
<td>157</td>
<td>(&quot;OHIP Schedule of Benefits for Physician Services,&quot;)</td>
</tr>
<tr>
<td>Per-procedure cost of abdominal CT Scan</td>
<td>449</td>
<td>(Saab et al., 2010)</td>
</tr>
<tr>
<td>Per-procedure cost of abdominal MRI</td>
<td>1,879</td>
<td>(Andersson et al., 2008)</td>
</tr>
<tr>
<td>Per-procedure cost of OLT</td>
<td>214,130</td>
<td>(Andersson et al., 2008)</td>
</tr>
<tr>
<td>Per-procedure cost of RFA</td>
<td>4,430</td>
<td>(Andersson et al., 2008)</td>
</tr>
<tr>
<td>Per-procedure cost of resection</td>
<td>51,686</td>
<td>(Andersson et al., 2008)</td>
</tr>
<tr>
<td>Per-procedure cost of abdominal Ultrasound</td>
<td>202</td>
<td>(Saab et al., 2010)</td>
</tr>
<tr>
<td>Per-day cost of ICU services</td>
<td>2,322</td>
<td>(Garland, 2013)</td>
</tr>
</tbody>
</table>

* based on 400mg two times daily regimen (Llovet, Ricci, et al., 2008); ICU: Intensive Care Unit

This table shows the cost values used in this model for calculations, the baselines together with the low and high ranges used for performing sensitivity analysis. Values are either from Canadian sources, or if not, transformed into 2014, Canadian dollar accordingly.
3.3.5.2 Probability Values

As also mentioned by Naglie and colleagues, (Naglie et al., 1997) probabilities are a quantitative estimation of the possibility of a health state transition defined in the model or an outcome described, to take place. Table 3.3-2 summarises the probability values used in the model together with their sources and also plausible ranges used in the sensitivity analyses. Rates and probabilities were converted whenever required through proper formula syntaxes in the TreeAge Pro® software to match properly with the model cycle length, i.e. one month.

Table 3.3-2: Annual probability and proportion values used in the model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Parameter Value</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCC incidence rate in the model population</td>
<td>0.005</td>
<td>0.001</td>
</tr>
<tr>
<td>Probability of death due to complications of OLT</td>
<td>0.11</td>
<td>0.086</td>
</tr>
<tr>
<td>Probability of death due to palliative Rx for incurable HCC</td>
<td>0.820</td>
<td>0.615</td>
</tr>
<tr>
<td>Mortality rate of HCC while on OLT waiting list</td>
<td>0.490</td>
<td>0.367</td>
</tr>
<tr>
<td>Probability of HCC relapse after OLT</td>
<td>0.050</td>
<td>0.037</td>
</tr>
<tr>
<td>Probability of developing OLT complications</td>
<td>0.220</td>
<td>0.049</td>
</tr>
<tr>
<td>Probability of HCC relapse after RFA</td>
<td>0.410</td>
<td>0.307</td>
</tr>
<tr>
<td>Probability of HCC relapse after surgical resection</td>
<td>0.200</td>
<td>0.100</td>
</tr>
<tr>
<td>Probability of receiving bridging Rx while on OLT waiting list</td>
<td>0.600</td>
<td>0.450</td>
</tr>
<tr>
<td>Probability of successful bridging Rx while on OLT waiting list</td>
<td>0.960</td>
<td>0.720</td>
</tr>
<tr>
<td>Probability of an HCC to convert from asymptomatic to symptomatic</td>
<td>0.600</td>
<td>0.100</td>
</tr>
<tr>
<td>Probability of death while on Sorafenib Rx for incurable HCC</td>
<td>0.640</td>
<td>0.480</td>
</tr>
<tr>
<td>Probability of availability of appropriate organ for OLT</td>
<td>0.450</td>
<td>0.337</td>
</tr>
<tr>
<td>Sensitivity of abdominal CT Scan</td>
<td>0.680</td>
<td>0.550</td>
</tr>
<tr>
<td>Specificity of abdominal CT Scan</td>
<td>0.930</td>
<td>0.890</td>
</tr>
<tr>
<td>Sensitivity of abdominal MRI</td>
<td>0.810</td>
<td>0.700</td>
</tr>
<tr>
<td>Specificity of abdominal MRI</td>
<td>0.850</td>
<td>0.770</td>
</tr>
<tr>
<td>Sensitivity of abdominal US</td>
<td>0.610</td>
<td>0.440</td>
</tr>
<tr>
<td>Specificity of abdominal US</td>
<td>0.970</td>
<td>0.950</td>
</tr>
<tr>
<td>Description</td>
<td>Proportion</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>----------------------------------------------------------------------------</td>
<td>------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Proportion of Pt. with single HCC ≤ 2 cm in &quot;Screen All&quot; group</td>
<td>0.680</td>
<td>0.510 0.8500</td>
</tr>
<tr>
<td>Proportion of Pt. with 2 &lt; HCC &lt; 5 cm in &quot;Screen All&quot; group</td>
<td>0.720</td>
<td>0.540 0.9000</td>
</tr>
<tr>
<td>Proportion of Pt. with ≤ 3 HCCs in &quot;Screen All&quot; group</td>
<td>0.790</td>
<td>0.592 0.9875</td>
</tr>
<tr>
<td>Proportion of Pt. with a single HCC in &quot;Screen All&quot; group</td>
<td>0.800</td>
<td>0.600 1.0000</td>
</tr>
<tr>
<td>Proportion of Pt. with portal hypertension</td>
<td>0.400</td>
<td>0.300 0.5000</td>
</tr>
<tr>
<td>Proportion of Pt. with single HCC ≤ 2 cm in &quot;Screen None/Non-Adherent&quot; groups</td>
<td>0.120</td>
<td>0.090 0.1500</td>
</tr>
<tr>
<td>Proportion of Pt. with 2 &lt; HCC &lt; 5 cm in &quot;Screen None/Non-Adherent&quot; groups</td>
<td>0.097</td>
<td>0.073 0.1213</td>
</tr>
<tr>
<td>Proportion of Pt. with ≤ 3 HCCs in &quot;Screen None/Non-Adherent&quot; groups</td>
<td>0.100</td>
<td>0.075 0.1250</td>
</tr>
<tr>
<td>Proportion of Pt. with a single HCC in &quot;Screen None/Non-Adherent&quot; groups</td>
<td>0.140</td>
<td>0.105 0.1750</td>
</tr>
<tr>
<td>Proportion of Pt. with &gt; 3 HCCs, all &lt;3cm in &quot;Screen All&quot; group</td>
<td>0.900</td>
<td>0.675 1.0000</td>
</tr>
<tr>
<td>Proportion of Pt. with &gt; 3 HCCs, all &lt;3cm in &quot;Screen None/Non-Adherent&quot; groups</td>
<td>0.200</td>
<td>0.150 0.2500</td>
</tr>
<tr>
<td>Proportion of Pt. receiving sorafenib vs. palliative Rx for incurable HCC</td>
<td>0.050</td>
<td>0.037 0.0625</td>
</tr>
<tr>
<td>Proportion of Pt. who die due to RFA complications</td>
<td>0.037</td>
<td>0.028 0.0463</td>
</tr>
<tr>
<td>Proportion of Pt. who die due to surgical resection complications</td>
<td>0.034</td>
<td>0.025 0.0425</td>
</tr>
<tr>
<td>Proportion of Pt. with PHTN, an HCC &lt; 2cm, eligible for OLT</td>
<td>0.050</td>
<td>0.037 0.0625</td>
</tr>
<tr>
<td>Proportion of Pt. with an HCC&lt; 2cm, no PHTN, eligible for surgical resection</td>
<td>0.300</td>
<td>0.225 0.3750</td>
</tr>
<tr>
<td>Proportion of Pt. with 2&lt;HCC&lt;5cm HCC, no PHTN, eligible for surgical resection</td>
<td>0.900</td>
<td>0.675 1.0000</td>
</tr>
<tr>
<td>Proportion of Pt. eligible for OLT with ≤ 3 HCCs, all ≤ 3cm</td>
<td>0.700</td>
<td>0.525 0.8750</td>
</tr>
<tr>
<td>Proportion of Pt. with &gt;3HCCs, all &gt;3cm, eligible for surgical resection</td>
<td>0.050</td>
<td>0.037 0.0625</td>
</tr>
<tr>
<td>Proportion of Pt. with single HCC &gt; 5 cm who are eligible for surgical resection</td>
<td>0.700</td>
<td>0.525 0.8750</td>
</tr>
<tr>
<td>Proportion of Pt. with complications of surgical resection in &quot;Screen All&quot; group</td>
<td>0.210</td>
<td>0.157 0.2625</td>
</tr>
</tbody>
</table>
Table 3.3-2; Continued

| Proportion of Pt. with RFA complications in "Screen All" group | 0.090 | 0.067 | 0.1125 | (Li et al., 2014) |

Pt. Patients; Rx: Therapy

In this table, probability values used in the model calculations, together with the references where they have been obtained are introduced. Furthermore, the low and high ranges of the values which were use in sensitivity analysis are also mentioned.

### 3.3.5.3 Utility Values

Health state utilities are used to measure quality of life and are usually assessed in relation to two extremes, referred to as anchor states. These so-called anchors are commonly death with an assigned value of "0" and full health with the assigned value of "1". (Chong, 2003; Naglie et al., 1997) Utilities have the advantage of being useful in decision analyses and cost-effectiveness studies (Chong, 2003) where their most frequent outcome, i.e. QALYs, are calculated through multiplying the time spent in a particular health state by the utility of that given state. On the other hand, as also discussed by Younossi and colleagues, (Younossi et al., 2001) anchoring utilities to death and full health states is quite significant since it offers the opportunity of measuring decreases in health related quality of life and the reductions in life-span, both in the same unit.

Although not an ideal method, utility values may be estimated through expert judgments; however, a clinician’s perception and estimation of a disease impact may be quite different from the patient’s feeling in the same setting. (Chong, 2003) In addition, these values can be measured, either directly using standard scaling techniques such as time trade-off, standard gamble or visual analog scale, or indirectly, thorough questionnaires such as Health Utility Index. (Chong, 2003; Thein, Krahn, Kaldor, & Dore, 2005)

It is important to remember that the adverse consequences of procedures should be incorporated into a model in addition to the beneficial effects, so that a precise picture can be produced. (Roberts et al., 2012) All surveillance programs, including this one for HCC, carry the possibility of imposing harm to the patients which can be due to the surveillance tests and therapeutic procedures and complications themselves or they can be psychological, related to the sense of anxiety accompanying the wait-time for results after each and every surveillance
event. (Sherman, 2014) Fortunately, in the specific case of surveillance for HCC, highly specific recall procedures recommended after detection of a nodule on ultrasound are supposed to minimize the potential harm of treating a falsely diagnosed and non-malignant nodule. (Bruix et al., 2011; Sherman, 2014) These unwanted effects, or the so-called disutilities as mentioned by Naglie and colleagues, (Naglie et al., 1997) have been incorporated into the structure of the current model and the parameter values are taken from the published literature and expert opinion, or whenever not available, calculated as "1-utility" value of the corresponding health event. The value of disutility was calculated according to the time span of the patient receiving or staying in that particular state of negative impact and then subtracted from the utility value of the same state. Table 3.3-3 summarises the utility/disutility parameters, their values and ranges.

### Table 3.3-3: Annual utility and disutility values used in the model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Parameter Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Utility of living while on palliative Rx for incurable HCC</td>
<td>0.40 0.20 0.60</td>
<td>(Bremner et al., 2007; Sarasin et al., 2001; Tengs &amp; Wallace, 2000)</td>
</tr>
<tr>
<td>Utility of living while on Sorafenib Rx for incurable HCC</td>
<td>0.76 0.57 0.95</td>
<td>(Camma et al., 2013)</td>
</tr>
<tr>
<td>Utility of living during the 1st post-OLT year</td>
<td>0.60 0.50 0.80</td>
<td>(Arguedas et al., 2003; Younossi et al., 2001)</td>
</tr>
<tr>
<td>Utility of living during the 2nd year &amp; onwards post-OLT</td>
<td>0.85 0.70 0.90</td>
<td>(Arguedas et al., 2003; Younossi et al., 2001)</td>
</tr>
<tr>
<td>Utility of living while on OLT waiting list</td>
<td>0.60 0.50 0.70</td>
<td>(Sarasin et al., 2001)</td>
</tr>
<tr>
<td>Utility of living with asymptomatic HCC, post-SVR</td>
<td>0.83 0.50 0.90</td>
<td>(Arguedas et al., 2003; Chong, 2003; Younossi et al., 2001)</td>
</tr>
<tr>
<td>Utility of living with symptomatic HCC, post-SVR</td>
<td>0.67 0.40 0.80</td>
<td>(Arguedas et al., 2003; Chong, 2003; Younossi et al., 2001)</td>
</tr>
<tr>
<td>Utility of living with compensated cirrhosis and no HCC, post-SVR</td>
<td>0.87 0.81 0.93</td>
<td>(Chong, 2003; Thein et al., 2005)</td>
</tr>
<tr>
<td>Utility of living after RFA as therapy for HCC</td>
<td>0.87 0.81 0.93</td>
<td>(Chong, 2003; Thein et al., 2005)</td>
</tr>
<tr>
<td>Utility of living after surgical resection as therapy for HCC</td>
<td>0.70 0.40 0.90</td>
<td>(Arguedas et al., 2003)</td>
</tr>
<tr>
<td>Disutility of OLT procedure</td>
<td>0.30 0.23 0.38</td>
<td>(Northup et al., 2009)</td>
</tr>
<tr>
<td>Disutility of living with OLT complications</td>
<td>0.15 0.11 0.19</td>
<td>(Northup et al., 2009)</td>
</tr>
<tr>
<td>Disutility of performing a screening or a diagnostic test</td>
<td>0.01 0.01 0.01</td>
<td>(Moore, Shenoy, Fanucchi, Tumeh, &amp; Flowers, 2009)</td>
</tr>
<tr>
<td>Disutility of performing RFA as therapy for HCC</td>
<td>0.10 0.08 0.13</td>
<td>(&quot;Toronto Liver Transplant Database;&quot;, 2014)</td>
</tr>
<tr>
<td>Disutility of living with RFA complications</td>
<td>0.14 0.11 0.18</td>
<td>(&quot;Toronto Liver Transplant Database;&quot;, 2014)</td>
</tr>
</tbody>
</table>
Table 3.3-3: Continued

| Disutility of surgical resection as therapy for HCC | 0.17 | 0.13 | 0.21 | (Northup et al., 2009) |
| Disutility of living with surgical resection complications | 0.20 | 0.15 | 0.25 | (Northup et al., 2009) |

Rx: Therapy

This table introduces the values used for utility and disutility variables in this model. Utilities are values changing from 0 to 1 where 0 is the utility of death and 1 shows complete health. Disutilities are values that refer to unwanted events or procedures as used in this model. Values, their references and high as well as low ranges used in sensitivity analyses are presented in the table.

3.3.5.4 Sensitivity Analysis

As discussed by Briggs and colleagues, (A. H. Briggs et al., 2012) evaluation and reporting of uncertainty are counted as important features of good modeling practice. In order to evaluate the impact of the uncertainties for the parameters used in the model and also to identify the most influential variables among them, both deterministic and probabilistic sensitivity analyses were performed within their plausible ranges and distributions.

Deterministic sensitivity analysis was used both as an important step for debugging the model (as one-way analyses on all parameter values over their "possible" ranges to evaluate the model behaviour) and as an important tool to evaluate and assess the uncertainty surrounding the parameters values in relation to the outcomes. This step, as will be elaborated on in the results section, was done in the form of deterministic, one-way sensitivity analyses on model parameters over their plausible ranges for values. (A. H. Briggs et al., 2012)

The ranges are taken from the same sources if available in the form of a proper range or 95% confidence intervals, (A. H. Briggs et al., 2012) and if not available, the baseline values were varied by the range of ±25%. In addition, probabilistic sensitivity analysis was conducted using appropriate distributions for model parameters values with 10,000 iterations. Gamma distribution was used to model cost variables and beta distribution for probabilities and normal distribution for time periods such as hospitalization days. (A. H. Briggs et al., 2012)
Probabilistic sensitivity analysis evaluates the chance of a strategy to be cost-effective in relation to different cost-effectiveness thresholds within a specific number of iterations, by changing all variable values randomly within their plausible ranges in their specific distributions. Monte Carlo simulations were used to examine both strategies in this model.

3.3.6 Model Transparency and Validation

In order to be successful, a healthcare model requires the building of trust and confidence. This can be achieved through transparency, i.e. everyone can see how the model has been structured and built, and validation which measures how well the model can reproduce the reality. (Caro et al., 2012; Eddy et al., 2012) In the first part, the current model has been extensively defined and explained step by step in the section on methods, in terms of the structure and transitions, parameter values and also assumptions to enable interested readers to understand the model, the steps which move the model towards transparency, to allow readers to assess the model accuracy, limitations and potential applications. (Eddy et al., 2012)

Moreover, transparency and validation are inseparably linked together since what is important is whether a model predicts what occurs in reality and whether predictions are accurate; this is the role assumed for validation. (Eddy et al., 2012) Validation assesses a model’s accuracy in making the predictions it is designed to make. In other words, transparency addresses what a model is and how a model works, whereas validation determines how well it works. Different types of validation can be implemented, as explained for the current model hereunder.

3.3.6.1 Face Validity

Face validity or clinical relevance, is the level to which the model structure, data input, problem formulation, assumptions and results correspond to the current science and evidence, as decided by experts in the related field. This will not only improve the trustworthiness of the model among professionals in the field, but also increases the acceptance of the results. The model structure and results were reviewed with the program advisory committee who are experts in hepatology, decision analysis and modeling, and also cost-effectiveness analysis.

In addition, other professionals have evaluated the inputs and results of the model during interviews carried out in the data collection phase. The model has been revised and parts added and deleted many times in order to make it the best possible match with the current medical and
decision analysis science available. However, face validity has some inherent limitations since all models simplify reality, which is true with the current model as well. (Eddy et al., 2012)

3.3.6.2 Internal Validity

Verification or internal validity refers to model implementation and whether its structure behaves as it is supposed to behave. In other words, it checks the extent to which calculations are done correctly and are consistent with the requirements of the model. (Eddy et al., 2012) Verification of this model was done in several steps to detect and minimize the presence of any problems or "bugs":

- Attention was paid to formulations and syntaxes used in calculations, checking individual equations several times in detail, character by character for probable typographical errors.
- The structure was controlled quite vigilantly to make sure every node and health state is correctly designed and nomenclature is consistent, transitions are routed where they are supposed to and state bindings are properly set.
- Data input were reviewed to see if rates and probabilities were converted to match precisely with the requirements.
- The structural balance and symmetry of the two strategies was also evaluated. For example, the results with zero adherence to screening were evaluated, the case in which the two strategies are practically the same and yielded near-identical results.
- As the main tool for "debugging", (Krahn, Naglie, Naimark, Redelmeier, & Detsky, 1997) one-way sensitivity analyses were conducted on all parameter values in the model over their possible ranges rather than their plausible ranges and the results were evaluated graphically to determine whether the behavior of the model in terms of its outputs is as expected or not, to find a clue of the presence and nature of a probable problem and also where it may be.
- As a means to check the health state transitions, quick-cohort analysis was performed and all the cycles (720 cycles in this model life time) were reviewed to see if movement of cohort members occurred in a logical manner in relation to the surveillance procedure.
- As another measure, the model was rolled back in "Life Year" format, to exclude the effect of utilities and isolate the effects of the model on life years.
Despite this type of rigorous approach to debugging, some bugs may remain undetected and unresolved. (Eddy et al., 2012; Krahn et al., 1997)

### 3.3.6.3 External Consistency

As discussed by Eddy and colleagues, (Eddy et al., 2012) external consistency or in other words, cross validity, examines different similar models addressing the same question and compares their results with the model under investigation to be validated. It is noteworthy that as already mentioned, there are no other studies available that evaluate surveillance for HCC in a post-SVR population, however, for validation purposes, the current model was run using the baseline parameters values. The behaviour and results of the model were compared to their counterparts, in the studies where the data input were obtained, as introduced in the section on data input, and the external studies in the literature. (Andersson et al., 2008; Kang et al., 1992; O. S. Lin et al., 2004; Nouso et al., 2008; Patel et al., 2005; Saab et al., 2003; Shih et al., 2010; Thompson Coon et al., 2008) The results of this model matched in terms of effectiveness of surveillance which will be further discussed and compared in the discussion section, though as mentioned, the final results cannot be compared due to the different population under study in this model.
4 Chapter Four: Results

4.1 Base Case Analysis

Cost-effectiveness analysis was performed for the base case in the model. If 10,000 patients are screened in this model, as summarized in Table 4.1-1, 93.2% of the tumors detected through screening in the "Screen all" group will be in a curable stage in comparison with 17.7% of the ones diagnosed through HCC-related symptoms in the "Screen none" group. In terms of liver-related mortality, there will be 1,100 deaths due to HCC in the "Screen all" group versus 1,297 in the screen none arm, that is a 15.2% decrease in tumor related mortality resulting from the surveillance program in the model population.

The analysis shows that biannual US screening offers, on average per patient, a gain of 0.090275 Life-Years or about 33 days of extra life, when compared to the group without any surveillance for HCC. If the calculations are adjusted for the quality of life, the gain is 0.070518 QALYs or about 26 quality-adjusted life days. It is important to keep in mind that these are average values for the whole model population in whom the annual incidence of HCC is quite low; the gain for individual affected patients will be much more noticeable.

Moreover, as expected based on the similar natural history of the disease in the two arms, the total number of HCCs is equal in both groups. The apparent 246 (14%) excess HCCs in the "Screen all" arm are actually the false positive diagnoses. The low incidence of HCC means that a high proportion of detected nodules prove to be false positives and hence the positive predictive value of a positive ultrasound is very low. These cases, stemming from the low incidence of HCC in the model population, are important because of the costs and morbidities related to the unnecessary treatments they receive.

The results of the base case analysis are shown in Table 4.1-2. The "Screen all" strategy offered 13.10 QALYs with a cost of $42,072 whereas the "Screen none" strategy offered 13.03 quality-adjusted life-years with a cost of $27,665. Therefore, the "Screen all" strategy is more effective but with higher expected costs, resulting in an ICER of $204,301/QALY.
Figure 4.1-1 illustrates the relationship between strategies in terms of their effectiveness and costs as an average per person. Again, as is evident from this graph, surveillance with biannual ultrasound in "Screen all" strategy is more effective than no surveillance (Screen none).

In order to provide a better perception of discounting in costs and effects, all the above mentioned values were calculated and compared with 5% and 0% annual discount rates and the results are summarized in Table 4.1-3.
Organ availability for liver transplantation is among the most important limited resources in any surveillance program which includes OLT as a treatment modality. There were two different values obtained for organ availability for Toronto and the whole of Canada. Therefore, as

![Graph showing cost-effectiveness analysis (Base Case)]

**Figure 4.1-1: Cost-effectiveness analysis (Base Case)**

This figure illustrates the relationship between strategies in terms of their effectiveness and costs as an average per person. Again, as is evident from this graph, surveillance with biannual ultrasound in "Screen all" strategy is more effective than no surveillance ("Screen none").

**Table 4.1-3: Base Case values discounted vs. not discounted**

<table>
<thead>
<tr>
<th>Discount %/Yr</th>
<th>Screen All Strategy</th>
<th>Screen None Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cost ($)</td>
<td>Effect (Life Year)</td>
</tr>
<tr>
<td>5</td>
<td>42,072</td>
<td>15.1067</td>
</tr>
<tr>
<td>0</td>
<td>86,672</td>
<td>31.2154</td>
</tr>
</tbody>
</table>

QALY: Quality Adjusted Life Year; Yr: Year

Discounting indicates the rate a society sets for time preference, which denotes the preference of receiving a benefit earlier or to incur a cost later. In order to show this idea in numbers, we have calculated the base case in this model with both 5% and 0% discount rate as a comparison.

**4.1.1 Scenario Analysis**

Organ availability for liver transplantation is among the most important limited resources in any surveillance program which includes OLT as a treatment modality. There were two different values obtained for organ availability for Toronto and the whole of Canada. Therefore, as
mentioned in the methodology section and in order for the results to be externally valid, the base case analysis uses the data for organ availability as reported by the Canadian Institute for Health Information (CIHI) (Canadian Institute for Health Information, 2012) for the whole country.

However, we also evaluated the comparators in the model with the values obtained from the Toronto General Hospital (TGH) Liver transplantation program, one of the largest programs in the country with higher rates of organ availability. Although the qualitative findings did not change with this scenario, as shown in Table 4.1-4, the gained QALYs increased 1.9 times, from 0.0705 to 0.1352, i.e. from 26 to 48 quality-adjusted life days (about 85% increase) and the ICER decreased to $153,089/QALY from $204,301/QALY (about 25% decrease).

The long-term prognosis of the two strategies can be examined using survival curves. As illustrated in Figure 4.1-2, the curves are almost superimposable with very small differences through the period of follow-up. However, in the third and fourth decade of follow-up, there appears to be a modest benefit in survival for the screened population.

![Survival Curves](image)

**Figure 4.1-2: Survival Curves (Screen All vs. Screen None); each stage is one month.**

There are two survival curves superimposed over each other in this figure. As illustrated, there is a minimal benefit for screening in terms of survival, obtained during the third decade after start of the screening program, when the incidence rate of HCC is notably low, as in the population under study in this model.
**4.2 Sensitivity Analysis**

4.2.1 Deterministic Sensitivity Analysis

Extensive one-way sensitivity analyses on all variables in the model demonstrated that the results were sensitive to some variables, the most important of which are the annual incidence rate of HCC and the annual probability of developing symptoms related to HCC in an initially asymptomatic patient with HCC or in other words, the probability of a tumor being diagnosed based on HCC-related symptoms within a year without screening. When HCC incidence rate is varied from the lowest up to the highest plausible value, the ICER changes from "Screen none" being dominant (more effective and less expensive) to $57,203/QALY; with increasing incidence, the ICER reaches the base case value of $204,301/QALY with HCC incidence of 0.5%. With an annual HCC incidence of 5.1%, the ICER drops to $57,203/QALY.

The annual probability of a patient with HCC to convert from asymptomatic to symptomatic status which is practically the probability of an HCC to be diagnosed based on tumor-related symptoms within one year, is also among the highly influential variables in this model. If this value is less than 30%, the model calculation will show that surveillance will be more expensive and less effective, i.e. dominated by the "Screen none" strategy. This will be further elaborated in the discussion section.

The table above shows the calculations for the base case in the model but with different values used for the availability of transplantation based on the data obtained from Toronto General Hospital Transplantation Program. This shows if in a screening program, there are more organ available for OLT, the ICER will decrease in favor of the surveillance program.

**Table 4.1-4: Cost-Effectiveness analysis (Scenario Analysis with the TGH data)**

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cost (CAN$)</th>
<th>Incremental Cost</th>
<th>Effect (QALY)</th>
<th>Incremental Effect</th>
<th>Incremental C/E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screen None</td>
<td>29,714.23</td>
<td>0</td>
<td>13.0527</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Screen All</td>
<td>50,414.50</td>
<td>20,700.27</td>
<td>13.1879</td>
<td>0.1352</td>
<td>153,089.32</td>
</tr>
</tbody>
</table>

The table above shows the calculations for the base case in the model but with different values used for the availability of transplantation based on the data obtained from Toronto General Hospital Transplantation Program. This shows if in a screening program, there are more organ available for OLT, the ICER will decrease in favor of the surveillance program.

Figure 4.2-1 reviews the most influential variables with their effects on the ICER in the "Screen all" strategy, using a tornado diagram. The vertical line in the figure shows the ICER in the base
case while the bars illustrate the variability of the ICER as a result of changes in the specific variable while all other variables are held constant.

![Tornado Diagram showing the effect of some variables on the ICER](image)

**Figure 4.2-1: Tornado Diagram showing the effect of some variables on the ICER (Base Case: 204,301.1709 $/QALY)**

When performing sensitivity analysis, TreeAge Pro® software keeps all variables other than the one under study, constant and varies that one particular one within the plausible range of low and high limits introduced for it. Then repeats the same procedure for each other variable and the results, which will be the range of changes in the ICER is illustrated in the so called "tornado diagram" as shown above. This reveals which variable or variables have the greatest effect on changing the ICER when they themselves change, i.e. effective variables in the model.

The annual discount rate was also modified during the process of sensitivity analysis. The value for this variable was decreased to 3% and 0% from the 5% used in the base case and these resulted in a decrease in the ICER value to $170,928/QALY and $125,762/QALY respectively. As far as the HCC incidence rate and surveillance effect are concerned, the incremental effectiveness of surveillance shows an increasing trend as the annual incidence increases within the plausible range of the variable. Figure 4.2-2 illustrates this relationship for the quality adjusted and discounted (5% annual rate) effects in the model.
Furthermore, the ICER starts to change from negative values (with 0.13% HCC incidence rate) where the "Screen all" strategy is actually dominated (more expensive and less effective) by the "Screen none" strategy, to positive values as the HCC incidence increases over 0.278% and the change continues in the plausible range of HCC incidence to be $103,503.27/QALY with the highest plausible HCC incidence (0.89%) in this setting. Although this ICER changes with a wide range within the plausible range for this HCC incidence, it is never below the cost-effectiveness threshold of $50,000/QALY for the "Screen all" strategy to be counted as cost-effective. Sensitivity analysis with a wide range of values for the annual incidence rate (0.1-10%) for HCC in the model showed that the lowest ICER ($57,203/QALY) can be achieved when this incidence is 5.1%. At this level, surveillance offers about 0.873436 QALY or about 319 extra quality-adjusted days of life.

**Figure 4.2-2: Effect of varying annual HCC incidence on incremental effectiveness**

As illustrated in the figure above, the incremental effectiveness of surveillance program for HCC increases as the annual HCC incidence increases, showing that when the incidence goes up, more effect will be achieved from "Screening All" strategy compared to "Screen None".
4.2.1.1 Model Start Age

The model start age is 50 years of age. However, we also evaluated the behaviour of the ICER and incremental effectiveness changes as the starting age was varied from 37 years up to 90 years of age. As is illustrated in Figure 4.2-3, the lowest ICER and the highest incremental effectiveness in the age range of 37 to 50 years is obtained with the already selected 50 years of age. With 37 years as the model start age, the ICER and incremental effectiveness will be $395,414/QALY and 0.044793 QALY respectively in comparison to the same values with 50 years as the start age, namely $204,301/QALY for the ICER with about 48% decrease 0.070518 QALY for the incremental effectiveness with an increase of about 58%. Obviously, with a very low incidence of HCC, cost of surveillance is remarkably high when screening starts at a younger age. On the other hand, as patients grow older, the ICER shows a decreasing trend down to $41,248/QALY if the model start age was set at 69 years and then starts to build up again. This decrease, as will be further elaborated in the discussion session, may in part be due to the lower cost of fewer screening tests required during the remaining life span of patients.
Adherence to surveillance has also been analysed separately to evaluate the behaviour of the model in regards to this variable. As is seen in Figure 4.2-4 and Figure 4.2-5, the cost and benefit of surveillance increase as adherence to surveillance increases. This is clinically expected and in part is due to more screening tests performed in the adherent patients and also more treatment instances, which are quite expensive in some modalities; however, since these increase together, as correctly captured during the sensitivity analyses, adherence to surveillance is not an influential variable in the whole model.

**Figure 4.2-3: Effect of model start age on the ICER**

The figure above shows the fluctuations in the ICER when the start age for screening changes from low values with highest ICERs to about 69 years old when the ICER in this model with the used values will be around $40,000/QALY, and then it climbs up again due to increasing age and higher probable complication rates for treatment options and also the higher cost of larger number of tests done for patients with higher age. Therefore, starting surveillance in a proper age may be cost effective as is shown in this figure.

**4.2.1.2 Adherence to Surveillance**

Adherence to surveillance has also been analysed separately to evaluate the behaviour of the model in regards to this variable. As is seen in Figure 4.2-4 and Figure 4.2-5, the cost and benefit of surveillance increase as adherence to surveillance increases. This is clinically expected and in part is due to more screening tests performed in the adherent patients and also more treatment instances, which are quite expensive in some modalities; however, since these increase together, as correctly captured during the sensitivity analyses, adherence to surveillance is not an influential variable in the whole model.
Figure 4.2-4: Surveillance adherence and incremental cost
As illustrated in the figure, the more the adherence to the surveillance program, the more tests are done and therefore, the higher the cost of the program would be. Although, as will be shown elsewhere, the effect obtained from the surveillance program will be higher when there is higher adherence will also increase.

Figure 4.2-5: Surveillance adherence and incremental effectiveness
This figure shows the relation between the adherence to the surveillance program and the incremental effect obtained from the program. Obviously, the more patients adhere to their surveillance program, the higher the incremental effectiveness of the surveillance will be.
4.2.2 Probabilistic Sensitivity Analysis

Figure 4.2-6 is the scatter plot showing the incremental cost-effectiveness of "Screen all" strategy compared to "Screen none" option. In this graph, each point represents a simulation of the model showing pairs of incremental cost and effectiveness values based on the comparator strategy ("Screen none"). The regions below the cost-effectiveness threshold line here are cost-effective iterations. The ellipse on the graph shows the 95% confidence interval in calculations. When parameter uncertainty was taken into account, the outcome did not differ significantly from the base case analysis.

![Figure 4.2-6: Scatter plot for ICER in "Screen all" vs. "Screen none" strategy](image)

Scatter plot in the figure above shows where most ICER values will be located (using the eclipse) if the model is run several times (in this case, 10,000 times), comparing them with the willingness to pay (WTP) threshold of $50,000/QALY. As seen here, ICER will be mostly above this threshold.

With 10,000 iterations, the "Screen all" strategy had less than 1% chance of costing less than $50,000/QALY, the WTP threshold in the model, when compared with "Screen none" strategy. Cost-effectiveness acceptability curves generally show the probability of each strategy being
cost-effective at different cost-effectiveness thresholds. (Fenwick, Claxton, & Sculpher, 2001; Fenwick, O'Brien, & Briggs, 2004) Therefore, as illustrated in Figure 4.2-7, if the cost-effectiveness threshold was to be more than about $220,000/QALY, the probability of the "Screen all" strategy being cost-effective is exceeding 50%.

Figure 4.2-7: Cost-Effectiveness Acceptability Curve for "Screen All" Strategy (WTP Threshold: $50,000/QALY)

Cost-effectiveness acceptability curves try to show that what happens if the model runs for a specific number of times, e.g. 10,000 times here; that is to say, what will the chances be that the procedure be cost-effective. As is shown in the figure, if our model runs for 10,000 time, there will be less than 1% chance that the results become cost-effective for "Screen All" strategy, taking into account all the variables and values used in the model and the willingness to pay threshold.
5 Chapter Five: Discussion

5.1 Discussion

This model showed that with 0.5% annual HCC incidence in patients with HCV-related cirrhosis, post-SVR, the strategy of biannual ultrasound surveillance for HCC would not be considered cost-effective at a cost-effectiveness threshold of $50,000/QALY.

HCC is a practical target for surveillance programs since it occurs in a well-defined population, most often in patients with cirrhosis, including cirrhosis due to HCV infection; it has a long subclinical and asymptomatic phase and fortunately, it has an improved prognosis if detected and treated early. (O. S. Lin et al., 2004) Therefore, surveillance programs for HCC have been recommended and are used in current practice. (Bruix et al., 2011) These programs, like any other interventions, need to be funded from the usually restricted healthcare budgets, therefore, cost-effectiveness analyses can be an important help to inform funding decisions for these programs. (Detsky & Naglie, 1990)

There is a comprehensive discussion in the section on surveillance about studies which have already shown that surveillance for HCC is both effective and cost-effective in the pre-SVR HCV-infected population with cirrhosis. The utility of HCC surveillance in patients with cirrhosis is not unexpected since the incidence of the tumor is high in this population. (Andersson et al., 2008) The current model was designed to evaluate the same question though in a different population, namely, CHC-related cirrhosis patients who have achieved SVR.

As mentioned above, with 0.5% annual HCC incidence in these patients, biannual US surveillance for HCC is not cost-effective at the commonly used cost-effectiveness threshold of $50,000/QALY. It is not surprising that this strategy costs more than the "Screen none" strategy; however, it offers noticeable life expectancy gains in the few patients who develop HCC in this population. Biannual US screening offers a gain of about 33 extra days of life or about 26 quality-adjusted life days compared to the group without surveillance. However, taking these results into consideration, it should be borne in mind that the gain obtained in the life expectancy is actually an average gain across a population of patients who receive the particular intervention. Because of the low-probability of HCC in patients after SVR, most of the
surveillance is done in patients who never develop HCC and thus never accrue benefit from screening. The small gain in life expectancy across the population still may correspond to experiencing a substantial gain for the small number of patients who do develop HCC. (Arguedas et al., 2003; D. Naimark, Naglie, & Detsky, 1994)

A main objective for HCC surveillance programs is to decrease the mortality from the disease. (Bruix et al., 2011; Sherman, 2014) This model showed that the liver-related mortality was decreased by about 15.2% using the "Screen all" strategy. This extra health benefit is gained because of early tumor detection and also the proper and timely management. Therefore, once more it was demonstrated that HCC surveillance is efficacious (achieving its goal in optimal circumstances such as full adherence to the program) and effective (doing more good than harm in usual, everyday life situations). Its efficiency (cost-effectiveness), (Detsky & Naglie, 1990) will be further discussed below.

Survival, in contrast to mortality rates, can be a surrogate endpoint since it will be affected by several sources of bias which do not affect mortality, including lead-time and length-time biases (Sherman, 2014) which have been discussed before in the related section. Naimark and colleagues, (D. Naimark et al., 1994) suggested that any procedure which increases longevity by about 100 days is clinically significant; bearing this in mind, the result of the current model would be a close call. Nevertheless, the benefits are comparable to the benefits in extra life-time obtained from well-established screening programs such as surveillance for diabetes mellitus, (Anderson, 2012) breast cancer, (Lindfors & Rosenquist, 1995) cervical cancer, (Eddy, 1990a) and also colorectal cancer (Eddy, 1990b) which have been shown to prolong survival of their target populations.

The calculated costs were $42,071 in "Screen all" and $27,664 in "Screen none" strategies, resulting in an ICER of $204,301/QALY. The high cost for OLT and post transplant maintenance in this model in part explain the increased cost of the "Screen all" strategy in comparison to that of the "Screen none" group, in addition to the costs from screening itself which also plays a role here. However, since HCCs are detected earlier in the "screen all" strategy and in a stage that can benefit from therapies other than OLT, the high cost of OLT, which applies to a few patients in this strategy, cannot significantly affect the final results. As
discussed in the results section, when the organ availability data from Toronto General Hospital with higher OLT rates, instead of the national data from the Canadian Institute for Health Information (Canadian Institute for Health Information, 2012) were used, the cost of "Screen all" strategy increased more (20%; from $42,071 to $50,414) than the "Screen none" strategy (7%; from $27,664 to $29,714) showing that more HCCs are diagnosed in time to be eligible for curative treatments like OLT which increases the benefits gained from therapy.

The ICER of $204,301/QALY is much higher than the conventional $50,000/QALY. (Braithwaite et al., 2008) This threshold, as discussed in the methodology section, has not changed since its introduction in 1982. (Ubel et al., 2003) Therefore, it may not be consistent with the current spending behaviour for health sector in some countries, like in the USA where in some instances, WTP thresholds may be up to $297,000 per QALY. (Braithwaite et al., 2008) Therefore, as Neumann and colleagues (Neumann et al., 2014) have also discussed, a practical approach is that the threshold should depend on the budget available to a decision maker in a particular jurisdiction who can evaluate the costs and benefits of alternative uses attributable to that budget. Moreover, they suggested that if a single threshold should be selected without an explicit resource constraint, $100,000 or $150,000 per QALY could be used. Therefore, there is the possibility of this surveillance strategy to be cost-effective in a jurisdiction where decision makers can afford higher thresholds for society’s willingness to pay for health services.

Probabilistic sensitivity analysis in this model showed that the "Screen all" strategy had a less than 1% chance of being cost-effective at the $50,000/QALY threshold. However, at a cost-effectiveness of $220,000/QALY, the probability of the screening strategy to be the cost-effective is 50%.

There have been many cost-effectiveness studies in patients with cirrhosis which have evaluated surveillance for HCC with different tests and protocols. (Andersson et al., 2008; Arguedas et al., 2003; Kang et al., 1992; O. S. Lin et al., 2004; Nouso et al., 2008; Patel et al., 2005; Saab et al., 2010; Saab et al., 2003; Sarasin et al., 1996; Shih et al., 2010; Thompson Coon et al., 2008) Notably, there are significant differences between the various models, confirming the difficulty of designing a truly comprehensive and scientifically satisfactory decision analysis model for this particular clinical issue. The published studies differ in not only the nature of the population
being investigated, but also in the interventions being applied including screening and diagnostic confirmatory tests and the treatment options incorporated into the models. It is important to know that when results of models from different settings are evaluated and compared with a specific study, even though costs are transformed to the appropriate local currency, different patterns of clinical practice and also different services and medication prices in specific jurisdictions may significantly hinder generalizability of the outcomes. (Roberts et al., 2012)

According to the current literature in this field, the present study is the only one thus far to evaluate surveillance for HCC in CHC-related cirrhosis patients who have achieved SVR. Consequently, since the study population is significantly different, the transition parameters, treatment allocations and in essence, the natural history of the disease will be different in this study, therefore, outcomes cannot be compared with other relevant studies. However, similarities and differences in terms of their concepts can be compared. Virtually, all these models have several results in common. All of these studies, including the current model, show that some form of surveillance is effective, in view of increase in life of the cohort through decrease in mortality therein, yet they differ in concluding which strategy is the most cost-effective one. Likewise, they all show that the cost-efficacy of the surveillance programs under investigation is highly dependent on the incidence of HCC development in whatever population of patients they assess. (Sherman, 2014) The current model has also reached the same result in the relation of cost-effectiveness of the surveillance and the incidence of HCC in the model population.

Among the mentioned studies, two of them are closer to the current model in terms of their population under investigation. Lin and colleagues, (O. S. Lin et al., 2004) assessed several screening tests including biannual and annual AFP and US, AFP and CT scan and combination of biannual AFP and annual US in patients with HCV-related cirrhosis, 40 years or older. They concluded that combination of AFP and US with the mentioned order is the cost-effective option among others with an ICER of less than $50,000/QALY. However, compared with the current model, other than a different patient population, they had not modelled adherence to screening, treatment of HCV and also many of the available treatment options for HCC in this model. They did not use a "No screening" strategy in their study and used a different discount rate (3% per
year) with a societal perspective. The second study was performed by Andersson and colleagues (Andersson et al., 2008) They chose patients older than 50 years with compensated cirrhosis to assess surveillance for HCC with annual and biannual US, biannual AFP and US, annual and biannual CT scan and annual MRI against no screening. They concluded that biannual US is the most cost-effective option with an ICER of $30,700/QALY. They assumed a 5% incidence of HCC development in their population. The current model found a similar result since it showed that if the HCC incidence increases over 5.1%, biannual US will be the cost-effective strategy in its target population. However, they did not have any treatment options for advanced tumor which accounts for a major difference with the model in the current study.

Nouso and colleagues, (Nouso et al., 2008) reviewed the strategies of no screening versus biannual US in patients with Child Pugh class A cirrhosis who were 45 years old or more. They did not include liver transplantation in their base case assessment and used surgical resection, RFA and TACE as treatment options. They used a 3% annual discount rate and concluded that with an HCC incidence of 4%, biannual US screening is the most cost-effective strategy with an ICER of $29,900/QALY; however, adding liver transplantation to their treatment portfolio increased their final ICER by about 50%. Thompson Coon and colleagues, (Thompson Coon et al., 2008) performed a study in which they evaluated HCC surveillance in patients with cirrhosis due to HBV, HCV and alcoholic liver disease, with several screening options against no screening, but only in those who were 70 years old or younger. It is true that, as Colombo and colleagues, (Colombo, 2007) stated, there is less gain from surveillance for HCC for those patients who are over 70 years of age. Nevertheless, in order to be more realistic and similar to the everyday clinical practice, the present model also includes patients older than 70 years and has anticipated appropriate treatment options for them to be followed up for their whole remaining life.

Another noteworthy conclusion that Thompson Coon and colleagues (Thompson Coon et al., 2008) stated is that the faster the tumor grows, the more cost-effective surveillance will be. This is similar to the present model where the higher the transition probability of an asymptomatic HCC to become symptomatic, the better and more favourable would be the ICER in terms of cost-effectiveness of biannual US surveillance, even in the target population of this model.
Saab and colleagues, (Saab et al., 2003) also performed a study on this theme which is different from the present model in several ways in terms of their population, patients with cirrhosis with advanced disease awaiting liver transplantation, and also they did not evaluate a "No screening" strategy among their evaluation options. Furthermore, they had not adjusted the outcomes for quality of life. However, they also shared with previous studies and also the current model that as the incidence of HCC increases in the target population, the surveillance, in their case with ultrasound, becomes more and more cost-effective.

The present model detects about 14% false positive diagnoses cases, which are often seen in screening programs especially for a disease with low incidence and prevalence which results in the positive predictive value of the screening tests to decrease and the results of a group of tests to turn out to be false positive. This is the case with HCC in this model population and therefore, there are a number of tests which are falsely confirmed as being positive. These cases are followed in the model while they receive RFA as their allocated treatment modality and are confirmed pathologically as false diagnoses cases during this procedure and then they return back to the screening program. This enables the model to incorporate all the costs, utilities and disutilities attributed to this group for a more realistic outcome report. In addition to the ICER itself, the high false positive rate among the "Screen All" group may be a deterrent to implement a surveillance program in patients after SVR. False negative cases will also return back to the screening process to be later diagnosed accordingly. Shih and colleagues (Shih et al., 2010) have reported a 10% false positive diagnosis with AFP and US. Among others, Argueda and colleagues (Arguedas et al., 2003) and Patel and colleagues (Patel et al., 2005) have also mentioned the false positive diagnoses in their studies however, the former study assumes them as regenerative nodules and the latter has not applied any particular treatment option for these cases.

As another important consideration in comparing different studies in this field and interpreting their results is what are and how they have allocated their treatment options. For example, in the current model, most of the available and appropriate treatment options have been incorporated for the model to be as comprehensive as possible. However, treatment allocation policies keep evolving throughout time. As an example, in many studies including the present one, Milan criteria (Mazzaferro et al., 1996) (single tumor of ≤ 5cm or three or fewer nodules, none more
(Yao et al., 2001) suggested that the criteria for OLT based on tumor size could be expanded and still expect outstanding survival post-transplantation. Yao and colleagues in another study (Yao, Ferrell, et al., 2002) suggested that if they allow for single tumors ≤ 6.5cm, or three or fewer nodules among which the largest tumor is ≤ 4.5cm and total lesion diameter of ≤ 8cm without gross vascular invasion, the so called University of California, San Francisco (UCSF) criteria, acceptable post transplant outcome would be better predicted in comparison to the Milan criteria. Because of the cost of transplant, studies that do not incorporate this important treatment option lack significant face validity.

Extensive one-way sensitivity analyses on all variables in the model demonstrated that the results were sensitive to some variables, the most important of which are the annual incidence rate of HCC and the probability of developing symptoms related to HCC in an asymptomatic patient with HCC within one year, which is actually the probability of the mentioned patient to obtain the indications to undergo diagnostic tests, without the surveillance program and just based on the HCC-related symptoms. If the HCC incidence is less that 0.278%, the screen all strategy will be dominated by "Screen none", i.e. "Screen all" is not only more expensive, but also less effective than no screening.

The effect of varying different values for annual discount rate was also reviewed in this process. Setting this variable to 0% and 3% annual rates resulted in ICER of $125,762/QALY and $170,928/QALY, respectively. Although these ICERs decreased in comparison to the main model value of $204,301/QALY, however, the overall outcome of the model did not change.

False positive diagnoses and disutilities attributed to the surveillance procedure may explain this finding. Sensitivity analysis with a wide range of values for the annual incidence rate for HCC in the model showed that the lowest ICER ($57,203/QALY /QALY) can be achieved when this incidence is about 5.1%. At this level, surveillance offers about 0.873436 QALY or about 319 extra quality-adjusted days of life. This effect is expected since with higher incidence rate, more and more patients will take benefit from the timely diagnosis and the appropriate treatment options available. The related ICER, though not still quite below the $50,000/QALY WTP threshold with the base-case, is possibly cost-effective. The annual incidence of HCC in the
model population (CHC-related cirrhosis patients, post-SVR) is 0.5%. (van der Meer et al., 2012) Although this 0.5% value may be uncertain, it is expected to be lower than the risk in patients who have not yet cleared the virus but have cirrhosis with estimates ranging from 1 to 4%, and possibly as high as 8% in some areas such as Japan. (Beasley et al., 1981; El-Serag, 2012; Fattovich, Giustina, Degos, Tremolada, et al., 1997; Mittal & El-Serag, 2013; Sherman, 2010c)

As mentioned before in the section on HCV-infection treatment, patients who have cleared their HCV through curative treatments and have achieved SVR, have a reduced risk of developing HCC. However, it is likely that the risk does not decline immediately and also probably increases with time as patients grow older. (van der Meer, 2013a) Therefore, it may become cost-effective to provide HCC surveillance facilities for these patients sometime in the course of their post-SVR life time. Unfortunately, that point in time cannot be determined with certainty, and these patients have to continue to undergo surveillance for HCC. (Bruix et al., 2011)

A recent study by van der Meer and colleagues, (van der Meer, 2013a) showed that the cumulative incidence of HCC in post-SVR patients increases as the patients grow older (2.6% in patients <45 years old, 9.7% in those 45-60 years old and 12.2% in patients older than 60 years old) and that the cost-effectiveness of HCC surveillance among patients with cirrhosis, post-SVR improves as this population with CHC ages. As was shown in the results section in the current model, surveillance started in younger ages (i.e. below 50 years) resulted in high ICER values such as $395,414/QALY when the start age is 37 years down to the $204,301/QALY for our base case (50 years old as start age). This decreasing trend continues to an ICER of $41,248/QALY when the model start age reached 69 years old. This may in part be due to the lower number of screening tests and intervention done during the shorter life-span of these patients. However, based on the discussion by van der Meer and colleagues, (van der Meer, 2013a) mentioned above, this decrease in the ICER may be explained by the increase in the HCC incidence as patients grow older when starting the surveillance program. Furthermore, as Colombo and colleagues, (Colombo, 2007) stated, there is less gain from surveillance for HCC for those patients who are over 70 years of age, the current model also shows an increasing trend in the ICER over the age 70 years as starting point for surveillance which can be explained by
the less gain offered to patients in this age by surveillance due to higher complications of therapeutic interventions.

Another noteworthy point is the reduced competing risk for mortality in post-SVR patients due to improvement of the liver disease itself in comparison to those who have not achieved SVR. Asahina and colleagues, (Asahina et al., 2010) also stated a similar concept when they concluded that elderly patients treated with interferon are at higher risk for HCC development. On the other hand, keeping in mind the risk factors for HCC development, there may be factors, other than age alone, such as state of cirrhosis, sex and some other biological factors playing a role. The annual probability of a patient with HCC to convert from asymptomatic to symptomatic status is also among the influential variables in this model. If this value is less than 30%, which results in the "Screen all" strategy being dominated which means it will be more expensive and less effective in comparison to the "Screen none" strategy. This is not surprising since if the tumor grows very slowly and it takes a long time for it to become symptomatic and therefore diagnosed, there is no benefit in biannual screening which in this case will add cost and discomfort for the population under surveillance. As this value increases, the benefit from screening starts to build up, though it may still not be cost-effective when the $50,000/QALY threshold for WTP is in effect.

By the time an HCC is diagnosed through its symptoms, over 85% of tumors will be unresectable due to multiple reasons including larger size, multifocality, liver decompensation or invasion to surrounding structures or portal vein. (Chlebowski et al., 1984; O. S. Lin et al., 2004; Solmi, Primerano, & Gandolfi, 1996) The current model is also in line with this finding in that patients move to the palliative treatment health state in screen none group notably more frequently than in the screen all strategy (82.3% versus 6.8% respectively, of the total tumors detected and diagnosed in the related strategies).

Myers and colleagues, (Myers et al., 2014) demonstrated that in Canada, the proportion of those patients with advanced HCV-related liver morbidity will rise between 2013 and 2035 related to the increase due to aging of infected population and the ensuing progression of the hepatic fibrosis. They have also mentioned that the incidence of decompensated cirrhosis, HCC and liver transplantation are all expected to peak sometime between 2031 and 2035. Arguedas and
colleagues, (Arguedas et al., 2003) have also reported a similar anticipation for HCC increase in the USA and other Western countries. Bearing all these in mind, together with improvements in efficacy of antiviral therapies in curing HCV infection, the importance of reconsidering HCC surveillance in cirrhosis patients post-SVR is much more highlighted, not only for policy makers, but also for clinicians.

Cost-effectiveness analyses may not be a favorite of clinicians engaged in the care of individual patients where, sometimes, interventions are selected based on their net benefit for the particular patients rather than considering alternate benefits those scarce resources could have for other patients. This clearly shows the struggle between wishes to maximize effectiveness for individual patients and the wishes of minimizing costs and maximizing the health benefits derived from a fixed budget to better allocate scant resources and benefits to larger groups of patients. However, even in extreme instances where some clinicians are not fond of the cost-effectiveness idea, they have to implement it in situations like "life boat scenario" where individual patients are in a queue for an intervention requiring a scarce resource like the only one empty bed in a cardiac care unit for a few eligible patients on a given day. (Detsky & Naglie, 1990)

5.2 Limitations

Similar to other studies, this current analysis also faces limitations. Some of these limitations are inherent in decision analysis models. Although this technique facilitates simulating real situations, however, no matter how complex they are, clinical realities cannot be perfectly and ideally reflected; this in part stems from the model inputs, such as costs and mortality rates and management routines, which vary in different populations and geographical areas and one way or the other, suffer from some level of uncertainties, leading to potential limitations. For example, some of the data used in the current model, such as general mortality rates, are from the Canadian population which may affect the external validity of the results; however, efforts have been made to collect the best available data from the literature or whenever not present, from well-known experts in the field and further supported by comprehensive sensitivity analyses, but when interpreting the results, this limitation should be kept in mind.
Another intrinsic limitation of cost-effectiveness models including the current one is the assumptions about the model parameters and conditions which are due to either lack of available data in the literature or the limits in the level of details which can be incorporated into the model structure. This model is quite complex with as many details as possible included, however, it suffers from some assumptions in the related calculations.

The current model is a Markov cohort evaluation thus, individual patients sampling or the so-called microsimulation, is not incorporated here. Therefore, it is actually not possible to account for patients’ population heterogeneity and also to deal with factors such as tumor growth rate, changes in some values as the patients grow older such as, mortality/morbidity rates, some probabilities and tumor incidence rate; furthermore, those parameters that may change in time, such as adherence to the surveillance program, have the same fate. Currently, these parameters are all assumed to remain constant in this model. By the same token, since interpersonal differences cannot be taken into account in a cohort analysis, characteristics of imaging test in different patients (e.g. ultrasound in thin vs. obese patients), as well as the previous health state of patients residing in a similar health state cannot be evaluated. For example, patients with different number of tumors with different stages are all transferred into a common health state for surgical resection.

Surveillance for HCC, like any other screening intervention for tumors, is subject to lead time bias. In this bias, some or even theoretically, all of the benefit in increased survival is credited to earlier diagnosis of the tumor, while death occurs at the same time whether the illness is diagnosed due to symptoms or through screening. (Sherman, 2014; Tong, Sun, Hsien, & Lu, 2010) In the current model, since HCC can be successfully cured in many instances if found early enough and is almost universally fatal otherwise, this bias may not be very strong; however, it is a valid caution to take when interpreting the results.

As another point to be remembered in this model is that therapeutic options are taken into account as similar in each category. For example, RFA or surgical resection therapies are meant to be performed with the same technique and outcome whereas they may differ in different settings and centers with different outcomes and complications. As another noteworthy example is the dramatic changes in transplantation techniques. Shortage of available organ donors is a
critical problem for cadaveric transplantation programs whereas this is less of an issue for living donor transplantation, and it has been reported to be more cost-effective. (Patel et al., 2005) Moreover, other screening approaches other than ultrasound have not been incorporated into this model and only the compensated liver disease at the time of HCV cure has been taken into account whereas with new antiviral treatment options, patients with more advanced underlying disease, like those with Child-Pugh B and C cirrhosis will be cured of their HCV infection and they likely have higher risk of HCC development.

5.3 Strengths

This study has several strengths. According to the current literature, this is the first analysis determining the cost-effectiveness of a surveillance program for HCC in patients with cirrhosis post-SVR. Efforts have been made to find model parameter values from the Canadian population or most likely to be applicable to the Canadian population and also to include as much details in the diagnosis and management of HCC as possible to simulate the natural history of the disease throughout the life-time of the patients. Although the life-time time horizon creates issue in calculating time dependent values such as utilities, however, it is long enough to capture major health and economic consequences which translate into the benefits from surveillance program.

Patients are offered the currently available treatment options according to their clinical status; furthermore, they have the option of receiving one or multiple therapies with different methods throughout the course of their illness when recommended. This helps to better justify any obtained survival benefit. Moreover, these benefits are estimated in QALYs instead of merely life-years so that the real gain from surveillance programs including their psychological impacts on patients, interpreted to disutilities in the model, can be evaluated. These together with inclusion of adherence to surveillance procedures into the model, helps preventing the overestimation about efficacy of surveillance which is a probable happening.

There are no strict exclusion criteria in the model. Therefore, real-life high risk behaviours such as alcohol intake and intravenous drug use can still have their role in the natural history of the disease, although reference to one of the abovementioned limitations, a cohort analysis cannot capture these influences as efficiently as microsimulation. Lastly, the structure of the model is
capable of incorporating age and time-related values for its parameters such as changes in HCC incidence rate with age of the patients, though due to lack of enough and strong data in the related literature, they are kept constant for the time being.
6 Chapter Six: Conclusion, Implications & Future Directions

6.1 Conclusion
The current simulation model was designed using the available knowledge about the natural history and epidemiology of HCC in affected patients. Moreover, most of the inputs for the calculations in the model are from the current diagnostic and therapeutic choices and their outcomes available in the related literature. Bearing all these in mind, this model found that with 0.5% HCC incidence in HCV-related cirrhosis patients post-SVR and using $50,000/QALY as the WTP threshold, biannual US surveillance for HCC in a cohort of 50-year-old HCV-related cirrhosis patients post-SVR is not cost-effective due to very low tumor incidence. In addition to the methods and tests used in a surveillance program, the extra quality-adjusted life years gained depend also on the properties of the tumor in the target population such as the incidence and prevalence of the tumor.

Therefore, as HCC incidence is an influential driver, identifying high-risk patients would be required to allow for targeted surveillance. This together with the rapid improvements in the efficacy of antiviral therapies in curing HCV infection highlight the importance of reconsidering HCC surveillance protocols in patients with cirrhosis, post-SVR which will be critical to development of effective guidelines and will help health policy makers to further optimize their resource allocation procedures.

6.2 Implications
6.2.1 Implications for Clinical Managements and Research
The current model suggests that with the incidence for HCC used in the calculations reflecting the population under study, screening all patients for HCC is unlikely to be cost-effective at a cost-effectiveness threshold of $50,000/QALY. Although decision analysis models, like the present one, cannot replace randomized controlled trials (RCT) in the level and quality of the results they produce, but, supported by sensitivity analyses, can show gaps in the data and identify which missing data are valuable enough to trigger prospective research protocols when possible.(Poustchi et al., 2011)
This model showed that the results are sensitive to the rate of asymptomatic to symptomatic conversion in patients with HCC and also the incidence rate of HCC in the population under surveillance. These data can be used to optimize the available management methods in post-SVR patients with cirrhosis and their follow-up procedures; they can emphasize the importance of future research on identifying high-risk population for surveillance protocols; yet it highlights the need for a thorough investigation of the natural history of cirrhosis post-SVR which may lead to interventions that may be more financially appealing.

6.2.2 Implications for Health Policy Makers

It has already been mentioned that due to the worldwide changes in HCV epidemiology, incidence and prevalence of HCC is increasing and improved diagnostic methods will result in more diagnosed cases. (Sherman, 2010a, 2010b; Umemura et al., 2009) On the other hand, taking into account all the favourable effects of SVR on all-cause mortality and incidence of HCC in this population of patients, (van der Meer et al., 2012) they are still at risk for developing HCC, (R. L. Morgan et al., 2013; T. R. Morgan et al., 2010) the fact that mandates paying attention to their follow-up, timely diagnosis and proper management. Although cost-effectiveness analyses from a third party payers’ perspective, due to difficulty of evaluation, do not calculate the opportunity costs of resources that are utilized by a specific intervention, which is logically lost in another setting, proper allocation of restricted healthcare budget is of utmost importance for efficient care provision and maximizing the quality of life offered through medical interventions. This model can be a sample of similar studies which assist health policy decision makers to better allocate available resources to the target groups who will take advantage of efficient and at the same time, costly treatments. At the end of the day, limited resources should be distributed in the fairest possible way to facilitate access to the greatest health benefit for a larger group of patients in need of these services. (Lens & Dawes, 2002)

6.3 HCC detection in the near future

Thanks to scientific endeavors and remarkable research done in this field so far, HCC has turned from an almost universal "death sentence" in the last decade into a malignancy that is preventable, can be detected early and if so, may be cured. (Bruix et al., 2011) However, as discussed before, the incidence of HCC is increasing in most countries. Although vaccination and preventive measures may possibly decrease the importance of HBV and HCV infections as
major risks factors for HCC worldwide in the coming future, other risk factors such as obesity and diabetes are simultaneously increasing fast throughout the world. (Nordenstedt et al., 2010)

At the same time, there are several areas in the field of hepatocellular carcinoma where active research is underway including but not limited to molecular pathogenesis, genomic studies, tumor detection through new biomarkers in the preclinical stage and also new radiologic methods like contrast-enhanced ultrasound, diagnosis and treatment that each and every single of them may have an influence in further elucidating transition of cells from non-malignant to malignant. This will definitely pave the road to new preventive and therapeutic strategies. (Bruix et al., 2011) In the long run, all these have a unique translation that is more HCC will be diagnosed in the coming years, even in the presence of practical preventive measures already described.

6.4 Strategies to meet the increasing demand

As far as HCC detection and treatment is concerned, healthcare systems will definitely be faced with an increased demand for required resources to fulfil surveillance and detection programs as well as implement therapeutic interventions which are both resource intensive and at some points mandate wise strategies and plans to efficiently allocated budgets and human resources.

Novel antiviral therapies which are improving with a fast pace will result in more patients who have been cured from their HCV infection and achieved SVR. On the other hand, ongoing genomic and proteomic studies will assist in better and more accurately characterizing HCC. This means that in the future, HCC patients may be classified based on their molecular profile and according to a rough estimation and evaluation of tumor burden or liver function. (Bruix et al., 2011) Moreover, studies are ongoing which have shown radiation therapy as an emerging and a possible therapeutic option for HCC. (Klein et al., 2015) Obviously, this may create further need for proper and timely diagnosis to take the utmost benefit from the therapeutic measures. These are also among a larger group of patients who are at risk for HCC due to other etiologic factors.

The present study as a representative of decision analysis modelling and also other studies such as the one performed by Lok AS and colleagues (Lok et al., 2009) who tried to create a risk
score for developing HCC in patients with CHC infection, can be further expanded and improved to find more efficient ways for identifying at risk populations, in this case, post-SVR, who require surveillance for HCC since this intervention is likely not cost-effective for all patients with cirrhosis. (Sherman, 2014) This seems to be a practical way to obtain the best possible results from the available and emerging treatment options.

Further research in this continuously evolving field may be required such as modelling studies with individual patient sampling methods to account for individual variability among patients and their tumor characteristics which may result in defining an optimal surveillance strategy in terms of methods and intervals. New and emerging diagnostic and therapeutic techniques will definitely assist future endeavors in this regard. On the other hand, further research may warrant to meet the assumptions and uncertainties in this and similar decision analysis models to make more accurate assessments of cost-effectiveness status for related interventions. These types of cost-effectiveness models can be further strengthened by preferably, long-term prospective studies on natural history and prognosis of HCC in post-SVR population.
References


Braithwaite, R. S., Meltzer, D. O., King, J. T., Jr., Leslie, D., & Roberts, M. S. (2008). What does the value of modern medicine say about the $50,000 per quality-adjusted life-year decision rule? Med Care, 46(4), 349-356. doi: 10.1097/MLR.0b013e31815c31a7


Fletcher, R. H., Fletcher, S. W., & Fletcher, G. S. (2014). Clinical Epidemiology, The Essentials (Fifth ed.).


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from malignant focal liver lesions. AJR. American Journal of Roentgenology, 186(1), 158-167. doi: 10.2214/ajr.04.1009


OHIP Schedule of Benefits for Physicians Services.


Paradis, V. (2013). Histopathology of hepatocellular carcinoma. Recent Results Cancer Res, 190, 21-32. doi: 10.1007/978-3-642-16037-0_2


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Selvarajah, S., & Busch, M. P. (2012). Transfusion transmission of HCV, a long but successful road map to safety. Antivir Ther, 17(7 Pt B), 1423-1429. doi: 10.3851/imp2459


Toronto Liver Transplant Database. (2014).


Van der Meer, A. J. (2013b). The risk for hepatocellular carcinoma among patients with chronic HCV infection and advanced hepatic fibrosis following sustained virological response. The AASLD Liver Meeting, Abstract #143.


Zangneh HF. (2014). Personal Enquiry from Princess Margaret Hospital, Toronto (August 2014).

Zangneh HF; Personal Enquiry, Dr. Sean Cleary & Dr. Jordan Feld. (2014).

