COMPARATIVE EFFECTIVENESS OF SURVEILLANCE AND CURRENT TREATMENT APPROACHES FOR THE DETECTION AND MANAGEMENT OF HEPATOCELLULAR CARCINOMA IN EAST ASIA

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ABSTRACT

Diana R. Chirovsky: COMPARATIVE EFFECTIVENESS OF SURVEILLANCE AND CURRENT TREATMENT APPROACHES FOR THE DETECTION AND MANAGEMENT OF HEPATOCELLULAR CARCINOMA IN EAST ASIA
(Under the direction of Kristen Hassmiller Lich)

Treatment approaches for hepatocellular carcinoma (HCC) in China are distinct in the use of resection with more advanced HCC, and continued research is needed to re-evaluate the appropriateness of guideline recommendations. Surveillance is recommended among individuals with chronic hepatitis B virus (HBV) infection in East Asia to improve early disease detection; however, only limited evidence exists to quantify its survival impact, and the ideal screening interval is not known. The overall objectives of this dissertation were to (1) compare the effectiveness of HCC treatment approaches in China, (2) evaluate the impact of 6-month and 12-month screening intervals compared with no surveillance among individuals with chronic HBV in China, and (3) examine the survival Impact of surveillance among HCC patients in Taiwan.

This dissertation used clinical data extracted from medical records for HCC patients in China and Taiwan, as part of the global BRIDGE to Better Outcomes in HCC (HCC BRIDGE) Study. Multivariate Cox proportional hazard models compared survival with treatment in China, stratified by disease stage, and propensity score (PS) analysis was conducted to address selection bias. An individual-based simulation model combined well-established data on chronic HBV progression and tumor growth in HCC with clinical data from the HCC BRIDGE study in China to project the survival impact of different surveillance strategies. Using the HCC BRIDGE study in Taiwan, survival according to surveillance status was assessed using the Kaplan-Meier method, controlling for selection bias through PS analysis and lead time bias using a range of tumor volume doubling time (DT) estimated across tumor growth studies.

The results revealed that patients with intermediate to advanced disease tolerate resection, and have better outcomes than with other HCC therapies. Surveillance improves survival with HCC, after applying lead time adjustments using a plausible range in DT. Results of model simulation suggest that surveillance performed at 12-month versus 6-month intervals can be more easily implemented with little impact on survival with HCC. These findings help inform efforts to ensure that individuals with chronic HBV are properly monitored for HCC given limited resources, and HCC patients receive appropriate treatment to improve survival outcomes in East Asia.

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AASLD	Association for the Study of Liver Disease
AFP	alpha-fetoprotein
AIC	akaike information criterion
ALD	alcoholic liver disease
ANOVA	analysis of variance
CI	confidence interval
CMH	China Ministry of Health
CP	Child-Pugh
CT	computed tomography
CVD	cardiovascular disease
DT	tumor volume doubling time
ECOG	Eastern Cooperative Oncology Group
HBV	hepatitis B virus
HCC	Hepatocellular carcinoma
HCC BRIDGE	BRIDGE to Better Outcomes in Hepatocellular Carcinoma Study
HCV	hepatitis C virus
HR	hazard ratio
MRI	magnetic resonance imaging
NAFLD	nonalcoholic fatty liver disease
PS	propensity score
REVEAL-HBV	Risk Evaluation of Viral Load Elevation and Associated Liver Disease/ Cancer-Hepatitis B Virus
RR	risk ratio
TA	trans-arterial

TM	tumor metastases
SE	standard error
US	ultrasound
VI	vascular invasion

CHAPTER 1: INTRODUCTION

Hepatocellular carcinoma (HCC) is highly prevalent and is the second leading cause of cancer-related death in East Asia, where hepatitis B virus (HBV) infection is endemic and is the primary etiological risk-factor for HCC.[1] Current approaches for improving survival with HCC are primarily focused on the early detection and treatment of HCC.[2,3] Recommended treatment approaches for HCC in China are largely distinct from those in other settings, particularly in the use of surgical resection among more advanced stage patients.[3-5] With recent advancements in resection and localized therapies for HCC, continued research is needed to re-evaluate the appropriateness of current guideline recommendations.[3]

Resection and tumor ablation are the main curative treatment options for HCC, but eligibility to receive curative therapy diminishes with more advanced disease.[2,3] Both the CMH and Taiwanese Department of Health have strived to improve the early detection of HCC by providing government-funded HCC surveillance in high-risk areas.[3,6,7] In both China and Taiwan, recommended screening tests include abdominal ultrasound (US) and measurement of serum alpha-fetoprotein (AFP), with a cut-point of ≥ 200 ng/mL.[2,3]

HCC surveillance is widely recommended; however, only limited evidence exists to quantify or even demonstrate its impact on survival with HCC.[2-4,8] An important limitation of prior studies assessing the impact of surveillance on the survival of patients with HCC is the potential for lead time bias.[9] This bias may occur if surveillance merely detects the tumor at an earlier stage without affecting the course of disease, leading in an overestimation of survival gains with surveillance.[2] To address this limitation, observational studies have approximately adjusted for lead time by applying different assumptions surrounding estimated tumor volume doubling time (DT) to the well-established formula

for tumor growth. [10-13] The results of these studies suggested that surveillance significantly improves survival, even after lead time adjustment. [10-13] However, such methods were based solely on current knowledge surrounding HCC tumor growth, and did not comprehensively incorporate the full range in DT seen across prior tumor growth studies in HCC. [14-27]

In addition, the ideal screening interval for HCC surveillance is not known. [2,4,8,28] Consensus guidelines suggest an interval of 6-12 months, based on average DT, [2,4,8] although there are no randomized studies that have determined the optimal interval. Guidelines acknowledge that the optimal interval for HCC surveillance should be assessed from the view of both resource use and survival outcomes, as it is clear that more frequent tests can detect HCC nodules of smaller size. [2,3] Thus, determining the optimal approach for HCC surveillance requires both an understanding of tumor development and progression over time, and an accurate assessment of treatment patterns and associated survival in clinical practice.

Thus, there are several gaps in the literature surrounding the appropriate treatment of patients diagnosed at various stages of disease, particularly for patients with intermediate to advanced HCC. [2-5] Surveillance among individuals at high-risk for HCC is recommended in East Asia, but further research is needed to understand its current impact on survival with HCC, and determine the optimal approach in light of the need to conserve resources. [2-4,8] Accordingly, this dissertation examined the comparative effectiveness of surveillance and current treatment approaches for the detection and management of HCC in East Asia. Specific aims included:

1. Compare the effectiveness of current treatment approaches for patients diagnosed with HCC in China
    a. Assess overall survival with primary treatment for patients diagnosed at various stages of HCC disease, controlling for selection bias
    b. Examine adherence to current treatment recommendations for HCC in China,

according to disease stage at diagnosis

c. Explore disease characteristics and current treatment approaches for HCC across different regions in China

2. Develop an Individual-based model to simulate a randomized trial of HCC surveillance among individuals with chronic HBV infection in China
    a. Provide a transparent overview of the model structure and input parameters
    b. Calibrate unknown parameters of HCC disease progression and incidental diagnosis
    c. Evaluate the impact of different screening intervals (i.e., 6 month vs. 12-month) for HCC surveillance based on current recommendations in China
3. Examine the current Impact of surveillance on the survival of patients diagnosed with HCC in Taiwan
    a. Estimate the survival benefit of surveillance, adjusting for lead time and selection bias
    b. Compare tumor characteristics and primary treatment approaches, by surveillance status

Clinical information for patients diagnosed with HCC were obtained from the global Bridge to Better Outcomes in HCC (HCC BRIDGE) study, a retrospective observational study of patients newly diagnosed with HCC from January 1, 2005 through June 30, 2011 across 14 countries in East Asia, Europe, and North America.[29,30] Data to assess Aims 1 and 2 were obtained from the HCC BRIDGE study in China, conducted across 10 tertiary hospital centers from 7 geographically diverse cities in mainland China. For the simulation model in Aim 2, comprehensive literature reviews were additionally conducted to obtain parameters surrounding chronic HBV progression, HCC development, tumor growth, and surveillance accuracy. Aim 3 analyses incorporated data from the HCC BRIDGE study in Taiwan, collected at the National Taiwan University Hospital, and the full range in tumor growth

parameters synthesized in Aim 2.

With advancements in the management of HCC in China, continued research is needed to assess current treatment patterns and re-evaluate the appropriateness of current guideline recommendations. To assess current treatment approaches (Aim 1), patients with HCC included in the HCC BRIDGE study were first stratified according to disease stage at diagnosis, based on categories defined in the China Ministry of Health (CMH) guidelines.[3] For each disease stage, trends in the frequency of primary treatments were compared with current guideline recommendations (Aim 1b). To compare survival with primary treatment, Kaplan-Meier curves were constructed for each disease stage; survival differences were assessed using the log-rank test (Aim 1a).[31] Multivariate Cox proportional hazard models further assessed the association between primary treatment and the hazard of death (aim 1a), controlling for underlying differences in patient characteristics across treatment groups.[31] Propensity score (PS) analysis, using the methods of propensity-based weighting and regression-based adjustment, were conducted to address residual selection bias.[32,33] PS for each treatment were estimated using multinomial logistic models.[32] Models for each disease stage controlled for patient demographics, co-morbidities, etiology, liver function, disease characteristics, and hospital site where treatment was received. Additional analyses explored disease stage at diagnosis and primary treatment across different regions in China; differences were assessed using the Chi^2 test (Aim 1c).[34]

Although HCC surveillance is widely recommended, few studies have shown a survival benefit, and the ideal screening interval is not known.[2,4,8,9,28] An individual-based simulation model was developed to project the impact of HCC surveillance on survival following HCC development among individuals with chronic HBV infection in China (Aim 2). The model incorporated well-established data on the natural disease course of chronic HBV infection and HCC development (Aim 2a).[35-37] A meta-analysis using a random effects model was conducted to synthesize estimates of DT from prior tumor growth studies in HCC (Aim 2a).[38,39] Model calibration was conducted to obtain additional unknown

parameters of HCC disease progression and incidental diagnosis, based on the distribution of tumor characteristics seen among HCC patients who did not receive surveillance from the HCC BRIDGE study in China (Aim 2b). The HCC BRIDGE study data was further used to assign HCC treatment probabilities and project survival with treatment using a series of parametric survival curves (2a).[31]

Based on the accuracy of diagnostic tests for HCC, the simulation model assessed three different strategies for HCC surveillance (Aim 2c): 1) no surveillance (for comparison), 2) 6-month US and AFP (with cutpoint ≥ 200 ng/mL), and 3) 12-month US and AFP. As the primary outcome, overall survival following HCC development was compared across surveillance strategies using the Kaplan-Meier method; survival differences were assessed using the log-rank test .[31] Additional analyses compared disease stage and primary treatment at diagnosis, with statistical differences evaluated using the Chi^2 test.[34] Probabilistic sensitivity analyses were conducted to provide estimates of uncertainly in the model-projected outcomes.[40]

A major limitation of prior studies assessing the survival impact of HCC surveillance is the potential for lead time bias related to the earlier diagnosis of HCC.[9] Using data from the HCC BRIDGE study in Taiwan, analyses assessed the impact of surveillance on survival, controlling for lead time bias (Aim 3a). Surveillance was defined as a binary variable, which indicated whether a patient received regular diagnostic imaging, with or without AFP, every 6-12 months. Lead time was approximated using the well-established formula for tumor growth and subtracted from the survival of patients in the surveillance group.[10,11,13] Analyses explored different assumptions surrounding the estimated lead time, using a range in median DT estimated across prior tumor growth studies (synthesized in Aim 2).[14-27] To address selection bias resulting from non-random allocation of HCC surveillance, PS analysis was conducted using the methods of propensity-based matching and propensity-based weighting.[33,41,42] The PS for each surveillance group were estimated using a logistic model, controlling for patient demographics, co-morbidities, etiology, liver function, and year of diagnosis. Kaplan-Meier curves

assessed survival according to surveillance status, controlling for both lead time and selection bias; survival differences were assessed using the log-rank test.[31] As secondary outcomes, the study also compared tumor characteristics and primary treatment approaches according to surveillance status; statistical differences were evaluated using the Chi^2 test (Aim 3b).[34]

Together, these studies can help improve the detection and management of HCC in East Asia, where HCC is one of the leading causes of cancer-related mortality.[43,44] Continued research is needed to re-evaluate the appropriateness of current guideline recommendations in China, particularly with limited evidence on the comparative effectiveness of therapies for intermediate to advanced disease.[3] Both China and Taiwan have implemented community-based surveillance to improve the early detection of HCC, but additional research is needed to examine the impact of HCC surveillance on survival outcomes.[3,6,7] Given the substantial clinical and economic burden of HCC in East Asia, this dissertation can help inform efforts to ensure that individuals at high-risk for developing HCC are properly monitored given limited resources, and patients with HCC receive appropriate treatment to improve survival.

Sections of the dissertation are organized as follows: Chapter 2 details the current literature on the burden of HCC in East Asia, consensus guidelines for HCC management, comparative effectiveness of current treatment approaches, survival impact of HCC surveillance, and decision models of HCC surveillance. Chapter 2 is intended to present background and justification for the dissertation study and to provide the reader with an understanding of the complexities and controversies involved when examining the impact of surveillance and treatment approaches on the survival of patients diagnosed with HCC. Chapters 3 through 5 are individual manuscripts corresponding to Aims 1-3, respectively, and are intended for submission to peer-reviewed journals. Chapter 6 summarizes the strengths and limitations of this work, policy relevance, and future research plans. References are provided in a generalized bibliography at the end of the dissertation.

CHAPTER 2: LITERATURE REVIEW

Overview

HCC is highly prevalent in East Asia, with more than one-half of all global cases occurring in China alone.[45] Recognizing the clinical and economic burden of HCC, the CMH has declared HCC as one of 5 tumors of high national importance and has published its newest Diagnosis and Treatment Guidelines for Primary Liver Cancers (2011 edition).[3] The guidelines are largely distinct from those in other settings, mainly in their recommendations for patients diagnosed with intermediate and advanced HCC.[3-5,8] With recent advancements in the treatment of HCC, continued research is needed to re-evaluate the appropriateness of current guideline recommendations. To this end, this study explored current treatment approaches and compared the effectiveness of primary treatment on overall survival for patients diagnosed at various stages of disease in China.

Both China and Taiwan have provided government-funded HCC surveillance in high-risk areas to improve the early detection of HCC.[3,6,7] Although HCC surveillance is widely recommended, few studies have provided direct evidence that surveillance improves survival.[2,4,5,8] Furthermore, the ideal screening interval for surveillance is not known.[2,4,8,28] Limitations of prior studies of HCC surveillance include: a relatively small number of patients diagnosed with HCC, data collected over a short follow-up, poor compliance to surveillance guidelines, suboptimal treatment following diagnosis, and potential lead time bias related to earlier diagnosis of HCC under surveillance.[9-12,46] As such, the current study addresses this gap in the literature by assessing the current impact of surveillance on the survival of patients diagnosed with HCC, using data from a large cohort of patients diagnosed with HCC in Taiwan. To control for potential lead time bias, different assumptions surrounding the estimated lead time were

explored, using a range in median DT estimated across prior tumor growth studies. [14-27] Using an individual-based model to simulate a randomized trial of surveillance, the study further examined the impact of different screening intervals among individuals with chronic HBV infection, based on current recommendations in China.

This dissertation collectively contributes to the existing literature in HCC by providing a more comprehensive outlook on the comparative effectiveness of current treatment approaches and surveillance for HCC, while addressing the limitations of prior studies. In terms of policy relevance, the results can be used to (1) inform clinicians about the appropriate used of current treatments options for HCC in comparison with guideline recommendations in China, (2) provide additional evidence on the current impact of HCC surveillance in clinical practice to inform ongoing policy efforts to improve the early detection of HCC, and (3) determine the optimal screening interval for surveillance to improve survival with HCC in the setting of limited resources.

Burden of Hepatocellular Carcinoma in East Asia

HCC is the third leading cause of cancer-related death worldwide. [47,48] HCC is highly prevalent in East Asia, with more than one-half of all global cases occurring in China alone. [45] HCC is the third most frequent cancer and the second leading cause of cancer-related death in China; an estimated 402,000 new cases were diagnosed and 372,000 HCC-related deaths occurred in 2008. [47] In Taiwan, HCC is the leading cause of cancer-related death among males and the second among females, with age-adjusted mortality rates of 40.8 and 14.1 per 100,000 persons, respectively. [49]

HCC is a highly complex and heterogeneous disease. Major etiological risk factors for HCC vary among different regions and most commonly include chronic infection with hepatitis B or C virus (HBV, HCV), alcoholic liver disease (ALD), nonalcoholic fatty liver disease (NAFLD), primary biliary cirrhosis, hemochromatosis, and inherited metabolic disorder. [2,3,5] Whereas HCV, ALD and NAFLD are the most

common factors contributing to HCC in North America and Europe, HCC in East Asia is primarily linked to a high prevalence of HBV infection (9.75%) and to a lesser extent HCV infection (prevalence: 3.2%).[45,50] Both chronic HBV or HCV infection can progress to liver cirrhosis, characterized by permanent scarring or fibrosis of liver tissue, which in turn can lead to the development of HCC. In 2006, more than 80% of HCC cases in China were related to HBV infection, whereas 17% were related to HCV infection.[45]

Although both HBV and HCV infection are direct risk factors for HCC, the mechanisms through which infection is contracted can lead to a different disease course. In East Asia, HBV is generally contracted through vertical transmission from mother to child, whereas HCV is generally contracted through needle contamination or injection drug use.[51,52] As a result, individuals with chronic HBV may develop HCC in late adulthood (≥40 years), whereas development of HCC in HCV generally occurs at a later age (mean age >60 years).[52] In addition, whereas HCC related to HCV almost always occurs with cirrhosis, HCC among individuals with chronic HBV can develop without the presence of underlying cirrhosis in approximately 10-20% of cases.[52]

During the past 3 decades, national campaigns to vaccinate infants in East Asia against HBV have diminished the incidence of new infection; however, effects on HCC incidence will not be seen until 20-30 years from now when these individuals reach late adulthood.[45,53] In addition, antiviral therapies to slow the progression of chronic HBV to the development of cirrhosis and HCC have demonstrated only a modest impact.[54] Therefore, current approaches to HCC management are primarily focused on the early detection and treatment of HCC.

Disease Staging for Hepatocellular Carcinoma

According to global consensus guidelines for the management of HCC, the main determinants of treatment selection and prognosis for HCC include tumor characteristics, underlying liver function and performance status at diagnosis.[2-5] Relevant tumor characteristics include tumor size (diameter in cm),

number of tumor nodules, and tumor spread, defined by the presence of vascular invasion (i.e., macrovascular invasion or invasion of the main branch of the hepatic vein, any portal vein, or any vascular or bile duct) and tumor metastases (i.e., hepatic lymph node, extrahepatic or any regional/distant metastases). An important consideration when evaluating therapeutic options for HCC is liver function.[2] A small percentage of patients (~10-20%) with chronic HBV may be diagnosed with HCC in the absence of cirrhosis.[52] The remaining patients are further staged based on degree of cirrhosis measured by the Child-Pugh (CP) scoring system, derived using laboratory values (i.e., international normalized ratio, bilirubin, albumin and prothrombin) and liver characteristics (i.e., presence of ascites and encephalopathy) at diagnosis.[3,55] Individuals with compensated cirrhosis with no or mild symptoms generally score in the range of CP A-B, whereas individuals with clinically significant decompensated cirrhosis generally score as CP C. Performance status is commonly measured using the Eastern Cooperative Oncology Group (ECOG) scoring criteria, with scores ranging from 0-2 = fully active/partially disabled to 3-4 = substantially/completely disabled, and 5 = dead.[3,56]

According to the CMH guidelines, disease stage following HCC diagnosis is categorized in five stages: 1) Very Early/Early, 2) Intermediate - Solitary, 3) Intermediate - Multinodular, 4) Advanced, and 5) Terminal (**Figure 2.1**).[3] Terminal stage includes patients with substantial performance status limitations (i.e., performance status = 3-4) or severely impaired liver function (i.e., CP C). Patients with no/moderate performance status limitations and liver function impairment (i.e., performance status <3, no cirrhosis or CP A/B) are further categorized according to tumor size, number, and spread. Advanced stage patients include those with tumor metastases or any vascular invasion. Disease stage for solitary tumors without vascular invasion and tumor metastases is defined according to tumor size: Very Early: diameter ≤2 cm, Early: >2 cm but ≤5 cm, and Intermediate: >5 cm. Multinodular tumors without vascular invasion and tumor metastases are categorized according to both tumor size and number:

Early: 2-3 tumors, with largest diameter ≤3 cm, and Intermediate: 2-3 tumors, with largest diameter >3 cm, or ≥4 tumors (of any size).

Guideline Recommended Treatment Approaches for Hepatocellular Carcinoma

Recommended treatment approaches for HCC in China are largely distinct from those in the United States and Europe (**Figure 2.1**).[3-5] Worldwide consensus guidelines consistently recommend resection as the primary treatment for patients with early HCC and well-preserved liver function, and acknowledge that ablation may be used as a less invasive alternative.[2-5] Liver transplant is also commonly recommended for early HCC, as it can both remove the cancerous tumor and cure the underlying liver disease; however, a shortage of suitable donors has limited its availability in China.[3]

The majority of patients worldwide are diagnosed with intermediate to advanced HCC, for which the most appropriate treatments remain controversial.[2-5] According to guidelines published in the United States and Europe, the primary treatment option for intermediate HCC, characterized by multinodular tumors (i.e., 2-3 tumors, with largest ≥3 cm or ≥4 tumors), is trans-arterial (TA) therapy, and the only recommended therapeutic option for advanced HCC is sorafenib.[4,5,8] In contrast, the CMH guidelines have adopted a more aggressive approach. Whereas the CMH guidelines agree that surgical resection may be recommended for large solitary HCC (i.e., > 5 cm), the guidelines further recommend resection for multinodular HCC, provided the tumors are in a suitable location and the patient has well-preserved liver function.[3] Furthermore, patients with advanced disease may receive resection, provided the same conditions apply, although treatment is mainly for palliative intent. TA therapy and systemic therapy are recommended for intermediate and advanced stage patients, respectively, who are not optimal surgical candidates or who elect to forgo surgical treatment.

In part, the apparent disagreement in treatment recommendations can be explained by distinctions in the clinical context surrounding HCC across different regions. In the United States and

Europe, where HCC is primarily linked to chronic HCV infection and ALD, nearly all patients present with cirrhosis.[57] In contrast, in China and other parts of East Asia, more than 80% of cases are related to chronic HBV infection; in this setting, HCC patients generally have well-preserved liver function, and approximately 10-20% of patients do not have evidence of cirrhosis.[52] Consensus guidelines agree that patients with significant liver function impairment, particularly portal hypertension, are poor candidates for surgical resection due to an increased risk of liver failure post resection.[4-7] Thus, in western settings, resection is often not recommended based on underlying liver impairment alone and/or portal hypertension, regardless of tumor characteristics.

Comparative Effectiveness of Treatments for Hepatocellular Carcinoma

Studies conducted in East Asia have assessed the effectiveness of surgical resection for patients with intermediate and advanced disease, with varying results. Prior research suggests that resection may be safely performed among patients with large solitary tumors with no evidence of vascular invasion, as the risk of recurrence is not significantly increased as compared to smaller tumors.[58,59] In contrast, earlier observational studies found that patients with multinodular HCC are poor candidates for resection, due to an increased risk of tumor recurrence.[58,60] With recent advancements in surgical techniques, however, a larger number of multinodular tumors are now considered resectable, with 3-year survival reaching as high as 35-56%.[61-63] Nevertheless, direct comparisons of survival with TA therapy have been limited. A recent prospective study conducted by Luo et al. (2011) in China compared survival with resection (n=85) and TA therapy (n=83) among patients with large (≥5 cm) and multiple (≥2) tumors that were deemed resectable based on extensive clinical discussion.[63] Overall 3- and 5-year survival for patients who received resection (35% and 24%, respectively) were higher than those for patients initially allocated to TA therapy (26% and 19%, respectively), although survival differences were non-significant (p=0.26). The authors noted, however, that 13 patients (16%) in the TA

therapy group subsequently received resection during follow-up. Although further evidence is needed, the authors suggested that TA therapy may be a better initial treatment for intermediate stage HCC, and resection should be recommended among patients who respond well to TA therapy.

Studies conducted among advanced stage patients with portal vein tumor thrombosis have reported modest survival benefits associated with resection; however, post-operative recurrence and post-surgical complications are common.[64,65] Thus, the role of resection remains controversial, particularly in the absence of head-to-head clinical trials comparing survival with that of sorafenib. A clinical trial of sorafenib conducted in East Asia demonstrated improved survival over placebo (p=0.014), with a reported median survival of 6.5 (5.6-7.6) months.[66] Other systemic treatments for HCC have been proven ineffective.[67,68]

Prior studies comparing long-term survival between resection and tumor ablation for early stage disease have largely reported conflicting results.[69-71] Clinical trials conducted in China noted higher survival rates with resection, but did not find a statistically significant difference in survival between the two groups.[72,73] In contrast, another trial found a substantial survival advantage with resection among early stage patients; 3-year survival rates for radiofrequency ablation versus resection were 69.6% and 92.2%, respectively (p=0.001).[74] It should be noted, however, that the trials enrolled different proportions of patients with very early stage disease, which may in part explain the conflicting results, since ablation beyond this stage is less effective in achieving complete tumor necrosis.[70] Subgroup analyses among patients with solitary tumors 3-5 cm and 2-3 tumors <3 cm were generally limited by small sample size, but reported a survival benefit with resection.[70,74] Whereas resection may provide better long-term efficacy than ablation, it should also be noted that resection is associated with increased complications and longer hospital stays.[69]

Surveillance to Detect Hepatocellular Carcinoma

Resection and tumor ablation are the main curative treatment options for HCC, but eligibility to receive curative therapy diminishes with more advanced disease.[2,3] Whereas survival with HCC is generally poor (5-year survival 16.2%), 5-year survival for patients diagnosed at an earlier stage who receive curative therapy can exceed 50%.[43,44] Both the CMH and Taiwanese Department of Health have strived to improve the early detection of HCC by providing government-funded HCC surveillance in high-risk areas.[3,6,7] In China, HCC surveillance is recommended every 6 months among men aged ≥40 years and women aged ≥50 years who are at high risk for HCC, including individuals with a history of chronic HBV or HCV infection, alcoholism and/or diabetes, or family history of HCC.[3] In Taiwan, HCC surveillance is also recommended every 6 months, but is primarily indicated among individuals with cirrhosis related to chronic HBV or HCV infection.[2]

In both China and Taiwan, recommended screening tests include abdominal US and measurement of serum AFP, with a cut-point of ≥200 ng/mL.[2,3] Additional screening modalities include computed tomography (CT) and magnetic resonance imaging (MRI) scan. However, these tests are generally not recommended as primary screening tests given their high cost, and are mainly used to confirm diagnosis. Guidelines acknowledge the use of additional biomarkers, such as des-c-carboxyprothrombin and lens culinaris agglutinin-reactive fraction of AFP as potential screening tools; however, they do not provide any specific recommendations surrounding these tests.[2]

Impact of Hepatocellular Carcinoma Surveillance on Survival Outcomes

HCC surveillance has been conducted in East Asia since the early 1970s. However, few studies have provided direct evidence that HCC surveillance improves survival. Early analyses evaluating the use of AFP alone among individuals at moderate risk for HCC found limited usefulness of this strategy provided the low incidence of disease among individuals at moderate risk and the low sensitivity and

specificity of the test.[75] Since the 1980s, the primary strategy for HCC surveillance evolved to the use of AFP in combination with US among individuals at high-risk for HCC.[76]

A randomized control trial among 18,816 participants with chronic HBV infection in China found that surveillance every 6 months with US and AFP was associated with a significant 37%-reduction in 5-year mortality.[9] Despite demonstrating survival benefit, the trial had several limitations, including potential lead time bias related to the earlier diagnosis of HCC, a relatively low number of HCC cases (n=153) collected over a short follow-up (5 years), and suboptimal adherence to the surveillance protocol (less than 60%). Nevertheless, the trial provides the best evidence of a survival benefit associated with surveillance in HCC. An earlier trial also conducted in China failed to show benefit with surveillance, largely because HCC patients did not undergo appropriate treatment.[46]

Controversies Surrounding Hepatocellular Carcinoma Surveillance

An important limitation to the seminal trial of surveillance in China, as well as other studies assessing the impact of surveillance, is the potential for lead time bias.[9] This bias may occur if surveillance merely detects the tumor at an earlier stage without affecting the course of disease, leading in an overestimation of survival gains with surveillance.[2] To address this limitation, observational studies have approximately adjusted for lead time by applying different assumptions surrounding estimated DT to the well established formula for tumor growth, first proposed by Schwartz (1961).[10-13]

$$t = \frac{\mathbf{DT} * \mathbf{3} * \mathbf{log}(\frac{\boldsymbol{D_1}}{\boldsymbol{D_0}})}{\mathbf{log}(\mathbf{2})}$$

where: t = time interval between measurements (days)

DT = tumor volume doubling time (days)

D_0 = tumor diameter at first measurement

D_1 = tumor diameter at last measurement

Using this formula, lead time represents the time interval (t, in days) for the primary tumor to grow from the median diameter among patients in the surveillance group (D_0) to the median diameter among patients in the no surveillance group (D_1). The estimated lead times are then subtracted from the survival of patients in the surveillance group. The results of observational studies suggest that surveillance significantly improves survival, even after lead time adjustment using a range in DT from 60 to 120 days. [10-13] However, such methods are based solely on current knowledge surrounding HCC tumor growth. Tumor growth in HCC is highly heterogeneous across individuals, and other aspects of HCC progression, including the development of multinodular HCC, vascular invasion and tumor metastases, are not fully understood. [14-27]

Although HCC surveillance is recommended, the ideal screening interval for surveillance is not known. Consensus guidelines suggest an interval of 6-12 months, based on average DT. [2,4,8] Prior clinical studies have adopted an interval of 6 months between periodic diagnostic tests, [9-11,28,30,77] although there are no randomized studies that have determined the optimal interval. Evidence from a small retrospective study in Italy suggests that survival is similar among HCC patients who receive surveillance at a 6-month interval, as compared with a 12-month interval. [28] However, clinical guidelines have been hesitant to make definite recommendations using the results of this study alone. [5] Guidelines acknowledge that the optimal interval for HCC surveillance should be assessed from the view of both resource use and survival outcomes, as it is clear that more frequent tests can detect HCC nodules of smaller size. [2,3]

Prior Decision Models of Hepatocellular Carcinoma Surveillance

Given the substantial clinical and economic burden of HCC in the Asia-Pacific region, clinical guidelines have explicitly considered evidence from prior cost-effectiveness studies when forming recommendations surrounding the use of different surveillance strategies. [2] Cost-effectiveness analyses

involve the systematic comparison of the costs and outcomes of two or more interventions, generally using decision modeling techniques.[40] In this case, each surveillance strategy is compared with the option of not providing surveillance.

In general, prior decision models of surveillance were developed using an aggregate state-transition (Markov) model, simulating the impact of alternative intervention scenarios on outcomes among specific patient cohorts (**Table 2.1**).[78-86] In all cases, individuals were initially assumed to have no HCC disease at the start of simulation. In turn, the progression of chronic liver disease was modeled, incorporating the risk of worsened liver function, HCC development and death. Specific high-risk populations incorporated in the models included individuals with cirrhosis, whereas one study additionally modeled individuals with chronic HBV without cirrhosis.[84]

Among the alternative surveillance strategies modeled, all models incorporated screening with US ± AFP in 6- or 12-month intervals;[78-86] additional strategies included the use of CT, MRI, and contrast enhanced US.[79-81,85] In evaluating the cost-effectiveness of these strategies, 5 studies assumed the perspective of the United States payer,[80,81,85-87] 2 studies modeled the perspective of the National Health Service in the United Kingdom,[82,83] 2 studies assumed the perspective of the national health insurance system in Japan,[78,79] and one study modeled the perspective of the National Health Insurance program in Taiwan.[84]

Key model inputs included: 1) sensitivity/specificity of surveillance, 2) transition probabilities, 3) tumor growth rates, 4) costs of surveillance, diagnosis, and treatment, and 5) health utilities related to disease and treatment states.[78-86] Model inputs for surveillance sensitivity/specificity inputs were largely similar, with one key difference. All but one study assumed the same sensitivity of US across tumor size when, in reality, the sensitivity of US is only 21-35% for small tumors (<2 cm).[88-90] Transition probabilities generally included the progression of compensated cirrhosis to decompensated cirrhosis, HCC incidence, probabilities of incidental and symptomatic diagnosis, treatment probabilities and death.

In modeling tumor progression, the majority of models incorporated evidence from prior tumor growth studies; however, the methods for incorporating this information varied considerably. Most authors manually calibrated the transition probabilities from small to large HCC tumors to reflect the expected tumor size over time. [81,85-87] Unfortunately, the details of these methods were largely unclear. In contrast, Thompson Coon et al. and Chang et al. developed a more sophisticated approach using individual-based sampling methods. [82-84] This method involved a two-dimensional representation of tumor growth: The authors assumed a relationship between tumor growth and time (e.g., exponential growth) and provided a scale parameter (i.e., DT) to adjust the rate of tumor growth. Although the methods employed by Chang et al. and Thompson Coon et al. were similar, the assumptions surrounding tumor growth and distribution of tumor doubling time were different (**Table 2.1**). [82-84] Using the tumor growth equation and a specified distribution of DT, the model would project tumor size for individuals with HCC. The results for different values of DT then were pooled across a series of simulations to estimate ranges in the costs and outcomes associated with surveillance versus no surveillance.

Whereas numerous studies have measured tumor growth in HCC, clinical data do not provide the necessary information to fully characterize the development of satellite tumors and tumor spread over time. The estimation of these parameters would require information regarding when each individual developed an HCC tumor and when further complications occurred. Such information is largely unavailable in clinical databases since most early stage patients are treated; even if patients elect to forgo treatment, large sample sizes would be needed to establish statistical power. As a result, prior decision models made simplified assumptions surrounding tumor progression in HCC. [81,85-87] For instance, both Chang et al. and Thompson Coon et al. observed that multinodular tumors and tumor metastases tended to occur with larger tumors. [70-72] Based on these relationships, the authors assumed that a large primary tumor > 5 cm could serve as a surrogate for more advanced HCC. [82-84] These assumptions, however, are problematic for two reasons. First, although there is a positive correlation

between tumor size and the presence of tumor-related complications in HCC, it is not uncommon for patients to present with multiple small tumors, with primary tumor size < 5 cm. [11,12,28] Secondly, treatment approaches and survival outcomes for patients with intermediate solitary HCC (> 5 cm) are vastly different than for individuals with other disease-related complications in addition to a large primary tumor. [2,3]

In addition, the rate at which HCC is detected outside of a surveillance program, either incidentally or based on clinical symptoms, cannot be directly measured. Doing so would require knowing the proportion of all HCC cases (undiagnosed and diagnosed) that are detected in regular clinical practice. A number of models excluded this parameter and assumed that all HCC patients in the no surveillance group were diagnosed with large HCC based on clinical symptoms. [85,86] In doing so, however, these models likely overestimated the impact of surveillance. To approximate this parameter, Thompson Coon et al. manually calibrated the probability of incidental diagnosis, by tumor size, to reflect the overall distribution of tumor size from a study of patients diagnosed incidentally in clinical practice. [82,83] However, the details surrounding the calibration procedures were not fully documented.

Another limitation of prior studies is that many did not appropriately account for the interaction between tumor characteristics and liver function in allocating treatments and projecting survival post treatment. Certain studies acknowledged differences in probabilities of receiving curative treatment according to degree of cirrhosis. [81,84,85] However, given limited data availability, survival probabilities with treatment were based on mean unadjusted estimates. As a result, survival with HCC treatment among patients with advanced cirrhosis and other risk factors, such as gender and age at diagnosis, was likely over-estimated, leading in an over-estimation of the survival impact of surveillance. Therefore, determining the optimal approach for HCC surveillance requires both an understanding of tumor development and progression over time, and an accurate assessment of treatment patterns and associated survival in clinical practice.

Advantages of an Individual-Based Model for Hepatocellular Carcinoma Surveillance

A major limitation of prior cohort-based models of HCC surveillance, which use Markov chains to model transitions through different health states, is that they cannot flexibly incorporate the impact of accumulating medical history in determining model transitions, and survival outcomes.[40] In HCC, treatment options and survival outcomes are highly dependent on tumor stage at diagnosis, liver function, gender, and age.[2] Prior Markov models have partially accounted for these interactions by stratifying HCC disease states according to degree of underlying cirrhosis when allocating treatment.[81,84,85] On the other hand, in the absence of detailed data in regular clinical practice, these studies have not accounted for differences in treatment outcomes related to patient age, gender, and degree of cirrhosis.

In addition, prior decision models have made simplifying assumptions about the rate of tumor growth in HCC,[85,86] when, in reality, rates of tumor progression are highly heterogeneous across individuals.[15,18,26] Indeed, in a scenario analysis performed by Thompson Coon et al.,[83] in which tumor growth rates were varied across ten simulated cohorts, the optimal intervals for HCC surveillance varied substantially when it was assumed that the majority of individuals had very slow growing versus fast growing tumors. Therefore, providing an accurate representation of tumor growth in HCC, as well as other aspects of tumor progression, is essential for understanding the optimal screening interval for HCC surveillance and the potential impact of non-compliance with surveillance protocols.

Individual-based models, sometimes described as agent-based or microsimulation models, provide an attractive alternative when the assumptions of Markov models prove to be limiting in this way.[40,91] As individuals move through the model one at a time, rather than as proportions of a cohort, the model can track individual-level characteristics (e.g., co-morbidities and medical history) and allow them to interact through a series of model transition rules (or transition logic) to simulate the life-course of disease.[40] Individual-based models generally consist of two components: a natural history

component and an intervention component. [92,93] The natural history model is developed first in the absence of an intervention. The intervention is then incorporated into the natural history model to alter the course of disease. Individual-based models are often complex, and the amount of complexity is largely governed by the disease process, specific questions to be addressed, and data available to inform model parameters. [40,91,93] As such, individual-based models are often used when large detailed datasets are available, as they can better incorporate the richness of the data to address a range of decision problems in the disease area as they emerge.

Significance and Contribution

With recent advancements in the treatment of HCC, continued research is needed to re-evaluate the appropriateness of current guideline recommendations. Studies conducted in East Asia have assessed the effectiveness of surgical resection for patients with intermediate and advanced disease, with varying results, and few studies have conducted direct survival comparisons with TA and sorafenib therapy. [58,60-65] Prior literature comparing long-term survival between resection and tumor ablation for early stage disease have also reported conflicting results. [69-71] The current study provides detailed comparative analyses of survival with HCC treatment for patients diagnosed at various stages of disease to clarify best treatment practices. The results of this study can provide valuable insights into the impact of disease characteristics and current treatment approaches on the prognosis of HCC in China, to help prioritize areas for improvement.

Both the CMH and Taiwanese Department of Health have sponsored government-funded HCC surveillance to reduce mortality associated with HCC. [3,6,7] Although surveillance is widely recommended, few studies have provided direct evidence that surveillance improves survival. [9-12] Limitations of prior studies of HCC surveillance include a relatively small number of patients diagnosed with HCC collected over a short follow-up, poor compliance, and potential lead time bias related to the earlier diagnosis of

HCC. The current study uses a large dataset of patients diagnosed with HCC in Taiwan to examine the survival impact of surveillance. The analyses leverage previously established methods for lead time bias adjustment using the well-established formula for tumor growth in HCC, [10-13] and further extend this work by incorporating the full range in median DT estimated across prior tumor growth studies. [14-27]

Although HCC surveillance is recommended, the ideal screening interval for surveillance is not known. [2,4,8] Determining the optimal approach for HCC surveillance requires both an understanding of tumor progression over time, and an accurate assessment of treatment patterns and associated survival in clinical practice. In the absence of more detailed data, prior Markov models of HCC surveillance have made simplifying assumptions surrounding tumor progression and the impact of patient characteristics in determining HCC treatment and survival outcomes. [83-86] The individual-based model of HCC surveillance, developed in this study, flexibly integrates accumulating medical history for individuals with chronic HBV infection, individual-level heterogeneity in tumor progression, and survival with treatment to accurately project survival for individuals who develop HCC. The simulation model then is used to simulate a randomized trial of HCC surveillance, controlling for lead time bias, to assess the impact of different screening intervals based on current recommendations in China. This simulation model not only helps to identify the optimal approach for HCC surveillance, but also provides a basis for exploring other issues surrounding surveillance, such as poor compliance and specific high-risk groups that should be targeted, as policy efforts to improve early detection evolve in China.

Table 2.1: Summary of overall structure and key model inputs from prior decision models of HCC surveillance. †

	Thompson Coon, 2007, 2008 [82,83]	Chang, 2011 [84]	Andersson, 2008 [85]	Patel, 2005 [86]
Perspective	United Kingdom National Health Service	Taiwan National Health Insurance	United States payer, Medicare costs	United States payer, Medicare costs
High-Risk Population(s)	Cirrhosis (HBV & HCV), ALD	Chronic HBV, cirrhosis (any etiology)	Cirrhosis (any etiology)	Cirrhosis & HCV
Initial Age of Cohort(s)	Mean Age at HCC diagnosis by etiology	50 years	50 years	45 years
Model Structure	Markov Model, Individual- Based Tumor Growth Component for Scenario Analyses	Markov Model, Individual-Based Tumor Growth Component	Markov Model	Markov Model
Cycle Length	1 month	3 months	6 months	6 months
Model Horizon	Lifetime	25 years	30 years	Until age 80 (i.e., 35 years)
Surveillance Strategies	6,12 month US, 6,12 month US + AFP	12 month US (3 months for individuals with chronic HBV who develop cirrhosis)	6,12 month US, 6 month US + AFP, 12 month CT, 12 month MRI	6 month US + AFP
Sensitivity/Specificity US	Sensitivity Small HCC: 0.18 Med. HCC: 0.37 Large HCC: 0.83 Specificity: 0.96	Sensitivity: 0.7 (.5-.9) Specificity: 0.8	Sensitivity: 0.75(.4-.81) Specificity: 0.95(.8-1.0)	Sensitivity: 0.79(.6-.9) Specificity: 0.87(.8-1.0)
Sensitivity/Specificity AFP	Based on distribution of AFP by tumor size, and among non-HCC cases from pooled tumor growth studies	N/A	Sensitivity: 0.6 (.4-.65) Specificity: 0.87(.63-.94)	Modeled with US
HCC Disease Stages Modeled	Small HCC: <2 cm Med. HCC: 2-5 cm Large HCC: >5 cm	Asymptomatic HCC Symptomatic HCC	Small HCC Large HCC	Small HCC: <2 cm Med. HCC: 2-5 cm Large HCC: >5 cm

	Thompson Coon, 2007, 2008 [82,83]	Chang, 2011 [84]	Andersson, 2008 [85]	Patel, 2005 [86]
Modeling Tumor Size	Probability HCC growth manually calibrated to tumor growth studies *Scenario Analyses:* Exponential tumor growth rate, normal & 2 beta distributions (fast, slow) of tumor doubling time *	Tumor growth rate piecewise linear & uniform distribution of tumor doubling time *	Probability HCC growth manually calibrated to tumor growth studies (details unclear)	Probability HCC growth manually calibrated to tumor growth studies (details unclear)
Inc./Symp. Diagnoses	Calibrated (manually) to reflect distribution of tumor size at diagnosis	Inc./symp. diagnoses incorporated (details unclear)	Symptomatic presentation only of large HCC tumors (details unclear)	Symptomatic presentation only of large HCC tumors
HCC Treatments	Resection, ablation TA therapy, supportive care	Resection, ablation, liver transplant, no treatment	Resection, ablation, liver transplant, supportive care	Resection, liver transplant, supportive care
Excess Mortality **	Decompensated cirrhosis, large HCC, HCC treatment	Compensated cirrhosis, decompensated cirrhosis, large HCC, HCC treatment	Decompensated cirrhosis, large HCC, HCC treatment	Decompensated cirrhosis, large HCC, HCC treatment

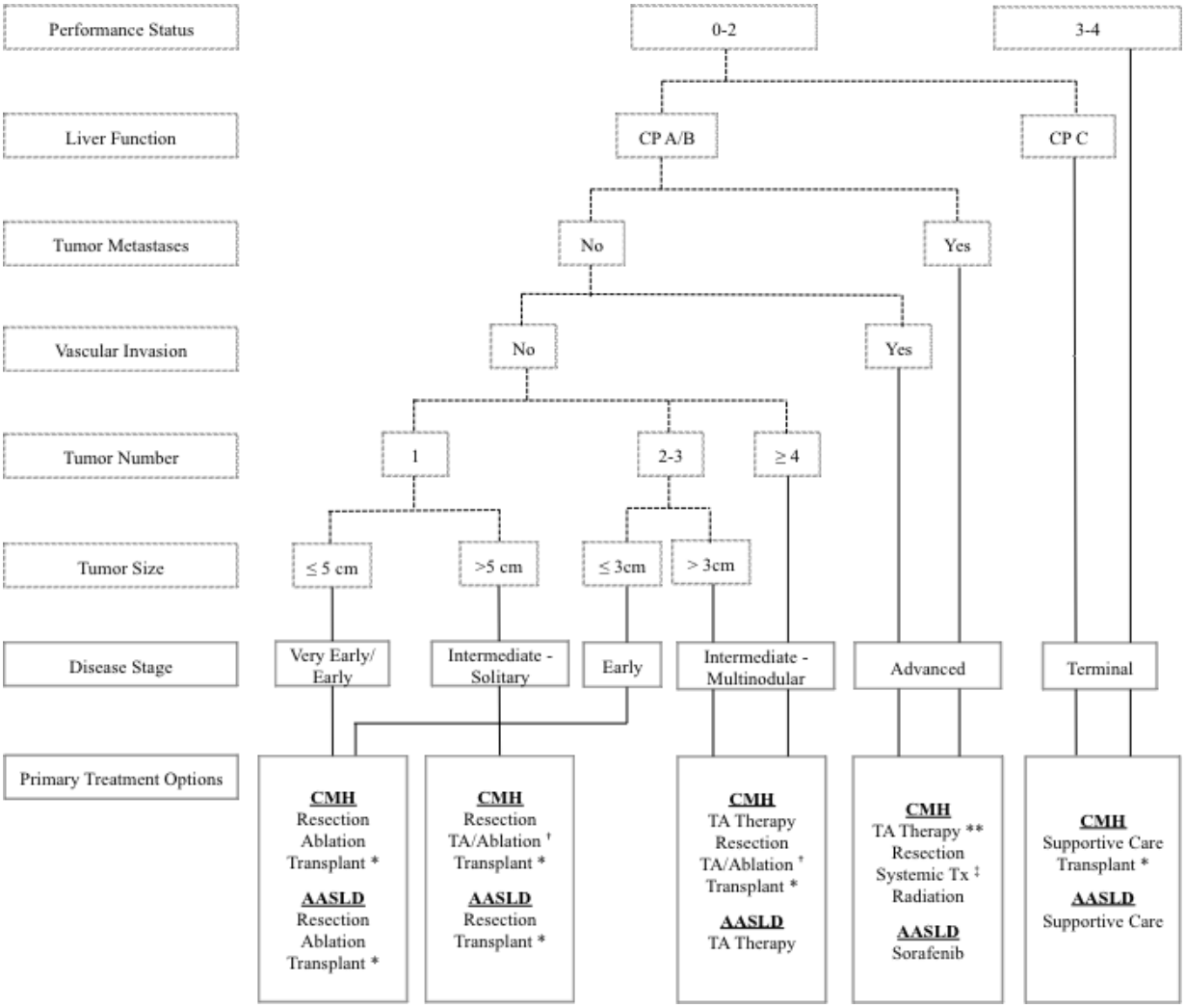
ALD = alcoholic liver disease, AFP = alpha-fetoprotein, CT = computed tomography scan, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, Med. = medium, Inc. = incidental, MRI = magnetic resonance imaging, Symp. = symptomatic, TA = trans-arterial, US = ultrasound

† A total of 10 decision models of HCC surveillance were identified; detailed comparisons were performed for the studies that provided the most appropriate model structure and transparent overview of the model methodology. [82-86]

* Tumor growth was varied at the individual level.

** In addition to all-cause mortality – in most cases, assumed to encompass mortality associated with compensated cirrhosis.

Figure 2.1: Summary of treatment recommendations for patients diagnosed with HCC based on the China Ministry of Health (CMH) [3] compared with the American Association for the Study of Liver Disease (AASLD) guidelines. [5,8]



AASLD = American Association for the Study of Liver Disease, CMH = China Ministry of Health, CP = Child-Pugh score, HCC = hepatocellular carcinoma, TA = trans-arterial therapy, Tx = treatment

* According to the AASLD guidelines, liver transplant is recommended for patients who fall within the Milan criteria. [5,94] The CMH guidelines primarily recommend liver transplant for patients with unresectable HCC or for those who cannot tolerate ablation or TA therapy due to poor liver function. [3]

† Combination therapy with trans-arterial therapy followed by ablation among patients who respond to treatment.

** TA therapy is recommended for patients without evidence of tumor metastases. [3]

‡ Recommended systemic treatments include sorafenib, other molecular targeted therapies, chemotherapy and Traditional Chinese medicine. [3]

CHAPTER 3: COMPARATIVE EFFECTIVENESS OF CURRENT TREATMENT APPROACHES FOR HEPATOCELLULAR CARCINOMA: RESULTS FROM A LONGITUDINAL OBSERVATIONAL STUDY IN CHINA

Introduction

Hepatocellular carcinoma (HCC) is one of the most prevalent and deadly cancers worldwide.[47,48] HCC is particularly common in Asian-Pacific countries, with more than one-half of all global cases occurring in China alone.[45] In China, HCC is the third most frequent cancer and the second leading cause of cancer-related death; an estimated 402,000 new cases were diagnosed and 372,000 HCC-related deaths occurred in 2008.[47]

In recent years, the China Ministry of Health (CMH) has declared HCC as one of 5 tumors of high national importance and has published its newest Diagnosis and Treatment Guidelines for Primary Liver Cancers (2011 edition).[3] Consistent with consensus guidelines published by other developed nations,[2,4,5] recommended therapeutic options for HCC are administered based on tumor stage, liver function and performance status (**Figure 3.1**).[3] Worldwide, clinical guidelines consistently recommend resection as the primary treatment for patients with early HCC and well-preserved liver function, and acknowledge that ablation may be used as a less invasive alternative.[4-7]

The majority of patients worldwide are diagnosed with intermediate to advanced HCC, for which the most appropriate treatments remain controversial.[4-7] According to guidelines published in the United States and Europe, the primary treatment option for intermediate HCC, characterized by multinodular tumors (i.e., 2-3 tumors, with largest ≥3 cm or ≥4 tumors), is trans-arterial (TA) therapy, and the only recommended therapeutic option for advanced HCC is sorafenib.[4,5,8] In contrast, the CMH guidelines have adopted a more aggressive approach. Whereas the CMH guidelines agree that surgical resection may be recommended for large solitary HCC (i.e., > 5 cm), the guidelines further recommend

resection for multinodular HCC, provided the tumors are in a suitable location and the patient has well-preserved liver function.[3] Furthermore, patients with advanced disease may receive resection, provided the same conditions apply, although treatment is mainly for palliative intent. TA therapy and systemic therapy are recommended for intermediate and advanced stage patients, respectively, who are not optimal surgical candidates or who elect to forgo surgical treatment.

In part, the apparent disagreement in treatment recommendations can be explained by distinctions in the clinical context surrounding HCC across different regions. In the United States and Europe, where HCC is primarily linked to chronic hepatitis C virus (HCV) infection and alcohol-related liver disease (ALD), nearly all patients present with cirrhosis.[57] In contrast, in China and other parts of East Asia, more than 80% of cases are related to chronic hepatitis B virus (HBV) infection; in this setting, HCC patients generally have well-preserved liver function, and approximately 10-20% of patients do not have evidence of cirrhosis.[52] Consensus guidelines agree that patients with significant liver function impairment, particularly portal hypertension, are poor candidates for surgical resection due to an increased risk of liver failure post resection.[4-7] Thus, in western settings, resection is often not recommended based on underlying liver impairment alone and/or portal hypertension, regardless of tumor characteristics.

Studies conducted in East Asia have assessed the effectiveness of surgical resection for patients with intermediate and advanced disease, with varying results. Earlier observational studies found that patients with multinodular HCC are poor candidates for resection, due to an increased risk of tumor recurrence.[58,60] With recent advancements in surgical techniques, however, a larger number of multinodular tumors are now considered resectable, with 3-year survival reaching as high as 35-56%.[61-63] Nevertheless, direct comparisons of survival with TA therapy have been limited.[63] Studies conducted among advanced stage patients with portal vein tumor thrombosis have reported modest survival

benefits associated with resection; however, post-operative recurrence and post-surgical complications are common.[64,65] Thus, the role of resection for advanced HCC remains controversial.

With recent advancements in the treatment of HCC, continuing research is needed to re-evaluate the appropriateness of current guideline recommendations. Therefore, the objective of this study was to explore current treatment approaches and to compare the effectiveness of primary treatment on overall survival for patients diagnosed at various stages of disease in China.

Methods

Study Sample

The study sample included data from the Bridge to Better Outcomes in Hepatocellular Carcinoma (HCC BRIDGE) study in China, a longitudinal cohort study of patients diagnosed with HCC across 12 tertiary hospital centers from 9 geographically diverse cities in mainland China. Details of the study design and complete inclusion criteria for the HCC BRIDGE study have been previously described.[29] Briefly, patients age $\geq$ 18 years who were newly diagnosed with HCC from January 1, 2005 through June 30, 2011 and received active treatment for HCC at one of the participating hospital sites were retrospectively enrolled in the study. Patients with unknown date of HCC diagnosis and/or date of first visit to the participating site or whose first HCC treatment was received via participation in a randomized clinical trial were excluded. All patients were followed until September 30, 2012 or date of death.

For the present study, additional inclusion criteria included complete clinical tumor characteristics, liver function and performance status information to appropriately classify disease stage at diagnosis, as well as available follow-up dates after date of diagnosis (**Figure 3.2)**. Two hospital sites in Changsha and Nanjing, respectively, were ultimately excluded due to overall poor data quality, including >50% missing information for disease characteristics and follow-up information, thus restricting the analyses to 10 hospital sites in 7 cities.

Data Collection

Data for the HCC BRIDGE study were systematically collected for all enrolled patients through a retrospective review of patient medical records. [29] Study data were entered into an electronic data capture system developed by Outcome Sciences, Inc. (Cambridge, MA, USA) and were subject to rigorous monthly data monitoring and cleaning. The institutional review boards from each participating hospital site approved the data collection for the HCC BRIDGE study. Data analyses for the present study were approved by The University of North Carolina Office of Human Research Ethics.

Available treatment approaches for HCC included: 1) surgical resection, 2) liver transplant, 3) ablation, 4) TA therapy, 5) systemic therapy, 6) supportive care, and 7) radiation/other locoregional therapy. The full list of therapies for each treatment approach are listed in **Appendix A**. The dates of all recorded treatments were compared to identify the primary and subsequent treatment approaches,. The primary treatment approach was generally defined as the first recorded treatment, with certain exceptions. Supportive care is often administered to reduce symptoms prior to or during primary therapy. [3] If patients received another therapy within one month (30 days) after supportive care, the other therapy was considered to be the primary treatment. In practice, TA therapy can be used to shrink the tumor(s) in preparation for surgical treatment. [3] For such cases, the primary treatment approach was considered to be surgical treatment, rather than TA therapy. Separate categories were created for patients who first received TA therapy then underwent resection, liver transplant or tumor ablation within 6 months (182 days) after the first administration of TA therapy. After this period, any additional treatment following TA therapy was considered to be a second-line approach either to treat the primary or de novo HCC lesions.

Clinical and laboratory assessments, including tumor characteristics, liver function, and performance status information, were obtained for all patients. Tumor characteristics included tumor size (diameter in cm), number of nodules and tumor spread, defined as the presence of vascular

invasion and/or tumor metastases. To measure liver function among individuals with cirrhosis, Child-Pugh (CP) scores were calculated, and presence of portal hypertension was documented at diagnosis.[3,55] Performance status was measured using the Eastern Cooperative Oncology Group (ECOG) scoring criteria.[3,56] Patients with incomplete data were excluded from the analyses. In cases where patients had multiple clinical assessments over time, only assessments obtained within 6 months (182 days) before and after date of diagnosis were considered, and the closest date to diagnosis was used. Laboratory values were taken within 1 month (30 days) before to 6 months (182 days) after date of diagnosis, and the earliest available laboratory values were selected. To maintain clinical validity, analyses and interpretation of clinical information at diagnosis were based on extensive discussions with an expert panel of gastroenterologists/hepatologists from China as well as other countries participating in the HCC BRIDGE study.

Patients were categorized according to five disease stages based on the CMH guidelines: 1) Very Early/Early, 2) Intermediate - Solitary, 3) Intermediate - Multinodular, 4) Advanced, and 5) Terminal (**Figure 3.1**).[3] Terminal stage included patients with substantial performance status limitations (i.e., performance status =3-4) or severely impaired liver function (i.e., CP C). Patients with no/moderate performance status limitations and liver function impairment (i.e., performance status <3, no cirrhosis or CP A/B) were further categorized according to tumor size, number, and spread. Advanced stage patients included those with tumor metastases or any vascular invasion, as defined above. Disease stage for solitary tumors without vascular invasion and tumor metastases was defined according to tumor size: Very Early: diameter ≤2 cm, Early: >2 cm but ≤5 cm, and Intermediate: >5 cm. Multinodular tumors without vascular invasion and tumor metastases were categorized according to both tumor size and number: Early: 2-3 tumors, with largest diameter ≤3 cm, and Intermediate: 2-3 tumors, with largest diameter >3 cm, or ≥4 tumors (of any size).

Additional patient demographic and clinical characteristics were collected at time of diagnosis or first visit to the hospital site, including patient age, gender, etiology, co-morbidities, and insurance status. Etiology of HCC included chronic HBV infection, chronic HCV infection, ALD, non-alcoholic fatty liver disease (NAFLD), primary biliary cirrhosis, hemochromatosis, inherited metabolic disorder or idiopathic disease, based on documented evidence in the patient medical record. Relevant co-morbidities included diagnosed diabetes mellitus, cardiovascular disease (CVD) and hypertension. [95,96] Patients who paid out of pocket for their treatment were considered uninsured.

Data Analyses

Descriptive analyses compared patient demographics, clinical characteristics, disease stage and primary treatment approaches across different cities in China. Statistical differences were assessed using analysis of variance (ANOVA) tests for continuous variables, and the $\chi 2$ or Fisher exact tests for categorical variables. [34] To assess compliance with the CMH guidelines for HCC treatment, additional analyses explored primary treatment approaches, according to disease stage, as well as additional treatment approaches following primary treatment.

Survival analyses were conducted to assess differences in survival, according to disease stage and primary treatment. Survival was estimated from the date of first treatment until death or censoring. Patients who did not die during follow-up were considered censored at the last known follow-up or study end (September 30, 2012). For each disease stage, unadjusted survival probabilities were estimated using the Kaplan-Meier method and compared by the log-rank test. [31] The life-table method was used to calculate yearly probabilities of survival; 95% confidence intervals (CI) were computed using the log-log transformation of the survivor function. [31]

For each disease stage, multivariate Cox proportional hazards models were constructed to assess the association between primary treatment and the hazard of death. [31] To maintain statistical

power, only analyses for treatments with an a priori minimum of n=50 patients were conducted; patients receiving other treatments were excluded. Models for all disease stages controlled for the following patient demographics and clinical characteristics: age, gender, co-morbidities, etiology, liver function (i.e., CP status and portal hypertension), and hospital site where treatment was received. Additional covariates for advanced stage disease included indicators for type of vascular invasion and/or tumor metastases. For all other disease stages, models controlled for tumor size and number of tumor nodules, based on the aforementioned categories outlined in the CMH guidelines.[3] Model fit for different specifications was assessed using the Akaike information criterion (AIC).[31] Model-estimated standard errors were adjusted using robust sandwich standard errors to account for patient clustering by hospital sites.[97] Log cumulative hazard plots stratified by treatment were estimated to test the proportional hazard assumption.[31]

In order to effectively control for selection bias arising from non-random allocation of primary treatment, two different methods for propensity score (PS) analysis were undertaken to adjust the survival analyses: 1) regression-based adjustment and 2) propensity-based weighting.[32,33] For each disease stage, PS for patients who received each primary treatment were estimated using multinomial logistic models, controlling for the variables included in the multivariate Cox proportional hazard models.[32] Histograms for the model-estimated PS were constructed to examine the overlap in the distribution of PS across treatment groups. To increase overlap in the PS, fully saturated models were estimated by adding higher order terms for age and interaction terms between liver function (i.e., CP status and portal hypertension) and tumor characteristics (i.e., tumor stage, vascular invasion and tumor metastases). Model fit for different model specifications was compared using the AIC, and likelihood ratio tests were performed to test the appropriateness of the interactions.[31] Once the models were correctly fitted, a series of Hausman tests were performed to test the Independence of Irrelevant Alternatives assumption.[98]

The model-estimated PS then were incorporated into the Cox proportional hazard models for each disease stage, in place of the model covariates specified above, to compare the hazard of death with treatment. Using regression-based adjustment, the estimated PS were directly included in the regression as a linear model covariate.[32] For the method of propensity-based weighting, patients were weighted using stabilized inverse probability weights, defined as the ratio of the marginal predicted probability of treatment (m) divided by the PS (i.e., m/PS).[33] Stabilized weights were chosen over standard inverse probability of treatment weights (i.e., 1/PS) to provide better estimates of the variance in treatment effect. To further remove selection bias from survival comparisons across treatments, patients were weighted by the stabilized inverse probability weights to form adjusted survival probabilities using the Kaplan Meier and life-table methods.[99]

All analyses were conducted using SAS version 9.2 (Cary, North Carolina, United States). An a priori 5% significance level was used for all statistical tests, as well as tests for model specification.

Results

A total of 6,194 patients from 10 hospital sites across 7 cities in China were included in the study (**Figure 3.2**). Primary treatment approaches for the full HCC BRIDGE study (n=7,251) compared with the final sample (n=6,194, 85.4%) were similar (p=0.09), suggesting that unavailable disease characteristics and follow-up dates were primarily missing at random (data not shown).

The majority of patients diagnosed with HCC were male (86.5%) with a mean age of 51.7 $\pm$ 11.9 years (**Table 3.1**). HCC etiology was primarily related to chronic HBV infection (88.7%). Most patients had well-preserved liver function (CP A/no cirrhosis: 87.8%), and few patients had comorbidities, including diabetes (6.0%), CVD (1.8%) or hypertension (9.5%). Patient characteristics appeared similar across different cities in China, although statistical differences were seen (all p<0.0001). Notably, insurance status varied substantially across different cities; whereas most HCC patients were uninsured

(71.1%), only 22.2% of patients treated in Beijing were uninsured. Additional differences included higher percentages of patients with underlying etiology related to chronic HCV infection in Harbin (11.9%), and moderate to severe liver impairment (i.e., CP B-C) in Xi'an (22.1%) and Nanning (24.6%).

Disease Characteristics

Nearly 40% of patients were diagnosed in the intermediate stages, and more than one- third of patients (34.5%) were diagnosed with advanced stage HCC characterized by vascular invasion (16.7%) and tumor metastases (17.8%) (**Table 3.2**). In contrast, less than one-quarter of patients (24.2%) were diagnosed in the early stages, when patients are prime candidates for curative surgical treatment. Disease stage at diagnosis varied significantly across the sampled cities ($p<0.0001$). In Beijing, a larger percentage of patients were diagnosed in the early disease stages (38.5%), and only 12.3% were diagnosed with advanced HCC. In Xi'an and Shanghai, on the other hand, nearly one-half of all patients were diagnosed with advanced HCC (Xi'an: 51.7%, Shanghai: 44.9%).

Current Treatment Approaches

TA therapy was the most common primary treatment approach, administered to approximately one-half (50.6%) of all patients, followed by surgical resection, performed among nearly one- third (32.8%) of all HCC patients (**Table 3.3**). Additional primary treatment approaches included tumor ablation (8.1%) and supportive care (4.7%); other primary treatments, including liver transplant (0.7%), systemic therapy (1.4%), and radiation/other (1.7%), were seldom used. Administration of TA therapy within 6 months prior to tumor ablation (39.8%) and liver transplant (32.6%) was common, but less common for resection (5.1%). Primary treatment approaches significantly differed across cities ($p<0.0001$).

Trends in primary treatment approaches, according to HCC disease stage, were generally consistent with the CMH clinical guideline recommendations (**Table 3.4**). Surgical resection and tumor

ablation were commonly performed for early and intermediate solitary HCC (<10 cm) and, to a lesser extent, among patients with 2-3 tumors. Palliative resection was performed among a small minority of patients with a massive solitary tumor (i.e., ≥ 10 cm; 26.2%), multiple tumors (i.e., ≥ 4; 17.7%) and advanced HCC (14.4%-14.6%), whereas ablation was seldom performed for these patients (1.6-8.0%). Palliative treatments, such as TA therapy, systemic therapy and supportive care, were primarily used to treat intermediate to advanced disease. Primary treatment for terminal stage patients with poor liver function (i.e., CP C) generally included supportive care (56.1%) or TA therapy (38.6%).

Approximately 29% of patients received at least one additional treatment after attempting primary therapy, of which 6% of patients received only supportive care. Across all primary treatments, the most common additional treatment approach was TA therapy (**Table 3.5**).

Survival with Primary Treatment

Median overall survival following primary treatment for the full study sample was 21.2 (95% confidence interval [CI]: 19.8-22.5) months, with 1- and 3-year survival of 62.9% (61.7-64.1%) and 40.9% (39.5-42.3%), respectively. Overall survival with treatment differed significantly according to disease stage at diagnosis (unadjusted p<0.001; **Figure 3.3**). As expected, patients diagnosed at an early stage experienced greater survival, with 1- and 3-year survival reaching 88.4% (86.6-90.0%) and 68.5% (65.6-71.3%), respectively. Among patients with intermediate stage disease, 1- and 3-year survival ranged from 67.8% (65.5-70.0%) and 42.6% (39.9-45.3%) for patients with a solitary tumor to 65.1% (61.6-68.4%) and 37.7% (33.9-41.6) for patients with multinodular tumors. Overall survival for patients with advanced and terminal stage HCC was generally poor; 1-year survival was only 42.6% (40.5-44.8%) and 26.3% (18.3-35.0%) for advanced and terminal stage patients, respectively.

After PS adjustment, overall survival across all disease stages varied substantially according to primary treatment (**Figure 3.4**). For early stage HCC, survival was markedly higher among patients who

underwent resection (3-year survival: 79.7%, 76.0-82.9%) compared with ablation (3-year survival: 57.6%, 49.4-65.0%) or TA therapy (3-year survival: 44.9%, 38.6-51.0%; p<0.0001 across groups). Similar trends were seen among intermediate stage patients with a solitary tumor, although differences in survival were less pronounced; 3-year survival was 58.6% (54.4-62.6%) for resection compared with 48.1% (31.6-62.8%) and 30.0% (26.3-33.7%) for ablation and TA therapy, respectively (p<0.0001 across groups). For intermediate multinodular HCC, overall 3-year survival was similar for resection (56.3%, 48.6-63.3%) and ablation (41.0%, 25.8-55.6%), but substantially lower for TA therapy (28.5%, 23.7-33.4%; p<0.0001 across groups). Significant differences in survival according to primary treatment were also seen for advanced stage disease (p<0.0001 across groups), with overall 3-year survival for resection and ablation reaching only 38.3% (32.0-44.6%) and 19.7% (12.3-28.5%), respectively.

Consistent with the results of the PS-adjusted survival analyses, differences in the hazard of death associated with primary treatment were significant across all disease stages (**Table 3.6**; p-values <0.0001 across treatment groups). Although results were slightly different across the multivariate and PS adjusted models, the 95% CIs surrounding the hazard ratios (HRs) generally overlapped, indicating consistent results for each disease stage.

Discussion

With advancements in the treatment of HCC, continuing research is needed to re-evaluate the appropriateness of current guideline recommendations. This study provides detailed survival comparisons from the HCC BRIDGE study, the most comprehensive longitudinal study of patients undergoing therapy for HCC in China, to clarify best treatment practices.[29] Overall, the significant findings were that patients with intermediate to advanced disease tolerated hepatic resection and had better outcomes than those who underwent alternative modalities of HCC therapy. Furthermore,

survival benefits associated with resection remained significant after PS adjustment, reducing concern that survival comparisons were biased by selection of better surgical candidates.

Treatment recommendations for HCC in China are distinct from those in the United States and Europe, particularly in the use of resection for intermediate stage HCC.[3] Prior research suggests that resection may be safely performed among patients with large solitary tumors with no evidence of vascular invasion, as the risk of recurrence is not significantly increased as compared to smaller tumors.[58,59] In the present study, resection was associated with a significant and substantial decrease in the hazard of death compared with TA therapy in this patient population, even after controlling for differences in patient characteristics at treatment selection.

As prior trials have suggested, primary treatment using TA therapy provided little to no survival benefit over supportive care.[100] It should be noted, however, that trials of TA therapy have been heterogeneous in terms of patient characteristics, treatment schedule, and agent used, leading to very different conclusions.[67] A meta-analysis of randomized controlled trials indicated that patient survival is significantly improved with TA therapy, with an objective response rate of 35%.[67] Thus, additional information is needed on the specific treatment schedules that were used among the hospital sites enrolled in this study to better assess the appropriateness of primary treatment using TA therapy in this patient population.

For patients with intermediate stage HCC, characterized by large multinodular tumors (i.e., 2-3 tumors, size >3 cm, or ≥4 tumors), without vascular invasion, tumor metastases or liver function impairment, the choice of treatment remains largely controversial. Based on previous evidence suggesting that the presence of multiple tumors is one of the most significant factors affecting survival, clinical guidelines in the United States and Europe consider patients with multinodular HCC to be poor candidates for resection, and TA therapy is recommended.[4,5] With recent advancements in surgical

techniques, however, a larger number of multinodular tumors are now considered resectable, with 3-year survival reaching as high as 35-56%. [61-63]

In the present study, overall survival was higher for resection than for TA therapy; likewise, TA therapy was associated with a significant increased hazard of death compared with resection, following multivariate adjustment. In interpreting these results, however, it is important to note that certain patients who received TA therapy in the present study may not have been candidates for surgical resection. Specifically, multicentric tumors, particularly those affecting multiple liver segments, are generally associated with inferior survival outcomes and may, in certain cases, preclude treatment with resection. [3,61] Thus, if a substantial number of patients who received TA therapy had unresectable tumors, differences in survival between resection and TA therapy were likely over-estimated.

A recent prospective study conducted by Luo et al. (2011) in China compared survival with resection (n=85) and TA therapy (n=83) among patients with large (≥5 cm) and multiple (≥2) tumors that were deemed resectable based on extensive clinical discussion. [63] Overall 3- and 5-year survival for patients who received resection (35% and 24%, respectively) were higher than those for patients initially allocated to TA therapy (26% and 19%, respectively), although survival differences were non-significant (p=0.26). The authors noted, however, that 13 patients (16%) in the TA therapy group subsequently received resection during follow-up. Although further evidence is needed, the authors suggested that TA therapy may be a better initial treatment for intermediate stage HCC, and resection should be recommended among patients who respond well to TA therapy.

Among patients with advanced stage HCC, characterized by vascular invasion and tumor metastases, overall survival in the current study was poor regardless of treatment. Patients who underwent resection achieved the largest survival benefit, with overall 3-year survival reaching 38%, whereas those who received TA or systemic therapy did not achieve a statistically significant survival benefit over supportive care. For patients with advanced disease, consensus guidelines currently

recommend systemic therapy with the multikinase inhibitor sorafenib.[3,4,8] A clinical trial of sorafenib conducted in East Asia demonstrated improved survival over placebo (p=0.014), with a reported median survival of 6.5 (5.6-7.6) months.[66] In the present study, sorafenib was only used by 3.5% of patients following its introduction in 2009, either as a primary or second-line therapy (data not shown), suggesting patients had limited access to treatment. Other systemic treatments have proven ineffective,[67,68] as was demonstrated in the current study.

In contrast with other consensus guidelines,[4,5] the CMH guidelines additionally recommend palliative resection among patients with vascular invasion and in certain instances, in the setting of tumor metastasis.[3] Previous studies conducted among patients with portal vein tumor thrombosis have reported 3-year survival rates of approximately 13-23%.[64,65,101,102] However, post-operative recurrence is common, occurring in more than one-half of patients within 6 months, with more than one-third experiencing post-surgical complications.[64,65] Thus, the role of resection remains controversial, particularly in the absence of head-to-head clinical trials comparing survival with that of sorafenib. In China, where access to sorafenib may be limited, the results of this study support the use of resection in this patient population, when clinically feasible.

Another significant finding was that, for early stage disease, patients who received tumor ablation did not derive the same benefit as patients who underwent resection. Prior literature comparing long-term survival between resection and tumor ablation for early stage disease have largely reported conflicting results.[69-71] Clinical trials conducted in China noted higher survival rates with resection, but did not find a statistically significant difference in survival between the two groups.[72,73] In contrast, another trial found a substantial survival advantage with resection among early stage patients; 3-year survival rates for radiofrequency ablation versus resection were 69.6% and 92.2%, respectively (p=0.001).[74] It should be noted, however, that the trials enrolled different proportions of patients with very early stage disease, which may in part explain the conflicting results, since ablation beyond this

stage is less effective in achieving complete tumor necrosis.[70] Subgroup analyses among patients with solitary tumors 3-5 cm and 2-3 tumors <3 cm were generally limited by small sample size, but reported a survival benefit with resection.[70,74] In the current study, the majority of early stage patients had solitary tumors 3-5 cm, which may explain the clear survival benefit seen with resection in this patient group. Whereas resection may provide better long-term efficacy than ablation, it should also be noted that resection is associated with increased complications and longer hospital stays.[69] Therefore, as currently recommended, ablation should be considered as a less-invasive alternative to resection, particularly among patients with very small tumors.[3]

This study is the largest to date of survival with HCC treatment in China and provides useful insights into the role of hepatic resection for more advanced disease and the limitations of all therapies when cancer is discovered in the later stages. The large number of HCC cases and meticulously collected data allowed for PS analysis to reduce elements of selection bias. Nevertheless the study has several limitations. First, as with any retrospective study of patient medical records, data on clinical characteristics were based solely on documented evidence in the patient medical record. As a result, potential miscoding of clinical characteristics across different hospital sites may have been present, and approximately 15% of the study sample was excluded due to missing disease stage or follow-up information. Likewise, only treatments provided to patients at the participating hospital site were generally documented; thus, the results may not reflect additional treatments if received from other sites.

Whereas the observational study design allowed an accurate portrayal of HCC management in regular clinical practice, survival comparisons across treatments were complicated due to non-random treatment allocation. In order to effectively control for underlying differences in patient characteristics across treatment groups, multivariate models were constructed, and PS analysis was further conducted to control for residual selection bias.[32] Nevertheless, residual confounding may still have been present,

leading to biased survival comparisons. Unfortunately, the HCC BRIDGE database did not capture information on tumor location, which as previously noted, may have lead to biased estimates of the impact of resection on survival among patients with multinodular tumors. More evidence is needed to better understand the comparative effectiveness of therapies for this patient population. Lastly, the study database exclusively captured treatment patterns and survival for patients treated across 10 large hospitals in China, and does not capture treatment patterns among patients treated in rural settings. Notably, over 70% of HCC patients included in the present study were uninsured, with wide differences in insurance status seen across the different cities that were sampled. Patients in rural settings are largely uninsured and may not have access to comprehensive treatment centers, which would further lead to disparities in treatment.

The results of this study can provide valuable insights into the impact of disease characteristics and current treatment approaches on the prognosis of HCC in China, to help prioritize areas for improvement. Overall, the significant findings of this comparative effectiveness analysis of HCC treatment are that patients with intermediate to advanced disease tolerate hepatic resection and have better outcomes than those who undergo alternative modalities of HCC therapy. Patients with early stage disease do not derive the same benefit from tumor ablation compared with patients who undergo resection. Despite advancements in the clinical management of HCC, the majority of patients are diagnosed with intermediate to advanced HCC in China, and survival is generally poor. Treatment patterns are generally consistent with current guideline recommendations in China. However, additional research is needed to determine whether published guidelines appropriately assign the primary treatment for intermediate stage patients with multinodular tumors.

Table 3.1: Demographics and clinical characteristics for patients diagnosed with HCC, across different cities in China.

Characteristic *	All Patients (n=6,194)	Guangzhou (n=1,523)	Shanghai (n=1,266)	Nanning (n=772)	Xi'an (n=737)	Chengdu (n=733)	Harbin (n=649)	Beijing (n=514)	p-value
Age years	51.7 ± 11.9	50.0 ± 12.1	52.7 ± 11.0	48.5 ± 12.0	51.7 ± 11.5	52.5 ± 12.5	54.3 ± 10.8	55.1 ± 12.1	<0.0001
Male Gender	5,360 (86.5)	1,393 (91.5)	1,070 (84.5)	695 (90.0)	633 (85.9)	628 (85.7)	527 (81.2)	414 (80.5)	<0.0001
Co-morbidities									
Diabetes mellitus	370 (6.0)	91 (6.0)	95 (7.5)	16 (2.1)	58 (7.9)	34 (4.6)	34 (5.2)	42 (8.2)	<0.0001
CVD	114 (1.8)	25 (1.6)	14 (1.1)	4 (0.5)	28 (3.8)	9 (1.2)	20 (3.1)	14 (2.7)	<0.0001
Hypertension	588 (9.5)	148 (9.7)	157 (12.4)	34 (4.4)	62 (8.4)	74 (10.1)	45 (6.9)	68 (13.2)	<0.0001
HCC Etiologies									
HBV	5,367 (88.7)	1,417 (93.0)	1,103 (87.1)	684 (88.6)	618 (83.9)	625 (85.3)	467 (72.0)	453 (88.1)	<0.0001
HCV	209 (3.4)	21 (1.4)	26 (2.1)	3 (0.4)	38 (5.2)	11 (1.5)	77 (11.9)	33 (6.4)	<0.0001
ALD	336 (5.4)	2 (0.1)	30 (2.4)	208 (27.0)	0 (0.0)	33 (4.5)	58 (8.9)	5 (1.0)	<0.0001
NAFLD	47 (0.8)	4 (0.3)	11 (0.9)	1 (0.1)	22 (3.0)	4 (0.6)	1 (0.2)	4 (0.8)	<0.0001
Other/Unknown	659 (10.6)	113 (7.4)	146 (11.5)	68 (8.8)	83 (11.3)	99 (13.5)	101(15.6)	49 (9.5)	<0.0001
Liver Function									<0.0001
CP A/No Cirrhosis	5,440 (87.8)	1,446 (94.9)	1,119 (88.4)	584 (75.6)	574 (77.9)	659 (89.9)	566 (87.2)	492 (95.7)	
CP B	693 (11.2)	77 (5.1)	141 (11.1)	156 (20.2)	153 (20.8)	68 (9.3)	76 (11.7)	22 (4.3)	
CP C	61 (1.0)	0 (0.0)	6 (0.5)	32 (4.2)	10 (1.3)	6 (0.8)	7 (1.1)	0 (0.0)	
Insurance Status									<0.0001
Insured	1,218 (19.6)	37 (2.4)	247 (19.5)	93 (12.1)	91 (12.4)	181 (24.7)	173 (26.7)	396 (77.0)	
Uninsured	4,402 (71.1)	1,466 (96.3)	694 (54.8)	661 (85.6)	640 (86.8)	502 (68.5)	325 (50.1)	114 (22.2)	
Unknown	574 (9.3)	20 (1.3)	325 (25.7)	18 (2.3)	6 (0.8)	50 (6.8)	151 (23.3)	4 (0.8)	

ALD = alcohol liver disease, CP = Child-Pugh score, CVD = cardiovascular disease, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, NAFLD = non-alcoholic fatty liver disease

* Values are expressed as mean ± standard deviation and n (%) for continuous and categorical variables, respectively.

Table 3.2: Disease characteristics for patients diagnosed with HCC, across different cities in China.

Disease Stage,* n (%)	All Patients (n=6,194)	Guangzhou (n=1,523)	Shanghai (n=1,266)	Nanning (n=772)	Xi'an (n=737)	Chengdu (n=733)	Harbin (n=649)	Beijing (n=514)	p-value
Very Early/Early †	**1,492 (24.2)**	**411 (27.0)**	**335 (26.5)**	**95 (12.4)**	**104 (14.1)**	**212 (29.0)**	**137 (21.1)**	**198 (38.5)**	**<.0001**
1 Tumor, ≤2 cm	258 (4.2)	80 (5.3)	65 (5.1)	5 (0.7)	15 (2.0)	29 (4.0)	19 (2.9)	45 (8.8)	
1 Tumor, 3-5 cm	1,113 (18.0)	305 (20.0)	219 (17.3)	80 (10.4)	79 (10.7)	176 (24.0)	115 (17.7)	139 (27.0)	
2-3 Tumors, ≤ 3 cm	121 (2.0)	26 (1.7)	51 (4.0)	10 (1.3)	10 (1.4)	7 (1.0)	3 (0.5)	14 (2.7)	
Interm./Solitary †	**1,675 (27.0)**	**445 (29.2)**	**221 (17.5)**	**282 (36.5)**	**138 (18.7)**	**165 (22.6)**	**201 (31.0)**	**223 (43.4)**	
1 Tumor, 6-9 cm	1,042 (16.8)	286 (18.8)	143 (11.3)	130 (16.8)	90 (12.2)	117 (16.0)	131 (20.2)	145 (28.2)	
1 Tumor, ≥ 10 cm	633 (10.2)	159 (10.4)	78 (6.2)	152 (19.7)	48 (6.5)	48 (6.6)	70 (10.8)	78 (15.2)	
Interm./Multinodular †	**787 (12.7)**	**154 (10.1)**	**125 (9.9)**	**217 (28.1)**	**94 (12.7)**	**58 (7.9)**	**110 (16.9)**	**29 (5.6)**	
2-3 Tumors, > 3 cm	376 (6.1)	75 (4.9)	87 (6.9)	106 (13.7)	32 (4.3)	33 (4.5)	15 (2.3)	28 (5.4)	
≥ 4 Tumors	411 (6.6)	79 (5.2)	38 (3.0)	111 (14.4)	62 (8.4)	25 (3.4)	95 (14.6)	1 (0.2)	
Advanced ‡	**2,134 (34.5)**	**513 (33.7)**	**568 (44.9)**	**143 (18.5)**	**381 (51.7)**	**275 (37.5)**	**191 (29.4)**	**63 (12.3)**	
Vascular Invasion	1,034 (16.7)	222 (14.6)	259 (20.5)	115 (14.9)	199 (27.0)	113 (15.4)	108 (16.6)	18 (3.5)	
Tumor Metastases	1,100 (17.8)	291 (19.1)	309 (24.4)	28 (3.6)	182 (24.7)	162 (22.1)	83 (12.8)	45 (8.8)	
Terminal	**106 (1.7)**	**0 (0.0)**	**17 (1.3)**	**35 (4.6)**	**20 (2.7)**	**23 (3.1)**	**10 (1.6)**	**1 (0.2)**	
CP C	57 (0.9)	0 (0.00)	5 (0.4)	32 (4.2)	9 (1.2)	6 (0.8)	5 (0.8)	0 (0.0)	
Perf. Stat. 3-4	49 (0.8)	0 (0.00)	12 (1.0)	3 (0.4)	11 (1.5)	17 (2.3)	5 (0.8)	1 (0.2)	

CP = Child-Pugh score, HCC = hepatocellular carcinoma, Interm. = intermediate, Perf. Stat. = performance status

* Disease stages are based on the China Ministry of Health Diagnosis and Treatment Guidelines for Primary Liver Cancers (2011 edition). [3]

† Patients in these categories have compensated cirrhosis (CP A/B), performance status 0-2, no venous invasion and no tumor metastases.

‡ Patients in these categories have compensated cirrhosis (CP A/B) and performance status 0-2.

Table 3.3: Primary treatment approaches for patients diagnosed with HCC across different regions in China.

Primary Treatment, n (%)	All Patients (n=6,194)	Guangzhou (n=1,523)	Shanghai (n=1,266)	Nanning (n=772)	Xi'an (n=737)	Chengdu (n=733)	Harbin (n=649)	Beijing (n=514)	p-value
Resection	2,029 (32.8)	675 (44.3)	244 (19.3)	283 (36.6)	145 (19.7)	364 (49.6)	144 (22.2)	174 (33.9)	**<0.0001**
TA Therapy*	103 (5.1)	54 (8.0)	7 (2.9)	13 (4.6)	13 (9.0)	1 (0.3)	7 (4.9)	8 (4.6)	
Transplant	46 (0.7)	3 (0.2)	4 (0.3)	2 (0.3)	2 (0.3)	35 (4.8)	0 (0.0)	0 (0.0)	
TA Therapy*	15 (32.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (25.7)	0 (0.0)	0 (0.0)	
Ablation	503 (8.1)	232 (15.2)	100 (7.9)	19 (2.4)	60 (8.1)	64 (8.7)	15 (2.3)	13 (2.5)	
TA Therapy*	200 (39.8)	111 (47.8)	43 (43.0)	6 (31.6)	30 (50.0)	2 (3.1)	5 (33.3)	3 (23.1)	
TA Therapy	3,135 (50.6)	538 (35.3)	856 (67.6)	325 (42.1)	482 (65.4)	230 (31.4)	401 (61.8)	303 (58.9)	
Systemic Therapy	88 (1.4)	16 (1.1)	7 (0.6)	9 (1.2)	39 (5.3)	0 (0.0)	7 (1.1)	10 (2.0)	
Supportive Care	289 (4.7)	49 (3.2)	28 (2.2)	131 (17.0)	7 (0.9)	8 (1.1)	66 (10.1)	0 (0.0)	
Radiation/Other	104 (1.7)	10 (0.7)	27 (2.1)	3 (0.4)	2 (0.3)	32 (4.4)	16 (2.5)	14 (2.7)	

HCC = hepatocellular carcinoma, TA = trans-arterial

* Proportion of patients who receive trans-arterial therapy within 6 months prior to resection, liver transplant or tumor ablation.

Table 3.4: Primary treatment approaches, according to disease stage,* for patients diagnosed with HCC in China.

	Very Early / Early†		Intermediate / Solitary†		Intermediate / Multinodular†		
Treatments, n (%)	**1 Tumor, ≤2 cm (n= 258)**	**1 Tumor, 3-5 cm (n=1,113)**	**2-3 Tumors, ≤ 3 cm (n=121)**	**1 Tumor, 6-9 cm (n=1,042)**	**1 Tumor, ≥ 10 cm (n=633)**	**2-3 Tumors, > 3 cm (n=376)**	**≥ 4 Tumors (n=411)**
Resection	118 (45.7)	628 (56.4)	35 (28.9)	544 (52.2)	166 (26.2)	143 (38.0)	73 (17.7)
TA Therapy**	2 (1.7)	13 (2.1)	1 (2.9)	29 (5.3)	8 (4.8)	9 (6.3)	8 (11.0)
Transplant	1 (0.4)	7 (0.6)	0 (0.0)	6 (0.6)	6 (0.9)	1 (0.3)	2 (0.5)
TA Therapy**	0 (0.0)	1 (14.3)	0 (0.0)	2 (33.3)	2 (33.3)	2 (50.0)	1 (20.0)
Ablation	74 (28.7)	168 (15.1)	27 (22.3)	49 (4.7)	10 (1.6)	25 (6.7)	33 (8.0)
TA Therapy**	15 (20.3)	35 (20.8)	8 (29.6)	30 (61.2)	9 (90.0)	12 (48.0)	19 (57.6)
TA Therapy	56 (21.7)	269 (24.2)	53 (43.8)	397 (38.1)	401 (63.4)	191 (50.8)	256 (62.3)
Systemic Therapy	0 (0.0)	2 (0.2)	1 (0.8)	5 (0.5)	7 (1.1)	4 (1.0)	8 (2.0)
Supportive Care	3 (1.2)	20 (1.8)	4 (3.3)	25 (2.4)	40 (6.3)	11 (2.9)	31 (7.5)
Radiation/Other	6 (2.3)	19 (1.7)	1 (0.8)	16 (1.5)	3 (0.5)	1 (0.3)	8 (2.0)

Table 3.4: (Continued).

Advanced‡		Terminal	
VI (n=1,034)	**TM (n=1,100)**	**CP C (n=57)**	**Perf. Stat. 3-4 (n=49)**
149 (14.4)	160 (14.6)	1 (1.8)	12 (24.5)
17 (11.4)	16 (10.0)	0 (0.0)	0 (0.0)
13 (1.3)	7 (0.6)	2 (3.5)	1 (2.0)
6 (46.2)	3 (42.9)	1 (50.0)	0 (0.0)
52 (5.0)	65 (5.9)	0 (0.0)	0 (0.0)
37 (71.2)	35 (53.9)	0 (0.0)	0 (0.0)
730 (70.6)	739 (67.2)	22 (38.6)	21 (42.9)
22 (2.1)	39 (3.6)	0 (0.0)	0 (0.0)
53 (5.1)	58 (5.3)	32 (56.1)	12 (24.5)
15 (1.5)	32 (2.9)	0 (0.0)	3 (6.1)

CP = Child-Pugh score, HCC = hepatocellular carcinoma, Perf. Stat. = performance status, TA = trans-arterial, TM = tumor metastases, VI = vascular invasion

* Disease stages are based on the China Ministry of Health Diagnosis and Treatment Guidelines for Primary Liver Cancers (2011 edition).[3]

** Proportion of patients who receive trans-arterial therapy within 6 months prior to resection, liver transplant or tumor ablation.

† Patients in these categories have compensated cirrhosis (CP A/B), performance status 0-2, no venous invasion and no tumor metastases.

‡ Patients in these categories have compensated cirrhosis (CP A/B) and performance status 0-2.

Table 3.5: Additional treatment approaches following primary treatment for patients diagnosed with HCC in China.

	Primary Treatment Approach						
Additional Treatment, n (%)	**Resection (n=2,029)**	**Transplant (n=46)**	**Ablation (n=503)**	**TA Therapy (n=3,135)**	**Systemic Therapy (n=88)**	**Supportive Care (n=289)**	**Radiation/ Other (n=104)**
Any Treatment	**833 (41.1)**	**13 (28.3)**	**233 (46.3)**	**618 (19.7)**	**62 (70.5)**	**7 (2.4)**	**44 (42.3)**
Resection	47 (2.3)*	0 (0.0)	15 (3.0)	18 (0.6)**	4 (4.6)	0 (0.0)	4 (3.9)
Transplant	8 (0.4)	1 (2.2)*	3 (0.6)	2 (0.06)**	0 (0.0)	0 (0.0)	0 (0.0)
Ablation	116 (5.7)	1 (2.2)	----	37 (1.2)**	1 (1.1)	1 (0.4)	5 (4.8)
TA Therapy	602 (29.7)	6 (13.0)	180 (35.8)	----	51 (58.0)	5 (1.7)	32 (30.8)
Systemic Therapy	86 (4.2)	3 (6.5)	28 (5.6)	144 (4.6)	----	1 (0.4)	3 (2.9)
Supportive Care	153 (7.5)	4 (8.7)	32 (6.4)	325 (10.4)	9 (10.2)	----	10 (9.6)
Radiation/Other	104 (5.1)	4 (8.7)	41 (8.2)	184 (5.9)	5 (5.7)	1 (0.4)	----

HCC = hepatocellular carcinoma, TA = trans-arterial

*Indicates that patient underwent a repeated resection or transplant, following primary resection or transplant.

** Indicates that patient underwent resection, ablation or transplant more than 6 months after the first administration of trans-arterial therapy.

Table 3.6: Cox proportional hazard models of the association between primary treatment and overall survival, according to disease stage, among patients diagnosed with HCC in China.

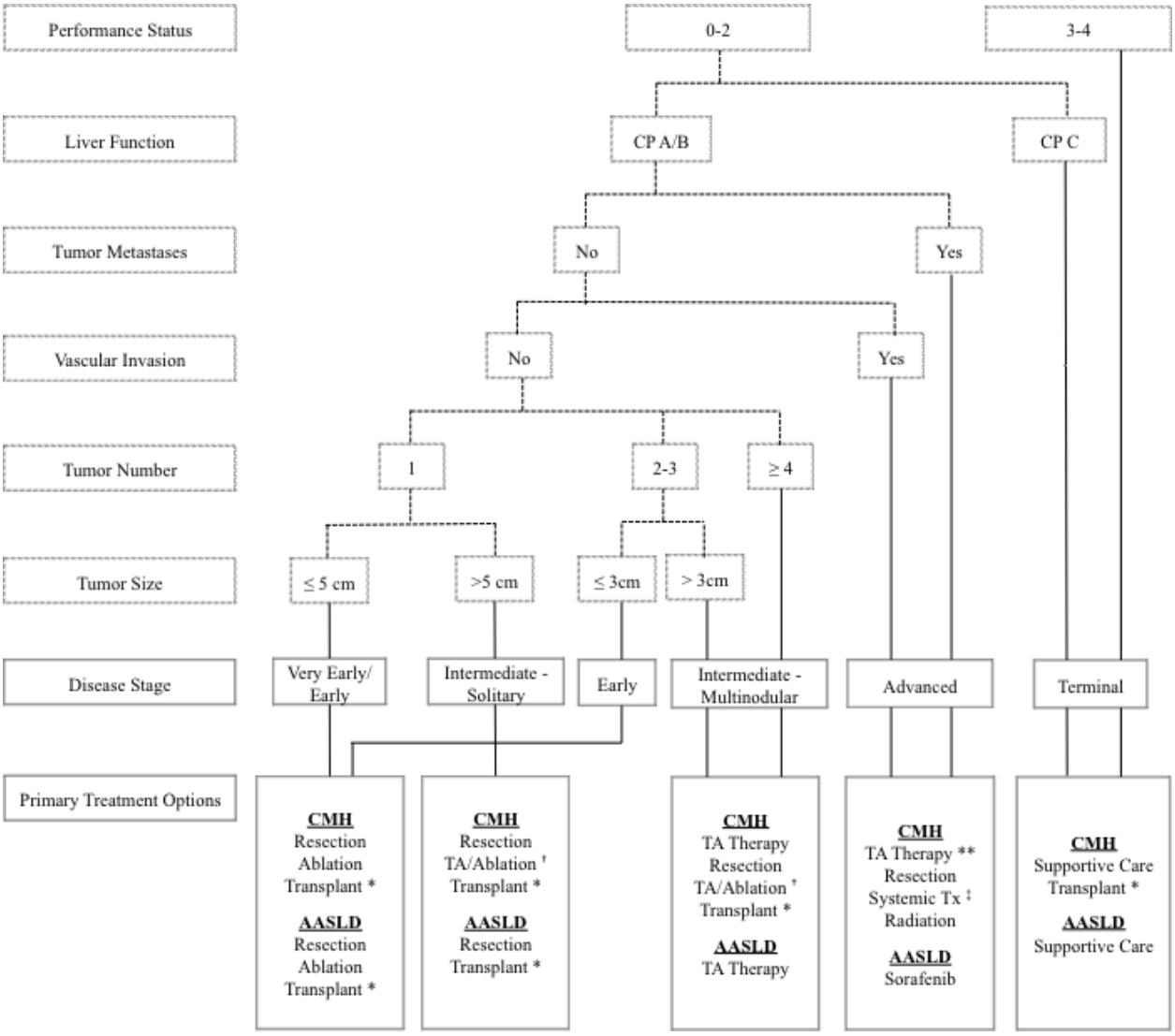
Disease Stage,* Treatment	Unadjusted** HR (95% CI)	Multivariate Adjusted** HR (95% CI)	Regression-Based Adjustment** HR (95% CI)	Propensity-Based Weighting** HR (95% CI)
Very Early/Early, n = 1,428				
Resection (Ref)				
Ablation	2.00 (1.60-2.50)	2.16 (1.71-2.73)	1.68 (1.33-2.14)	2.06 (1.72-2.48)
TA Therapy	3.16 (2.46-4.06)	3.21 (2.39-4.31)	2.87 (2.15-3.82)	3.55 (2.49-5.07)
Ablation (Ref)				
TA Therapy	1.58 (1.16-2.15)	1.49 (1.16-1.90)	1.70 (1.34-2.17)	1.72 (1.24-2.39)
Interm./Solitary, n = 1,632				
Resection (Ref)				
Ablation	1.40 (1.14-1.73)	1.52 (1.16-1.99)	1.20 (0.93-1.55)	1.31 (0.88-1.94)
TA Therapy	2.43 (1.88-3.13)	2.42 (2.06-2.85)	2.46 (2.01-3.02)	2.21 (2.06-2.36)
Supportive Care	3.79 (2.82-5.09)	2.30 (1.68-3.16)	3.27 (2.35-4.55)	2.57 (1.35-4.86)
Ablation (Ref)				
TA Therapy	1.73 (1.23-2.43)	1.59 (1.16-2.19)	2.05 (1.47- 2.87)	1.69 (1.15-2.47)
Supportive Care	2.70 (1.80-4.04)	1.51 (1.06-2.14)	2.72 (1.76-4.23)	1.96 (0.80-4.80)
TA Therapy (Ref)				
Supportive Care	1.56 (0.98-2.49)	0.95 (0.60-1.51)	1.33 (0.87-2.03)	1.16 (0.59-2.29)
Interm./Multinodular, n = 721				
Resection (Ref)				
Ablation	1.25 (0.91-1.71)	1.20 (0.79-1.82)	1.21 (0.89-1.65)	1.46 (1.06-2.02)
TA Therapy	2.31 (1.91-2.79)	2.16 (1.77-2.64)	2.36 (2.08-2.68)	2.13 (1.57-2.92)
Ablation (Ref)				
TA Therapy	1.85 (1.23-2.78)	1.81 (1.16-2.82)	1.95 (1.38-2.78)	1.47 (0.98-2.20)
Advanced, n = 2,067				
Resection (Ref)				
Ablation	1.38 (1.07-1.78)	1.38 (1.11-1.70)	1.45 (1.09-1.93)	1.55 (1.30-1.86)
TA Therapy	2.11 (1.65-2.72)	2.03 (1.71-2.42)	1.66 (1.27- 2.18)	1.84 (1.44-2.36)
Systemic Therapy	2.52 (1.88-3.37)	1.90 (1.46-2.47)	2.73 (1.95- 3.81)	2.05 (1.27-3.32)
Supportive Care	3.23 (2.24-4.64)	2.50 (1.91-3.27)	3.35 (2.32-4.83)	2.78 (1.86-4.15)
Ablation (Ref)				
TA Therapy	1.53 (1.05-2.24)	1.48 (1.07-2.04)	1.15 (0.69-1.92)	1.19 (0.84-1.68)
Systemic Therapy	1.82 (1.58-2.11)	1.38 (1.13-1.69)	1.88 (1.60-2.22)	1.32 (0.83-2.11)
Supportive Care	2.34 (1.57-3.48)	1.82 (1.36-2.44)	2.31 (1.51-3.53)	1.79 (1.29-2.48)
TA Therapy (Ref)				
Systemic Therapy	1.19 (0.84-1.68)	0.94 (0.69-1.28)	1.64 (0.97-2.77)	1.12 (0.71-1.75)
Supportive Care	1.53 (0.97-2.40)	1.23 (0.87-1.74)	2.01 (1.24-3.27)	1.51 (0.98-2.31)
Systemic Therapy (Ref)				
Supportive Care	1.28 (0.88-1.86)	1.32 (1.03-1.68)	1.23 (0.82-1.85)	1.35 (0.87-2.10)

CI = confidence interval, HCC=hepatocellular carcinoma, HR = hazard ratio, Interm. = intermediate, TA = trans-arterial, Ref = referent category

*Disease stages are based on the China Ministry of Health Diagnosis and Treatment Guidelines for Primary Liver Cancers (2011 edition). [3]

**For all disease stage regressions, p-values were <0.0001 for comparisons across treatment groups.

Figure 3.1: Summary of treatment recommendations for patients diagnosed with HCC based on the China Ministry of Health (CMH)[3] compared with the American Association for the Study of Liver Disease (AASLD) guidelines.[5,8]



AASLD = American Association for the Study of Liver Disease, CMH = China Ministry of Health, CP = Child-Pugh score, HCC = hepatocellular carcinoma, TA = trans-arterial therapy, Tx = treatment

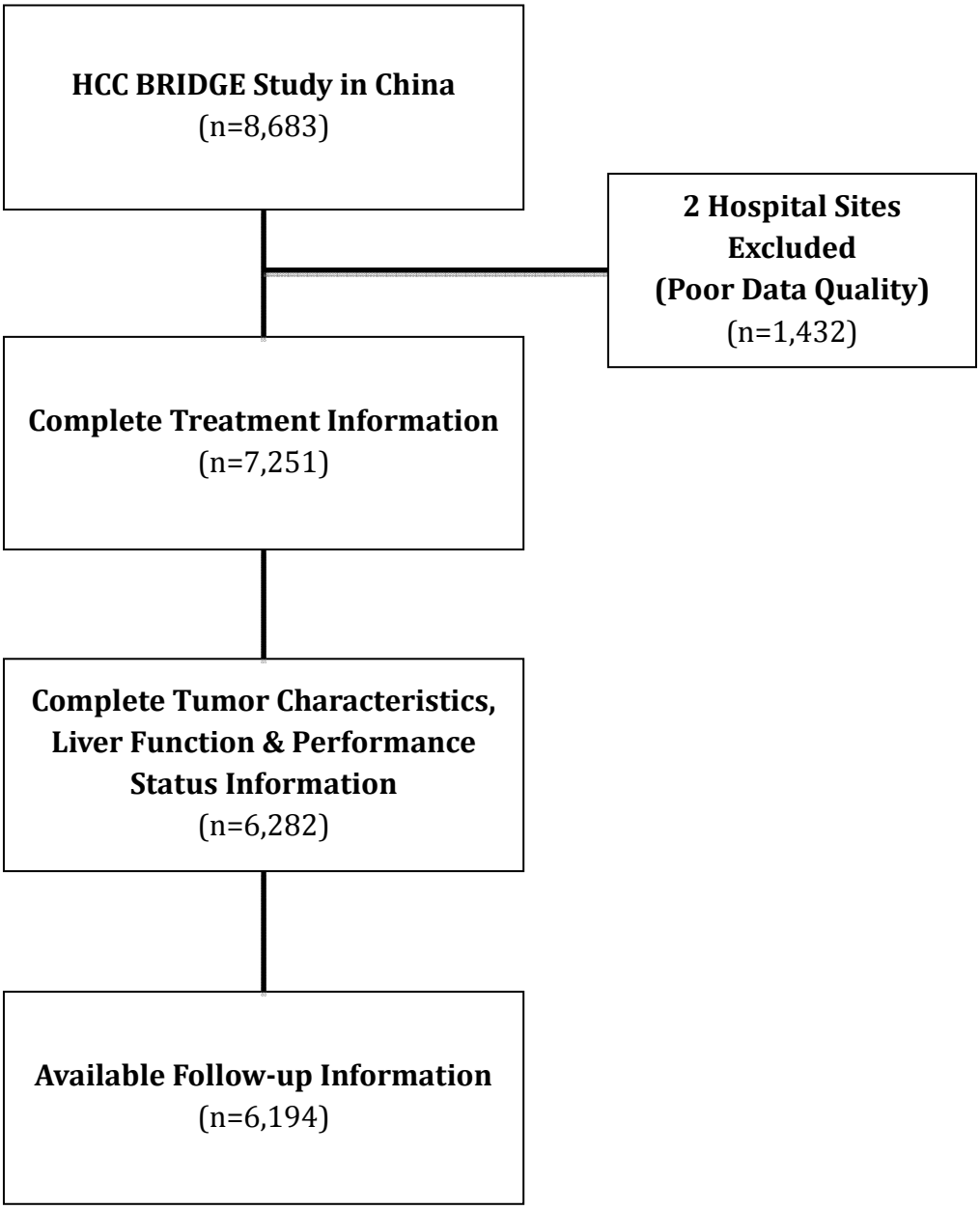
* According to the AASLD guidelines, liver transplant is recommended for patients who fall within the Milan criteria.[5,94] The CMH guidelines primarily recommend liver transplant for patients with unresectable HCC or for those who cannot tolerate ablation or TA therapy due to poor liver function.[3]

† Combination therapy with trans-arterial therapy followed by ablation among patients who respond to treatment.

** TA therapy is recommended for patients without evidence of tumor metastases.[3]

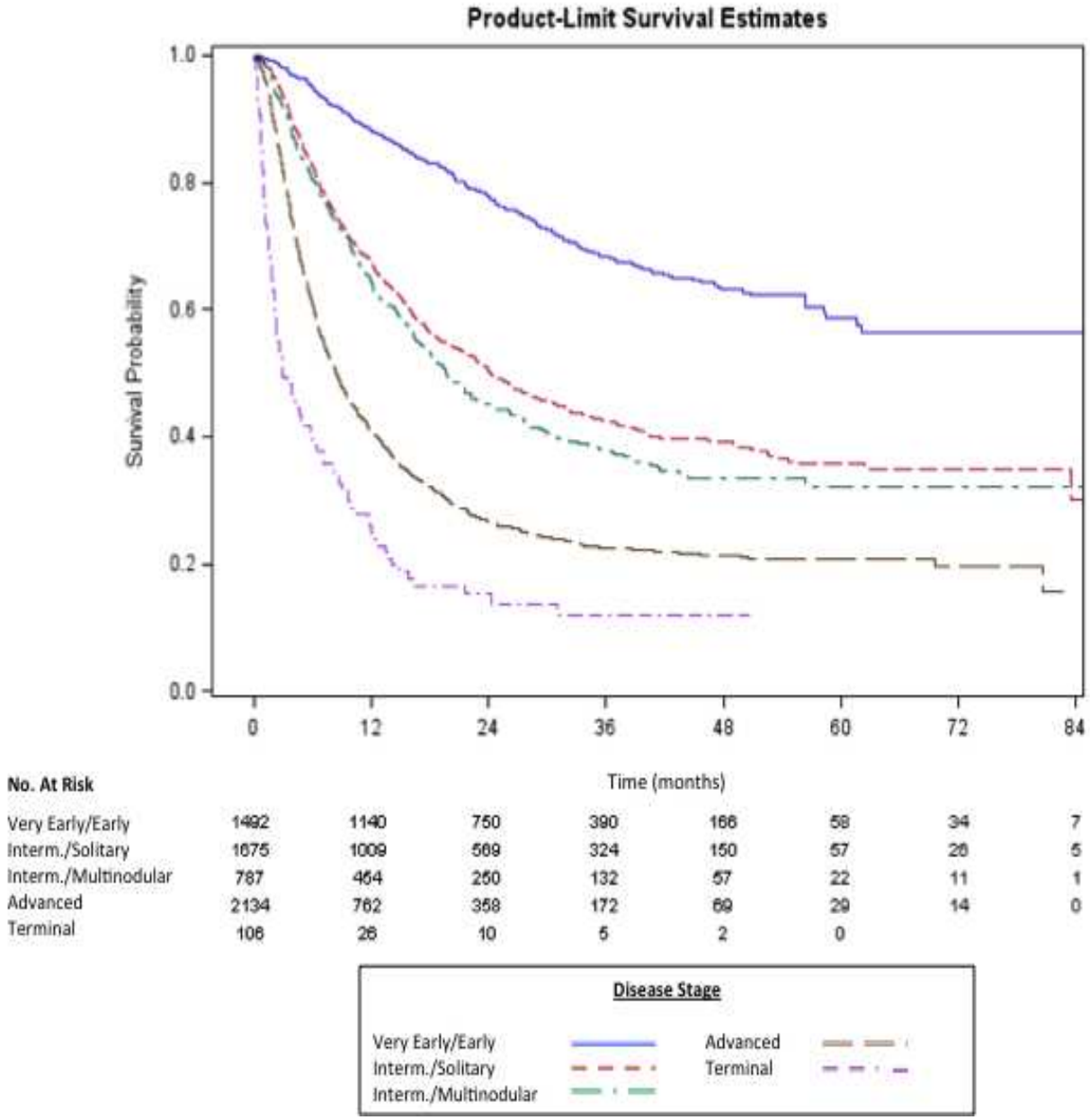
‡ Recommended systemic treatments include sorafenib, other molecular targeted therapies, chemotherapy and Traditional Chinese medicine.[3]

Figure 3.2: Sample selection from the HCC BRIDGE study in China.



HCC = hepatocellular carcinoma, HCC BRIDGE = The Bridge to Better Outcomes in Hepatocellular Carcinoma Study

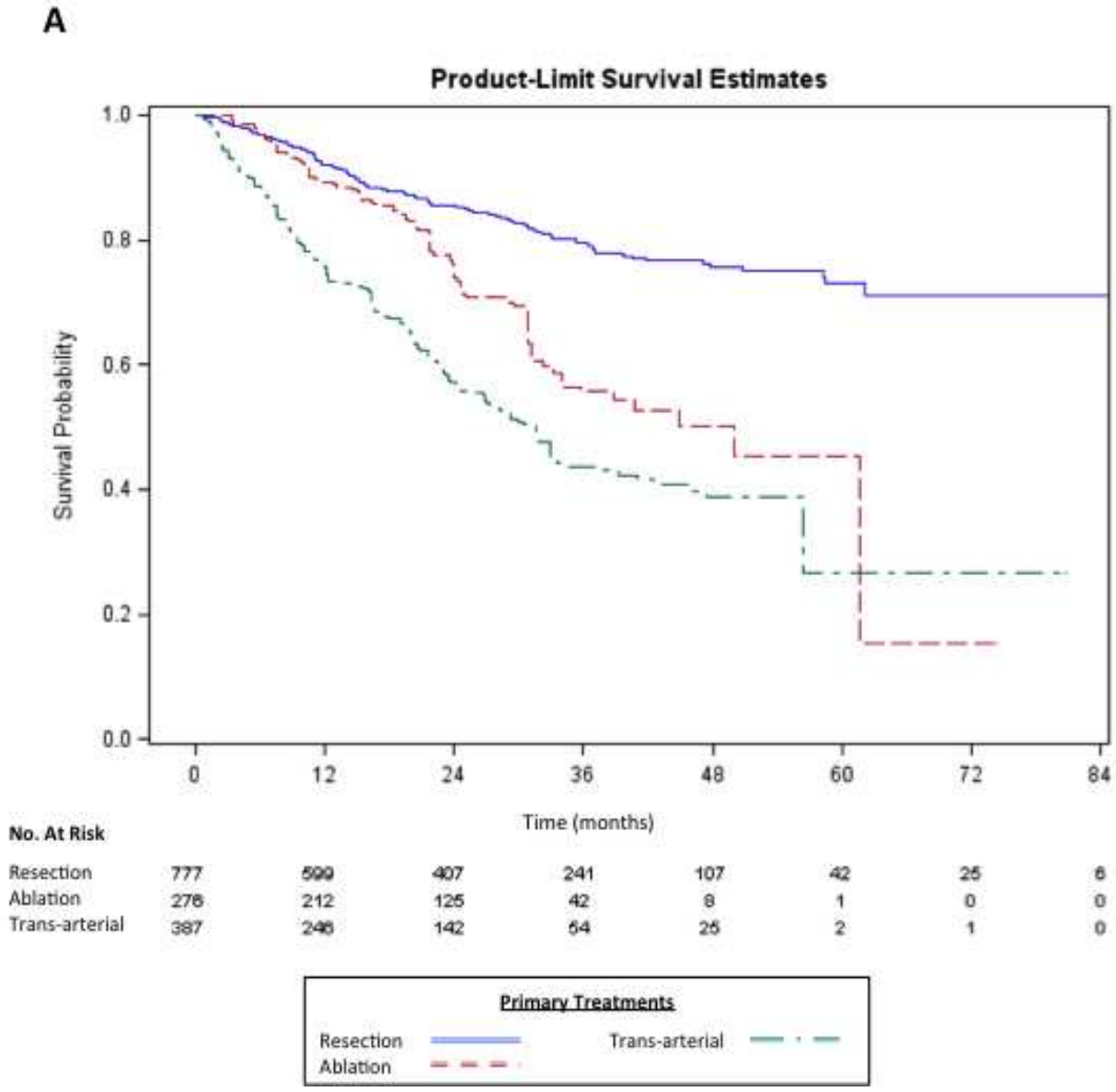
Figure 3.3: Unadjusted Kaplan-Meier survival curves for patients diagnosed with HCC in China, according to disease stage.*



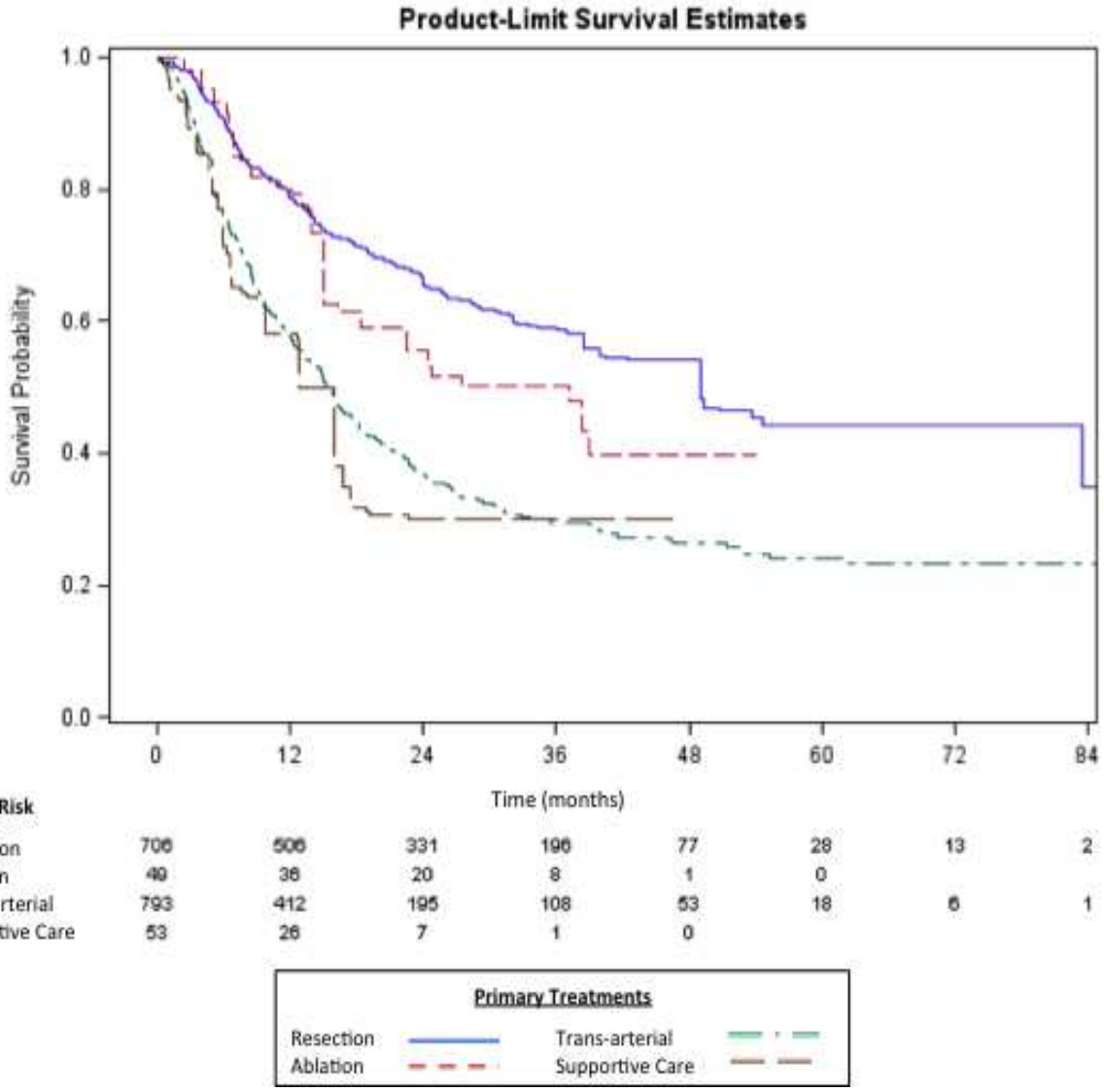
HCC = hepatocellular carcinoma, Interm. = intermediate, No. = number

* Disease stages are based on the China Ministry of Health Diagnosis and Treatment Guidelines for Primary Liver Cancers (2011 edition). [3]

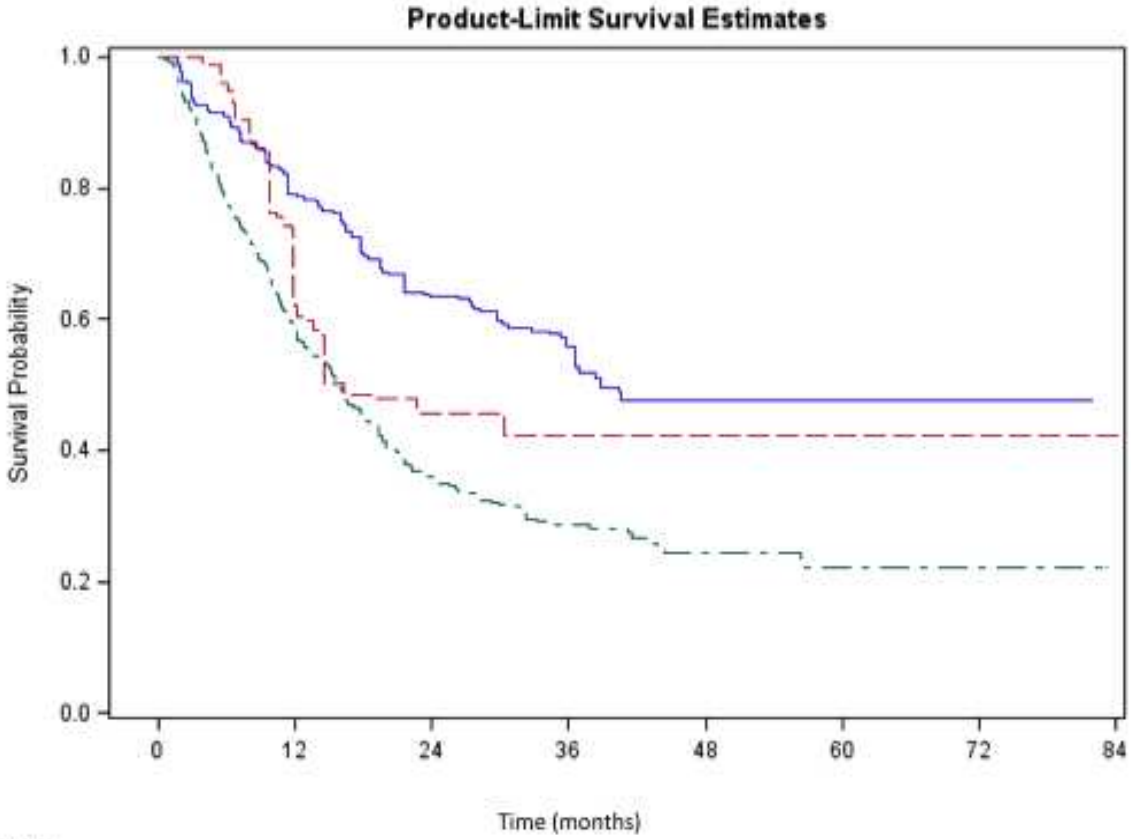
Figure 3.4: Propensity Score Adjusted† Kaplan-Meier survival curves for patients diagnosed with HCC, according to disease stage and primary treatment: A) Very Early/Early Stage, B) Intermediate Stage - Solitary Tumor > 5cm, C) Intermediate Stage – Multinodular Tumors, D) Advanced Stage.



B

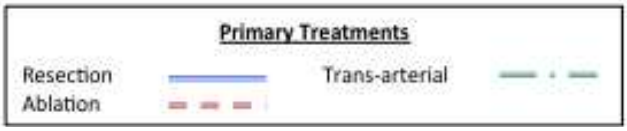

Product-Limit Survival Estimates
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
48
60
72
84
Time (months)
No. At Risk
Resection 706 506 331 196 77 28 13 2
Ablation 49 36 20 8 1 0
Trans-arterial 793 412 195 108 53 18 6 1
Supportive Care 53 26 7 1 0
Primary Treatments
Resection
Ablation
Trans-arterial
Supportive Care

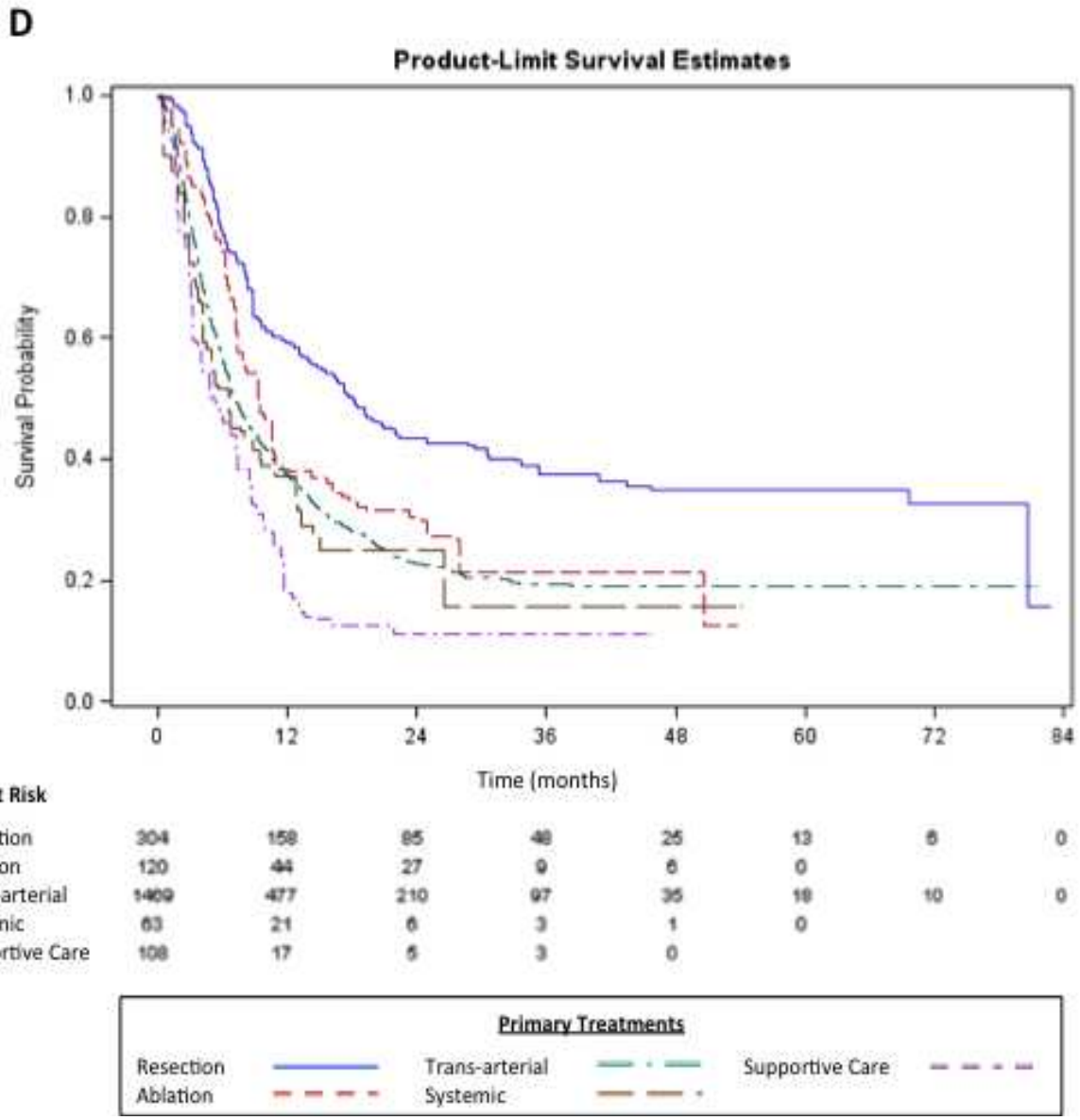
C



No. At Risk

Resection	213	157	106	53	16	7	3	0
Ablation	55	28	13	9	3	0	0	0
Trans-arterial	443	232	112	54	29	10	6	0





HCC = hepatocellular carcinoma, No. = number

* Disease stages are based on the China Ministry of Health Diagnosis and Treatment Guidelines for Primary Liver Cancers (2011 edition). [3]

† The Kaplan-Meier survival curves were adjusted using stabilized inverse probability weights.[99]

CHAPTER 4: INDIVIDUAL-BASED MODEL OF SURVEILLANCE TO DETECT HEPATOCELLULAR CARCINOMA AMONG INDIVIDUALS WITH CHRONIC HEPATITIS B VIRUS INFECTION IN CHINA

Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide.[103] In China, where hepatitis B virus (HBV) infection is endemic and is the leading etiological risk-factor for HCC, HCC is the second most common malignancy.[45] China alone contributes more than 55% of diagnosed cases of HCC worldwide.[103] Resection and tumor ablation are the main curative treatment options for HCC, but eligibility to receive curative therapy diminishes with more advanced disease.[3] Whereas current survival with HCC in China is generally poor (5-year survival 16.2%), 5-year survival for patients diagnosed at an earlier stage who receive curative therapy can exceed 50% (**Chapter 3**).[43,104]

The China Ministry of Health (CMH) has strived to improve the early detection of HCC by providing government-funded HCC surveillance in high-risk areas and publishing its newest Diagnosis and Treatment Guidelines for Primary Liver Cancers (2011 edition).[3] According to the CMH guidelines, HCC surveillance is recommended every 6 months among men aged ≥40 years with a history of chronic HBV infection and women aged ≥50 years with a history of chronic HBV infection. Recommended screening tests include abdominal ultrasound (US) and measurement of serum alpha-fetoprotein (AFP), with a cut-point of ≥200 ng/mL.

HCC surveillance has been conducted in China since the early 1970s, though only limited evidence exists to quantify or even demonstrate its impact on survival. A randomized control trial conducted among 18,816 participants with chronic HBV infection in China found that surveillance every 6 months with US and AFP was associated with a significant 37% reduction in 5-year mortality.[9] Despite demonstrating survival benefit, the trial had several limitations, including potential lead time bias

related to the earlier diagnosis of HCC, a relatively low number of HCC cases (n=153) collected over a short follow-up (5 years), and suboptimal adherence to the surveillance protocol (less than 60%). On one hand, the results likely underestimate the survival benefit from surveillance, because of poor compliance; on the other hand, potential lead time bias could have resulted in an overestimation of survival with surveillance. An earlier trial also conducted in China failed to show benefit with surveillance, largely because HCC patients did not undergo appropriate treatment. [46]

Although HCC surveillance is recommended, the ideal screening interval for surveillance is not known. Consensus guidelines suggest an interval of 6-12 months, based on average tumor volume doubling time (DT). [2,4,8] However, evidence from a small retrospective study suggests that survival is similar among HCC patients who receive surveillance at a 6-month interval, as compared with a 12-month interval. [28] More research is needed to inform the optimal interval. DT in HCC can vary considerably across individuals, and clinical data do not provide the necessary information to fully characterize other components of HCC disease progression, such as the development of multinodular tumors, vascular invasion (VI), and tumor metastases (TM). [14-27]

Determining the optimal approach for HCC surveillance requires both an understanding of tumor development and progression over time, and an accurate assessment of treatment patterns and associated survival in clinical practice. The objective of this study was to develop and calibrate an individual-based simulation model of surveillance to detect HCC among individuals with chronic HBV infection in China. The model then was used to simulate a randomized trial of HCC surveillance, controlling for lead time bias, to assess the impact of different screening intervals based on current recommendations in China, using no surveillance as a basis for comparison.

Methods

Model Overview

In the absence of more detailed data, prior Markov models of HCC surveillance have made simplifying assumptions surrounding the rate of tumor growth in HCC and the impact of patient characteristics, such as liver function, age and gender, in determining HCC treatment and survival outcomes. [83-86] Individual-based models provide an attractive alternative when the assumptions of Markov models prove to be limiting. [40,91] As individuals move through the model one at a time, rather than as part of a cohort, the model can track individual-level characteristics and allow them to change over time through a series of transition rules to simulate the life-course of disease. [40] The individual-based model of HCC surveillance, further described below, flexibly integrates accumulating medical history with individual-level heterogeneity in tumor growth to accurately project the impact of surveillance on disease stage at diagnosis, treatment selection, and survival for individuals who develop HCC.

The model incorporates well-established data on the natural disease course of chronic HBV infection, HCC development, and tumor growth in HCC. [14-27,35-37] Model calibration was conducted to provide estimates of unknown parameters surrounding the progression and detection of HCC disease outside of a surveillance program, based on the distribution of tumor characteristics among a cohort of patients diagnosed in clinical practice in China (**Chapter 3**). [29] The clinical data were further used to accurately portray treatment selection and associated survival with HCC in China. The model then was used to simulate a randomized trial of HCC surveillance, using different screening intervals.

Model Structure

The individual-based model of HCC surveillance in China was developed and calibrated using AnyLogic simulation software version 6.8.1 (© XJ Technologies Co., www.anylogic.com, St. Petersburg,

Russia). The structure of the individual-based model includes three parallel components designed to simulate: 1) the natural progression of chronic HBV infection, cirrhosis, and death; 2) the development, progression, and diagnosis of HCC; and 3) treatment and survival following HCC diagnosis. Three different surveillance strategies then were incorporated into the model, based on the CMH recommendations: 1) no surveillance (for comparison), 2) 6-month US and AFP (with cutpoint ≥ 200 ng/mL), and 3) 12-month US and AFP.[3] HCC tumors detected based on a positive US and/or AFP test were assumed to undergo confirmatory imaging with a computed tomography (CT) and/or magnetic resonance imaging (MRI) scan.

The model simulated a hypothetical cohort of 10,000 individuals, representative of the general population with chronic HBV infection in China, from time of chronic HBV diagnosis (based on a positive HBV surface antigen test) until death. At the start of the simulation, all individuals were in the chronic HBV state, without evidence of cirrhosis or HCC. With time, individuals could develop cirrhosis with no or mild symptoms (i.e., Child-Pugh [CP] A/B status), progress to clinically significant decompensated cirrhosis (i.e., CP C), or die (**Figure 4.1**). At any stage of progressive liver disease, individuals could simultaneously develop HCC. At the time of HCC development, individuals were assumed to have a solitary, very early stage tumor, which would grow continuously over time. Individuals with HCC could further develop satellite tumors (i.e., multinodular HCC), VI and/or TM, and with more advanced disease, die due to liver disease complications. At any stage of HCC progression, individuals could be diagnosed incidentally or through surveillance with US and AFP; individuals without HCC or whose HCC tumors were not detected would remain in their current health state. Treatment options for patients diagnosed with HCC were allocated according to disease stage, as defined by the current CMH guidelines, based on liver function and tumor characteristics at diagnosis (**Figure 4.2**).[3] Once allocated to treatment, HCC patients would remain in the post-treatment state until death.

Input Parameters

Input parameters for the simulation model were obtained from observational data and literature reviews, and were further verified by expert opinion from gastroenterologists and hepatologists. The following sections provide an overview of the methodologies for obtaining the model parameters for each model component.

Chronic HBV Progression

Literature searches of the Medline (PUBMED) and EMBASE databases were conducted to identify peer-reviewed articles that assessed the natural history of chronic HBV disease [**Appendix B**]. In order to maximize study relevance to the clinical context in China, specific emphasis was placed on prospective cohort studies conducted in East Asia. The natural disease course of chronic HBV infection has been extensively studied (**Table 4.1**). Model parameters for the incidence rate of HCC and cirrhosis among individuals with chronic HBV infection were obtained from the REVEAL-HBV (Risk Evaluation of Viral Load Elevation and Associated Liver Disease/ Cancer-Hepatitis B Virus) study, a prospective cohort study (n=3,683) conducted across seven counties in Taiwan over 11 years of follow-up. [36,37] A larger prospective cohort study (n=11,506) also assessed HCC development in chronic HBV in China; however, the study was ultimately excluded as the primary outcome was HCC mortality, and there was no evidence of screening in the baseline period to detect prevalent cases of HCC. [105]

Consistent with population-based studies of HCC prevalence, [1] the risk of both HCC and cirrhosis development in chronic HBV were substantially higher for males compared with females. [36] To adjust for gender, risk ratios (RR) reported in the REVEAL-HBV study were incorporated in the model. [36,37] The REVEAL-HBV study additionally provided gender-stratified annual rates for HCC incidence, but not for cirrhosis incidence. As a result, the annual rate of cirrhosis among males was obtained from an earlier prospective study conducted in Taiwan (n=1,506) [106], which provided a similar rate (0.70 per 100

person/years) to the pooled estimate from the REVEAL-HBV study (0.91 per 100 person/years).[37] After the development of cirrhosis, the incidence rate of HCC was considerably higher than among individuals with chronic HBV, but did not differ significantly according to gender (males vs. females: RR = 1.8, 0.4-8.6).[35] Likewise, gender differences in the rate of marked clinical decompensation (CP C) were also non-significant (RR = 0.7, 0.1-3.7).[35] As a result, these rates were not adjusted by gender.

All individuals who were not treated for HCC were subject to an annual rate of death due to all causes, adjusted by age and gender, based on China-specific estimates reported by the World Health Organization.[107] Studies have cited complications related to cirrhosis decompensation and advanced HCC disease as the main causes of death among individuals with chronic HBV; in contrast, mortality among individuals without cirrhosis, compensated cirrhosis or early stage HCC is generally similar to that of the general population.[108,109] Accordingly, an excess mortality rate, based on survival probabilities reported in retrospective studies of patient medical records, were applied to individuals with significantly decompensated cirrhosis (CP C) and advanced HCC.[110-112] Separate mortality rates were applied during the first and subsequent years following decomposition to account for the increased hazard of death within the first year following decomposition.[111,112] The hazard of death among individuals with undiagnosed advanced HCC was assumed to be the same as for patients diagnosed with advanced HCC who received supportive care, and was projected using parametric survival curves as further described below.

Initial Population

Baseline characteristics of the study population at the start of simulation were based on the distribution of age (67% ≥ 40 years) and gender (62% male) from the REVEAL-HBV study (**Table 4.1**).[36] Consistent with the CMH recommendations, HCC surveillance was provided among men and women with chronic HBV aged ≥ 40 and ≥ 50 years, respectively.[3] Therefore, the distribution of baseline

characteristics incorporated in the simulation model captured the broad population of individuals with chronic HBV who would undergo HCC surveillance in China.

HCC Disease Progression

Model parameters for the progression of HCC disease included tumor growth rates to project the size of the primary tumor, rates for the development of satellite tumors, VI, and TM, as well as incidental/symptomatic diagnosis rates. The following section describes the methodology for projecting tumor growth over time. Methods for obtaining the additional HCC-related parameters are later described in the calibration procedures.

Based on the seminal work by Schwartz (1961), HCC tumors are generally assumed to grow exponentially with time, at a rate governed by the tumor volume doubling time (DT), such that, at any time t (in days), tumor diameter (D_t) can be predicted as follows: [13]

$$D_t = D_0 * 2^{t/(3*DT)}$$

where: D_t = tumor diameter at time t

D_0 = tumor diameter at initial measurement

DT = tumor volume doubling time (days)

t = time (days)

Literature searches were conducted to identify peer-reviewed articles that assessed tumor growth in HCC using multiple measurements of tumor diameter (or volume) over time and calculated DT using the tumor growth formula (or equivalent, using tumor volume [13]) (**Appendix C**). The search identified 26 studies that met these criteria, of which 9 were excluded, as they were not conducted among the general population of HCC tumors, [113-117] or focused on the growth of macroregenerative nodules of which only a minority were later diagnosed as HCC. [118-121]

The results of the 17 remaining studies are summarized in **Appendix D**.[14-27,122-124] DT was highly variable across study samples, with mean/median DT ranging from 71 to 272 days, as well as across individuals, evidenced by a wide range of DT. Several studies noted that DT varied within individuals over follow-up;[14,15,18,19,21] however, the studies did not identify any definite trends. The majority of studies were conducted in East Asia, and 6 studies were from the United States or Europe.[18,25,26,122-124] Although HCC patients in China display different disease characteristics than patients in western settings due to differences in HCC etiology,[52,57] studies assessing the predictors of DT did not find an association between HCC etiology/degree of cirrhosis and DT.[18,21,122,124] Therefore, regional differences in HCC etiology were assumed to have no impact on HCC tumor growth, and all 17 studies were considered for a pooled meta-analysis.

The pooled meta-analysis was conducted using Microsoft Excel for Mac 2011 (version 14.3.9) (**Figure 4.3**).[38] Differences in the initial tumor size and characteristics across study samples suggested that a random effects model was more appropriate than a fixed effects model.[39] Most studies noted that the distribution of DT in HCC was highly skewed, suggestive of a log-normal distribution.[14,15,17-20,22-24,26] Thus, to satisfy the normality assumption for the random effects model, the meta-analysis was conducted using the geometric mean ± SD for DT to achieve normality at the log-scale.[39,125] Studies were included if they directly estimated the geometric mean,[24,26] or provided raw data to allow estimation of the geometric mean.[14,15,17,19-23] For studies that provided only the arithmetic mean ± SD,[16,18,25,27] the geometric mean and 95% CI were approximated using previously validated methods.[125] Three studies that provided only the median and range for DT were ultimately excluded.[122-124]

Using the mean and standard error (SE) estimates from the pooled meta-analysis (**Figure 4.3**), DT was incorporated into the formula for tumor growth to project primary tumor size over time for all individuals who developed HCC. Consistent with prior evidence, DT was randomly assigned using a log-normal distribution.[14,15,17-20,22-24,26] Initial tumor size (D_0) was assigned using a uniform distribution,

based on the range in the minimum detected tumor size across all tumor growth studies (0.3-1.5 cm; **Appendix D**).

Diagnostic Accuracy of HCC Surveillance

As diagnostic imaging techniques for the detection of HCC are rapidly evolving, literature searches to identify the diagnostic accuracy of HCC surveillance were restricted to studies published since the year 2000 (**Appendix E**). To project the impact of surveillance, it was critical to capture the sensitivity of abdominal US in detecting tumors of various sizes. Six studies assessing US accuracy met these criteria, of which 3 studies included an insufficient sample of HCC cases (n<30) to reliably estimate differences across tumor size. [126-128] The remaining three studies provided different sensitivity estimates for very early tumors ranging from 21% to 35%. [88-90] The lower sensitivity estimate was conservatively chosen, and sensitivity analyses incorporated the full range in sensitivity across studies (**Table 4.1**). For AFP ≥ 200 ng/mL, sensitivity analyses also assessed the full range in sensitivity (20%-36%), with the lowest estimate assumed in the base-case analysis. [90,129-132] Earlier studies, using different AFP cut-points, have suggested variations in AFP sensitivity according to HCC etiology; however, these associations have not been consistent. [132-134] Therefore, HCC etiology originating from chronic HBV infection was not considered a relevant inclusion criteria. Although both CT and MRI scan can exhibit a significant false-negative rate when used in first-line assessments, when used as confirmatory imaging, the sensitivity of both CT and MRI is as high as 91-100%. [89]

HCC Treatment

Treatment probabilities and survival with treatment incorporated in the simulation model were based on a prior analysis of the BRIDGE to Better Outcomes in HCC (HCC BRIDGE) study in China, a retrospective cohort study of patients diagnosed with HCC at 10 hospital centers across 7 cities in mainland China (see **Chapter 3**). Details of the study design and complete inclusion criteria for the HCC

BRIDGE study have been previously described (see **Chapter 3**). [29] For the present analyses, the cohort was further restricted to HCC patients with documented evidence of chronic HBV infection and complete tumor characteristics, liver function, and follow-up information (n=4,797; 80%) (**Appendix F**). Analyses were conducted using SAS version 9.2 (Cary, North Carolina, United States). An a priori 5% significance level was used for all statistical and model specification tests.

For each disease stage at diagnosis, probabilities of HCC treatment were incorporated in the simulation model based on the frequency of primary treatment approaches found in the HCC BRIDGE study (**Table 4.2**). Primary treatment was generally defined as the first recorded treatment, with certain exceptions, as previously described (see **Chapter 3**). Prior analyses of the HCC BRIDGE study found that HCC treatment patterns are generally consistent with the CMH guideline recommendations (see **Chapter 3**). [3] Common primary treatment approaches include resection, ablation, trans-arterial therapy and supportive care. Although recommended, liver transplant (n=38, 0.8%), systemic therapy (n=59, 1.2%) and radiotherapy/other loco-regional therapy (n=74, 1.5%) are rarely provided and, therefore, did not warrant inclusion in the simulation model.

Additional analyses explored treatment delays from diagnosis to first treatment. Treatment delays were minimal across all primary treatments (mean (95% CI): 10.2, 9.6-10.9 days) with the vast majority (95.4%) of patients receiving treatment within one month following diagnosis. Therefore, treatment delays were not incorporated in the model, and patients were assumed to receive treatment immediately following diagnosis.

To assess differences in survival across disease stage and primary treatment, initial survival curves were fitted to individual-level data from the HCC BRIDGE study. Kaplan-Meier survival curves were estimated for each primary treatment, and pair-wise log-rank tests were conducted to identify significant differences in survival across disease stages. [31] Using the same procedure, additional Kaplan-Meier curves compared survival with treatment for each disease stage. Survival differences were

generally significant across the disease stage and treatment strata, with some exceptions. For resection, ablation and trans-arterial therapy, survival for patients with intermediate-solitary and intermediate-multinodular tumors was similar (all $p>0.05$). In addition, survival did not significantly differ across all disease stages for patients allocated to supportive care, and survival was poor regardless of treatment for terminal stage patients. Where survival differences were non-significant, patients were pooled together, resulting in a total of 11 treatment/disease stage groups (**Figure 4.4**).

In order to project survival beyond the 3-5 year follow-up of the HCC BRIDGE Study, parametric survival curves were fitted separately for each treatment/disease stage group. Candidate model distributions included the exponential, Weibull, log-normal, log-logistic and generalized gamma models.[135] Comparisons between fitted distributions were quantitatively judged using the Akaike Information Criteria (AIC).[31,135] In cases where models (Weibull, exponential, and log-normal) were nested within a parent model (generalized gamma), likelihood ratio tests were performed to further compare model fit.[31,135] To qualitatively assess model fit, the unadjusted parametric survival curves were graphed against the corresponding non-parametric survival curves, estimated using the life-table method (**Figure 4.4**).

Based on the quantitative test results, the log-normal model generally provided the best fit to the HCC BRIDGE data.[31,135] As exceptions, gamma models provided the best fit for terminal stage patients and for intermediate stage patients receiving trans-arterial therapy. Despite these results, the unadjusted gamma survival curves were qualitatively similar to the log-normal models. To maintain consistency in the assumptions surrounding the hazard of death across models, log-normal models were ultimately chosen across all treatment and disease stage categories. The hazard of death for individuals with undiagnosed advanced HCC was additionally assumed to be the same as for patients diagnosed with advanced HCC who receive supportive care, and was therefore, projected from time of VI/TM development using the log-normal model for supportive care.

All of the final parametric survival curves were adjusted for age and gender. The terminal stage model additionally controlled for primary treatment (i.e., TA therapy or supportive care). All other models controlled for tumor size, number of nodules, and tumor spread (i.e., VI and TM), based on the tumor stage categories outlined in the CMH guidelines (**Figure 4.2, Table 4.2**).[3] Probability plots, using a modified Kaplan-Meier method that adjusts for covariates, were used to graphically assess model fit for each parametric curve at different values of the model covariates.[31] Quantitative comparisons of model fit for each fitted distribution were re-conducted, as described above. Model fit results were qualitatively similar with those of the unadjusted models.

Calibration Procedures

Whereas numerous studies have measured tumor growth in HCC, clinical data do not provide the necessary information to fully characterize the development of satellite tumors and VI/TM over time. The estimation of these parameters would require information regarding when each individual developed an HCC tumor and when further complications occurred. Such information is largely unavailable in clinical databases since most early stage patients are treated; even if patients elect to forgo treatment, large sample sizes would be needed to establish statistical power. In addition, the rate at which HCC is detected outside of a surveillance program, either incidentally or based on clinical symptoms, cannot be directly measured. Doing so would require knowing the proportion of all HCC cases (undiagnosed and diagnosed) that are detected in regular clinical practice.

Unknown parameters surrounding HCC disease progression were estimated through model calibration, a process that involves the systematic adjustment of model parameters to maximize consistency between simulated and observed data.[136] The following parameters were estimated by calibrating the simulation model: 1) the annual growth rate of an additional tumor if 1, 2 and ≥ 3 tumors are present; 2) the annual rates of VI and TM development; and 3) annual incidental/symptomatic

diagnosis rates. All parameters were adjusted by primary tumor size (≤5 cm, >5 and ≤ 10cm, >10 cm). Given that these unknown parameters cannot be measured in clinical practice, there were no prior data to inform plausible ranges. Thus, ranges for all 18 unknown parameters initially explored every possible value (rate per person: 0-1 per year) using continuous step sizes; base case values and plausible ranges were iteratively adjusted based on initial calibration results.

Through model calibration, the unknown parameters were chosen to produce model outputs optimized to reflect the distribution of tumor characteristics found in the HCC BRIDGE study data. The HCC BRIDGE data were first restricted to HCC patients who were not enrolled in a HCC surveillance program prior to HCC diagnosis (n=3,288; **Appendix F**). The data were then stratified into 27 mutually exclusive categories by tumor size, number of tumor nodules, and tumor spread (**Table 4.3**). Trends in tumor characteristics revealed that the majority of patients were diagnosed with a solitary tumor, and the frequency of VI and TM generally increased with tumor size. The frequency of multinodular tumors tended to increase with primary tumor size, presumably with the increased likelihood of VI/TM development; however, the development of satellite tumors in early HCC was also common.

Based on these trends, the following assumptions were made to reduce the complexity of the calibration process: 1) All individuals with HCC were initially assumed to have a solitary (primary) tumor, the size of which was projected using the tumor growth formula and the randomly assigned DT.[13] With time, individuals could develop satellite tumors, VI and/or TM. 2) As most patients present with a solitary tumor, individuals with a solitary tumor had a lower rate of developing an additional tumor than those who already had multiple nodules, 3) Satellite tumors were assumed to be the same size or smaller than the primary tumor, and were assumed to vary according to the primary tumor size. 4) The rates of VI and TM development were assumed to vary with primary tumor size. 5) The growth rate of the primary tumor was assumed to be independent of any satellite tumors and VI/TM. 6) The rates of incidental/symptomatic diagnosis increased with primary tumor size to reflect differences in the

sensitivity of diagnostic imaging with tumor size, as well as an increase in disease-related complications leading in symptomatic disease. [3,89]

The model calibration was conducted using the Optquest Optimization Engine (© OptTek Systems, Inc., www.opttek.com, Boulder, CO, United States) incorporated in the AnyLogic simulation software. The parameter search strategy is proprietary to Optquest, and uses a modified Newton method for optimization (www.opttek.com). Goodness of fit for the model outputs compared with the observed data was measured using the method of least squares. [136] To obtain the optimal parameter set, multiple iterations were run, each with different combinations of the calibrated parameters, for a total of 10,000 iterations. To account for underlying model stochasticity, multiple replications were run per iteration until the 95% CI of the least squares value had been reached with 0.5% error, with a minimum of 10 replications. The mean least squares value across all replications was used to search for the minimum value across model iterations.

Parameter sets that produced local minimum least square values that fell within a 0.001 relative change from the global minimum least squares value were compared. [136] As the acceptance criteria, the parameter set that produced the lowest percentage point differences in the distribution of tumor characteristics compared with the HCC BRIDGE data, within a maximum 5 percentage-point radius for each of the 27 strata, was ultimately retained. The resultant optimal set of parameters was used to conduct the model analyses.

Model Verification

Throughout development, the simulation model was run with enhanced animation to identify errors, oversights, or bugs in the model logic. Extreme value testing was performed to ensure the model behaved as expected as input parameters changed, both one at a time and in combination. Gastroenterologists/hepatologists were additionally consulted to ensure the model provided a clinically

valid representation of the natural disease course for chronic HBV infection and outcomes for HCC patients.

Model Analyses

Model Outcomes

All model outcomes were exported from AnyLogic into text files and read into SAS. Model outcomes included the 18 unknown parameters of HCC disease progression, and the model projected distribution of tumor characteristics following HCC diagnosis. Following model calibration, the model was used to project the impact of 3 different surveillance strategies from time of chronic HBV diagnosis until death: 1) no surveillance (for comparison), 2) 6-month US and AFP (with cutpoint ≥ 200 ng/mL), and 3) 12-month US and AFP. The primary model outcome was the survival time for individuals who developed HCC from time of HCC development until death. Survival was measured from time of HCC development, as opposed to time of diagnosis (as in clinical trial settings), to eliminate lead-time bias and incorporate cases of undiagnosed HCC that died prior to diagnosis. To account for underlying model stochasticity, multiple replications were run per iteration until the 95% CI of the mean survival estimate had been reached with 0.5% error, with a minimum of 10 replications. The maximum number of replications needed across all HCC surveillance strategies was then used to compare survival across strategies. For each strategy, the resultant individual-level survival estimates were pooled across replications and analyzed using the Kaplan-Meier method; differences in survival across HCC surveillance strategies were compared using the log-rank test.[31] Overall survival probabilities (1-, 3-, 5-, 10-, and 20-year) were calculated using the Life-Table method.[31]

Additional model outcomes for each surveillance strategy included disease stage at diagnosis, primary treatment following diagnosis, and the total number of screening tests needed to detect one

case of HCC. Statistical differences across surveillance strategies were assessed using the Chi^2 test. An a priori 5% significance level was used for all statistical tests.

Probabilistic Sensitivity Analyses

Probabilistic sensitivity analyses, using Monte-Carlo simulation, were conducted to provide estimates of uncertainty in the model-projected outcomes. The simulation model was run for 100 iterations with model parameters drawn from fitted parameter distributions reported in **Table 4.1**. Probabilities of HCC treatment, according to disease stage at diagnosis, were drawn from Dirichlet distributions, using frequencies reported in **Table 4.2**. To incorporate probabilistic uncertainty in the hazard of death following HCC treatment, the covariance matrices of the estimated log-normal survival curves were estimated. [40] Cholesky decomposition was then applied to the covariance matrices to account for correlation between the model parameters, when sampled using a normal distribution. [40] The same procedures, described above, were used to analyze survival for individuals who develop HCC across iterations to form ranges surrounding the base-case model outcomes.

Results

Model Calibration

After a total of 10,000 iterations, the model calibration resulted in 12 best fitting solutions (local minima), of which 5 iterations produced calibrated output with minimum least square values within a 0.001 relative change of the global minimum value (sum of square errors [SSE] = 0.005). The optimal calibrated distribution of tumor characteristics, compared with results from the HCC BRIDGE data, are presented in **Table 4.4.** The model-estimated distribution of tumor characteristics for the best fitting solution (sum of square errors = 0.006) fell well within the maximum 5 percentage point tolerance radius for each of the 27 strata, suggesting an acceptable model fit to the data. The resultant model-

estimated optimal parameter set is listed in **Table 4.5**. As expected, the rates of HCC disease progression and incidental/symptomatic diagnosis generally increased with tumor size. The rates of satellite tumor development were initially low for patients with a solitary tumor, and then increased among individuals with multinodular tumors.

Model-Projected Outcomes

Using the base-case model parameters, the results of the simulation model suggest that HCC surveillance with US and AFP, compared with no surveillance, provides a clear survival benefit among individuals who develop HCC (**Figure 4.5a**; log-rank: $p < 0.0001$). Overall survival following HCC development was also significantly higher among patients who received surveillance with US and AFP every 6 months, as compared with 12 months ($p < 0.0001$); however, the magnitude of the survival difference was small (median survival for 6- vs. 12-month interval: 4.60 vs. 4.11 years). Short-term differences in survival for individuals with HCC who did not receive surveillance compared with individuals who received surveillance every 6 or 12 months were minimal, but increased substantially over follow-up. Overall survival 5 and 10 years following HCC development was only 28.9% and 13.5% in the no surveillance group, compared with 48.1% and 30.1% for surveillance conducted using a 6-month interval, and 44.2% and 27.0% using a 12-month interval, respectively (**Table 4.6**).

Consistent with these results, a markedly higher proportion of HCC patients who underwent surveillance were diagnosed with early stage HCC (6- and 12-month interval: 84.6% and 73.8%), compared with patients who did not undergo surveillance (29.7%), and fewer patients were diagnosed with advanced HCC (**Table 4.6;** overall $p < 0.0001$ for all comparisons). Surveillance was also associated with increased use of curative resection and ablation as the primary treatment (overall $p < 0.0001$ for all comparisons). Despite these benefits, approximately 399 screening tests would be needed to detect

one case of HCC for surveillance using a 6-month interval; using a 12-month interval, the ratio in the number of screening tests is reduced to 218 per HCC case detected.

Probabilistic Sensitivity Analyses

Survival results from the probabilistic sensitivity analyses, conducted across a series of 100 iterations, were consistent with results from the base case analyses. Both surveillance conducted using a 6-month and 12-month interval, compared with no surveillance, consistently improved survival with HCC (**Figure 4.5b-c**). On the other hand, survival following HCC development for individuals who received 6-month as compared with 12-month surveillance was similar (**Figure 5d**). Overall survival 5 and 10 years following HCC development ranged from 26.9-29.3% and 12.2-14.4% in the no surveillance group, respectively, compared with 45.4-51.8% and 40.9-47.5% for surveillance conducted using a 6-month interval, and 40.9-47.5% and 24.2-30.7% using a 12-month interval, respectively.

Discussion

This individual-based simulation model of HCC surveillance combines well established data on the natural progression of chronic HBV infection and HCC disease, along with detailed clinical data from patients diagnosed with HCC in China, to provide an accurate portrayal of the impact of surveillance on survival outcomes for individuals who develop HCC. The results of this model suggest that surveillance with ultrasound and AFP is associated with both earlier disease detection and an increased rate of curative surgical treatment. As a result, surveillance markedly improves the survival of patients who develop HCC. Despite the clear survival benefit, however, a large number of screening tests are needed to detect one case of HCC, suggesting that resource use is an important consideration. In the setting of limited resources, the results of this model suggest that surveillance performed at 12-month as opposed to 6-month intervals, as currently recommended in China, can be more easily implemented with little impact on the survival of patients who develop HCC.

Although HCC surveillance is widely recommended, few studies have demonstrated that surveillance improves survival. [2-5,8] The seminal clinical trial of surveillance in China, conducted by Zhang et al. (2004), found a 37% reduction in HCC mortality associated with surveillance every 6 months with US and AFP. [9] Among patients diagnosed with HCC, surveillance was associated with a significant survival benefit ($p<0.01$); 5-year survival among patients who received surveillance was 46.4% compared with 0% in the no surveillance group. In comparison with these results, 5-year survival following HCC development in the current study was similar among individuals who received surveillance using a 6-month interval (45.4-51.8%), but was substantially higher in the no surveillance group (26.9-29.3%). In interpreting these survival differences, it is important to note that HCC treatment approaches have evolved substantially since Zhang et al. conducted the trial in 1993-1998. In particular, local ablation has emerged as a less invasive alternative to resection for individuals with early stage tumors. [2,71] With advancements in surgical techniques, a larger number of multinodular tumors are now considered resectable, with 3-year survival reaching as high as 56%. [61-63] Further advancements in curative treatment options for HCC will likely increase the survival advantages associated with HCC surveillance.

An important limitation to the trial conducted by Zhang et al., as well as other studies assessing the impact of surveillance, is the potential for lead time bias. [9] This bias may occur if surveillance merely detects the tumor at an earlier stage without affecting the course of disease, leading in an overestimation of survival gains with surveillance. [2] To address this limitation, observational studies have approximately adjusted for lead time by applying different assumptions surrounding estimated DT to the well-established formula for tumor growth (see **Chapter 5**). [10-13] The results of these studies suggest that surveillance significantly improves survival, even after lead time adjustment using a range in DT from 60 to 120 days. However, such methods are based solely on current knowledge surrounding HCC tumor growth. Tumor growth in HCC is highly heterogeneous across individuals, and other aspects of HCC progression, including the development of multinodular HCC, vascular invasion and tumor

metastases, are not fully understood. [14-27] In the current model, survival with HCC was defined from the time of HCC development, as opposed to diagnosis, to effectively remove lead time bias and also account for cases of HCC-related mortality prior to HCC diagnosis. Thus, the results of this model not only overcome controversies surrounding potential lead time bias, but also provide a more accurate portrayal of the true benefit of surveillance among the full population of HCC tumors.

Further advantages of this simulation model include the detailed representation of tumor growth in HCC, based on evidence synthesized across published tumor growth studies. [14-27] Whereas prior decision models of HCC surveillance have made simplifying assumptions surrounding tumor growth in HCC, [83-86] the current model sought to expand the representation of disease progression in HCC by incorporating individual-level heterogeneity in tumor growth and disease-related complications through model calibration. The model-based projections were generally concordant with trends in the distribution of tumor characteristics seen in clinical practice in China (see **Chapter 3**); [45] nevertheless, several assumptions were incorporated to simplify the calibration process. Thus, further research on the biological mechanisms surrounding HCC progression, if feasible, would help test and inform the model-based assumptions. Likewise, additional large-scale datasets of patients diagnosed with HCC are needed to cross-validate the model-based outcomes.

In interpreting the results of this study, it is important to note that survival outcomes incorporated in the model were based on data from HCC patients diagnosed and treated at large tertiary hospitals in China. Thus, the results may represent a more ideal scenario in which patients were routinely provided appropriate care. Physician's level of experience in staging and treating HCC patients can have a profound impact on survival outcomes. [46,137] An earlier trial conducted in China noted that screening with AFP led to earlier diagnosis, but did not result in an overall reduction in mortality largely due to ineffective treatment. [46] Community-based screening projects conducted in Taiwan have suggested that two-stage screening programs consisting of AFP followed by US among suspected cases

of HCC is economically feasible with a large proportion of HCC cases detected in the early disease stage.[7,138-140] On the other hand, the lack of a suitable comparator group has limited survival comparisons to establish the survival impact of surveillance in this setting.[7]

Lastly, the current model was designed to assess survival among individuals who develop HCC as a result of chronic HBV infection, the most common etiology of HCC disease in China, representing over 80% of all HCC cases (see **Chapter 3**).[45] Further research is needed to understand the impact of surveillance among the population of HCC patients with other underlying risk factors, including chronic HCV infection and alcohol liver disease, which generally present with more advanced liver disease (CP B/C: 30-49%).[10,28,30,77] Advanced liver disease has been found to reduce the survival benefit associated with surveillance, as these patients are generally not optimal candidates for surgical resection and experience higher mortality from liver-disease related complications.[11]

In conclusion, the results of this simulation model of HCC development among individuals with chronic HBV in China reveal that surveillance using abdominal US and AFP is associated with earlier disease detection, increased use of curative treatment, and improved survival. Based on current knowledge surrounding HCC tumor progression, HCC surveillance conducted using a 12-month interval is associated with similar survival benefits, as compared with surveillance conducted every 6 months. Therefore, surveillance using a 12-month interval among individuals with chronic HBV infection can be more easily implemented with little impact on the survival of patients who develop HCC. Additional large-scale studies are needed to establish whether survival gains associated with surveillance withstand differences in the underlying etiology of HCC disease and access to effective HCC treatments in China

Table 4.1: Model parameters incorporated in the simulation model to project the natural history of chronic HBV disease and sensitivity of diagnostic imaging for surveillance.

		Probabilistic Sensitivity Analyses		
Model Inputs	**Base Case**	**Distribution**	**Parameters**	**Sources**
Demographics				
Gender Distribution (% Male)	61.9	Beta	α = 2,260, β = 1,393	Chen et al., 2006 [36]
Age Distribution (years) *				
30-39	33.3	Dirichlet	α List = (1,216, 1,014, 1,058, 365)	Chen et al., 2006 [36]
40-49	27.7			
50-59	29.0			
60-79	10.0			
Cirrhosis Incidence **				
Annual Rate – Comp. Cirrhosis				
Male	0.70	Beta	α = 89, β = 12,625	Yu et al., 1997; [106] Iloeje et al., 2006 [37]
RR Male vs. Female	2.5	Log-Normal	Normal Mean = 0.9, SD = 0.1 †	Iloeje et al., 2006 [37]
Annual Rate – Decomp. Cirrhosis	1.5	Beta	α = 12, β = 788	Chen et al., 2007 [35]
HCC Incidence **				
Annual Rate in Chronic HBV				
Male	0.53	Beta	α = 135, β = 25,337	Chen et al., 2006 [36]
RR Male vs. Female	3.0	Log-Normal	Normal Mean = 1.1, SD = 0.2 †	Chen et al., 2006 [36]
Annual Rate in Cirrhosis	2.7	Beta	α = 21, β = 757	Chen et al., 2007 [35]
Mortality Rates				
Annual Mortality – Decomp. Cirrhosis				
≤ 1 year After First Decompensation	0.60 ‡	Beta	α = 75, β = 91 ‡	Jiang et al., 2008; [110] Fattovich et al., 2002; [111] Tsai et al., 1988 [112]
> 1 year After First Decompensation	0.25 ‡	Beta	α = 7, β = 26 ‡	Fattovich et al., 2002; [111] Tsai et al., 1988 [112]
Mortality UnDxed Advanced HCC	Survival Curves Adjusted for Gender, Age & Tumor Stage			HCC BRIDGE Study ¶

Annual All-Cause Mortality in China		Gender & Age Adjusted		World Health Organization, 2011 [107]
Sensitivity of Diagnostic Imaging				
Abdominal US				
<2 cm	0.21	Beta	α = 33, β = 86 §	Di Martino et al., 2013; [88] Yu et al., 2011; [89] Snowberger et al., 2007 [90]
2-4 cm	0.62	Beta	α = 44, β = 27	Yu et al., 2011 [89]
>4 cm	0.85	Beta	α = 28, β = 5	Yu et al., 2011 [89]
AFP ≥ 200 ng/mL	0.20	Beta	α = 30, β = 85 §	Sterling et al., 2009; [129] Arrieta et al., 2007; [130] Nguyen et al., 2002; [131] Trevisani et al., 2001; [132] Cedrone et al., 2000 [133]
CT/MRI	0.91	Beta	α = 85, β = 4 §	Yu et al., 2011 [89]

AFP = alpha-fetoprotein, Comp. = compensated, Decomp. = decompensated, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCC BRIDGE = BRIDGE to Better Outcomes in Hepatocellular Carcinoma Study, RR = risk ratio, SD = standard deviation, UnDxed = undiagnosed, US = ultrasound

* Within each age category, age was randomly assigned using a uniform distribution.

** Annual rates are per 100 person/years.

† Parameters were estimated using the 95% confidence intervals for the RR estimates: Annual Rate Compensated Cirrhosis, RR = 2.5 (1.9-3.3); Annual Rate HCC in Chronic HBV, RR = 3.0 (2.0-4.5).

‡ Annual mortality rates were estimated using the reported 1-year (0.55) [110] and 5-year (0.28) [111] survival probabilities, assuming a standard constant hazard of death within each time interval. [40]

¶ The hazard of death among individuals with undiagnosed advanced HCC was assumed to be the same as for patients diagnosed with advanced HCC who received supportive care, and was projected using parametric survival curves fitted to the HCC BRIDGE Study data.

§ The distribution surrounding the sensitivity of diagnostic imaging was derived using the method of moments fitting for the beta distribution with parameters approximated using the mean and range across studies: US for size < 2cm = 21%-35%; AFP ≥ 200 ng/mL = 20-36%; CT/MRI = 91-100%. [40]

Table 4.2: Frequency of primary treatment approaches for patients diagnosed with HCC, according to tumor characteristics and liver function, incorporated in the simulation model: results from the HCC BRIDGE study in China, (n=4,797).

	Very Early/Early†			Intermediate/ Solitary†		Intermediate/ Multinodular†		Advanced‡		Terminal
Treatments, n (%)*	**1 tumor, ≤2 cm (n=226)**	**1 tumor, 3-5 cm (n=931)**	**2-3 tumors, ≤ 3 cm (n=111)**	**1 tumor, 6-9 cm (n=871)**	**1 tumor, ≥ 10 cm (n=525)**	**2-3 tumors, > 3 cm (n=319)**	**≥ 4 tumors (n=292)**	**VI (n=724)**	**TM (n=755)**	**CP C (n=43)**
Resection **	112 (49)	571 (61)	33 (30)	476 (55)	140 (27)	119 (37)	64 (22)	128 (18)	133 (18)	–
Ablation **	63 (28)	142 (15)	26 (23)	43 (5)	9 (2)	22 (7)	26 (9)	48 (6)	43 (6)	–
TA Therapy	51 (23)	218 (23)	52 (47)	334 (38)	343 (65)	168 (53)	180 (62)	514 (71)	538 (71)	15 (35)
Supportive Care	–	–	–	18 (2)	33 (6)	10 (3)	22 (7)	34 (5)	41 (5)	28 (65)

CP = Child-Pugh, HCC = hepatocellular carcinoma, HCC BRIDGE = BRIDGE to Better Outcomes in Hepatocellular Carcinoma Study TA = trans-arterial therapy, TM = tumor metastases, VI = vascular invasion

* The frequency of other primary treatments, including liver transplant (n=38, 0.8%), systemic therapy (n=59, 1.2%),and radiotherapy/other loco-regional therapy (n=74, 1.5%), were not incorporated in the decision model, as these treatments were rarely provided.

** Includes patients who received trans-arterial therapy within 6 months prior to resection or ablation.

– Frequency of primary treatment was insufficient to warrant inclusion (all <2%).

† Patients in these categories have compensated cirrhosis (CP A/B), no venous invasion and no tumor metastases.

‡ Patients in these categories have compensated cirrhosis (CP A/B).

Table 4.3: Distribution of tumor characteristics among HCC patients who did not undergo surveillance incorporated in the model calibration: results from the HCC BRIDGE study in China (n=3,288).

	Number of Tumor Nodules, n (%)		
Tumor Size & Spread	1 tumor (n = 2,340)	2 - 3 tumors (n = 439)	≥ 4 tumors (n = 419)
≤ 5 cm (n = 1,239)			
No VI/TM	837 (25.46)	156 (4.74)	78 (2.37)
VI*	54 (1.64)	11 (0.33)	9 (0.27)
TM	28 (0.85)	33 (1.00)	33 (1.00)
> 5 & < 10 cm (n = 1,177)			
No VI/TM	581 (17.67)	88 (2.68)	70 (2.13)
VI*	147 (4.47)	30 (0.91)	34 (1.03)
TM	112 (3.41)	49 (1.49)	66 (2.01)
≥ 10 cm (n = 872)			
No VI/TM	341 (10.37)	28 (0.85)	49 (1.49)
VI*	205 (6.23)	20 (0.61)	39 (1.19)
TM	125 (3.80)	24 (0.73)	41 (1.25)

HCC = hepatocellular carcinoma, HCC BRIDGE = BRIDGE to Better Outcomes in Hepatocellular Carcinoma Study, TM = tumor metastases, VI = vascular invasion

* Includes patients with vascular invasion, but without tumor metastases.

Table 4.4: Distribution of tumor characteristics among HCC patients who did not undergo surveillance: results from the HCC BRIDGE study in China compared with model output after calibration.†

	Number of Tumor Nodules					
Tumor Size & Spread	1 tumor	% Point Difference	2-3 tumors	% Point Difference	≥ 4 tumors	% Point Difference
≤ 5 cm						
No VI/TM	25.46 (29.28)	3.82	4.74 (3.24)	-1.5	2.37 (0.45)	-1.92
VI*	1.64 (2.26)	0.62	0.33 (0.46)	0.13	0.27 (0.07)	-0.2
TM	0.85 (1.07)	0.22	1.00 (0.14)	-0.86	1.00 (0.01)	-0.99
> 5 & < 10 cm						
No VI/TM	17.67 (17.02)	-0.65	2.68 (4.63)	1.95	2.13 (1.1)	-1.03
VI*	4.47 (5.66)	1.19	0.91 (1.47)	0.56	1.03 (0.43)	-0.6
TM	3.41 (3.65)	0.24	1.49 (1.25)	-0.24	2.01 (0.23)	-1.78
≥ 10 cm						
No VI/TM	10.37 (6.4)	-3.97	0.85 (2.32)	1.47	1.49 (0.88)	-0.61
VI*	6.23 (4.48)	-1.75	0.61 (1.76)	1.15	1.19 (0.92)	-0.27
TM	3.80 (6.12)	2.32	0.73 (2.42)	1.69	1.25 (2.26)	1.01

HCC = hepatocellular carcinoma, HCC BRIDGE = BRIDGE to Better Outcomes in Hepatocellular Carcinoma Study, TM = tumor metastases, VI = vascular invasion

* Includes patients with vascular invasion, but without tumor metastases.

† Note: Data represent the percentages of patients with each tumor characteristic: % HCC BRIDGE Data (% Model Output). Model output was pooled across a series of 10 replications, based on the minimum number of replications needed per iteration for the 95% CI of the least squares value to be reached with 0.5% error.

Table 4.5: Model estimated rates of HCC disease progression and incidental/symptomatic diagnosis: results of model calibration.

Model Parameter	Calibrated Results
HCC Disease Progression Rates (annual) *	
Rate Additional Tumor	
For Primary tumor: ≤ 5 cm	
1 tumor present	0.12
2 tumors present	0.37
≥ 3 tumors present	0.66
For Primary tumor: > 5 cm, ≤ 10 cm	
1 tumor present	0.027
2 tumors present	0.33
≥ 3 tumors present	0.45
For Primary tumor: > 10 cm	
1 tumor present	0.14
2 tumors present	0.56
≥ 3 tumors present	0.63
Rate of VI development	
Primary tumor: ≤ 5 cm	0.17
Primary tumor: > 5 cm, ≤ 10 cm	0.43
Primary tumor: > 10 cm	0.38
Rate of TM development	
Primary tumor: ≤ 5 cm	0.058
Primary tumor: > 5 cm, ≤ 10 cm	0.34
Primary tumor: > 10 cm	0.38
Incidental/Symptomatic Diagnosis Rate (annual) *	
Primary tumor: ≤ 5 cm	0.091
Primary tumor: > 5 cm, ≤ 10 cm	0.48
Primary tumor: > 10 cm	0.44

HCC = hepatocellular carcinoma, TM = tumor metastases, VI = vascular invasion

* Rates were calibrated to produce model outputs optimized to reflect the distribution of tumor characteristics among individuals who did not participate in surveillance found in the HCC BRIDGE study.

Table 4.6: Comparison of model outcomes across surveillance strategies for the detection of hepatocellular carcinoma among individuals with chronic HBV infection.

	Surveillance Strategy			p-value **		
Model Outcome	**No Surveillance**	**6 mo. US + AFP**	**12 mo. US + AFP**	**No Surv. vs. 6 mo.**	**No Surv. vs. 12 mo.**	**6 mo. vs. 12 mo.**
Median Survival, years †	3.26	4.60	4.11	<.0001	<.0001	<.0001
1-year, %	86.55	87.31	87.19			
3-year, %	54.94	62.87	60.36			
5-year, %	28.92	48.13	44.24			
10-year, %	13.45	30.12	27.04			
20-year, %	6.46	13.79	12.62			
Disease Stage at Dx, %				<.0001	<.0001	<.0001
Very Early/Early	29.7	84.6	73.8			
Intermediate - Solitary	24.4	1.8	6.0			
Intermediate - Multinodular	10.6	2.2	5.2			
Advanced	34.2	10.3	13.9			
Terminal	1.1	1.1	1.1			
Primary Treatment, %				<.0001	<.0001	<.0001
Resection	36.4	47.5	46.2			
Ablation	10.9	21.1	18.5			
Trans-arterial Therapy	49.1	29.9	33.6			
Supportive Care	3.6	1.5	1.7			
No. Surv. Tests per HCC Case	–	399	218	–	–	–

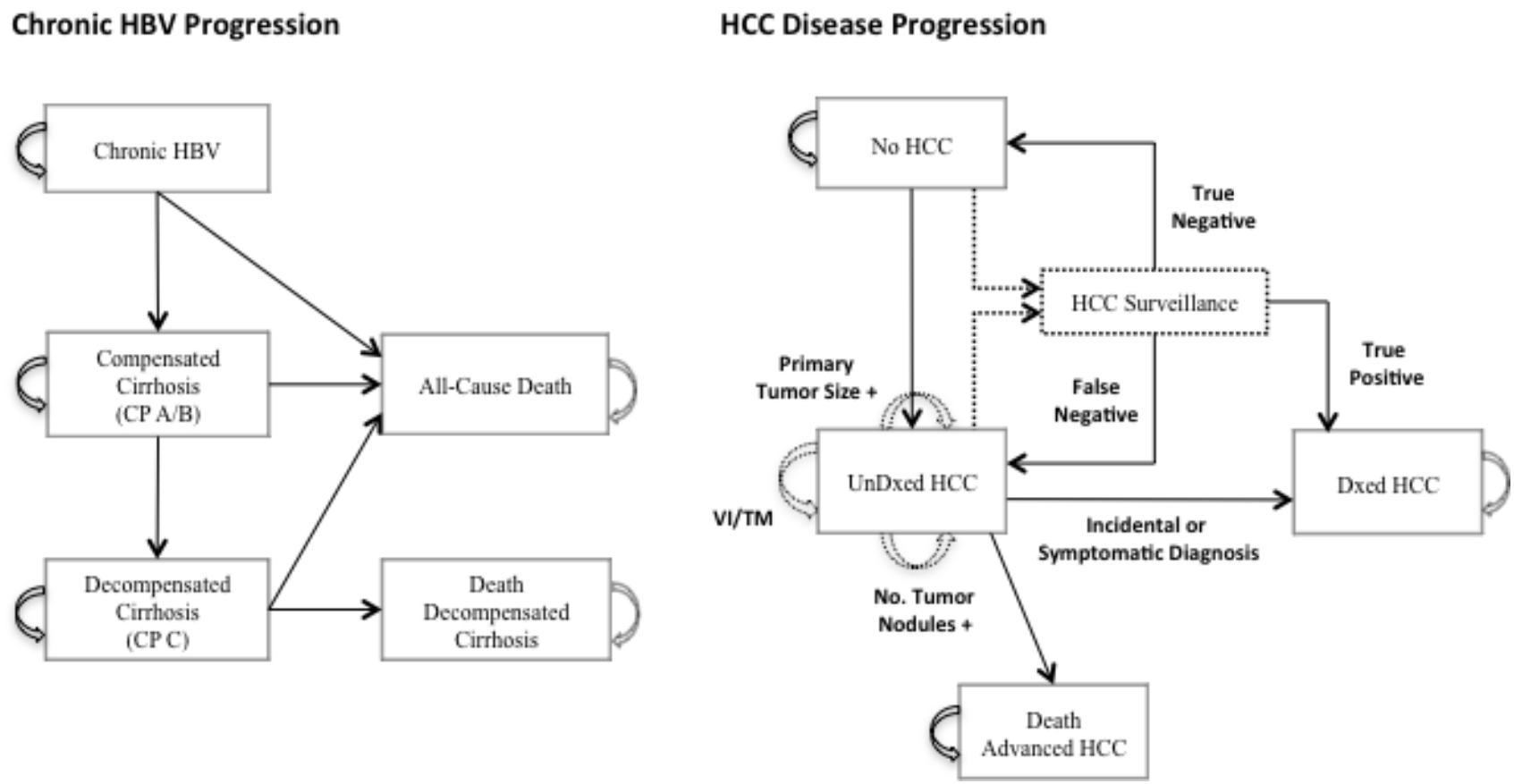
alpha-fetoprotein = AFP, Dx = diagnosis, HCC = hepatocellular carcinoma, HR = hazard ratio, mo. = month, No. = number, Surv. = surveillance, US = ultrasound

* Represents the base case model outcomes pooled across a series of 30 replications, based on the maximum number of replications needed for the 95% CI of the mean survival estimate across all surveillance strategies to be reached with 0.5% error.

** Statistical differences were assessed using the Chi^2 test for categorical model outcomes, and differences in overall survival were assessed using the log-rank test.

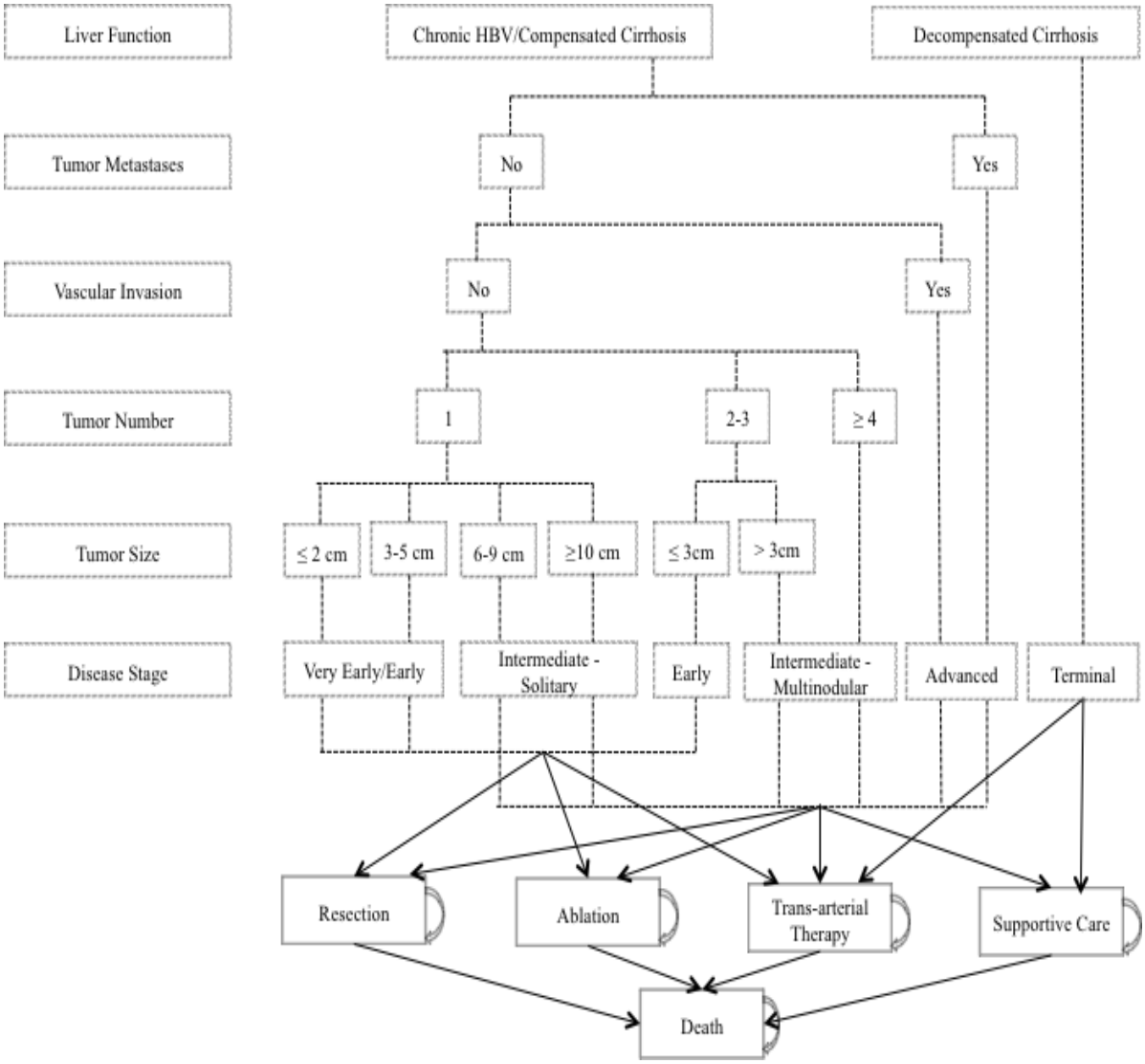
† For individuals who develop HCC, survival was measured from time of HCC development until death.

Figure 4.1: Model health states for the chronic HBV and HCC disease progression components of the simulation model.



CP = Child-Pugh status, Dxed = diagnosed, TM = tumor metastases, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, No. = number, UnDxed = undiagnosed, VI = vascular invasion

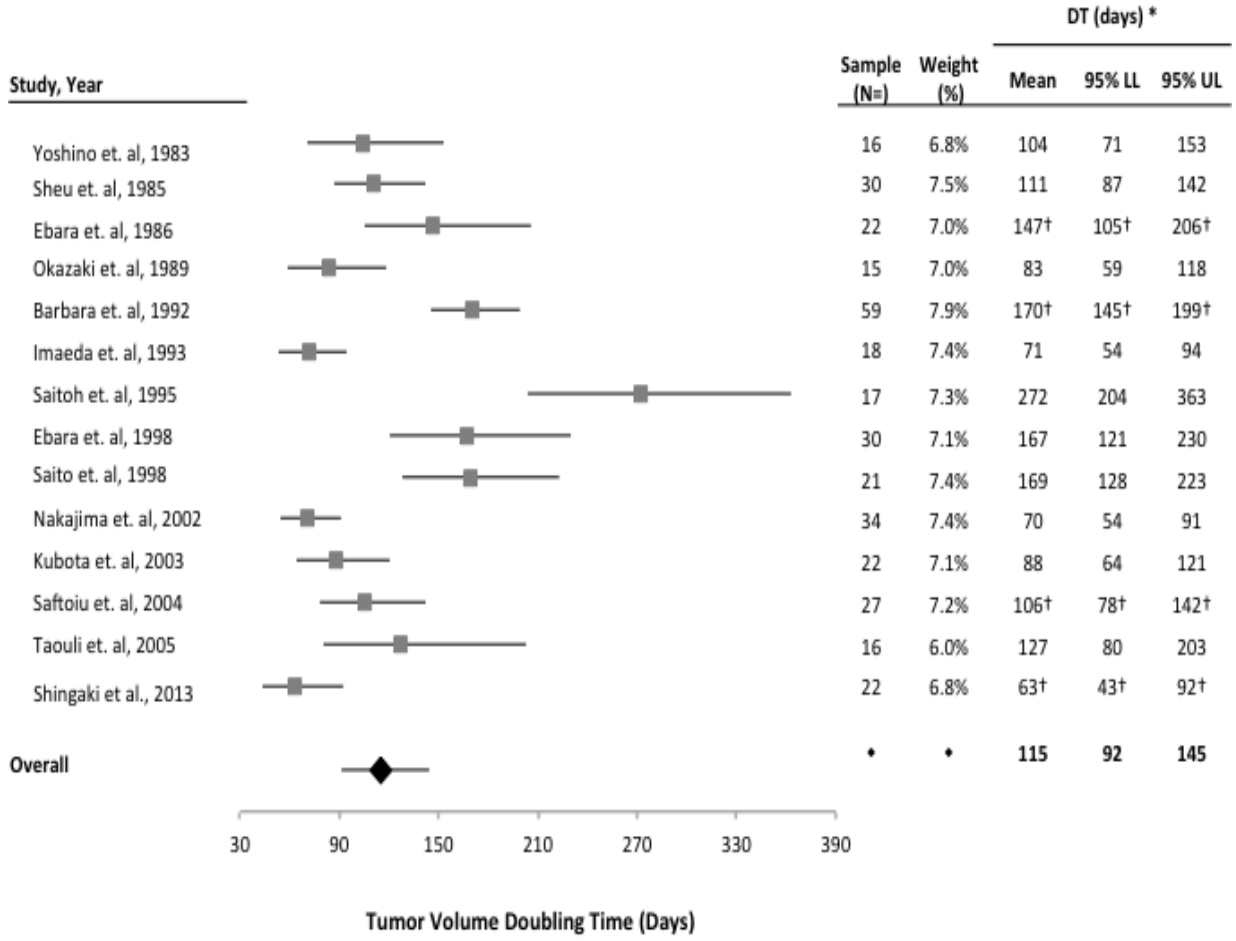
Figure 4.2: Model health states and transition logic for the HCC treatment component of the simulation model.



HBV = hepatitis B virus, HCC = hepatocellular carcinoma

Note: Solid rectangles represent health states, whereas dotted rectangles indicate model transition logic.

Figure 4.3: Results of the pooled random effects meta-analysis for tumor volume doubling time (DT) conducted among studies that assessed tumor growth in HCC.



DT = tumor volume doubling time, HCC = hepatocellular carcinoma, 95% LL = 95% confidence interval lower limit, 95% UL = 95% confidence interval upper limit

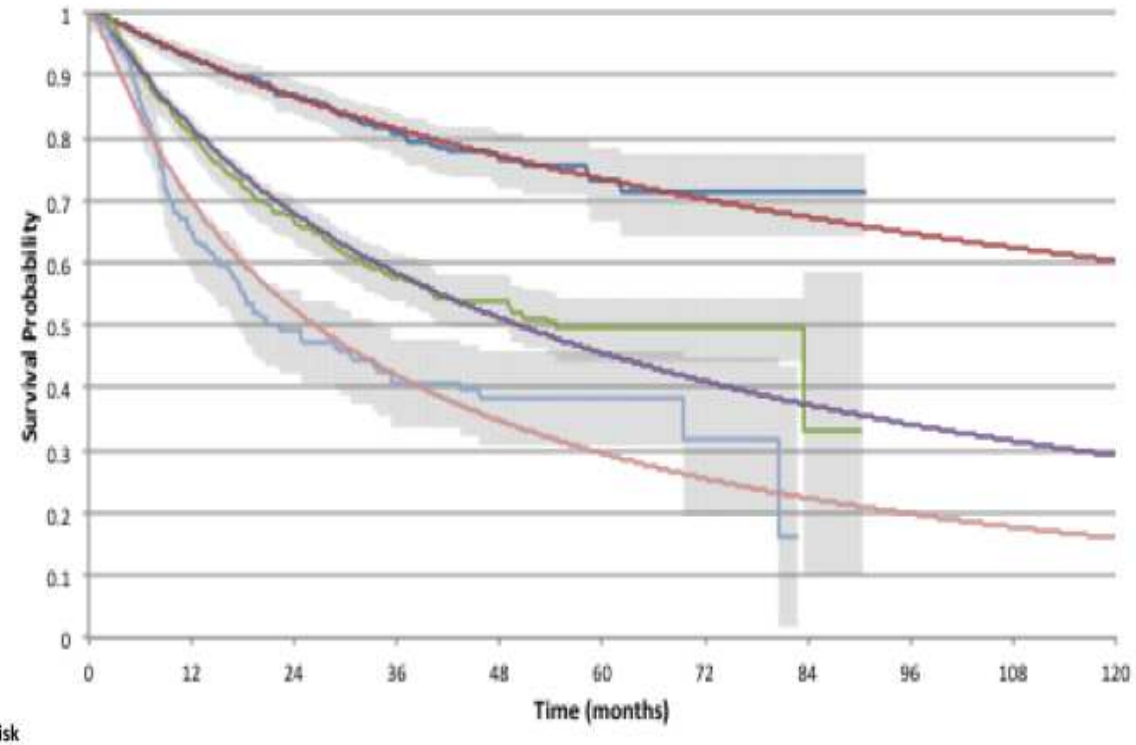
Random Effects Model Statistics: Q = 124.48, p = <0.0001, Tau^2 = 0.17

* Represents the geometric mean and 95% confidence interval for tumor volume doubling time.

† Geometric mean and standard deviation were approximated using the arithmetic mean and standard deviation, using previously validated methods. [125]

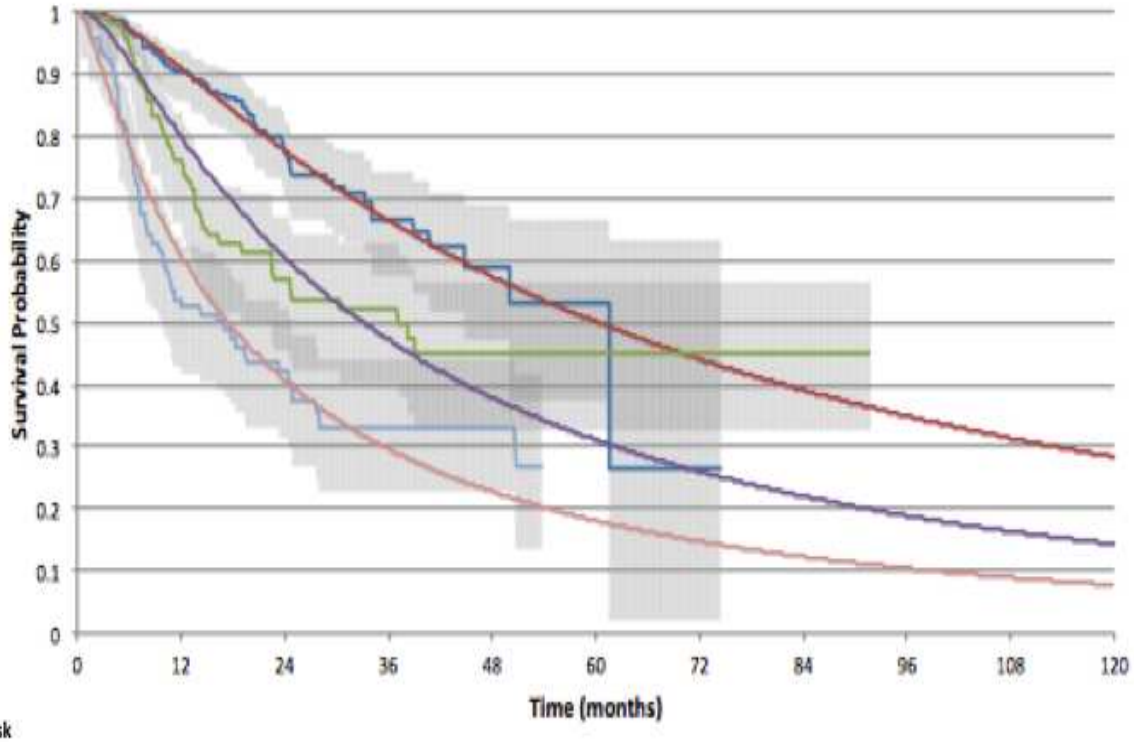
Figure 4.4: Graphical assessment of model fit for the unadjusted parametric survival curves[†] in comparison with the life-table survival curve estimates for each primary HCC treatment and disease stage: results from the HCC BRIDGE study in China (n=4,797). A) Resection, B) Ablation, C) Trans-arterial Therapy, D) Supportive Care and Terminal Disease Stage.

A



No. At Risk								
Very Early/Early	716	561	393	244	113	50	30	6
Intermediate	799	577	377	217	91	39	18	2
Advanced	261	146	82	45	24	11	4	

B

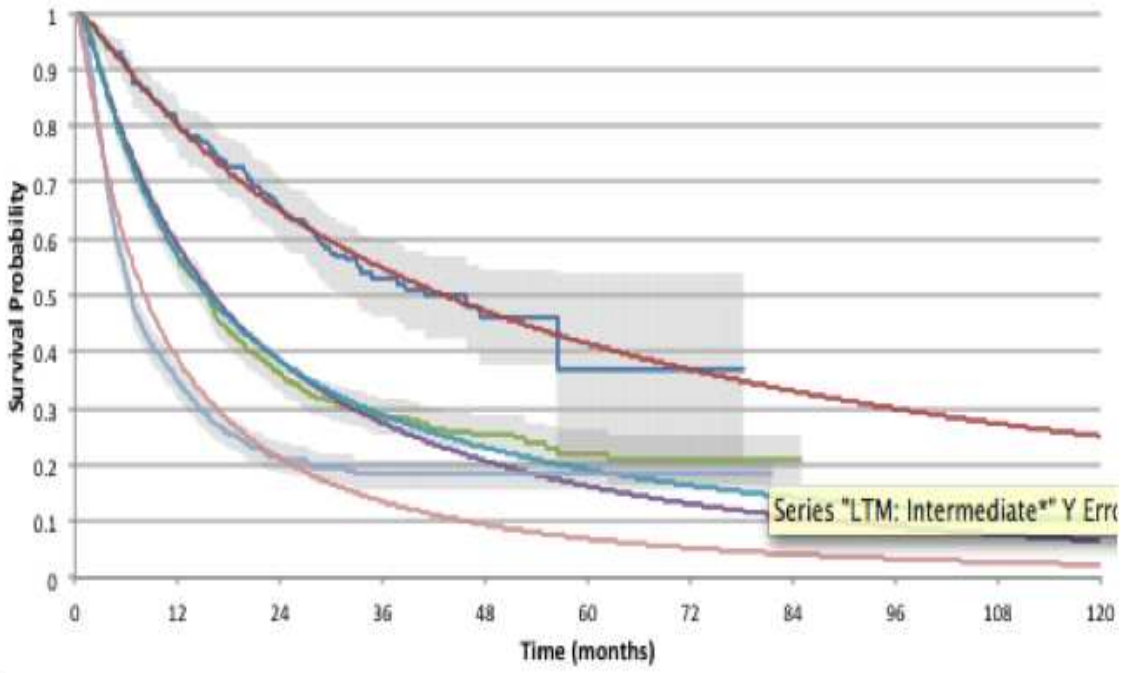


No. At Risk

Very Early/Early	231	178	105	40	11	2	1	
Intermediate	100	64	37	25	7	1	1	1
Advanced	91	45	27	10	6			

LTM: Very Early/Early
LN: Very Early/Early
LTM: Intermediate*
LN: Intermediate*
LTM: Advanced
LN: Advanced

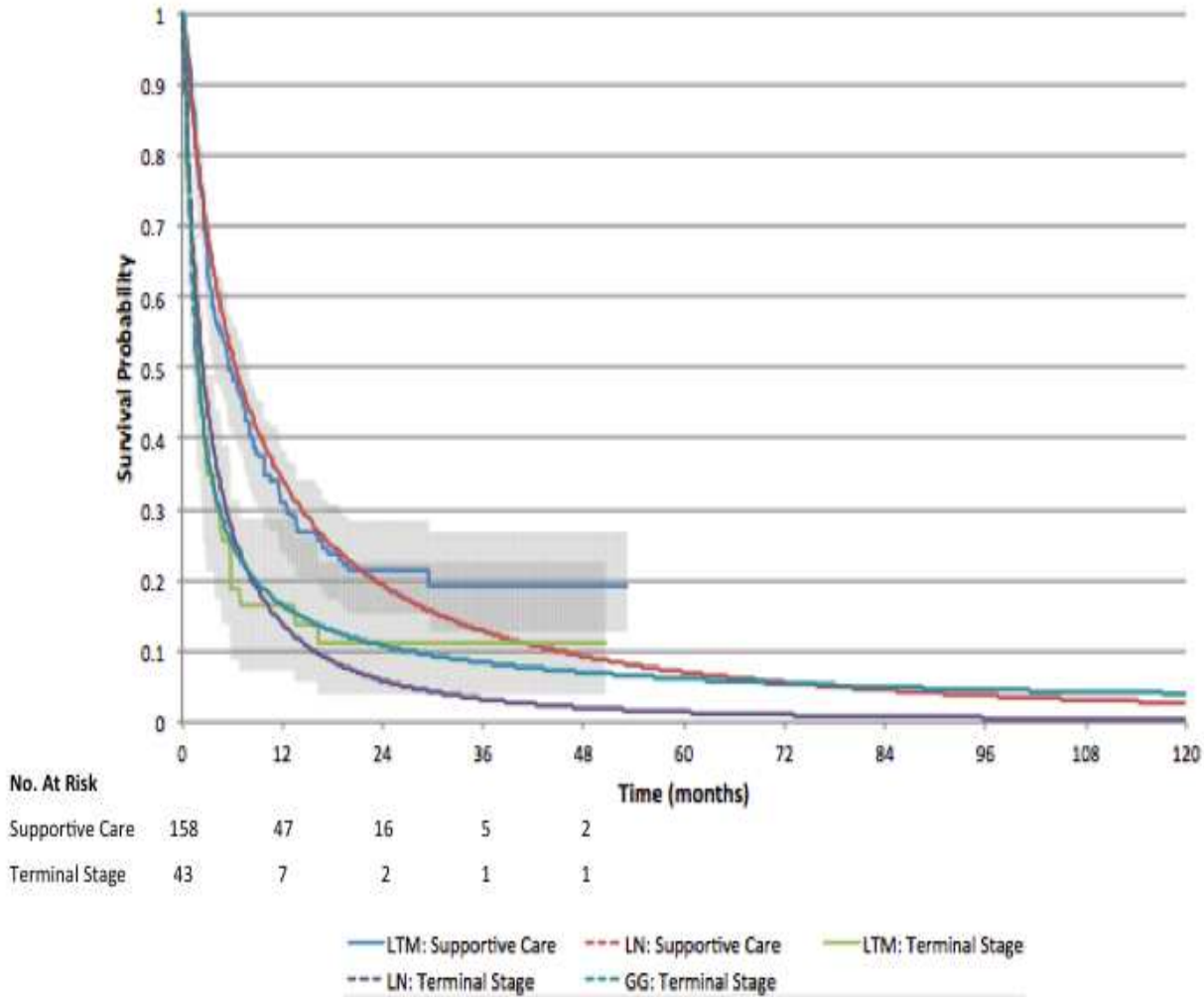
C



No. At Risk

Very Early/Early	321	233	143	60	23	2	1	
Intermediate	1,025	522	247	126	64	20	8	1
Advanced	1,052	312	132	62	23	10	7	

D



GG = generalized gamma model, HCC = hepatocellular carcinoma, HCC BRIDGE = BRIDGE to Better Outcomes in Hepatocellular Carcinoma Study, LTM = life-table method, LN = log-normal model

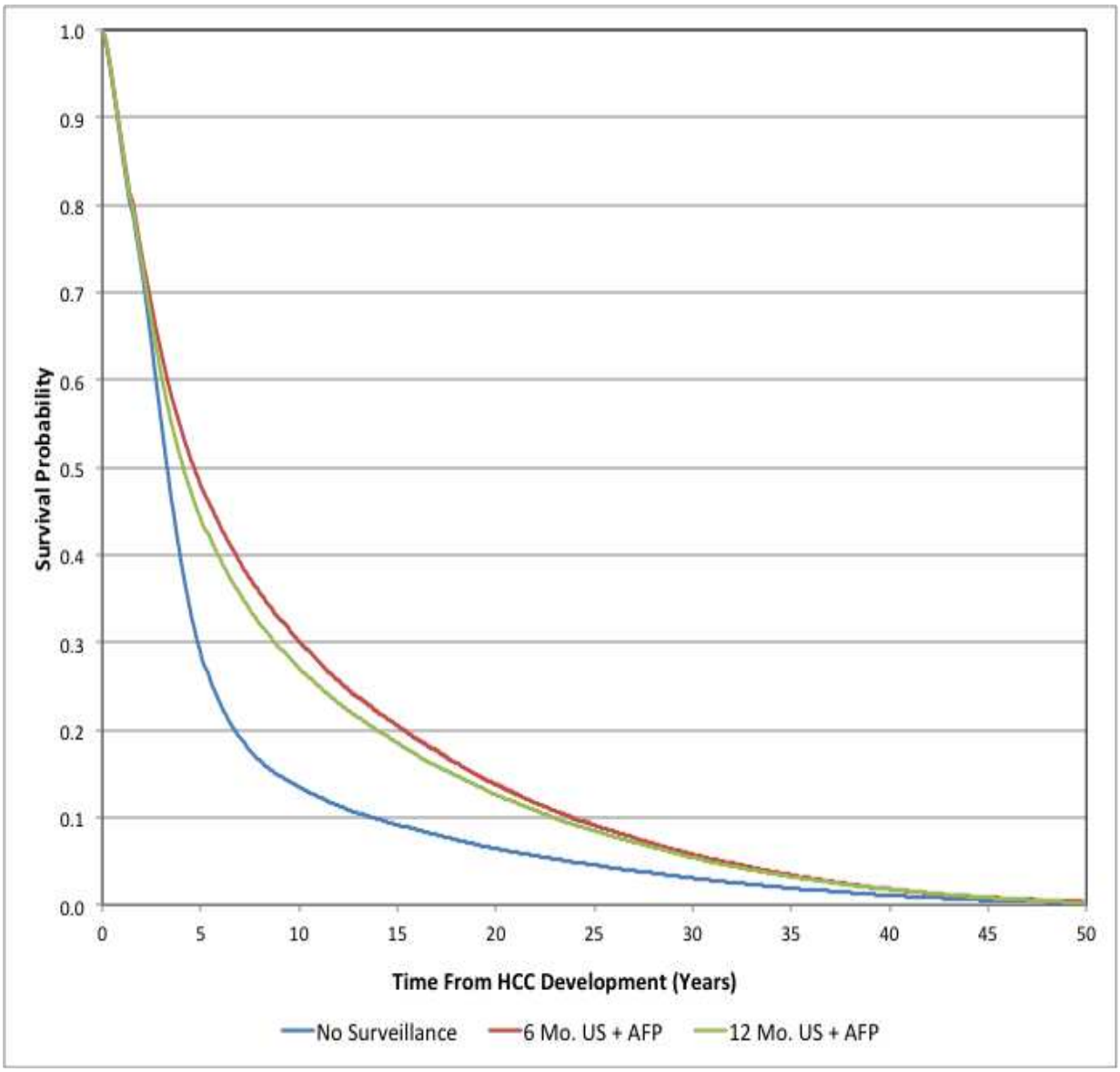
NOTE: Grey areas represent the 95% confidence intervals using the log-log transformation of the survival function estimated using the life-table method. [31]

* Intermediate stage HCC with solitary (> 5cm) or multi-nodular tumors (2-3 tumors, > 3 cm or ≥ 4 tumors). [3]

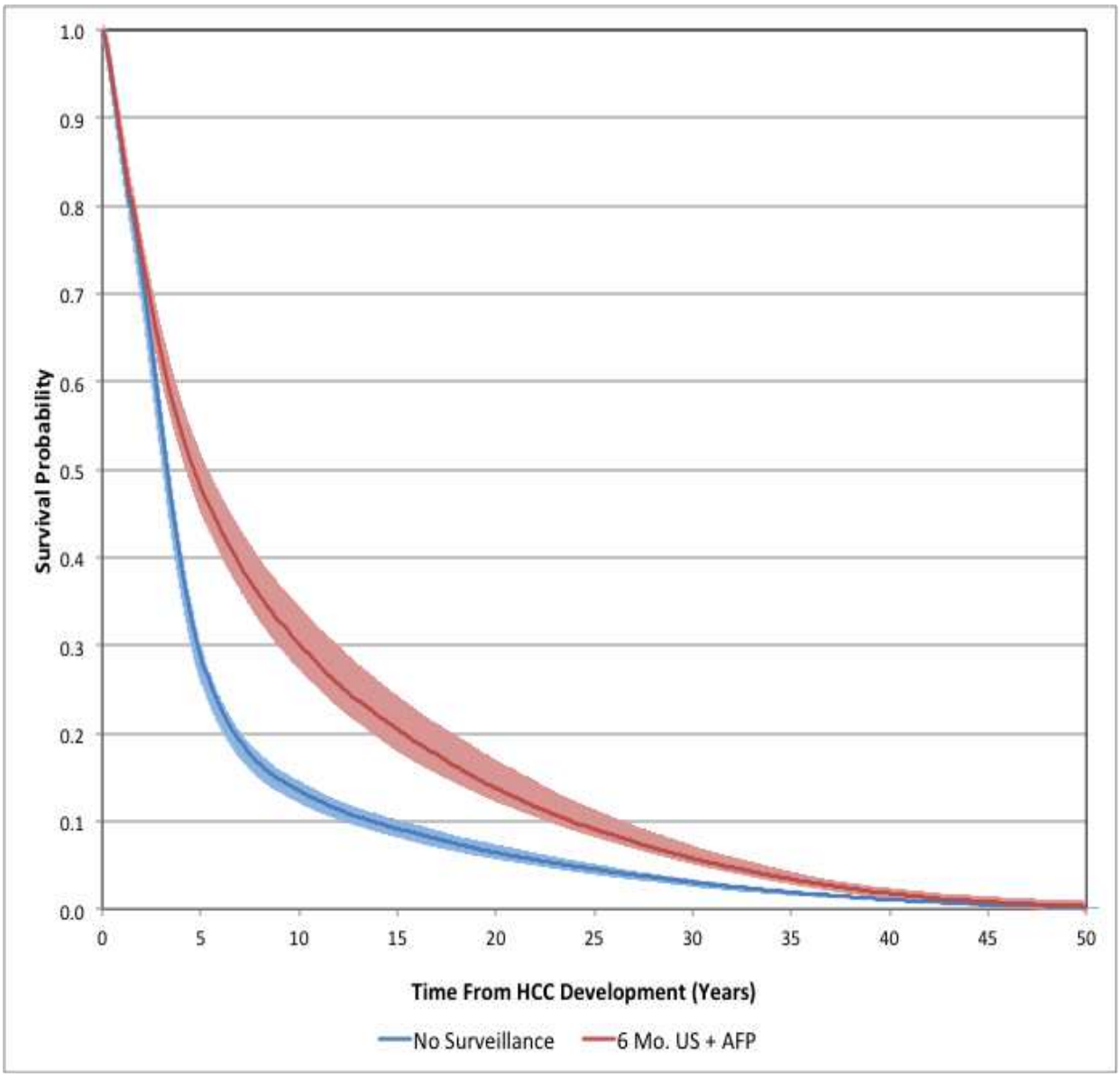
† Based on results of the Akaike Information Criteria (AIC) and likelihood ratio tests, the Log-normal model generally provided the best fit to the HCC BRIDGE data. [31,135] As exceptions, gamma models provided the best fit for terminal stage patients as well as for intermediate stage patients receiving trans-arterial therapy. Despite these results, the unadjusted gamma survival curves were qualitatively similar to the log-normal model. Log-normal models were ultimately chosen across all treatment and disease stage models to maintain consistency in the assumptions surrounding the hazard of death across models.

Figure 4.5: Comparison of model-projected overall survival across surveillance strategies among individuals who developed HCC, analyzed using the Life-Table method. A) Base Case Analyses, and Probabilistic Sensitivity Analyses: B) No Surveillance vs. 6-Month US + AFP, C) No Surveillance vs. 12-Month US + AFP, and D) 6-Month US + AFP vs. 12-Month US + AFP.

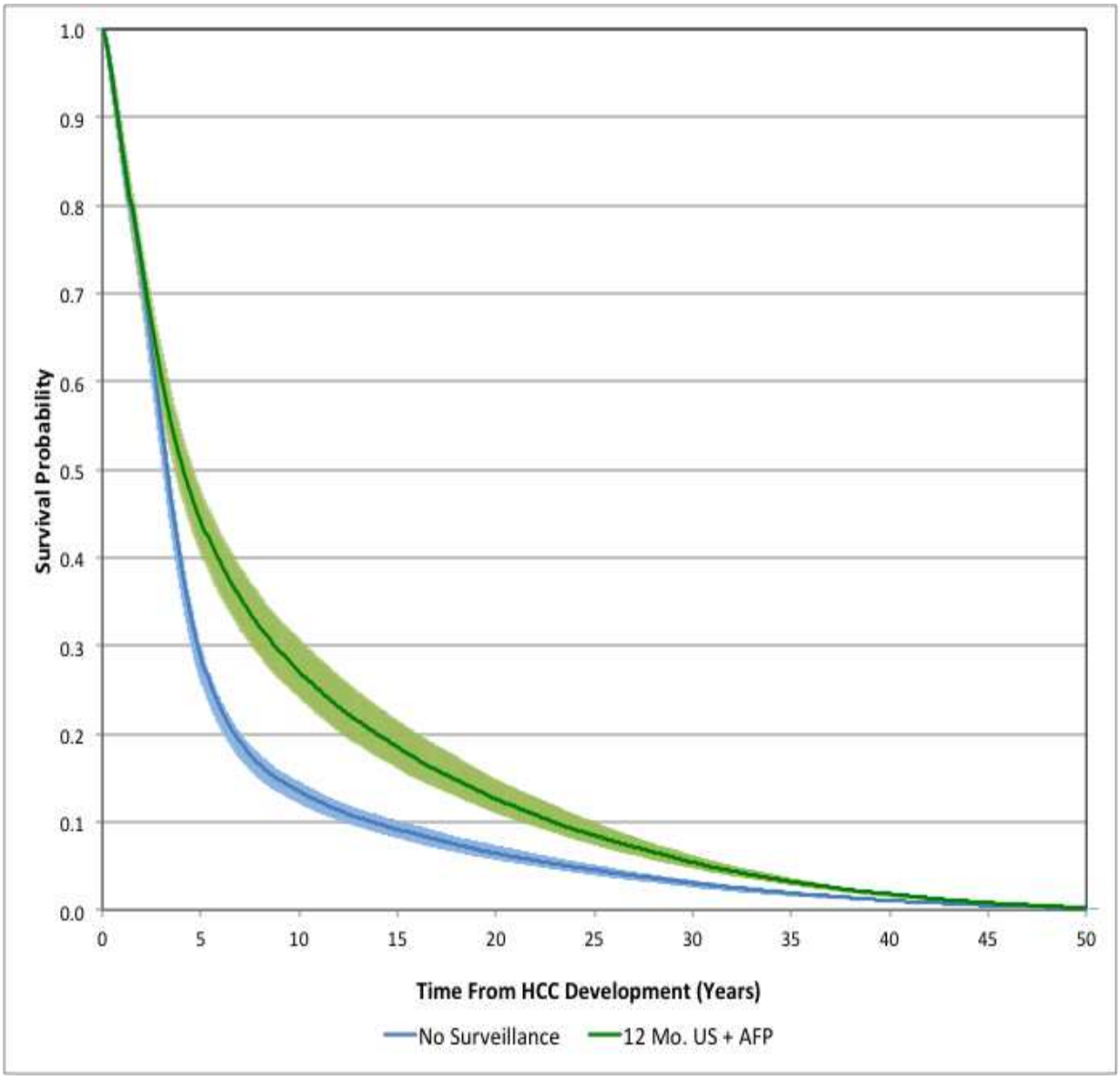
A



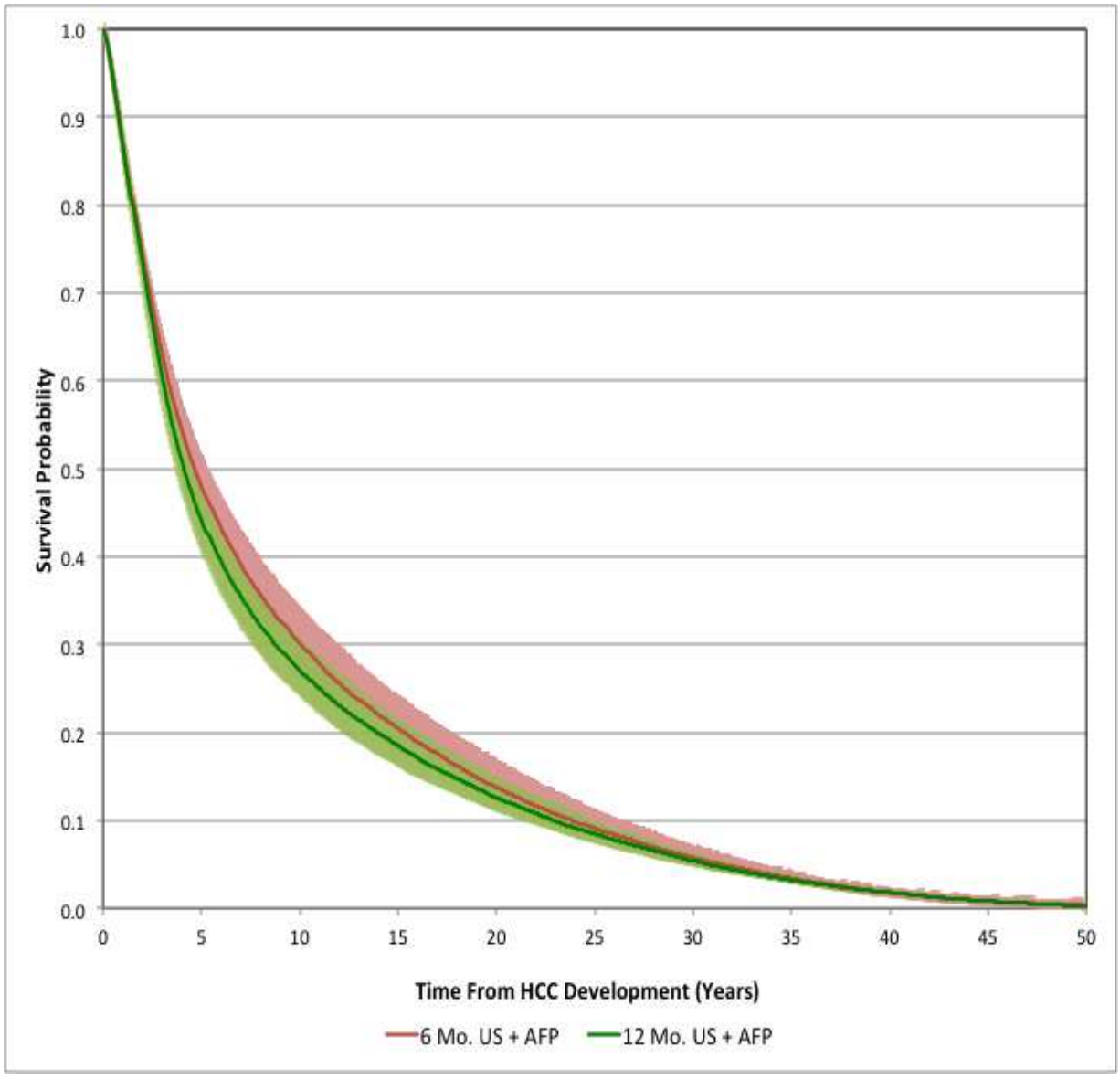
B


1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Survival Probability
0
5
10
15
20
25
30
35
40
45
50
Time From HCC Development (Years)
No Surveillance
6 Mo. US + AFP

C


1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Survival Probability
0
5
10
15
20
25
30
35
40
45
50
Time From HCC Development (Years)
No Surveillance
12 Mo. US + AFP

D



alpha-fetoprotein = AFP, HCC = hepatocellular carcinoma, US = ultrasound

* Note: Shaded areas represent the range in survival estimates across the 100 iterations used in probabilistic sensitivity analyses. For each iteration, survival outcomes were pooled across a series of 30 replications, based on the maximum number of replications needed per iteration for the 95% CI of the mean survival estimate, across all surveillance strategies, to be reached with 0.5% error.

CHAPTER 5: IMPACT OF SURVEILLANCE ON THE SURVIVAL OF PATIENTS WITH HEPATOCELLULAR CARCINOMA: RESULTS FROM A LONGITUDINAL STUDY IN TAIWAN

Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide. [103] HCC is highly prevalent in East Asia, where hepatitis B virus (HBV) infection is endemic and is the primary etiological risk-factor for HCC. [1] In Taiwan, HCC is the leading cause of cancer-related death among males and the second among females, with age-adjusted mortality rates of 40.8 and 14.1 per 100,000 persons, respectively. [49] Resection and tumor ablation are the main curative treatment options for HCC, but eligibility to receive curative therapy diminishes with more advanced disease. [2] Whereas survival with HCC in Taiwan is generally poor (5-year survival 16.2%), 5-year survival for patients diagnosed at an earlier stage who receive curative therapy can exceed 50%. [43,44]

To improve the early detection of HCC, the Taiwanese Department of Health has funded community-based surveillance since 1991 to identify and monitor individuals at high-risk for HCC, as part of the Taiwan Community-Based Cancer Screening project. [6,7] HCC surveillance currently is recommended every 6 months among individuals with cirrhosis related to chronic HBV or hepatitis C virus (HCV) infection. [2] Recommended screening tests include abdominal ultrasound (US) and measurement of serum alpha-fetoprotein (AFP), with a cut-point of ≥200 ng/mL.

Although HCC surveillance is widely recommended, few studies have provided direct evidence that surveillance improves survival. [2,4,5,8] A randomized control trial conducted among 18,816 participants with chronic HBV infection in China found that surveillance every 6 months with US and AFP was associated with a 37% - reduction in 5-year mortality. [9] Despite demonstrating survival benefit, the trial had several limitations, including potential lead time bias related to the earlier diagnosis of HCC, a

relatively low number of HCC cases (n=153), and suboptimal adherence to the surveillance protocol (less than 60%). On one hand, the results likely underestimate the survival benefit from surveillance because of poor compliance; on the other hand, potential lead time bias could have resulted in an overestimation of survival with surveillance.

The objective of this study was to evaluate the impact of HCC surveillance in current clinical practice in Taiwan on the survival of patients diagnosed with HCC. To control for potential lead time bias, we explored different assumptions surrounding the estimated lead time, using a range in median tumor volume doubling time (DT) estimated across prior tumor growth studies (synthesized in **Chapter 4**). [14-27] Propensity score (PS) analysis was also conducted to address selection bias resulting from non-random allocation of HCC surveillance. As secondary outcomes, the study compared tumor characteristics and primary treatment approaches according to surveillance status.

Methods

Study Sample

The study sample was collected at the National Taiwan University Hospital in Taipei, Taiwan, as part of the Bridge to Better Outcomes in Hepatocellular Carcinoma (HCC BRIDGE) study, a retrospective cohort study of patients diagnosed with HCC across 14 countries in East Asia, Europe, and North America. [29,30] Inclusion criteria for the HCC BRIDGE study included patients age $\geq$ 18 years who were newly diagnosed with HCC from January 1, 2005 through June 30, 2011 and received active treatment for HCC. Patients with unknown date of HCC diagnosis and/or date of first visit or whose first HCC treatment was received via participation in a randomized clinical trial were excluded. For the present study, additional inclusion criteria included documented surveillance status prior to HCC diagnosis, complete patient characteristics and liver function information at diagnosis, and available follow-up information (**Figure 5.1**). All patients were followed until September 30, 2012 or date of death.

Data Collection

Data for the HCC BRIDGE study were systematically collected for all enrolled patients through a retrospective review of patient medical records. [29,30] Study data were entered into an electronic data capture system developed by Outcome Sciences, Inc. (Cambridge, MA, USA) and were subject to rigorous monthly data monitoring and cleaning. The institutional review boards from each participating hospital site approved the data collection for the HCC BRIDGE study. Data analyses for the present study were approved by The University of North Carolina Office of Human Research Ethics Institutional Review Board.

Surveillance status was collected prior to HCC diagnosis. The general surveillance protocol within the Department of Hepatology and Gastroenterology at the National Taiwan University Hospital included abdominal ultrasound and AFP examination every 6-12 months. Patients were considered to be diagnosed under HCC surveillance if imaging by abdominal ultrasound computed tomography and/or magnetic resonance imaging, with or without AFP, was repeated at regular intervals of 6-12 months and the most recent imaging study was documented within 12 months prior to HCC diagnosis. Patients with unknown surveillance status, due to unavailable clinical information prior to HCC diagnosis, were excluded from the study (**Figure 5.1**).

Clinical and laboratory assessments, including tumor characteristics and liver function information, were obtained for all patients. Tumor characteristics included tumor size (diameter in cm), number of nodules and tumor spread, defined as the presence of vascular invasion and/or tumor metastases. To measure liver function among individuals with cirrhosis, Child-Pugh (CP) scores were calculated. [2,55] In cases where patients had multiple clinical assessments over time, only assessments obtained within 6 months (182 days) before and after date of diagnosis were considered, and the closest date to diagnosis was used. Laboratory values were taken within 1 month (30 days) before to 6 months (182 days) after date of diagnosis, and the earliest available laboratory values were selected.

Available treatment approaches for HCC included: 1) surgical resection, 2) liver transplant, 3) ablation, 4) trans-arterial (TA) therapy, 5) systemic therapy, 6) supportive care, and 7) radiation/other locoregional therapy. The full list of therapies for each treatment approach are listed in **Appendix A**. The primary treatment approach was generally defined as the first recorded treatment, with certain exceptions. Supportive care is often administered to reduce symptoms immediately prior to and following primary therapy.[2,5] If patients received another therapy within one month (30 days) after supportive care, the other therapy was considered to be the primary treatment. In practice, TA therapy can be used to shrink the tumor(s) in preparation for surgical treatment.[2] The primary treatment approach was considered to be surgical treatment, rather than TA therapy, if patients underwent resection, liver transplant or tumor ablation within 6 months (182 days) after the first administration of TA therapy.

Additional patient demographic and clinical characteristics, including patient age, gender, etiology, and co-morbidities, were collected at time of diagnosis or first visit to the hospital site. Etiology of HCC included chronic HBV infection, chronic HCV infection, alcohol-related liver disease (ALD), non-alcoholic fatty liver disease (NAFLD), primary biliary cirrhosis, hemochromatosis, inherited metabolic disorder or idiopathic disease, based on documented evidence in the patient medical record. Relevant co-morbidities included diagnosed diabetes mellitus, cardiovascular disease (CVD), and hypertension.[95,96]

Data Analyses

Descriptive analyses compared patient demographics, clinical characteristics, tumor characteristics, and primary treatment approaches according to surveillance status. Statistical differences were assessed using analysis of variance (ANOVA) tests for continuous variables, and the χ^2 or Fisher exact tests for categorical variables.[34] All analyses were conducted using SAS version 9.2 (Cary,

North Carolina, United States). An a priori 5% significance level was used for all statistical tests, as well as tests for model specification.

Survival analyses were conducted to assess differences in survival, according to surveillance status. Survival was estimated from the date of diagnosis until death or censoring. Patients who did not die during follow-up were considered censored at the last known follow-up or study end (September 30, 2012). Unadjusted survival probabilities were estimated using the Kaplan-Meier method and compared by the log-rank test.[31] The life-table method was used to calculate yearly probabilities of survival; 95% confidence intervals (CI) were computed using the log-log transformation of the survivor function.[31]

Cox proportional hazards models were constructed to assess the association between surveillance status and the hazard of death, controlling for the following patient demographics and clinical characteristics: age, gender, co-morbidities, etiology, liver function (i.e., CP status), and year of diagnosis.[31] Model fit for different specifications was assessed using the Akaike information criterion (AIC).[31] To test the proportional hazard assumption, log cumulative hazard plots stratified by surveillance status were estimated.[31]

Propensity Score Analysis to Address Selection Bias

Two different methods for PS analysis were undertaken to control for selection bias arising from non-random allocation of surveillance: 1) propensity-based weighting (PBW), and 2) propensity-based matching (PBM).[33,41,42] In the absence of unmeasured confounding, both methods control for selection bias; however, the methods produce distinct estimates of the treatment effect. Applied to surveillance, the PBW method estimates the average effect of surveillance among the population of HCC patients with the same distribution of risk factors found in the full study sample (i.e., average treatment effect).[33,41] In contrast, the PBM method estimates the effect of surveillance for patients with the same

distribution of risk factors found in the surveillance group (i.e., average effect of treatment among the treated). [42]

The PS for patients who underwent surveillance and no surveillance were estimated using a logistic model, controlling for the variables included in the multivariate Cox proportional hazard model. [32] Histograms for the model-estimated PS were constructed to examine the overlap in the distribution of PS across surveillance groups. For the PBW method, patients were weighted using stabilized inverse probability weights, defined as the ratio of the marginal predicted probability of treatment (m) divided by the PS (i.e., m/PS). [33] Stabilized weights were chosen over standard inverse probability of treatment weights (i.e., 1/PS) to provide better estimates of the variance in the effect of surveillance. [34]

PBM was conducted using the nearest available neighbor approach: Patients in the no surveillance group were matched with patients in the surveillance group using a 1:1 ratio with sample replacement. [42,141] To avoid bad matches, patients were matched within a ± 0.05 range (i.e., caliper) of the PS. This commonly used range (± 0.05) was chosen because it produced a reasonable balance of baseline characteristics across surveillance groups, while maximizing the number of successful matches. [32] Additional analyses explored a smaller caliper (± 0.01), with and without sample replacement, which did not produce meaningfully different results from those reported below (data not shown).

Following both PS analysis methods, ANOVA and χ^2 tests were conducted to examine differences in baseline characteristics according to surveillance status. [32,42] Using the survival analysis methods described previously, patients were weighted by the stabilized inverse probability weights to form adjusted hazard ratios and survival probabilities. [99] For the PBM method, survival analyses were restricted to patients who were matched based on the PS.

Lead Time Bias Adjustments

An important consideration when estimating the impact of surveillance on survival is the potential for lead time bias. This bias may occur if surveillance merely detects the tumor at an earlier stage without affecting the course of disease, leading in an overestimation of survival gains associated with surveillance.[2] Using a similar approach described by Trevisani et al. (2004, 2007), "lead time" was approximated using the well-established formula for tumor growth, first proposed by Schwartz (1961):[10,11,13]

$$t = \frac{\mathbf{DT} * \mathbf{3} * \mathbf{log}(\frac{D_1}{D_0})}{\mathbf{log}(\mathbf{2})}$$

where: t = time interval between measurements (days)

DT = tumor volume doubling time (days)

D_0 = tumor diameter at first measurement

D_1 = tumor diameter at last measurement

Using the formula, lead time represents the time interval (t, in days) for the primary tumor to grow from the median diameter among patients in the surveillance group (D_0) to the median diameter among patients in the no surveillance group (D_1). Sensitivity analyses assessed different assumptions about the DT, based on the range of median DT (i.e., 60, 130, 200 days) estimated across published tumor growth studies conducted among the general population of HCC tumors (synthesized in **Chapter 4**).[14-27] The estimated lead times were subtracted from the survival of patients in the surveillance group. For cases in which survival became negative, time of death/censoring was reassigned to 1 day. Survival curves were re-estimated using the lead time adjusted survival estimates, as described above.

Results

A total of 1,533 patients from the HCC BRIDGE study in Taiwan met the study inclusion criteria (**Figure 5.1**). Primary treatment approaches for the full HCC BRIDGE study (n=1,587) compared with the final sample (96.6% of full sample) were not statistically different (p=0.8), suggesting that unavailable patient characteristics and follow-up information were primarily missing at random (data not shown).

The majority of patients diagnosed with HCC were male (72.0%) with a mean age of 61.0 $\pm$ 12.4 years (**Table 5.1**). HCC etiology was primarily related to chronic HBV (64.0%) and HCV (31.5%) infection. Most patients had well-preserved liver function (CP A/no cirrhosis: 92.2%), and a moderate percentage of patients had co-morbidities, such as diabetes (20.3%), CVD (10.6%), and hypertension (35.0%), with 16.4% of patients presenting with more than one comorbidity.

A total of 829 patients (54.1%) underwent HCC surveillance prior to HCC diagnosis (**Table 5.1**). Patients who received surveillance were slightly older (mean age: 62.1 years vs. 59.7; p=0.0002), with a lower percentage of males (66.8% vs. 78.1%; p<0.0001) compared with patients who did not receive surveillance. HCC etiology also significantly differed according to surveillance status; chronic HCV infection was more frequent (38.6% vs. 23.2%; p<0.0001), and ALD (3.3% vs. 5.5%; p=0.03) was slightly less frequent in the surveillance group than in the no surveillance group. In addition, the frequency of advanced liver cirrhosis (CP B-C) was significantly lower among patients who received surveillance versus no surveillance (4.5% vs. 11.6%; p<0.0001).

Following PS adjustment, baseline characteristics were generally balanced across the surveillance groups (**Appendix G**). As expected, baseline characteristics for the PS weighted sample were similar to the original study sample, whereas characteristics of patients who were matched based on the PS were similar to those of the surveillance group.

Tumor Characteristics and Primary Treatment

A higher percentage of patients who underwent surveillance were diagnosed with early HCC, defined as a solitary tumor ≤ 5 cm (66.1% vs. 28.8%), and fewer patients had advanced HCC (5.9% vs. 25.5%), compared with patients who did not undergo surveillance (**Table 5.2;** overall p<0.0001). Likewise, primary tumor size was significantly smaller in the surveillance group (median, interquartile range: 2.6, 2.0-3.8 cm) compared with the no surveillance group (5.8, 3.3-10.0 cm). Surveillance resulted in a higher percentage of patients receiving tumor ablation as the primary treatment (25.1% vs. 7.1%). On the other hand, the frequency of surgical resection was similar across the surveillance groups (surveillance: 52.1% vs. no surveillance: 53.3%), and few patients received liver transplant (1.2% vs. 0.4%, respectively).

Survival Benefit of Surveillance

Overall 1- and 3-year survival following HCC diagnosis for the full study cohort was 86.6% (95% confidence interval [CI]: 84.7-88.2%) and 75.0% (72.4-77.4%), respectively. Unadjusted survival was significantly higher among patients who received surveillance (3-year survival: 85.5%, 82.3-88.2%) than among patients who did not undergo surveillance (62.0%, 57.7-65.9%, p<0.0001; **Figure 5.2a**). After multivariate adjustment, surveillance was associated with a significant 67% - reduction in the hazard of death (hazard ratio [HR], 95% CI: 0.33, 0.25-0.42; p<0.0001), compared with no surveillance (**Table 5.3**). Additional significant factors affecting survival included etiology related to NAFLD (HR, 95% CI: 0.42, 0.33-0.53), and poor liver function (CP B vs. No Cirrhosis/CP A: 3.93, 2.92-5.28; CP C: 6.73, 1.93-23.45). Survival differences according to surveillance status were less pronounced but remained highly significant after PS adjustment, using both the PBW (HR, 95% CI: 0.40, 0.32-0.50; p<0.0001) and PBM methods (HR, 95% CI: 0.42, 0.33-0.53; p<0.0001).

Lead Time Bias Adjustment

The survival benefit associated with surveillance remained significant after lead time bias adjustment using a range in DT of 60-200 days, corresponding to an estimated lead time of 6.8-22.7 months (all p<0.0001; **Figure 5.2b**). Overall 3-year survival in the surveillance group was 83.3% (79.7-86.3%), 82.0% (78.2-85.3%) and 81.0% (76.5-84.7%) using a DT of 60, 130, and 200 days, respectively, compared with 62.0% (57.7-65.9%) in the no surveillance group.

After PS adjustment, however, survival differences according to surveillance status were sensitive to assumptions surrounding the estimated lead time (**Figure 5.2c-d**). Using a DT of 130 days, 3-year survival after PBW and PBM adjustments was 79.0% (75.0-82.5%) and 82.0% (78.2-85.3%) in the surveillance group compared with 66.3% (62.1-70.3%) and 71.7% (67.8-75.2%) in the no surveillance group, respectively (log-rank p<0.0001 and p<0.001). When using a DT of 200 days, however, survival differences were significant using the PBW method (p=0.02), but were not significant using the PBM method for adjustment (p=0.19). Despite statistical differences in the estimated impact of surveillance, survival estimates were consistent across the two PS analysis methods, evidenced by overlap in the CIs surrounding the survival probabilities. Using the PBW method, 1- and 3-year survival for a DT of 200 days were 83.7% (80.6-86.4%) and 75.8% (70.8-80.0%) in the surveillance group compared with 80.1% (76.8-82.9%) and 66.3% (62.1-70.3%) in the no surveillance group, respectively. Corresponding 1- and 3-year survival for surveillance, using the PBM method and a DT of 200 days, were 85.7% (82.7-88.2%) and 81.0% (76.5-84.7%) versus 84.7% (81.9-87.1%) and 71.7% (67.8-75.2%) for no surveillance, respectively. Differences in survival using the two PS analysis methods can be explained by slightly different baseline characteristics in the underlying sample of HCC patients (**Appendix G**).

Discussion

In this cohort of patients diagnosed with HCC in Taiwan, HCC surveillance was associated with earlier disease detection, increased rate of curative treatment, and improved survival. To the best of our knowledge, this is the first study to assess the current impact of surveillance on the survival of HCC patients in clinical practice in Taiwan, controlling for both selection bias through PS analysis and lead time bias using DT adjustments. The results suggest that the survival benefit associated with surveillance is consistent when using different methods of lead time and PS adjustment, with one exception. Using a DT of 60 or 130 days to correct for lead time, survival differences across surveillance groups remained statistically significant, regardless of PS analysis method used. On the other hand, when assuming a DT of 200 days, differences in survival across surveillance groups were marginal and even non-significant, depending on the method of PS adjustment.

In interpreting these results, it is important to note that the lead time adjustments used in this study were approximated based on current knowledge surrounding HCC tumor growth. The range in DT (60-200 days) to estimate lead time was chosen based on the full range of median DT estimated across tumor growth studies (see **Chapter 4**).[14-27] Using the well established formula for tumor growth and differences in median tumor size across surveillance groups, this range in DT translated to a broad range in estimated lead time from approximately 7 to 23 months.[13] Thus, the expected lead time resulting from earlier HCC diagnosis remains uncertain. Tumor growth in HCC is highly heterogeneous across individuals, and other aspects of HCC progression, including the development of multinodular HCC, vascular invasion and tumor metastases, are not fully understood.[14-27]

Prior observational studies of surveillance, using similar methods for lead time bias adjustment, have used a smaller range in DT from 60 to 120 days.[10-12] A smaller study conducted in Hong Kong found that surveillance among HCC patients with chronic HBV (n=492) was associated with a significant increase in survival when using a DT up to 90 days (estimated lead time = 8 months; $p<0.0001$).[12] On

the other hand, when assuming a DT of 120 days (lead time = 10 months), survival differences across surveillance groups were no longer significant (p=0.18). To some extent, the lower survival benefits associated with surveillance may be explained by differences in the surveillance protocol employed. In the current study, surveillance was generally conducted every 6 months using US with or without AFP, whereas in the prior study, surveillance was conducted with AFP every 6 months and US every 1-2 years. As a result, the prior study noted a larger median tumor diameter in the surveillance group (4.2 cm vs. 2.6 cm in the current study), and much lower use of surgical resection (20% vs. 52%). Additional large-scale studies conducted in regular clinical practice are needed to establish whether survival gains associated with surveillance withstand assumptions surrounding estimated lead time.

After PS adjustment to address nonrandom allocation of surveillance, the survival benefit associated with surveillance in this study was also slightly higher compared with results reported in the seminal trial of HCC surveillance in China, conducted by Zhang et al.[9] In the current study, surveillance was associated with a 58% - reduction in the hazard of death prior to lead time bias adjustment (HR, 95% CI: 0.42, 0.33-0.53, using PBM method). In contrast, Zhang et al. found a 37% - reduction in HCC mortality associated with surveillance (relative risk [RR], 95% CI: 0.63, 0.41–0.98).[9] There are several possible explanations for the larger survival benefit associated with surveillance in the current study. Although Zhang et al. initially recruited a large sample of high-risk patients, a relatively small number of HCC cases were detected (n=153); thus, the trial may have been underpowered to detect survival differences. In addition, compliance with the trial protocol for surveillance was poor (less than 60%), which may have lead to the lower frequency of early HCC (tumor < 5 cm) among individuals who received surveillance (45.3% in prior trial vs. 66.1% in the current study). Lastly, HCC treatment approaches have evolved substantially since Zhang et al. conducted the trial in 1993-1998. In particular, local ablation has emerged as a less invasive alternative to resection for individuals with early stage tumors.[2,71] In addition, with advancements in surgical techniques, a larger number of multinodular

tumors are now considered resectable, with 3-year survival reaching as high as 56%. [61-63] Further advancements in curative treatment options for HCC will likely increase the survival advantages associated with HCC surveillance.

In interpreting the results of this study, it is important to note that HCC patients were treated at a large tertiary hospital with an established liver care center. Thus, the results may represent a more ideal scenario in which patients were routinely screened and provided appropriate care. Whereas more than half of all patients included in this study received surveillance prior to HCC diagnosis, prior research suggests that patient compliance with surveillance is often poor. [9] Furthermore, physician's level of experience in staging and treating HCC patients can have a profound impact on survival outcomes. [46,137] An earlier trial conducted in China noted that screening with AFP led to earlier diagnosis, but did not result in an overall reduction in mortality largely due to ineffective treatment. [46] Community-based screening projects conducted in Taiwan have suggested that two-stage screening programs consisting of AFP followed by US among suspected cases of HCC is economically feasible with a large proportion of HCC cases detected in the early disease stage. [7,138-140] On the other hand, the lack of a suitable comparator group has limited survival comparisons to establish the survival impact of surveillance in this setting. [7] Therefore, additional research is needed to understand the current impact of non-compliance and geographical variations in access to effective HCC treatments on the survival benefits associated with surveillance in Taiwan.

This study provides valuable insights into the current impact of surveillance on the survival of patients diagnosed with HCC, using a broad range of assumptions surrounding tumor growth in HCC to address lead time bias. In addition, the large number of HCC cases and detailed clinical data allowed for PS adjustment to reduce elements of selection bias. Nevertheless the study has several limitations. First, as with any retrospective study of patient medical records, data on clinical characteristics were based solely on documented evidence in the patient medical record. As a result, potential miscoding of

clinical characteristics may have been present, and approximately 3% of the study sample was excluded due to missing surveillance status, disease stage, or follow-up information.

Another limitation is the incomplete definition of HCC surveillance, which indicates whether the patient underwent surveillance prior to diagnosis, but does not account for the duration and frequency of surveillance. For patients treated at the University hospital, surveillance was provided using a standard protocol (i.e., US and AFP every 6 months); however, surveillance provided to patients diagnosed at another hospital/clinic prior to referral may have differed and was not consistently recorded. As a result, there is some possibility that certain patients in the no surveillance group had some monitoring of liver disease. Thus, the true benefit of HCC surveillance may be slightly greater than the observed benefit found in this study. Lastly, this study identifies the impact of HCC surveillance on survival, based on current practice, but does not distinguish differences in the impact of surveillance among different risk groups and factors that affect their implementation. A better understanding of these associations can help target and increase participation in surveillance programs among the broad population of individuals at high-risk for HCC in Taiwan.

In conclusion, currently recommended surveillance strategies in Taiwan, using abdominal US and AFP, are associated with earlier disease detection, increased use of curative treatment, and improved survival. The results of this study suggest that the survival benefit associated with surveillance remains significant following adjustment using a plausible range in estimated lead time and methods to control for selection bias. However, when assuming the upper range in median DT estimated across prior tumor growth studies, the survival gains associated with surveillance are only marginal or even non-significant, depending on the method of PS adjustment. Additional large-scale studies, using similar methods for lead time and selection bias adjustment, are needed to establish whether survival gains associated with surveillance withstand differences in compliance with surveillance and access to effective HCC treatments in Taiwan.

Table 5.1: Demographics and clinical characteristics for patients diagnosed with HCC in Taiwan, according to surveillance status.

Characteristic *	All Patients (n=1,533)	Surveillance (n=829)	No Surveillance (n=704)	p-value
Age (years)	61.0 ± 12.4	62.1 ± 11.7	59.7 ± 13.1	0.0002
Male Gender	1,104 (72.0)	554 (66.8)	550 (78.1)	<0.0001
Co-morbidities				
Diabetes mellitus	311 (20.3)	165 (19.9)	146 (20.7)	0.7
CVD	162 (10.6)	80 (9.7)	82 (11.7)	0.2
Hypertension	536 (35.0)	282 (34.0)	254 (36.1)	0.4
HCC Etiologies				
HBV	981 (64.0)	532 (64.2)	449 (63.8)	0.9
HCV	483 (31.5)	320 (38.6)	163 (23.2)	<0.0001
ALD	66 (4.3)	27 (3.3)	39 (5.5)	0.03
NAFLD	126 (8.2)	62 (7.5)	64 (9.1)	0.3
Other/Idiopathic	114 (7.4)	20 (2.4)	94 (13.4)	<0.0001
Liver Function				
CP A/No Cirrhosis	1,414 (92.2)	792 (95.5)	622 (88.4)	
CP B	114 (7.4)	37 (4.5)	77 (10.9)	<0.0001
CP C	5 (0.3)	0 (0.0)	5 (0.7)	

ALD = alcohol liver disease, CP = Child-Pugh score, CVD = cardiovascular disease, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, NAFLD = non-alcoholic fatty liver disease

* Values are expressed as mean ± standard deviation and n (%) for continuous and categorical variables, respectively.

Table 5.2: Tumor characteristics and primary treatment approaches for patients diagnosed with HCC in Taiwan, according to surveillance status.

Characteristic *	All Patients (n=1,533)	Surveillance (n=829)	No Surveillance (n=704)	p-value
Tumor Characteristics, n = 1,502**				
Tumor Size	**3.4 (2.2-6.5)**	**2.6 (2.0-3.8)**	**5.8 (3.3-10.0)**	**<0.0001**
Solitary HCC †	**993 (66.1)**	**609 (75.0)**	**384 (55.6)**	**<0.0001**
≤ 5 cm	736 (49.0)	537 (66.1)	199 (28.8)	
> 5 cm	257 (17.1)	72 (8.9)	185 (26.8)	
Multinodular HCC †	**285 (19.0)**	**155 (19.1)**	**130 (18.8)**	
2-3 Tumors, size ≤ 3 cm	101 (6.7)	77 (9.5)	24 (3.5)	
2-3 Tumors, size > 3 cm	101 (6.7)	46 (5.7)	55 (8.0)	
≥ 4 Tumors	83 (5.5)	32 (3.9)	51 (7.4)	
Advanced HCC	**224 (14.9)**	**48 (5.9)**	**176 (25.5)**	
Vascular Invasion	129 (8.6)	35 (4.3)	94 (13.6)	
Tumor Metastases	95 (6.3)	13 (1.6)	82 (11.9)	
Primary Treatment				**<0.0001**
Resection	807 (52.6)	432 (52.1)	375 (53.3)	
Transplant	13 (0.8)	10 (1.2)	3 (0.4)	
Ablation	258 (16.8)	208 (25.1)	50 (7.1)	
TA Therapy	357 (23.3)	169 (20.4)	188 (26.7)	
Systemic Therapy	73 (4.8)	10 (1.2)	63 (8.9)	
Supportive Care	21 (1.4)	0 (0.0)	21 (3.0)	
Radiation/Other	4 (0.3)	0 (0.0)	4 (0.6)	

HCC = hepatocellular carcinoma, TA = trans-arterial

* Values are expressed as median (interquartile range) and n (%) for continuous and categorical variables, respectively.

** Represents the sample size with complete tumor characteristics information at diagnosis.

† Patients in these categories have no venous invasion or tumor metastases.

Table 5.3: Cox proportional hazards model of the association between surveillance status and overall survival for patients diagnosed with HCC in Taiwan, controlling for other patient characteristics.

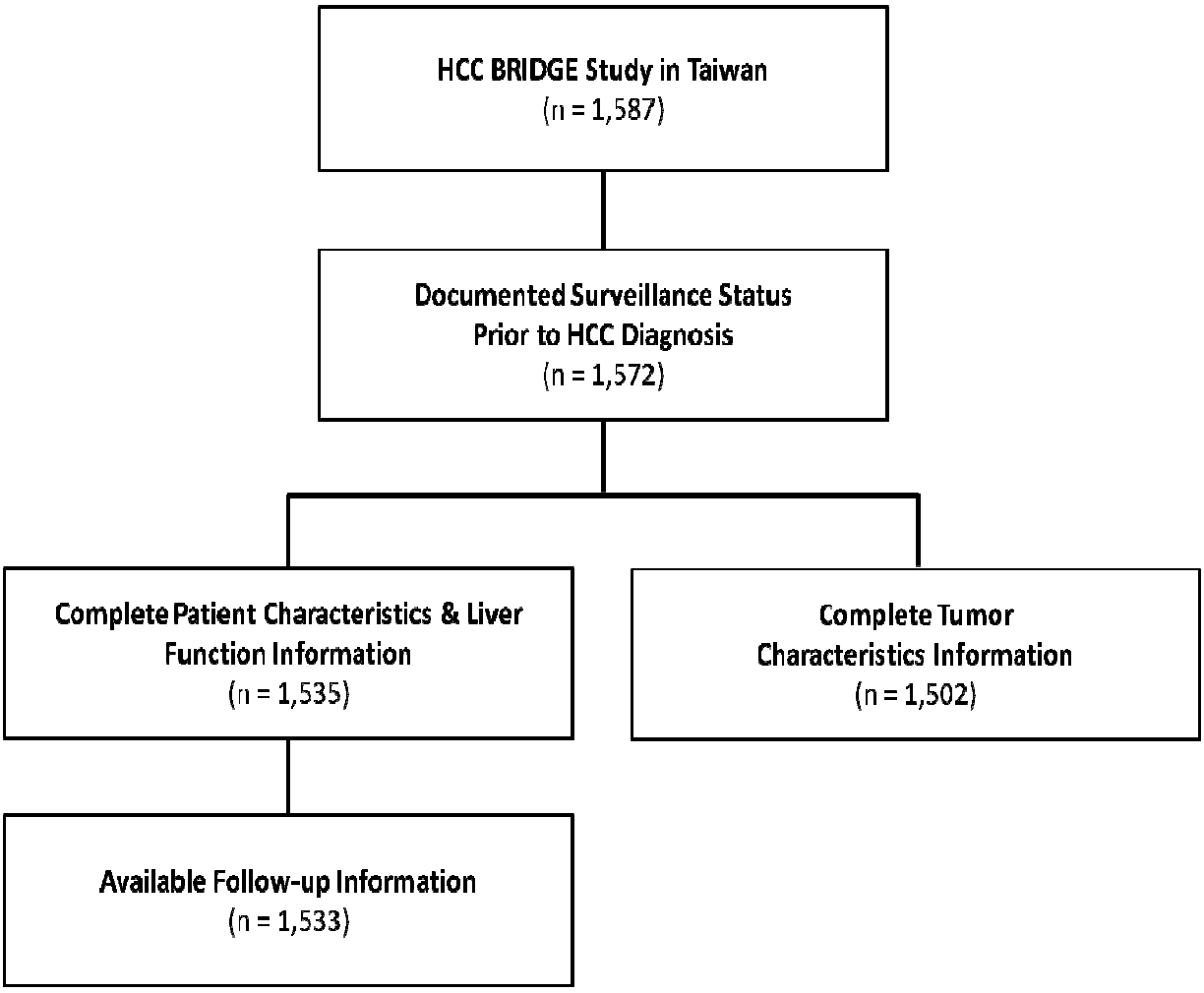
	All Patients (n = 1,533)	
Characteristics *	**HR (95% CI) ****	**p-value**
Surveillance		
Surveillance (vs. No Surveillance)	0.33 (0.25-0.42)	<0.0001
Characteristics		
Age (per 1 year)	1.00 (0.99-1.01)	0.67
Male gender	1.20 (0.92-1.59)	0.19
Co-morbidities		
Diabetes mellitus	1.24 (0.94-1.64)	0.13
CVD	1.26 (0.88-1.80)	0.21
Hypertension	0.98 (0.76-1.27)	0.89
HCC Etiology		
HBV	0.74 (0.47-1.16)	0.19
HCV	0.85 (0.54-1.31)	0.46
ALD	0.96 (0.57-1.61)	0.87
NAFLD	0.23 (0.12-0.42)	<0.0001
Other/Idiopathic	0.66 (0.36-1.20)	0.18
Liver Function		
CP B (vs. CP A/No Cirrhosis)	3.93 (2.92-5.28)	<0.0001
CP C	6.73 (1.93-23.45)	0.0028

ALD = alcohol liver disease, CI = confidence interval, CP = Child-Pugh score, CVD = cardiovascular disease, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, HR = hazard ratio, NAFLD = non-alcoholic fatty liver disease

* Analyses additionally controlled for year of HCC diagnosis.

** To test the proportional hazard assumption, log cumulative hazard plots stratified by surveillance status were estimated; the plots were approximately parallel, suggesting little evidence of departure from the proportional hazard assumption. [31]

Figure 5.1: Sample selection from the HCC BRIDGE study in Taiwan.

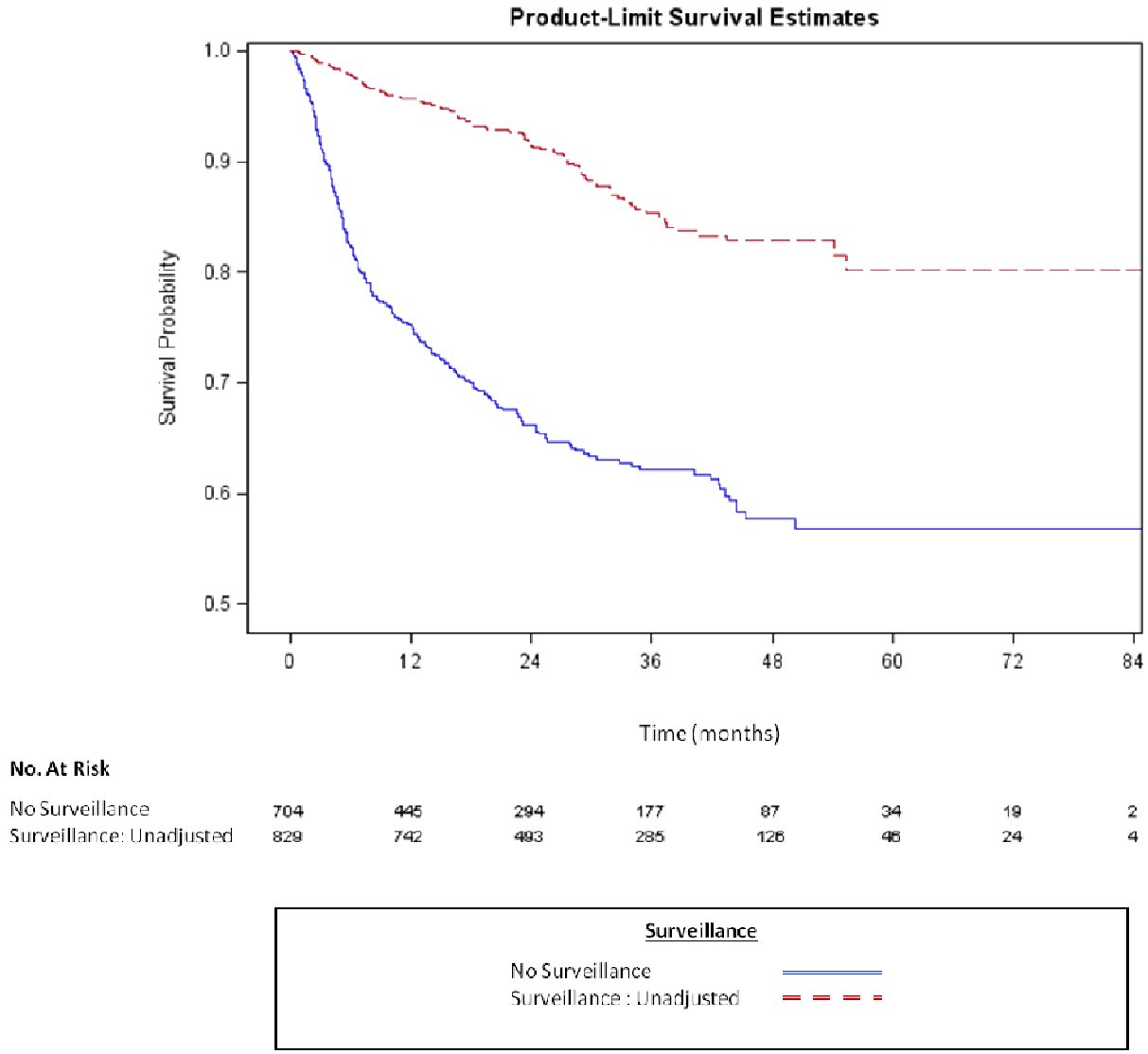


HCC = hepatocellular carcinoma, HCC BRIDGE = The Bridge to Better Outcomes in Hepatocellular Carcinoma Study

* Note: According to the inclusion criteria for the HCC BRIDGE study, the study sample included complete information on primary treatments following HCC diagnosis.

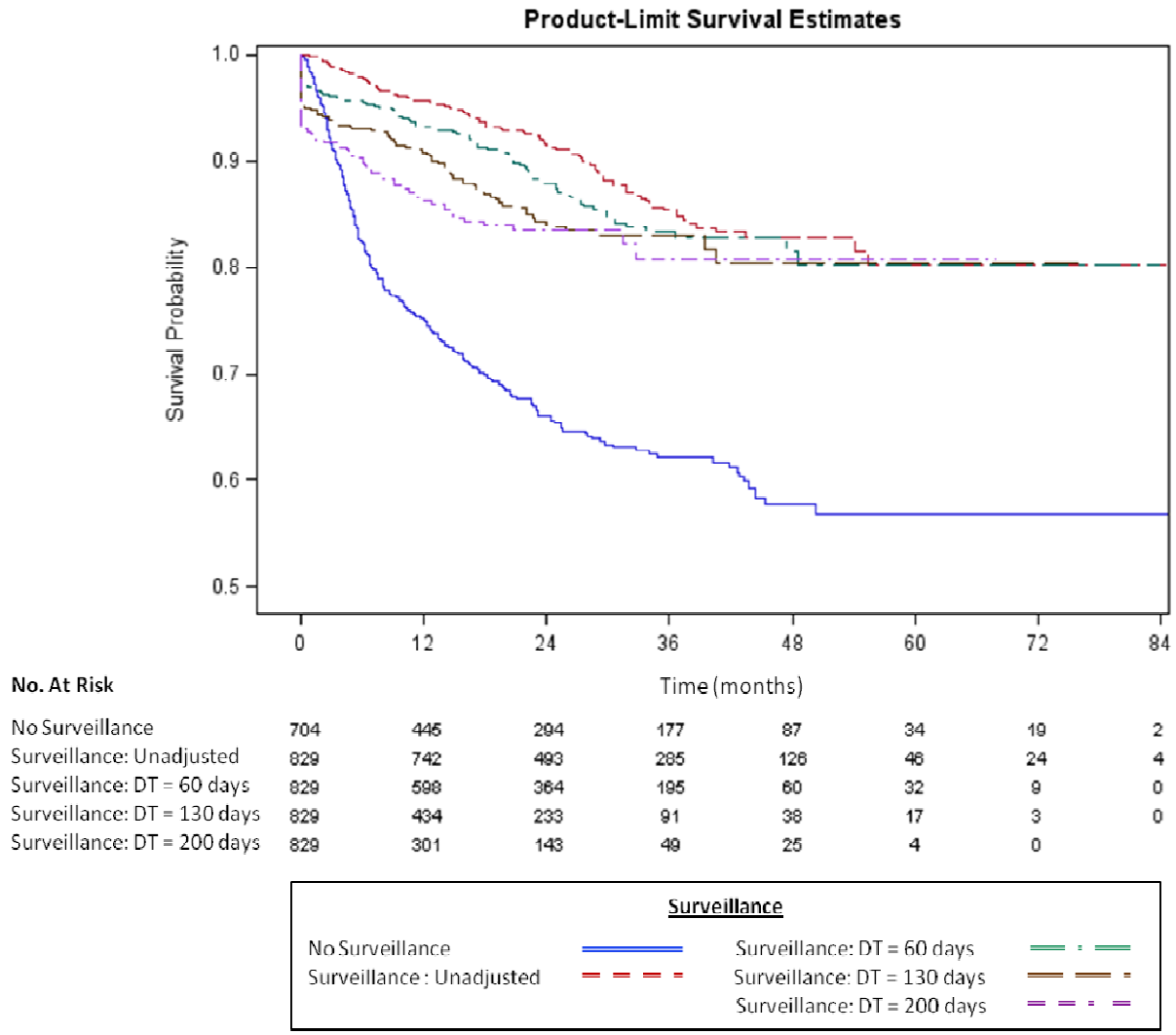
Figure 5.2: Kaplan-Meier survival curves for patients diagnosed with HCC, according to surveillance status: A) Unadjusted for Lead Time Bias and Selection Bias, B) Lead Time Bias Adjustment, using DT = 60-200 days,* C) Propensity-Based Weighting and Lead Time Bias Adjustment, using DT = 60-200 days,* D) Propensity-Based Matching ** and Lead Time Bias Adjustment, using DT = 60-200 days.*

A



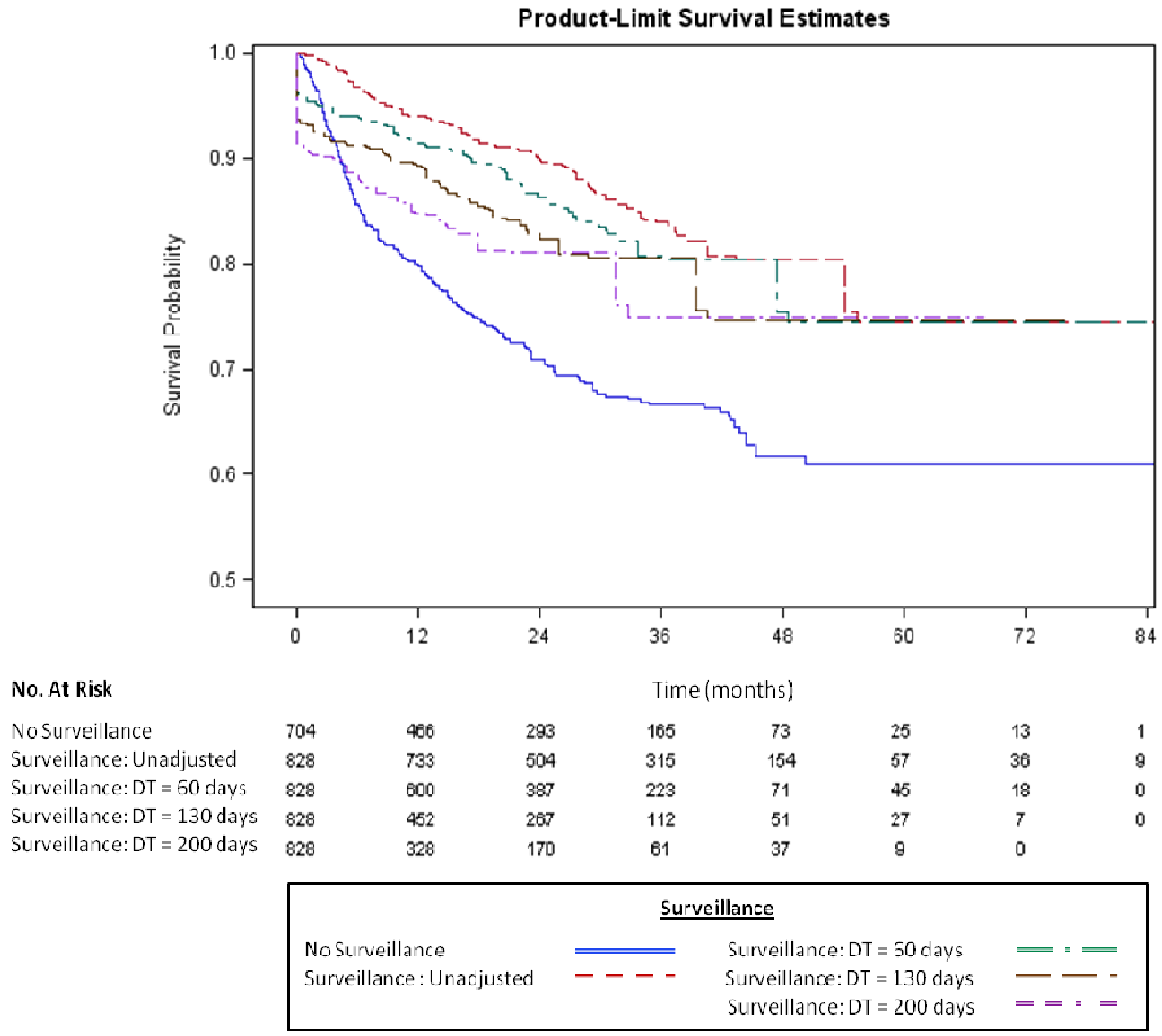
log-rank test:[†] p<0.0001

B



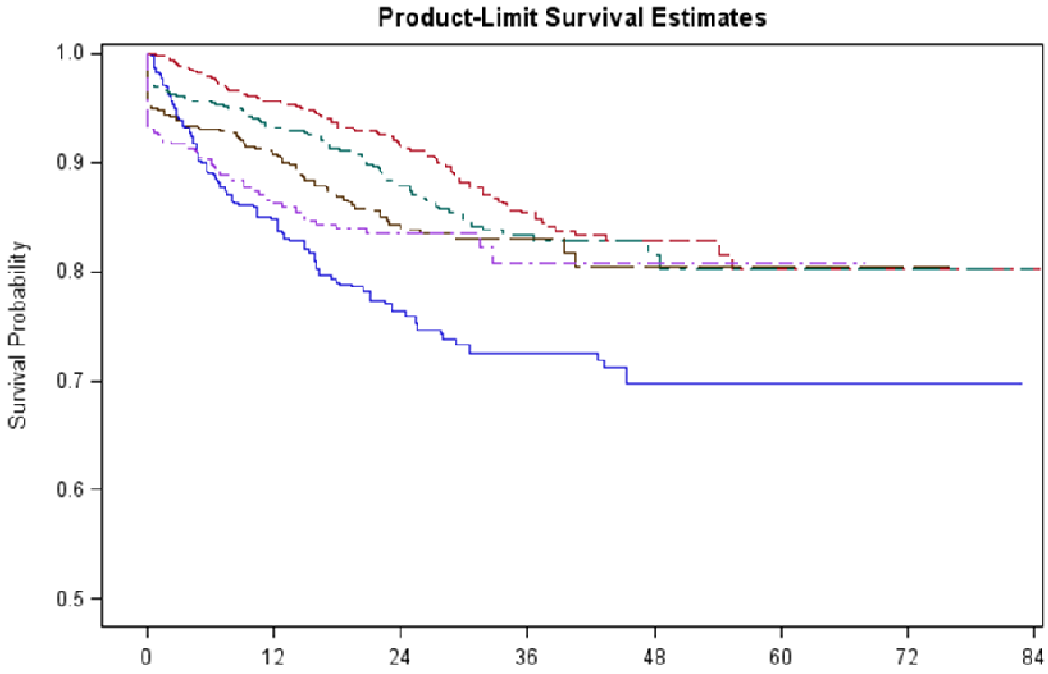
log-rank test:† DT=60 days, p<0.0001; DT=130 days, p<0.0001; DT=200 days, p<0.0001

C

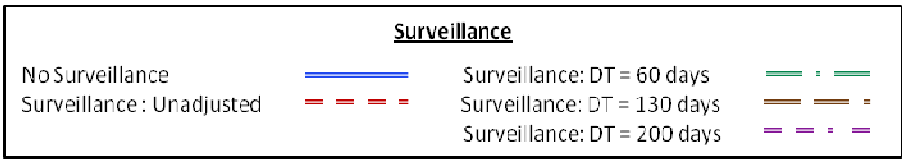


log-rank test:[†] DT=60 days, p<0.0001; DT=130 days, p<0.0001; DT=200 days, p=0.02

D



No. At Risk								
No Surveillance	829	301	143	49	25	4	0	
Surveillance: Unadjusted	829	434	233	91	38	17	3	0
Surveillance: DT = 60 days	829	598	364	195	60	32	9	0
Surveillance: DT = 130 days	829	571	368	188	78	23	7	0
Surveillance: DT = 200 days	829	742	493	285	126	46	24	4



log-rank test:[†] DT=60 days, p<0.0001; DT=130 days, p<0.001; DT=200 days, p=0.19

DT = tumor volume doubling time, HCC = hepatocellular carcinoma, No. = number

* The range in median tumor volume doubling time (DT) from HCC tumor growth studies (60, 130 and 200 days) was applied to the tumor growth formula, using the median tumor size in the surveillance (2.6 cm) and no surveillance groups (5.8 cm), respectively. The resultant estimated lead times (6.8, 14.7, and 22.7 months, respectively) were then subtracted from the survival of patients who underwent surveillance. For cases in which survival became negative, occurring among n= 48, 136, and 310 patients for DT= 60, 130, and 200 days, respectively, time of death/censoring was reassigned to 1 day.

** Patients in the no surveillance group were matched with patients in the surveillance group within a ± 0.05 range of the PS; [42,141] a total of 526 patients from the no surveillance group (74.7%) were identified as matches. To retain the full sample of patients in the surveillance group, patients in the no surveillance group were sampled with replacement to achieve a 1:1 ratio of patients in the two groups.

[†] Pair-wise statistical comparisons between each estimated survival curve for surveillance versus no surveillance were conducted using the log-rank test. [31]

CHAPTER 6: POLICY IMPLICATIONS, LIMITATIONS, AND CONCLUSIONS

Summary of Findings, Policy Implications and Limitations

This study used data from the HCC BRIDGE study, the largest longitudinal study of patients diagnosed with HCC in China and Taiwan, to examine the impact of HCC surveillance and clarify best treatment practices.[29] The analyses conducted in this study represent one of the most comprehensive attempts to compare the impact of current treatment approaches on the survival of patients diagnosed at various stages of HCC disease. Furthermore, this study is the first to examine the survival impact of different surveillance strategies using multiple approaches to correct for lead time bias, based on current knowledge of HCC tumor growth.

In Chapter 3, we conducted detailed survival comparisons across current treatment approaches, for patients diagnosed at various stages of HCC disease, to re-evaluate the appropriateness of current guideline recommendations. Overall, the significant findings were that patients with intermediate to advanced disease tolerated surgical resection and had better outcomes than those who underwent alternative modalities of HCC therapy. Furthermore, survival benefits associated with resection remained significant after PS adjustment, reducing concern that survival comparisons were biased by selection of better surgical candidates. For intermediate solitary and multinodular HCC, trans-arterial therapy significantly increased the hazard of death over resection (hazard ratio [HR] = 2.13, 95% confidence interval: 1.57 - 2.92; HR = 2.21,2.06-2.36), following PS adjustment using the method of propensity-based weighting. Another significant finding was that, for early stage disease, patients who received tumor ablation did not derive the same benefit as patients who underwent resection (HR=3.55,

2.49-5.07). Despite advancements in the clinical management of HCC, however, the majority of patients are diagnosed with intermediate to advanced HCC in China, and survival is generally poor.

In Chapter 4, we developed and calibrated an individual-based simulation model of HCC surveillance, which combined well-established data on the natural progression of chronic HBV infection and HCC disease, along with detailed clinical data from patients diagnosed with HCC in China, to provide an accurate portrayal of the impact of surveillance on survival outcomes for individuals who develop HCC. The results of this model suggested that surveillance with US and AFP was associated with earlier disease detection, increased use of curative treatment, and improved survival. Whereas overall 5- and 10-year survival following HCC development for individuals who did not receive surveillance was only 28.9% (26.9-29.3%) and 13.5% (12.2-14.4%), 5- and 10-year survival for 6-month US+AFP was as high as 48.1% (45.4-51.8%) and 30.1% (40.9-47.5%), respectively (log-rank test: $p<0.0001$). In comparison, survival for 12-month US+AFP was similar to using a 6-month interval, with 5- and 10-year survival reaching 44.2% (40.9-47.5%) and 27.0% (24.2-30.7%), respectively. Thus, in the setting of limited resources, surveillance performed at 12-month as opposed to 6-month intervals as currently recommended in China, can be more easily implemented with little impact on the survival of patients who develop HCC.

In Chapter 5, we assessed the current impact of surveillance on the survival of HCC patients in clinical practice in Taiwan, controlling for both selection bias through PS analysis and lead time bias using current knowledge surrounding HCC tumor growth. The results of this study suggest that the survival benefit associated with surveillance remains significant following adjustment using a plausible range in estimated lead time and methods to control for selection bias. Using a DT of 130 days to adjust for lead time bias, 3-year survival after PS adjustment using propensity-based matching was 79.0% (75.0-82.5%) in the surveillance group compared with 66.3% (62.1-70.3%) in the no surveillance group, respectively (log-rank $p<0.0001$).

This dissertation makes several important contributions to the literature. The HCC BRIDGE study is currently the largest and most comprehensive longitudinal study of patients diagnosed and treated for HCC in current clinical practice in China.[29] The large number of HCC cases and meticulously collected data allowed for detailed survival comparisons according to disease stage at diagnosis, as well as PS analysis to reduce elements of selection bias. The database included data for HCC patients diagnosed across 10 tertiary hospitals from 7 geographically diverse cities in mainland China, increasing the generalizability of the study outcomes, while also facilitating geographic comparisons in disease stage and primary treatment following diagnosis. Thus, the results of this study can help guide current clinical and policy efforts to improve the management of HCC disease and reduce disparities across different regions in China.

To the best of our knowledge, this is the first study to assess the current impact of surveillance on the survival of HCC patients in clinical practice in Taiwan, controlling for both selection bias through PS analysis and lead time bias using DT adjustments. Importantly, the HCC BRIDGE study in Taiwan included a large number of HCC patients who underwent surveillance to facilitate propensity-based matching without sacrificing a large number of HCC cases. The analyses additionally leveraged previously established methods for lead time bias adjustment using the well-established formula for tumor growth in HCC,[10-13] and further extended this work by incorporating the full range in median DT estimated across prior tumor growth studies.[14-27] As a result, the study provides an accurate portrayal of the survival benefit of surveillance using current strategies in Taiwan, controlling for a plausible range in estimated lead time.

Additionally, the detailed clinical information from the HCC BRIDGE study in China, combined with well-established data on the epidemiology of chronic HBV infection and tumor growth in HCC, presented the unique opportunity to develop an in-depth representation of the natural disease course of HCC through the use of an individual-based model. One of the main strengths of this model was the

ability to flexibly incorporate individual-level heterogeneity in HCC disease progression and survival outcomes. Recognizing that previous estimates of tumor growth in HCC are highly variable across studies, analyses incorporated a meta-analysis to synthesize estimates of DT in HCC. Additional unknown parameters of HCC disease progression and incidental diagnosis, which cannot be directly measured in clinical practice, were calibrated based on clinical data from the HCC BRIDGE study in China. The HCC BRIDGE study data was further used to model individual-level heterogeneity in survival with treatment using a series of parametric survival curves, which controlled for the main determinants of survival with HCC: patient demographics, disease characteristics and liver function.[2,3] Lastly, by defining survival with HCC from the time of HCC development, as opposed to diagnosis, the model effectively removed lead time bias and also accounted for cases of HCC-related mortality prior to HCC diagnosis to provide a more accurate portrayal of the true benefit of surveillance among the full population of HCC tumors. This simulation model not only helps to identify the optimal approach for HCC surveillance, but also provides a basis for exploring other issues surrounding surveillance, such as poor compliance and specific high-risk groups that should be targeted, as policy efforts to improve early detection evolve in China.

There are several limitations to the analyses described in this dissertation. First, as with any retrospective chart review study, data included in the HCC BRIDGE study were based solely on documented evidence in the patient medical record. As a result, potential miscoding of clinical characteristics across different hospital sites may have been present. Approximately 15% of the study sample in China was excluded due to missing disease stage or follow-up information; in contrast, only 3% of the study sample for the hospital site in Taiwan was excluded due to missing relevant information. In addition, only treatments provided to patients at each of the participating hospital sites were generally documented; thus, the results may not reflect additional treatments if received from other sites.

For the Aim 3 analyses using the HCC BRIDGE study data in Taiwan, another limitation was the incomplete definition of HCC surveillance, which indicated whether patients underwent surveillance prior to diagnosis, but did not account for the duration and frequency of surveillance. For patients treated at the University hospital, surveillance was provided using a standard protocol (i.e., US and AFP every 6 months); however, surveillance provided to patients diagnosed at another hospital/clinic prior to referral may have differed and was not consistently recorded. As a result, there was some possibility that certain patients in the no surveillance group had some monitoring of liver disease. Thus, the true benefit of HCC surveillance may be slightly greater than the observed benefit found in this study.

Whereas the observational study design of the HCC BRIDGE study allowed an accurate portrayal of HCC management in regular clinical practice, survival comparisons were complicated due to non-random allocation of treatment and surveillance. In order to effectively control for underlying differences in patient characteristics across treatments for Aim 1 and between surveillance groups for Aim 3, multivariate models were constructed, and PS analysis was further conducted to control for selection bias.[32] Nevertheless, residual confounding may still have been present, leading to biased survival comparisons. For Aim 1, the HCC BRIDGE database did not capture information on tumor location, which may have lead to biased estimates of the impact of resection on survival among patients with multinodular tumors. More evidence is needed to better understand the comparative effectiveness of therapies for this patient population. In addition, information on socioeconomic status would provide relevant context surrounding the decision to undergo surveillance in Aim 1 and treatment decisions affecting survival in Aim 3.

A major concern when assessing the impact of surveillance on survival is inherent lead time bias related to the earlier diagnosis of HCC.[8] To address this bias, lead time adjustments for the Aim 3 analyses were approximated using the full range of median DT (60-200 days) estimated across tumor growth studies, synthesized in Aim 2.[14-27] The results suggested that survival gains with surveillance are

consistent across these assumptions; however, such methods are based solely on current knowledge surrounding HCC tumor growth. Tumor growth in HCC is highly heterogeneous across individuals, and other aspects of HCC progression, including the development of multinodular HCC, vascular invasion and tumor metastases, are not fully understood. [14-27]

An advantage of the simulation model, described in Aim 3, was that survival with HCC could be defined from the time of HCC development, as opposed to diagnosis, to effectively remove lead time bias and also account for cases of HCC-related mortality prior to HCC diagnosis. The model provided a detailed representation of tumor growth in HCC, based on evidence synthesized across published tumor growth studies, [14-27] and further sought to expand the representation of disease progression in HCC by incorporating individual-level heterogeneity in tumor growth and disease-related complications through model calibration. The model-based projections were generally concordant with trends in the distribution of tumor characteristics seen in clinical practice in China (as seen in Aim 1); nevertheless, several assumptions were incorporated to simplify the calibration process. Thus, further research on the biological mechanisms surrounding HCC progression, if feasible, would help test and inform the model-based assumptions. Likewise, additional large-scale datasets of patients diagnosed with HCC are needed to cross-validate the model-based outcomes.

In interpreting the results of this dissertation, it is important to note that survival outcomes from the HCC BRIDGE study were based on data from HCC patients diagnosed and treated at large tertiary hospitals in China and Taiwan. Thus, the results may represent a more ideal scenario in which patients were routinely provided appropriate care. Physician's level of experience in staging and treating HCC patients can have a profound impact on survival outcomes. [46,137] A trial conducted in China noted that screening with AFP led to earlier diagnosis, but did not result in an overall reduction in mortality largely due to ineffective treatment. [46]

In addition, the analyses in Aim 2 and Aim 3 identified the impact of HCC surveillance on survival, based on current practice, but did not distinguish differences in the impact of surveillance among different risk groups and factors that affect their implementation. In Aim 2, for patients treated at the University hospital in Taiwan, surveillance was provided using a standard protocol (i.e., US and AFP every 6 months). Data from community-based screening projects in Taiwan have suggested that two-stage screening consisting of AFP followed by US among suspected cases of HCC is economically feasible with a large proportion of HCC cases detected in the early disease stage. [7,138-140] On the other hand, the lack of a suitable comparator group has limited survival comparisons to establish the survival impact of surveillance in this setting. [7] Whereas individuals incorporated in the simulation model of HCC surveillance were assumed to be fully adherent to the surveillance protocol, results from the seminal trial of surveillance in China, which arguably represents a more ideal scenario for patient follow-up, suggests that patient compliance with surveillance is often poor (only ~60%). [9] Therefore, additional research is needed to understand the current impact of non-compliance and geographical variations in access to effective HCC treatments on the survival benefits associated with surveillance in East Asia.

Lastly, the simulation model in Aim 3 was designed to assess survival among individuals who develop HCC as a result of chronic HBV infection, the most common etiology of HCC disease in China, representing over 80% of all HCC cases. [45] With the implementation of vaccination programs against the spread of HBV infection in most parts of East Asia, the underlying risk factors surrounding HCC disease will likely change in future generations. [45,53] Further research is needed to understand the impact of surveillance among the population of HCC patients with other underlying risk factors, including chronic HCV infection and alcohol liver disease, which generally present with more advanced liver disease (CP B/C: 30-49%). [10,28,30,77] Advanced liver disease has been found to reduce the survival benefit associated with surveillance, as these patients are generally not optimal candidates for surgical resection and experience higher mortality from liver-disease related complications. [11]

Despite these limitations, this study is a policy-relevant and timely contribution to the literature surrounding the comparative effectiveness of surveillance and current treatment approaches for the detection and management of HCC in East Asia. From this study, it is clear that surveillance among individuals at high-risk for HCC significantly improves the survival of patients who develop HCC. In addition, current treatment approaches for HCC in China, which are distinct from other settings in the use of surgical resection among more advanced stage patients, are both clinically valid and consistent with current guideline recommendations.

Future Research Agenda

Considering current issues of poor compliance with surveillance programs in China and other settings, a natural extension of this work would be to incorporate assumptions surrounding non-adherence with surveillance to the simulation model.[9] Doing so would provide a more accurate portrayal of survival outcomes with surveillance in actual clinical practice, and could help quantify the potential impact of increasing compliance with surveillance protocols. As a starting point, the randomized controlled trial of surveillance in China provides information on the proportion of individuals who participated in surveillance over the 5-year trial period.[9] Using this information as a guide, unknown parameters surrounding surveillance program drop-out and general non-attendance can be calibrated to reflect the trends seen in the randomized trial. Following calibration, the survival results from the simulation model could be further compared with the results of the randomized trial to assess model validity.

Another natural extension of this work would be to assess the cost-effectiveness of HCC surveillance. Currently, the results of the simulation model suggest that resource use is a concern when comparing surveillance conducted in 12-month as opposed to 6-month intervals, given that a large number of screening tests are needed to detect one case of HCC with little additional survival benefit.

Indeed, clinical guidelines have explicitly considered evidence from prior cost-effectiveness studies when forming recommendations surrounding the use of different surveillance strategies. [2,8] Likewise, assessing the cost-effectiveness in the setting of poor compliance would provide additional context surrounding the potential cost and outcomes of increasing participation in surveillance programs.

As the landscape surrounding HCC disease evolves over time in China, the simulation model can also serve as the foundation for evaluating public health policies and clinical decision making. HBV is endemic in China and is a direct risk factor for HCC disease, resulting in a high clinical and economic burden to society. [1] In response to this challenge, health authorities in East Asia have instituted national vaccination campaigns to prevent HBV transmission and effectively lower the incidence of HCC disease in the next 20-30 years. [45,53] In addition, government-funded community-based programs in HBV endemic areas are actively screening patients at high-risk for developing HCC and working to increase the use of antiviral treatment for HCC prevention. [6,87-89] With the availability of additional data, the simulation model can be adapted to facilitate future analyses of HCC surveillance, in addition to the effects of antiviral treatment, as HCC disease characteristics and available treatments options evolve over time.

The analyses incorporated in this dissertation identify the impact of surveillance and treatment approaches for HCC, based on current practice, but do not distinguish differences in the application of surveillance and treatment among different risk groups as well as factors that affect their implementation. Future research should assess the impact of regional differences in access to surveillance and HCC treatment, as well as disparities among individuals with various etiologies of disease and comorbidities to provide a broader representation of survival outcomes with HCC in East Asia. Qualitative research could further elucidate the contextual factors, such as socioeconomic status and cultural beliefs, that affect the decision to undergo regular surveillance and treatment decisions following diagnosis in East Asia.

Conclusions

This dissertation revealed that current treatment approaches for patients with HCC in China, which largely differ from approaches in other settings, are both clinically appropriate and consistent with consensus guideline recommendations. Patients with intermediate to advanced disease tolerate surgical resection and have better outcomes than those who undergo alternative modalities of HCC therapy. The results additionally showed that surveillance to detect HCC leads to earlier diagnosis, increased use of curative treatment and, consequently, improved survival among individuals who developed HCC. In the setting of limited resources, surveillance performed at 12-month as opposed to 6-month intervals as currently recommended in China, can be more easily implemented with little impact on the survival of patients who develop HCC. This dissertation provides a unique contribution to the clinical literature surrounding HCC in that it helps identify optimal approaches for the early detection and treatment of HCC. The findings can help policymakers and clinicians better target efforts to ensure that individuals who are at high-risk for developing HCC are properly monitored, and patients with HCC receive appropriate treatment to improve survival outcomes.

APPENDIX A: TREATMENT APPROACHES CAPTURED IN THE HCC BRIDGE STUDY DATABASE.

Treatments	
Surgical Resection	
Liver Transplant	
Tumor Ablation	radiofrequency ablation (RFA), microwave ablation, cryoablation, or percutaneous ethanol injection (PEI)
Trans-arterial (TA) Therapy	transcatheter arterial chemoembolization (TAE), transcatheter arterial embolization (TAE), trans-artieral radioembolization (TARE), or intrarterial chemotherapy
Systemic Therapy	sorafenib, oxorubucin, gemcitabine, cisplatin, oxaliplatin, capecitabine, interferon, sunitinib, bevacizumab, cetuximab, erlotinib, fluorouracil, daunorubicin, epirubicin, mitomycin C, carboplatin, lobaplatin, floxuridine, thalidomide, lenalidomide, and other
Supportive Care	narcotic and non-narcotic analgesics, laxatives, anti-diarrhea medications, antihistamines, antidepressants, anxiolytics, sedative/hypnotics, oxygen, and other
Radiation Therapy/Other	radiation therapy, conformal radiation therapy or other loco-regional therapy

HCC BRIDGE = The Bridge to Better Outcomes in Hepatocellular Carcinoma Study

APPENDIX B: SUMMARY OF RESULTS FOR THE LITERATURE SEARCH ON PUBLISHED ARTICLES THAT ASSESSED THE NATURAL HISTORY OF HEPATOCELLULAR CARCINOMA AMONG INDIVIDUALS WITH CHRONIC HEPATITIS B VIRUS INFECTION.

PubMed Search– conducted on May 22, 2012 and updated on February 13, 2014

#	Facet	Search Terms	Results 5/22/12	Results* 2/13/14
1	Hepatitis B	“Hepatitis B”[MESH]	41,660	2,340
2	Hepatocellular carcinoma	“Carcinoma, Hepatocellular” [MESH]	51,046	4,490
3	Liver Cirrhosis	“liver cirrhosis” [MESH]	65,710	3,016
4	HBV/Cirrhosis/HCC	#1 OR #2 OR #3	145,937	8,805
5	Epidemiology, Incidence, natural history	“epidemiology”[MESH] OR “natural history"[MESH] OR “incidence"[MESH] OR “disease progression"[MESH]	264,858	26,932
6	HBV/Cirrhosis/HCC epidemiology	#4 AND #5	5,095	677
7	HBV/Cirrhosis/HCC epidemiology	Limited to English Language	4,538	648

Embase Search– conducted on May 22, 2012 and updated on February 13, 2014

#	Facet	Search Terms	Results 5/22/12	Results* 2/13/14
1	Hepatocellular Carcinoma	'hepatocellular carcinoma'/exp	75,010	14,881
2	Hepatitis B	'hepatitis b'/exp	60,352	10,058
3	Liver Cirrhosis	'liver cirrhosis'/exp	108,121	15,016
4	HBV/Cirrhosis/HCC	#1 AND #2 AND #3	3,986	852
5	Epidemiology, Incidence	'incidence'/exp	224,560	36,733
6	HBV/Cirrhosis/HCC incidence	#4 AND #5	395	74

Total on May 22, 2012 (after removal of duplicates): 4,687 Articles

Total on February 13, 2014 (after removal of duplicates): 5,246 Articles

* Searches conducted on February 13, 2014 were restricted to studies published as of May 1, 2012 (PubMed) and January 1, 2012 (Embase), respectively.

APPENDIX C: SUMMARY OF RESULTS FOR THE LITERATURE SEARCH ON PUBLISHED ARTICLES THAT ASSESSED TUMOR GROWTH IN HEPATOCELLULAR CARCINOMA.

PubMed Search – conducted on November 8, 2012 and updated on February 13, 2014

#	Facet	Search Terms	Results 11/8/12	Results* 2/13/14
1	Hepatocellular carcinoma	"Liver Neoplasms"[Mesh] OR "hepatocellular carcinoma"[Title/Abstract] OR "hepatic carcinoma"[Title/Abstract] OR "liver carcinoma"[Title/Abstract] OR "liver cancer"[Title/Abstract] OR "hepatic cancer"[Title/Abstract] OR hepatoma[Title/Abstract]	134,454	13,297
2	Tumor Growth	"growth rate"[Title/Abstract] OR "doubling time" [Title/Abstract] OR "tumor volume" [Title/Abstract]	47,704	5,619
3	HCC & Tumor Growth	#1 AND #2	1,321	139
4	Filter to Human Studies/Exclude Animal Studies	Filters: Humans	788	81
5		#4 NOT (rat[Title/Abstract] OR mice[Title/Abstract])	569	58
6	Exclude HCC Treatments	#5 NOT ("Hepatectomy"[Mesh] OR "resection" [Title/Abstract] OR "Liver Transplantation"[Mesh] OR "transplant" [Title/Abstract] OR "Ablation Techniques"[Mesh] OR ablat* [Title/Abstract] OR "cryoablation" [Title/Abstract] OR "percutaneous ethanol injection"[Title/Abstract] OR "PEI"[Title/Abstract] OR "chemoembolization, therapeutic"[Mesh] OR "TACE" [Title/Abstract] OR chemoemboliz*[Title/Abstract] OR "transarterial" [Title/Abstract] OR "trans-arterial" [Title/Abstract] OR radioemboliz*[Title/Abstract] OR "TARE" [Title/Abstract] OR "chemotherapy" [Title/Abstract] OR "erlotinib"[Title/Abstract] OR "tarceva"[Title/Abstract] OR "sorafenib"[Title/Abstract] OR "nexavar"[Title/Abstract] OR "brivanib"[Title/Abstract] OR linifanib[Title/Abstract] OR "everolimus"[Title/Abstract] OR "afinitor"[Title/Abstract] OR "ramucirumab"[Title/Abstract])	342	26

Embase Search – conducted on November 8, 2012 and updated on February 13, 2014

#	Facet	Search Terms	Results 11/8/12	Results* 2/13/14
1	Hepatocellular Carcinoma	'hepatocellular carcinoma'/exp OR 'hepatocellular carcinoma'	90,442	19,662
2		'liver cancer'/exp OR 'liver cancer'	138,073	28,302
3		'liver carcinoma'/exp OR 'liver carcinoma'	84,109	18,440
4		'liver cell carcinoma'/exp OR 'liver cell carcinoma'	83,711	18,367
5		#1 OR #2 OR #3 OR #4	143,800	29,435
6	Tumor Growth	'growth rate'/exp OR 'growth rate'	98,578	13,473
7		'tumor growth'/exp OR 'tumor growth'	87,595	20,726
8		'tumor volume'/exp OR 'tumor volume'	77,617	23,969
9		#6 OR #7 OR #8	180,797	53,804
10	HCC & Tumor Growth	#5 AND #9	13,206	4,209
11	Exclude Animal Studies & Non-Peer-reviewed Articles	#10 NOT ('animal cell'/de OR 'animal experiment'/de OR 'animal model'/de OR 'animal tissue'/de OR 'case report'/de OR 'in vitro study'/de OR 'nonhuman'/de OR 'book'/it OR 'conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'editorial'/it OR 'erratum'/it OR 'letter'/it OR 'note'/it OR 'short survey'/it)	5,785	1,458
12		#11 NOT ('mice'/exp OR 'mice' OR 'rat'/exp OR 'rat')	2,333	1,404
13	HCC Treatments (for exclusion)	'liver'/exp OR liver AND ('resection'/exp OR resection)	247,451	44,560
14		'liver transplantation'/exp OR 'liver transplantation'	70,416	14,080
15		'radiofrequency ablation'/exp OR 'radiofrequency ablation'	17,186	5,293
16		'cryoablation'/exp OR cryoablation	3,450	1,097
17		'microwave therapy'/exp OR 'microwave therapy'	1,243	463
18		'percutaneous ethanol injection'	1,407	117
19		'chemoembolization'/exp OR chemoembolization	7,563	2,505
20		radioembolization	693	505
21		'embolization'/exp OR embolization	59,138	11,464
22		'chemotherapy'/exp OR chemotherapy	557,379	94,157
23		'sorafenib'/exp OR sorafenib	11,148	5,077
24		'brivanib'/exp OR brivanib	338	248
25		'radiotherapy'/exp OR radiotherapy	496,002	72,327
26		'systemic therapy'/exp OR 'systemic therapy'	13,313	4,823
27		#12 thru #26 connected with OR	1,216,062	191,114
28	Exclude HCC Treatments	#12 NOT #27	1,701	370

Total (after removal of duplicates): 1,912 Articles

Total on February 13, 2014 (after removal of duplicates): 2,186 Articles

* Searches conducted on February 13, 2014 were restricted to studies published as of November 1, 2012 (PubMed) and January 1, 2012 (Embase), respectively.

APPENDIX D: SUMMARY OF PUBLISHED STUDIES THAT ASSESSED TUMOR GROWTH IN HEPATOCELLULAR CARCINOMA AND REPORTED ESTIMATES FOR TUMOR VOLUME DOUBLING TIME (N=19), GROUPED ACCORDING TO INCLUSION STATUS IN THE POOLED META-ANALYSIS.†

Study, Year	Country	Imaging Modality	N = tumors (n=patients)	Follow-up (months)	Initial Tumor Size, diameter (cm)	Tumor Volume Doubling Time (DT, days) *
Included Studies (n=14) †						
Yoshino et al., 1983 [14]	Japan	US or CT	N = 16 (n = 13)	Mean ± SD: 5.2 ± 3.1 Range: 0.3-9.6	Mean ± SD: 3.0 ± 1.5 Range: 0.9-6.5	Mean, 95% CI: 104, 71-153 Median: 112.5 Range: 41-315
Sheu et al., 1985 [15]	Taiwan	US	N = 30 (n = 28)	Mean: 7.8 Range: 1.2-28.3	Mean ± SD: 2.3 ± 0.8 Range: 1.1-4.1	Mean, 95% CI: 111, 87-142 Median: 117 Range: 29-398
Ebara et al., 1986 [16]	Japan	US	N = 22	Mean: 21.6 Range: 6-37	Mean ± SD: 1.9 ± 0.6 Range: 1.0-3.0	Mean ± SD: 196 ± 173 Range: 30-593
Okazaki et al., 1989 [17]	Japan	US & CT	N = 15	Range: 1.0-13.0	Mean ± SD: 2.8 ± 1.0 Range: 1.3-4.5	Mean, 95% CI: 83, 59-118 Median: 71 Range: 41-305
Barbara et al., 1992 [18]	Italy	US	N = 59 (n = 39)	Mean ± SD: 12.0 ± 7.5 Range: 3.0-31.6	Range: 0.7-5.0	Mean ± SD: 204 ± 135 Median: 172 Range: 27-606
Imaeda et al., 1993 [19]	Japan	CT	N = 18	Mean ± SD: 12.1 ± 8.3 Range: 3.8-35.0	Mean ± SD: 1.9 ± 0.7 Range: 0.4-3.0	Mean, 95% CI: 71, 54-94 Median: 67 Range: 28-230

Study, Year	Country	Imaging Modality	N = tumors (n=patients)	Follow-up (months)	Initial Tumor Size, diameter (cm)	Tumor Volume Doubling Time (DT, days) *
Saitoh et al., 1995 [20]	Japan	CEUS or CT	N = 17 (n = 12)	Mean ± SD: 10.2 ± 4.3 Range: 4.2-22.3	Mean ± SD: 1.6 ± 0.6 Range: 1.0-3.1	Mean, 95% CI: 272, 204-363 Median: 299 Range: 89-607
Ebara et al., 1998 [21]	Japan	US	N = 30	Mean ± SD: 20.9 ± 11.5 Range: 6-48	Mean ± SD: 1.8 ± 0.6 Range: 0.8-2.9	Mean, 95% CI: 167, 121-230 Range: 30-1,086
Saito et al., 1998 [22]	Japan	US	N = 21	Mean ± SD: 7.6 ± 6.0 Range: 2.0-25.1	Mean ± SD: 1.8 ± 0.8 Range: 0.6-3.0	Mean, 95% CI: 169, 128-223 Median: 143 Range: 76-720
Nakajima et al., 2002 [23]	Japan	US, CT or MRI	N = 34	Mean ± SD: 3.9 ± 2.3 Range: 0.4-8.3	Mean ± SD: 2.4 ± 1.2 Range: 0.4-5.9	Mean, 95% CI: 70, 54-91 Median: 74 Range: 17-274
Kubota et al., 2003 [24]	Japan	CT	N = 22	Mean ± SD: 9.4 ± 9.1 Range: 0.9-35.7	Mean ± SD: 1.0 ± 0.7 Range: 0.3-3.0	Mean, 95% CI: 88, 64-121 Median: 83 Range: 33-496
Saftoiu et al., 2004 [25]	Romania	US	N = 27	≥ 6	Mean ± SD: 6.8 ± 2.3 Range: 1.5-12.7	Mean ± SD: 140 ± 122 Median: 160 Range: 28-580
Taouli et al., 2005 [26]	United States	CT or MRI	N = 16 (n = 11)	Mean, 95% CI: 5.8, 1.6-20.5 Range: 2.5-15.5	Mean, 95% CI: 3.0, 2.4-3.7 Range: 1.4-8.0	Mean, 95% CI: 127, 80-203 Range: 17-541
Shingaki et al., 2013 [27]	Japan	CT	N = 22	Mean ± SD: 1.5 ± 0.8 Range: 0.5-3.7	Mean ± SD: 2.6 ± 1.4	Mean ± SD: 91 ± 94 Range: 9-406

Study, Year	Country	Imaging Modality	N = tumors (n=patients)	Follow-up (months)	Initial Tumor Size, diameter (cm)	Tumor Volume Doubling Time (DT, days) *
Excluded Studies (n=3)						
Cucchetti et al., 2005 [122]	Italy	CT or MRI	N = 62	Median: 2.6 Range: 0.7-4.1	Median: 3.2 Range: 1.2-6.8	Median: 80 Range: 13-356
Choi et al., 2007 [123]	United States	MRI	N = 33 (n = 21)	Mean: 12.4	Mean: 1.1 Range: 0.6-1.9	Mean: 285, Median: 188 Range: 69-2,042
Furlan et al., 2012 [124]	United States	MRI	N = 69 (n = 48)	Mean: 8.8 Range: 1.3-33.3	Mean ± SD: 1.2 ± 0.3 Range: 0.5-2.0	Median: 210, Range: 30-2,671

Cat. = category, CI = confidence interval, CT = computed tomography, HCC = hepatocellular carcinoma, MRI = magnetic resonance imaging, SD = standard deviation, US = ultrasound

† To satisfy the normality assumption for the random effects model, the meta-analysis was conducted using the geometric mean ± SD for DT to achieve normality at the log-scale. [39,125] Studies were included in the meta-analysis if they directly estimated the geometric mean, [24,26] or provided raw data to allow estimation of the geometric mean. [14,15,17,19-23] For studies that only estimated the arithmetic mean ± SD, [16,18,25,27] the geometric mean and 95% CI were approximated using previously validated methods. [125] Studies that provided only the median and range for DT were ultimately excluded. [122-124]

* Mean, 95% CI represents the geometric mean and 95% confidence interval, unless where noted, [16,18,25,27] mean ± SD represents the arithmetic mean and standard deviation.

APPENDIX E: SUMMARY OF RESULTS FOR THE LITERATURE SEARCH ON PUBLISHED ARTICLES THAT ASSESSED THE ACCURACY OF DIAGNOSTIC IMAGING MODALITIES FOR THE DETECTION OF HEPATOCELLULAR CARCINOMA.

PubMed Search – conducted on November 18, 2012 and updated on February 13, 2014

#	Facet	Search Terms	Results 11/18/12	Results* 2/13/14
1	Hepatocellular carcinoma	“Liver Neoplasms”[Mesh] OR “hepatocellular carcinoma”[Title/Abstract] OR “hepatic carcinoma”[Title/Abstract] OR “liver carcinoma”[Title/Abstract] OR “liver cancer”[Title/Abstract] OR “hepatic cancer”[Title/Abstract] OR hepatoma[Title/Abstract]	134,622	13,297
2	AFP	"alpha-Fetoproteins"[Substance Name] OR alpha-fetoprotein[Title/Abstract] OR α-fetoprotein[Title/Abstract] OR α-foetoprotein[Title/Abstract] OR alpha-foetoprotein[Title/Abstract] OR “alpha fetoprotein”[Title/Abstract] OR “α fetoprotein”[Title/Abstract] OR “α foetoprotein”[Title/Abstract] OR “alpha foetoprotein”[Title/Abstract] OR alphafetoprotein[Title/Abstract] OR alphafoetoprotein[Title/Abstract] OR AFP[Title/Abstract]	20,645	1,539
3	Ultrasound	Ultrasonography[Mesh] OR ultrasound[Title/Abstract] OR “ultrasonography”[Title/Abstract] OR “ultrasonographic”[Title/Abstract] OR “ultrasonic”[Title/Abstract]	365,903	37,431
4	CT	"Tomography, X-Ray Computed "[MESH] OR “computed tomography”[Title/Abstract] OR “computerized tomography”[Title/Abstract] OR “computer tomography”[Title/Abstract] OR “Computed axial tomography” [Title/Abstract] OR “CT”[Title/Abstract]	399,941	53,745
5	MRI	"Magnetic Resonance Imaging"[Mesh] OR "magnetic resonance imaging"[Title/Abstract] OR “MRI”[Title/Abstract]	330,612	49,056
6	Biopsy	Biopsy[Mesh] OR biopsy[Title/Abstract]	331,470	26,173
7	Combine Imaging	#2 OR #3 OR #4 OR #5	1,242,312	143,083
8	HCC Imaging	#1 AND #7	29,872	3,006
9	Diagnostic Imaging Accuracy	"Sensitivity and Specificity"[Mesh] OR “Predictive Value of Tests”[Mesh] OR “False Negative Reactions”[Mesh] OR “False Positive Reactions”[Mesh] OR sensitivity[Title/Abstract] OR specificity[Title/Abstract] OR “predictive value”[Title/Abstract] OR “false	962,505	110,324

		positive”[Title/Abstract] OR “false negative”[Title/Abstract]		
10	HCC Imaging Accuracy	#8 AND #9	4,472	658
12	Exclude Colorectal Cancer Metastases	#10 NOT ("colon"[Title/Abstract] OR "colorectal"[Title/Abstract] OR "Colorectal Neoplasms"[Mesh] OR "Colonic Neoplasms"[Mesh])	3,888	593
11	Published as of 01/01/2000 *	#10 Filters: Publication date from 2000/01/01	2,538	----

Embase Search – conducted on November 18, 2012 and updated on February 13, 2014

#	Facet	Search Terms	Results* 11/8/12	Results** 2/13/14
1	Hepatocellular Carcinoma	'hepatocellular carcinoma'/exp OR 'hepatocellular carcinoma'	90,442	19,662
2		'liver cancer'/exp OR 'liver cancer'	138,073	28,302
3		'liver carcinoma'/exp OR 'liver carcinoma'	84,109	18,440
4		'liver cell carcinoma'/exp OR 'liver cell carcinoma'	83,711	18,367
5		#1 OR #2 OR #3 OR #4	143,800	29,435
6	AFP	'alpha fetoprotein'/exp OR 'alpha fetoprotein'	10,997	3,074
7		afp	9,758	3,264
8		#6 OR #7	16,917	5,219
9	Ultrasound	'ultrasonography'/exp OR ultrasonography	305,439	83,383
10		'ultrasound'/exp OR ultrasound	175,438	51,656
11		ultrasonographic	11,474	2,469
12		'ultrasonic'/exp OR ultrasonic	71,449	23,834
13		#9 OR #10 OR #11 OR #12	398,626	112,001
14	CT	'computer assisted tomography'/exp OR 'computer assisted tomography'	365,298	102,980
15		'computed tomography'/exp OR 'computed tomography'	378,174	106,695
16		ct	275,181	86,504
17		#14 OR #15 OR #16	523,678	152,047
18	MRI	'magnetic resonance imaging'/exp OR 'magnetic resonance imaging'	375,963	113,592
19		'mri'/exp OR mri	375,451	113,551
20		#18 OR #19	387,984	116,711
21	Biopsy	'biopsy'/exp OR biopsy	305,771	84,091
22	Combine Imaging	#8 OR #13 OR #17 OR #20 OR #21	1,305,103	371,561
23	HCC Imaging	#5 AND #22	27,670	9,144
24	Diagnostic Imaging Accuracy	'sensitivity and specificity'/exp OR 'sensitivity and specificity'	164,355	43,533

25		'predictive value'/exp OR 'predictive value'	61,232	34,066
26		'false negative'	16,113	4,796
27		'false positive'	27,129	7,981
28		#24 OR #25 OR #26 OR #27	231,926	73,593
29	HCC Imaging Accuracy	#23 AND #28	2,352	948
30	Exclude Colorectal Cancer Metastases	'colon'/exp OR colon	435,653	71,245
31		colorectal AND ('cancer'/exp OR cancer)	123,772	30,574
32		colorectal AND ('carcinoma'/exp OR carcinoma)	42,865	8,691
33		#30 OR #31 OR #32	448,573	75,133
34		#29 NOT #33	1,955	789

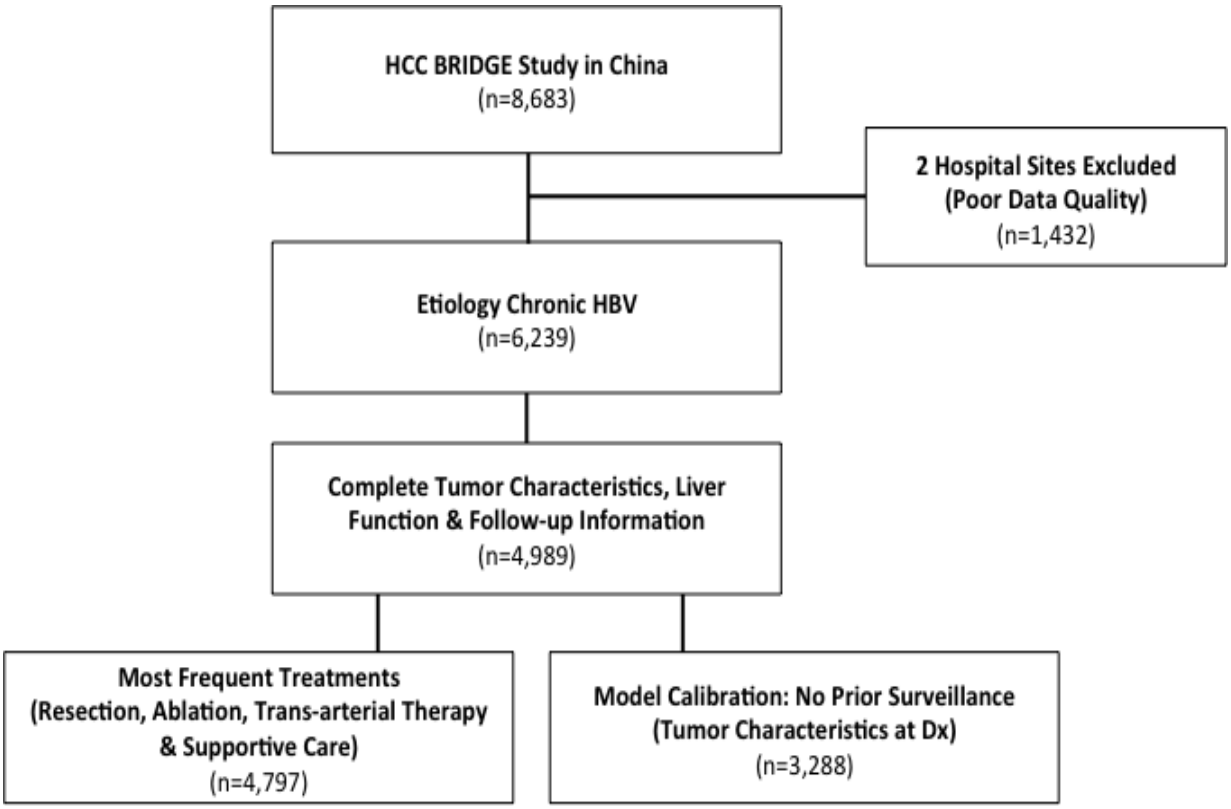
Total on November 18, 2012 (after removal of duplicates): 3,564 Articles

Total on February 13, 2014 (after removal of duplicates): 4,341 Articles

* Both the PubMed and Embase searches were restricted to articles published as of January 1, 2000 to ensure both accurate and current assessments of the diagnostic accuracy of the HCC imaging modalities listed above. The year 2000 was deemed an appropriate cut-point based on a review of HCC diagnostic imaging studies referenced in a prior health technology assessment of HCC surveillance conducted in the United Kingdom. [83]

** Searches conducted on February 13, 2014 were restricted to studies published as of November 1, 2012 (PubMed) and January 1, 2012 (Embase), respectively.

APPENDIX F: HCC BRIDGE STUDY SAMPLE SELECTION FOR MODEL PARAMETERS INCORPORATED IN THE SIMULATION MODEL.



Dx = diagnosis, HBV = hepatitis B virus, HCC BRIDGE = BRIDGE to Better Outcomes in Hepatocellular Carcinoma Study

APPENDIX G: DEMOGRAPHICS AND CLINICAL CHARACTERISTICS FOR PATIENTS DIAGNOSED WITH HCC IN TAIWAN, ACCORDING TO SURVEILLANCE STATUS, AFTER PROPENSITY SCORE ANALYSIS.

	Propensity-Based Weighting			Propensity-Based Matching **		
Characteristic *	**Surveillance (n=829)**	**No Surveillance (n=704)**	**p-value**	**Surveillance (n=829)**	**No Surveillance (n=829)**	**p-value**
Age years	61.1 ± 11.6	61.0 ± 12.9	0.9	62.1 ± 11.7	61.9 ± 13.0	0.7
Male Gender	594 (71.7)	509 (72.3)	0.8	554 (66.8)	594 (71.7)	0.03
Co-morbidities						
Diabetes mellitus	162 (19.5)	143 (20.3)	0.7	165 (19.9)	154 (18.6)	0.5
CVD	92 (11.1)	77 (10.9)	0.9	80 (9.7)	81 (9.8)	0.9
Hypertension	289 (34.9)	246 (35.0)	0.9	282 (34.0)	251 (30.3)	0.1
HCC Etiologies						
HBV	524 (63.2)	451 (64.1)	0.9	532 (64.2)	538 (64.9)	0.8
HCV	261 (31.5)	223 (31.7)	0.9	320 (38.6)	324 (39.1)	0.8
ALD	43 (5.2)	31 (4.4)	0.5	27 (3.3)	23 (2.8)	0.6
NAFLD	69 (8.3)	60 (8.5)	0.9	62 (7.5)	67 (8.1)	0.6
Other/Idiopathic	59 (7.1)	52 (7.4)	0.8	20 (2.4)	23 (2.8)	0.6
Liver Function						
CP A/No Cirrhosis	765 (92.3)	650 (92.3)		792 (95.5)	622 (97.0)	
CP B	64 (7.7)	52 (7.4)	0.3	37 (4.5)	25 (3.0)	0.1
CP C	0 (0.0)	2 (0.3)		0 (0.0)	0 (0.0)	

ALD = alcohol liver disease, CP = Child-Pugh score, CVD = cardiovascular disease, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, NAFLD = non-alcoholic fatty liver disease

* Values are expressed as mean ± standard deviation and n (%) for continuous and categorical variables, respectively.

** Patients in the no surveillance group were matched with patients in the surveillance group within a ± 0.05 range of the PS; [42,141] a total of 526 patients from the no surveillance group (74.7%) were identified as matches. To retain the full sample of patients in the surveillance group, patients in the no surveillance group were sampled with replacement to achieve a 1:1 ratio of patients in the two groups.

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