Epidemiology of Hepatitis B related hepatocellular carcinoma in South Australia: Strategies for improved outcomes based on optimizing treatment uptake, screening program and percutaneous interventions

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CONTENTS:

SUMMARY

Background & aims: The aims of this thesis were to investigate five clinically relevant questions concerning chronic hepatitis B (CHB) - related hepatocellular carcinoma (HCC); (1) what is the epidemiology of CHB- related HCC in South Australia (SA)? (2) What are the estimated clinical benefits of increasing treatment uptake in CHB? (3) Is there a survival benefit within a dedicated HCC screening program in high risk groups? (4) What are the local recurrence rates and disease free survival rates following percutaneous ablation therapies in HCC? and (5) what type of thermal ablation therapy provides superior outcomes?

Methods: For aim 1, subjects notified with CHB between 1996 and 2010 in SA were probabilistically linked with cancer and death registry records to calculate the survival, crude and age-standardized incidence rates. Using a Markov mathematic model for aim 2, the cost-effectiveness of increasing treatment uptake in CHB was assessed. The current level of treatment uptake (2.9%) was compared with recommended targets of 10% and 15% to calculate the incremental cost per quality-adjusted life years (QALYs) gained. Aim 3 was assessed by comparing the overall survival (OS), tumour stage at diagnosis and the proportion of patients having curative therapy between those diagnosed within and outside of a dedicated HCC screening program. Aim 4 was investigated with a multicentre retrospective cohort study investigating local recurrence rates following percutaneous ablation. For aim 5, a meta-analysis was performed to assess differences in local tumour progression rates (LTP) post radiofrequency (RFA) and microwave ablation (MWA).

Results: The overall crude and age-standardized CHB- related HCC incidence was 111.3/100,000 and 189.1/100,000 person-years respectively, and rates for men were significantly higher than for women. CHB- related HCC incidence increased in a linear fashion during the study period with an annual percentage change of 20.8%. Median OS was 12.5 months, with a trend towards longer survival between 2006 and 2010 (21.8 months).

Increasing HBV treatment uptake to 15% was associated with the highest mean QALY gained (8.20) compared to 10% (7.99) and 2.9% (7.68) uptake rates. The corresponding mean cost/person over 10 years was AU$60,133 v AU$61,964 and AU$64,597 respectively. Higher treatment uptake was cost-effective with at least 2 years of increased uptake rates.

HCC diagnosed within a dedicated screening program had a better median OS compared to those diagnosed outside the program [26.8 v 11.5 months, p=0.01]. Subjects within the program had an earlier stage HCC and a significantly greater proportion were treated with curative intent. Propensity score adjustment using baseline clinical characteristics estimated a 58% real reduction in HCC mortality for patients diagnosed within the program.

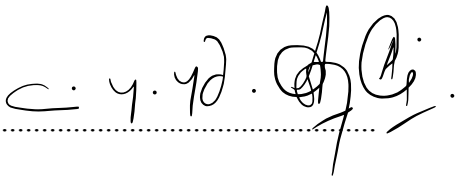
With respect to outcomes following percutaneous thermal ablation, the local recurrence rate was 23.4%. Overall mean (±SD) local recurrence-free survival was 46.9 (±3.6) months and this was marginally higher in nodules ≤2cm. Poorly differentiated HCC and pre-treatment AFP >50 kIU/L were independent predictors of local recurrence.

Meta-analysis comparing RFA and MWA suggested that both techniques were equally safe and effective; MWA was more effective in preventing local recurrence when treating larger tumours. Other outcomes including completion ablation rates and adverse events were similar between the groups.

Conclusions: CHB- related HCC has been progressively increasing in SA over the past two decades. Increasing treatment uptake rates in CHB improves the survival by reducing the number of expected clinical events. Dedicated, centralised HCC screening programs provide improved HCC outcomes relative to an unscreened HCC population. There is a relatively high local recurrence rate following percutaneous ablation therapy for HCC and both MWA and RFA provide similar clinical outcomes.

DECLARATION

I certify that this thesis does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text.

Signed 

[Dr Mohamed Asif Chinnaratha]

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PUBLICATIONS

Full-text:

- **Chinnaratha MA**, Graham C, Fraser RJ, Woodman RJ, Wigg AJ. Rising incidence of hepatitis B related hepatocellular carcinoma in South Australia: 1996-2010. *Intern Med J.* 2016 Aug; 46(8):902-8 [Incorporated into chapter 2].

- **Chinnaratha MA**, Kaambwa B, Woodman RJ, Fraser RJ, Wigg AJ. Assessing the clinical and economic impact of increasing treatment uptake in chronic hepatitis B infection using a Markov model. *J Gastroenterol Hepatol*. Accepted article – 12/12/2016. [Incorporated into chapter 3].

- **Chinnaratha MA**, Sathananthan D, Pateria P, Tse E, MacQuillan G, Mosel L, Pathi R, Madigan D, Wigg AJ. High local recurrence of early stage hepatocellular carcinoma post percutaneous thermal ablation in routine clinical practice. *Eur J Gastroenterol and Hepatol* 2015 Mar; 27(3):349-54 [Incorporated into chapter 5].

- **Chinnaratha MA**, Chuang M-Y, Fraser RJ, Woodman, RJ, Wigg AJ. Percutaneous thermal ablation for primary hepatocellular carcinoma: A Systematic review and Meta-analysis. *J Gastroenterol Hepatol.* 2016 Feb; 31(2):294-301 – one of the featured articles in this issue with a commentary (Incorporated into chapter 6]

Abstracts:

- **Chinnaratha MA** et al., Improved survival of hepatocellular carcinoma patients diagnosed with a dedicated surveillance program. *J Gastroenterol Hepatol* 2015; 30 (Suppl. 3): 186.

- **Chinnaratha MA** et al., Trends in the incidence and mortality of Hepatitis B related Hepatocellular Carcinoma in South Australia: 1996–2010. *J Gastroenterol Hepatol* 2015; 30 (Suppl. 3): 186 – 187.

- **Chinnaratha MA** et al., Percutaneous thermal ablation for hepatocellular carcinoma: A systematic review and meta-analysis. *Hepatology*, Oct 2014; 60 (4) (Suppl): 154A.

- **Chinnaratha MA** et al., Percutaneous thermal ablation for primary hepatocellular carcinoma: a systematic review and meta-analysis. *J Gastroenterol Hepatol* 2014; 29 (Suppl. 2): 71.

- **Chinnaratha MA** et al., Predictors of Hepatocellular carcinoma recurrence post thermal ablation. *Hepatology*, Oct 2013; 58 (4) (Suppl): 202A.

  Chinnaratha MA et al., Predictors of hepatocellular carcinoma recurrence post thermal ablation. *J Gastroenterol Hepatol* 2013; 28 (Suppl. 2): 66.

PRESENTATIONS

Oral presentations:

- **Chinnaratha MA**, Very early stage HCC: When to resect, ablate or transplant – AGW 2016: Innovations in Medicine (Adelaide, SA)

- **Chinnaratha MA**, HCC surveillance in chronic hepatitis B: in whom and why? **-** 2016 South Australia GUT club (State-wide Gastro meeting - Adelaide, SA)

- **Chinnaratha, MA** et al., Trends in the incidence and survival of hepatitis B related hepatocellular carcinoma in South Australia: 1996-2010 – Gastro 2015 AGW-WGO International congress (Brisbane, Qld)

- **Chinnaratha, MA** et al., Economic impact of increasing treatment uptake in chronic hepatitis B infection – Gastro 2015 AGW-WGO International congress (Brisbane, Qld)

- **Chinnaratha, MA** et al., Percutaneous thermal ablation for primary hepatocellular carcinoma: A systematic review and meta-analysis – AGW 2014 (Gold Coast, Qld)
- **Chinnaratha** MA, Current role of thermal ablation in HCC management: Microwave – not just for popcorn anymore – 2014 South Australian GUT club (Adelaide, SA)

- **Chinnaratha MA** et al., Predictors of Hepatocellular carcinoma recurrence post percutaneous thermal ablation – AGW 2013 (Melbourne, Vic)

Posters:

- **Chinnaratha, MA** et al., Improved survival of hepatocellular carcinoma patients diagnosed with a dedicated surveillance program – Gastro 2015 AGW-WGO International congress (Brisbane, Qld)

- **Chinnaratha, MA** et al., Percutaneous thermal ablation for hepatocellular carcinoma: A systematic review and meta-analysis – The Liver Meeting ®, AASLD 2014 (Boston, USA)

- **Chinnaratha, MA** et al., Predictors of hepatocellular carcinoma recurrence post thermal ablation - The Liver Meeting ®, AASLD 2013 (Washington, USA)

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2015 **Best student publication award** from the Faculty of Medicine, Nursing and Health Sciences, Flinders University of South Australia

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ABBREVIATIONS

AASLD	American Association for the Study of Liver Disease
AE	Adverse events
AFP	Alpha feto-protein
ALT	Alanine transaminase
Anti-HBe	Hepatitis B e antibody
APASL	Asian Pacific Association for the Study of Liver
APC	Annual percentage change
ASR	Age-standardized rate
ATSI	Aboriginal and Torres Strait Islanders
BCLC	Barcelona Clinic Liver Cancer (staging)
BDM	Births, deaths and marriages (registry)
CA	Complete ablation
CC	Compensated cirrhosis
CDCB	Communicable Disease Control Branch
CEAC	Cost-effectiveness acceptability curves
CEP	Cost-effectiveness plane
CHB	Chronic hepatitis B

CHC	Chronic hepatitis C
CI	Confidence interval
CT	Computed tomography
CUA	Cost utility analysis
DALY	Disability-adjusted life-years
DC	Decompensated cirrhosis
DOB	Date of birth
EASL	European Association for the Study of Liver
EU	European Union
GP	General Practitioner
HBeAg	Hepatitis B e antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Hazard ratio
ICER	Incremental cost-effectiveness ratio
IDR	Intra-hepatic distant recurrence

IDU	Injecting drug use
IHR	Intra-hepatic recurrence (overall)
INR	International normalized ratio
IQR	Inter-quartile range
LT	Liver transplant
LTP	Local tumour progression
MELD	Model for end-stage liver disease
MOOSE	Meta-analysis of observational studies in epidemiology
MRI	Magnetic resonance imaging
MSM	Men who have sex with men
MWA	Microwave ablation
NASH	Non-alcoholic steatohepatitis
NOM	Net overseas migration
NSW	New South Wales
OR	Odds ratio
OS	Overall survival
PBS	Pharmaceutical benefits scheme
PCR	Polymerase chain reaction
PEI	Percutaneous ethanol injection

PTA	Percutaneous thermal ablation
QALY	Quality-adjusted life-years
QoL	Quality of life
RCT	Randomized controlled trial
RFA	Radiofrequency ablation
SA	South Australia
SALHN	Southern Adelaide Local Health Network
SIR	Standardized incidence rate
SIRT	Selective internal radiotherapy
TACE	Trans-arterial chemo-embolization
UCSF	University of California San Francisco
UK	United Kingdom
USA	United States of America
USS	Ultrasound scan
WHO	World Health Organization

1. LITERATURE REVIEW

1.1 HEPATITIS B EPIDEMIOLOGY:

Chronic hepatitis B virus (HBV) infection, defined as hepatitis B surface antigen (HBsAg) positivity for at least 6 months, is a global public health problem. Since the HBV vaccines were developed and peri-natal vaccination programs were implemented from the 1980s, there has been a significant reduction in new infection in some countries. However, given the long latency period to the development of complications like hepatocellular carcinoma (HCC), and delayed introduction of infant vaccination programs in some countries, the disease burden from the existing chronic hepatitis B (CHB) will pose a significant challenge for the next few decades.

1.1.1 Global Prevalence:

According to a recent estimate from the World Health Organization (WHO), updated in July 2015, there are approximately 240 million people worldwide who are chronically infected with hepatitis B with a global prevalence of 3.24% (1). There is an overall decline in the global prevalence of the disease as the previous WHO report from 2009 estimated the chronic carriers to be around 360 million people (2). However, the prevalence of CHB is highly variable ranging from <1% in low endemic areas to up to 30% in high endemic areas (3) **(Figure 1.1)**. The prevalence of CHB and mode of HBV transmission varies widely by geographic distribution and by population subgroups.

In areas of high HBV endemicity, like sub-saharan Africa, most of Asia, the Amazon basin and the western Pacific (except Australia and Japan), the usual mode of transmission is at the time of birth (vertical transmission) or in early childhood. The majority of the world's population (~45%) live in high HBV endemic areas, where the HBV prevalence is >8% and their life time risk of developing HBV infection would be >60% (3). Only 12% live in low HBV endemic areas like western Europe, North America and Australia, where the HBV prevalence is <1% and their life time risk of HBV infection is <20% (3). In these low endemic areas, the common mode of transmission is horizontal and in adulthood, either by sexual transmission or by the use of contaminated needles.

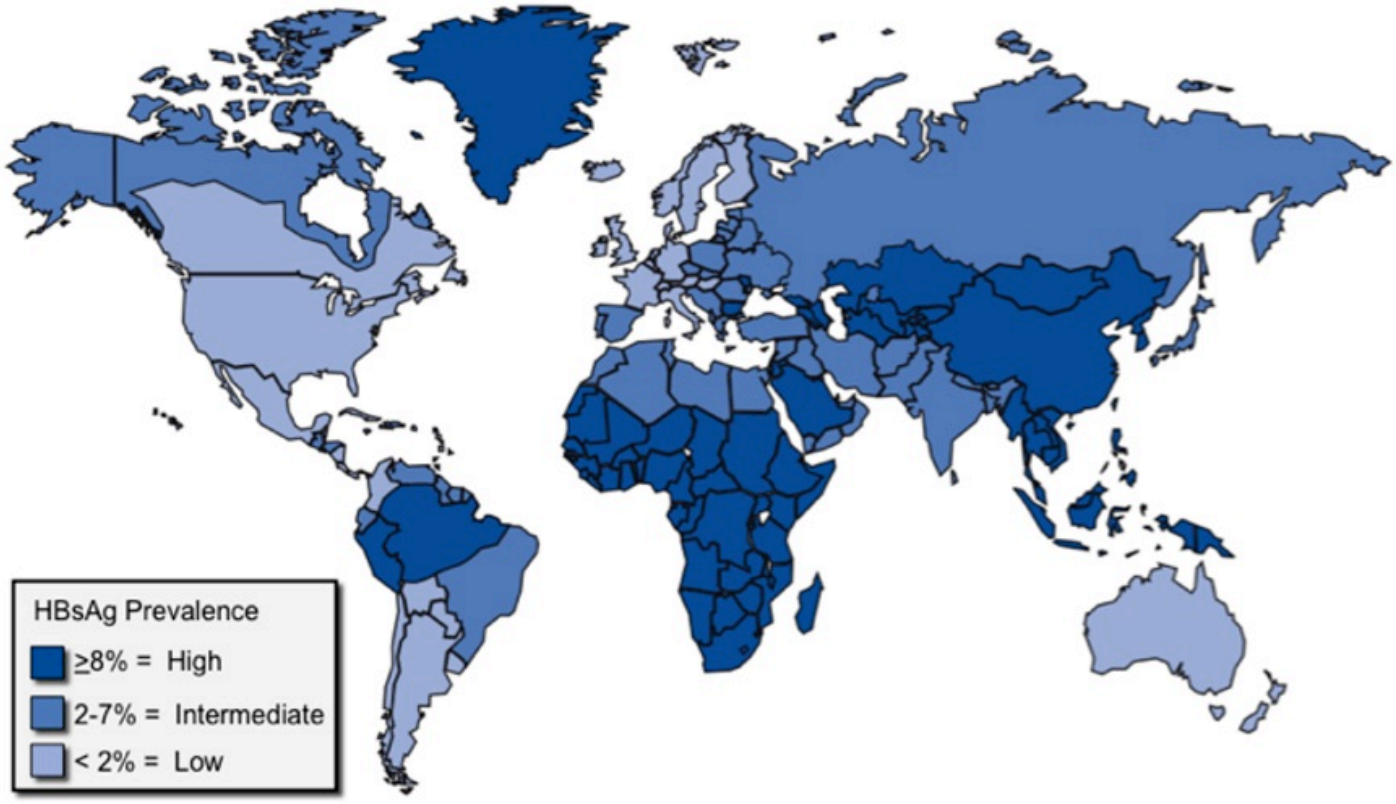

Figure 1.1: Global prevalence estimates of chronic hepatitis B

(Adapted from World Health Organization (http://www.who.int/csr/disease/hepatitis/en/)

The remainder of the world's population (~43%) live in areas of intermediate HBV endemicity, (Eastern and Central Europe, the Middle-East and the Indian sub-continent), where the HBV prevalence is 1-7% and their life time risk of developing HBV infection ranges from 20-60% (3).

There are 8 HBV genotypes (A-H) and each has a distinctive geographical distribution **(Figure 1.2)**. These can be further divided into sub genotypes. It is important to understand the HBV genotypes as they exhibit different clinical and virological manifestations. Genotypes A and B respond better to treatment with Interferon compared to genotypes C and D (4). Further, HBV pre-core mutations commonly occur in genotype D followed by genotypes C, B and A and hence HBeAg –ve CHB most commonly occurs in genotype D dominant regions (eg., Mediterranean areas) (5). Liver disease is more severe in genotype B and C compared to genotype A (6); however, cirrhosis and HCC develop more frequently with genotype C (6-8).

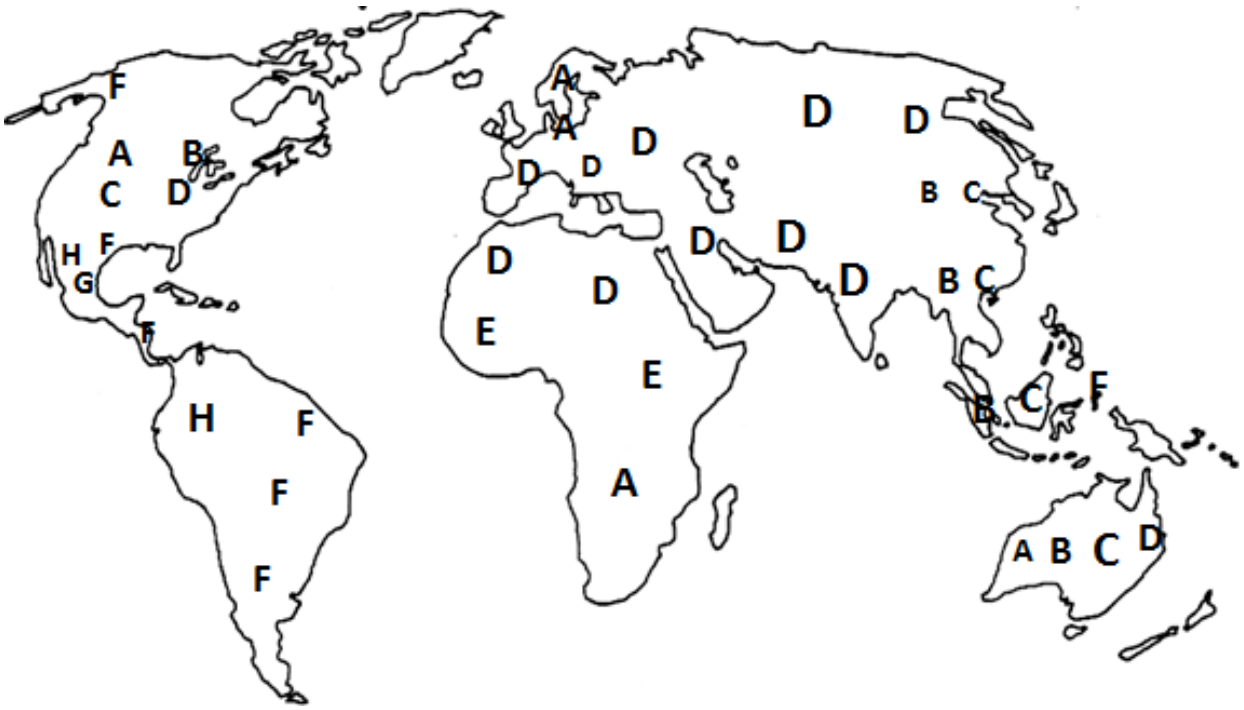

Figure 1.2: Chronic hepatitis B genotype distribution across the globe

1.1.2 Hepatitis B in Australia:

HBV was discovered in 1965 and was initially named the "Australia antigen" as it was first seen in the serum of Australian Indigenous population (9). Since then, the prevalence of CHB continues to increase, predominantly related to the increase in immigration from high endemic areas (10, 11). An accurate estimate of the number of people with CHB in Australia is limited as there is a lack of large scale, good quality population-level epidemiological data. Also, the notifications of CHB are dependent on levels of hepatitis B testing and reporting. Based on the CHB notification data, the population rate of diagnosis was 32 per 100,000 population (12). However, approximately 45% of cases remain undiagnosed and hence untreated (13). According to a recently released national report, based on a modelled estimate, there are approximately 218,000 people in Australia currently with CHB which would equate to a prevalence of 1.02% (14).

The current modelled estimate has increased significantly compared to a decade ago (2004) which estimated the number of people with CHB in Australia to be between 90,000 and 160,000 representing a population prevalence of 0.5%-0.8% (15). This is likely due to an ageing CHB population as the notification rate has remained steady at national level in recent years, with around 6000-7000 new notifications per year. Even though the rate of CHB notification varies significantly between the states and territories, there is no significant variation in the population prevalence among them **(Figure 1.3)**. Highest CHB prevalence was seen in Northern territory and lowest prevalence was in Tasmania.

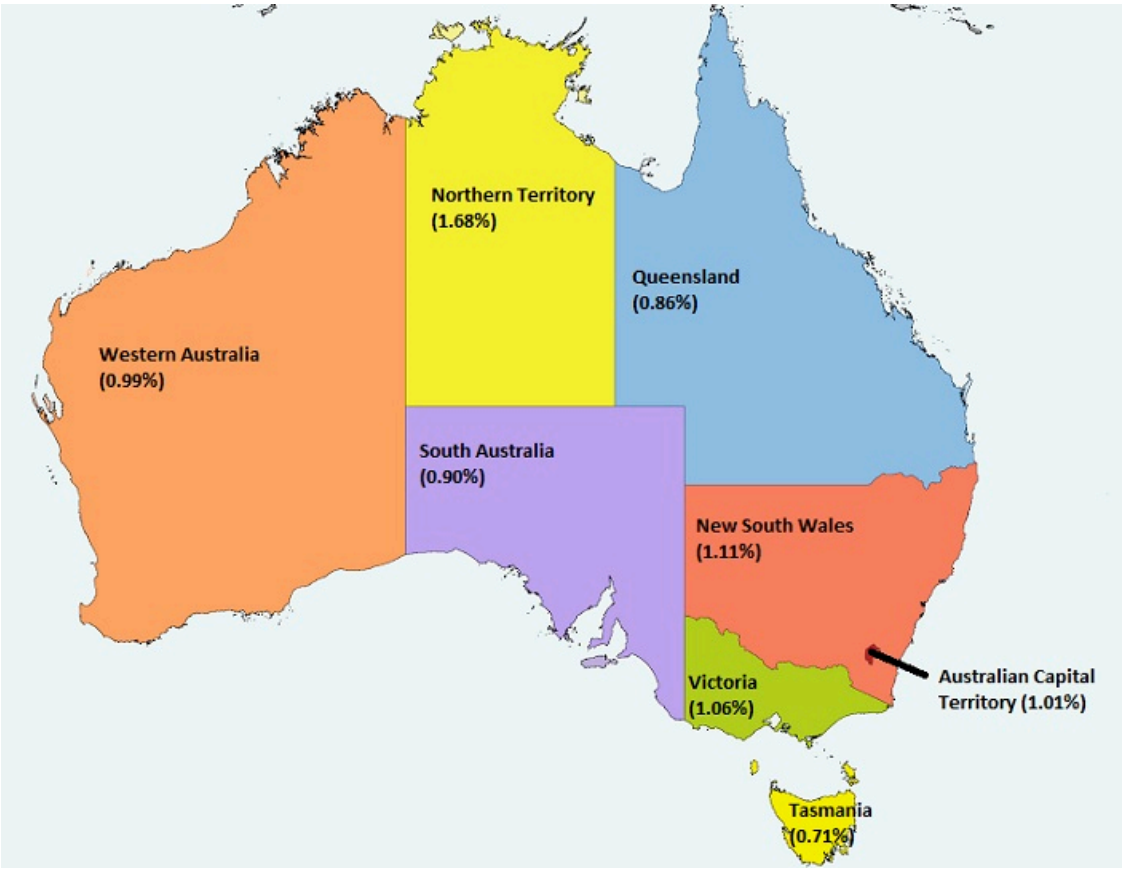

Figure 1.3: Estimated prevalence of chronic hepatitis B in Australia

In South Australia (SA), based on the recent modelled estimates, there were 14,400 people with CHB and the population prevalence (0.90%) is marginally lower than the national prevalence. Also, the population rate of diagnosis based on the notification data has remained relatively stable (15-20 per 100,000 population) over the past 15 years. However, this is expected to increase significantly over the next few years as the net overseas migration (NOM) remains the main mode of population growth in SA. The majority of this overseas migration to SA occurs from high/intermediate HBV prevalence areas like China, Vietnam, India and Italy (16).

1.1.3 High risk groups for hepatitis B in Australia:

The majority of people with CHB in Australia were born overseas, particularly in China and Vietnam where the CHB prevalence is high (15-20%) (15, 17). Increasing migration from HBV

endemic areas, particularly from the Asia-pacific region and Africa, along with the Aboriginal and Torres Strait Islanders (ATSI) represent approximately two thirds of those living with CHB in Australia (13, 15, 18). Other specific populations, particularly unvaccinated adults, considered to be at high risk include: injecting drug users (IDU), men who have sex with men (MSM), sex workers, those with HIV and/or hepatitis C infection and people in custodial settings (15, 18-22). A cross-sectional estimate of the proportions of CHB prevalence in Australia showed that 46% were born in south-east or north-east Asia, 16% were from ATSI population, 8% were MSM, 5% were IDU and the remaining 25% had other risk factors (15). Specific prevalence estimates among these groups are high including 8-10% in ATSI, 3% in MSM, 1.6-3.0% in IDU, 5-11% among migrants born in Asia and 3% in custodial settings (14, 15, 23-26). The CHB prevalence among the high risk groups is expected to increase further. This is mainly because of the large proportion of undiagnosed HBV infection, delayed introduction of vaccination programs in high endemic countries like China and Vietnam and sub-optimal vaccination coverage within other high-risk cohorts (20, 27).

1.2 NATURAL HISTORY:

The presentation of acute hepatitis B infection ranges from asymptomatic infection to self-limiting hepatitis to fulminant hepatitis. Approximately one third of acute infections in adults are symptomatic however, fulminant hepatitis is rare (<1%) but with a high mortality (~70%) (28). HBV is predominantly transmitted by blood and other body fluids like saliva and semen. Chronicity of the infection is closely correlated with the age of the patient at the time of infection. CHB is seen in 90% of infants infected at birth, 20-30% of children infected between 1 and 5 years of age, 6-10% in children aged 6-15 years and <5% of patients infected as adults (29). Natural history studies on the risk of peri-natal infection have shown that it is much higher in infants born to HBeAg +ve mothers (65-85%) compared to HBeAg -ve/Anti-HBe +ve mothers (4-18%) (30-32).

1.2.1 Stages of disease progression:

The natural course of chronic HBV infection acquired perinatally or during infancy is complex and variable and has 4 distinct phases **(Figure 1.4)** (33-35). These phases result from a complex interplay between the virus (genotype, viral load, mutations), hepatocyte and the host (age of infection, gender, immune status).

a. Immune-tolerant phase: Individuals in the immune-tolerant phase are usually young and asymptomatic and this phase can last for 20 to 30 years. A cross-sectional assessment among the Australian CHB population would reveal that only 3.6% would be in this phase (36) **(Figure 1.5)**. The duration of this phase is highly variable, but longest in those who acquire infection in the peri-natal period. They are HBeAg seropositive with a high viral load. There is active viral replication in the liver but because of little immune response to the virus, there is minimal or no liver disease activity. Hence, they have a normal serum ALT level and near normal liver histology. Individuals in this phase would not require any anti-viral therapy as the risk of liver disease progression is low.
b. Immune-clearance phase: This phase is associated with declining/fluctuating HBV DNA levels. There may be acute, intermittent flares in the serum ALT levels but patients are mostly asymptomatic. Higher ALT levels usually implies a strong host immune response to the virus and more extensive hepatocyte damage (37). This results in moderate-to-high levels of liver inflammation and can result in rapid liver disease progression. These recurrent hepatitis flares will eventually lead to HBeAg seroconversion to Anti-HBe. Not all individuals will achieve HBeAg seroconversion, as some will develop recurrent exacerbations with intermittent disappearance of serum HBV DNA without loss of HBeAg. These repeated episodes of hepatitis flares increase the risk of developing cirrhosis and HCC. The current recommendation from the American Association for the Study of Liver Disease (AASLD) is to treat adults in this phase with anti-viral therapy to decrease the risk of liver-related complications (38). The annual probability of spontaneous HBeAg seroconversion varies from 2-15% depending on factors like

age, serum ALT levels and HBV genotypes (37, 39-41). The median age of onset for this phase is 30 years and is reached in the majority before 40 years.

c. Immune-control phase: The majority of patients with chronic HBV infection will eventually enter this inactive state with low/undetectable HBV DNA, normal serum ALT level (low levels of liver inflammation) and a low risk of developing advanced liver disease (42). A cross-sectional assessment among the Australian CHB population would reveal that the majority (76%) would be in this phase (36) **(Figure 1.5)**. During this phase, spontaneous HBsAg seroclearance can occur and the reported incidence in a recent study was 1.2%/year (43). Again, this depends on the HBV genotype as patients with genotype A and B have a higher likelihood of seroclearance compared to other genotypes (44, 45).

d. Immune-escape phase: A small proportion (1-4%) of HBeAg –ve patients will have sero-reversion whereby they develop HBeAg seropositivity again. However, a significant proportion of patients will develop HBeAg –ve CHB, because of the development of pre-core and core promoter mutations with reported incidence of 2-3%/year (34, 41). In this phase, there is an increase in the HBV DNA and serum ALT levels and the liver biopsy characteristically demonstrates moderate to severe histological activity with variable amounts of fibrosis. Patients with HBeAg –ve CHB have lower serum HBV DNA levels than those with HBeAg +ve CHB and are more likely to experience a fluctuating course. Since the risk of liver disease progression is increased in this phase, the majority of these patients require anti-viral therapy for viral suppression.

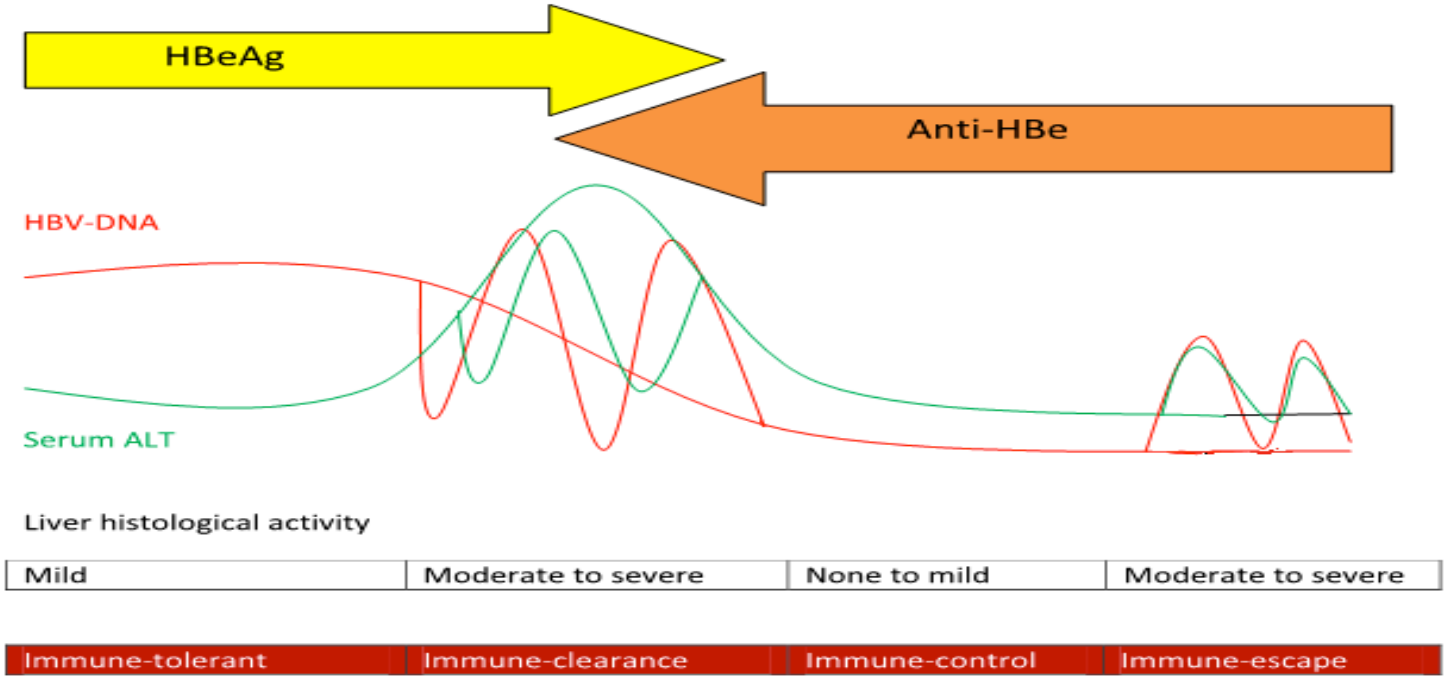

Figure 1.4: Phases of disease progression in chronic hepatitis B

Adult-acquired CHB has a similar clinical course except that there is no apparent immune-tolerant phase as this coincides with the incubation period [41]. Although HBsAg seroclearance usually confers excellent long-term prognosis, cirrhosis and HCC have been reported years after seroclearance in a small proportion of people. In this cohort, small amounts of HBV DNA can still be detected by PCR in the serum and peripheral mononuclear cells, indicating a state of occult infection and reactivation may occur with immunosuppressive therapy [42].

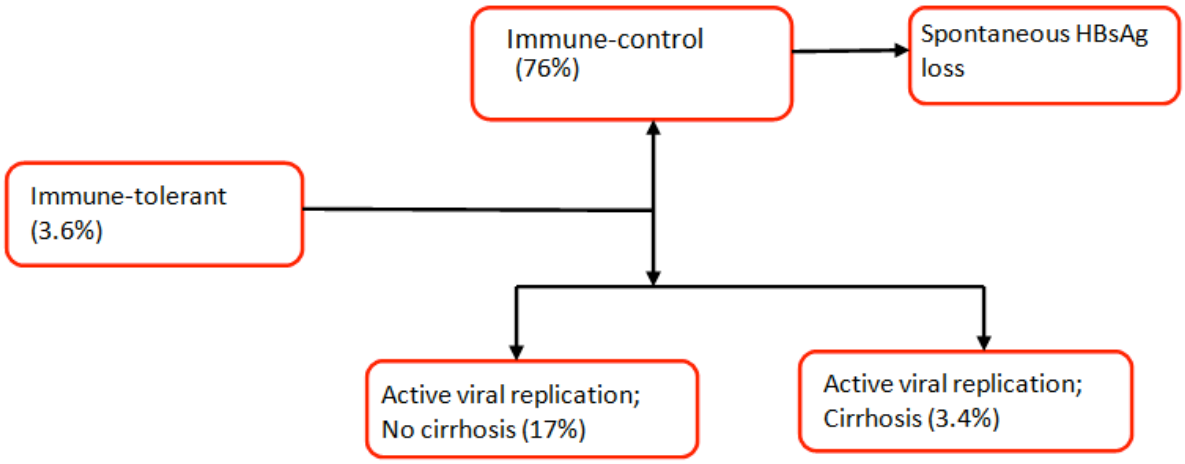

Figure 1.5: Australian cross-sectional estimates of phases in chronic hepatitis B

1.2.2 Complications:

Cirrhosis and HCC are the two major complications which may develop during the natural course of CHB. The lifetime risk of developing serious complications is 40-50% in men and 15% in women. The risk of developing these complications is variable and is influenced by host factors such as increasing age (46-48), male gender, serum ALT levels and co-factors like obesity, diabetes and increased alcohol consumption (49); viral factors such as high HBV DNA levels (46), persistent seropositivity for HBeAg (50), genotype C (51-53) and other viral co-infections (54). Among untreated adults with CHB, 5- year cumulative incidence of cirrhosis is 8%-20%. Among those

diagnosed with cirrhosis at presentation by liver biopsy, non-invasive markers or on radiological grounds, the 5- year cumulative risk of developing hepatic decompensation is 15-20% and this risk is higher in those with active viral replication compared to those without (19). The cumulative 5-year survival rate for patients with compensated cirrhosis is 80-85% but this decreases to 30-50% in those with decompensated cirrhosis (55). The annual risk of development of CHB- related complications and mortality is shown in **Figure 1.6.**

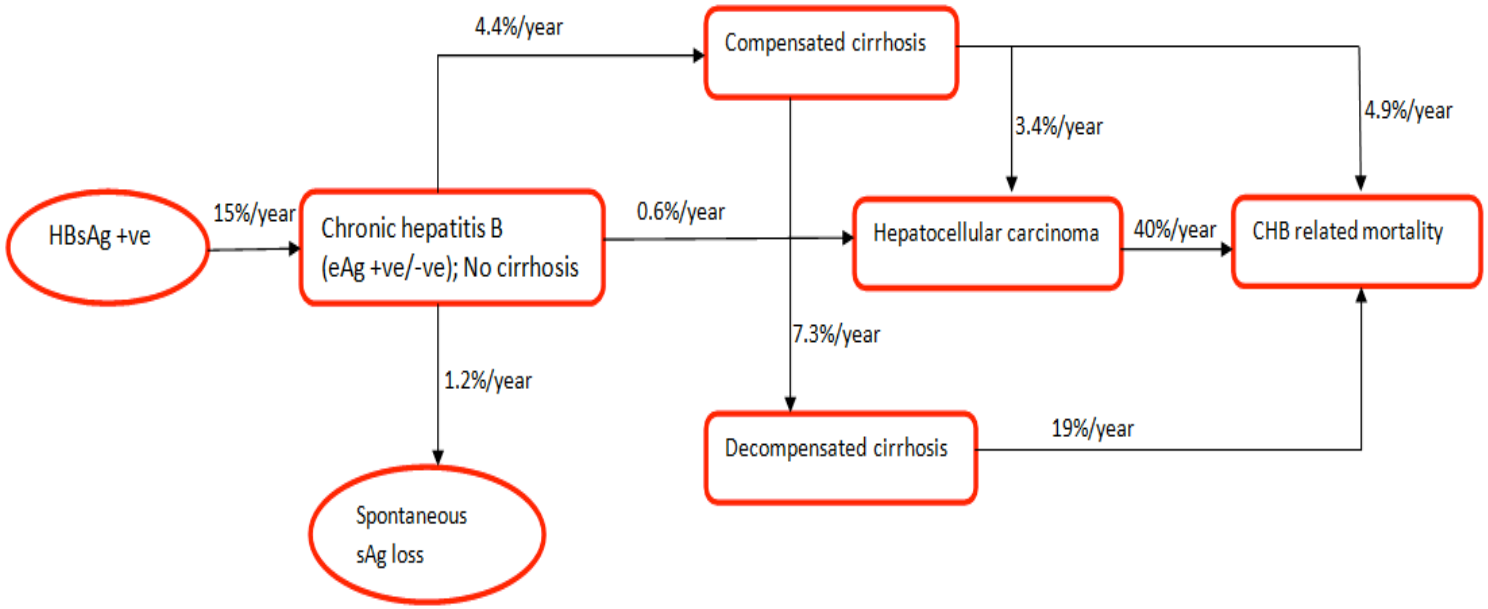

Figure 1.6: Annual risk of complications in chronic hepatitis B

1.3 HEPATITIS B RELATED HCC AND MORTALITY:

The annual risk of HCC occurrence in those with cirrhosis is 3-6% (55, 56). Two meta-analyses of cross-sectional and case-control studies showed a summary odds ratio of 22.5 (95% CI: 19.5-26.0) and 15.6 (95% CI: 11.5-21.3) respectively, for HCC development in HBsAg positive and anti-HCV/ HCV RNA negative patients (57, 58). However, the incidence rates of HBV- related HCC varies depending on the age, gender, ethnicity, underlying cirrhosis and duration of follow-up.

HCC mostly develops in those with cirrhosis and hence HCC and cirrhosis share the common risk factors (as above), with family history of HCC being an additional risk factor (59). However, HCC can also develop in non-cirrhotic livers and the major risk factors in this setting include HBV DNA level, genotype, country of origin and naturally occurring pre and basal core promoter mutations (60-62). HBV- related HCC in non-cirrhotic liver is more common in southern Africa (~40% have minimal liver damage at HCC diagnosis) compared to Asia, America and Europe (~90% have underlying cirrhosis) (63). Overall, the incidence rates of HBV- related HCC are much higher in those with cirrhosis (820-2247/ 100,000 person-years) compared to those without cirrhosis (280-474/ 100,000 person-years) (64, 65).

1.3.1 Global prevalence of hepatitis B related HCC:

Globally, HCC is the fifth most common cancer and the third most common cause of cancer related mortality (66). CHB accounts for more than 50% of HCC cases worldwide and 70-80% of HCC cases in areas with high HBV prevalence (67-69). There is a wide variability in the prevalence of HBV- related HCC with the highest prevalence seen in eastern Asia, middle and some countries of Western Africa. Among patients with HCC, HBsAg positivity is low (<25%) in Europe, United States and Japan, and high (>40%) in Greece, Asia and Africa (66). Even in countries with a low HBV prevalence such as United States and Australia, approximately 70-80% of HBV- related HCC cases are seen in the migrant Asian population (70-72). Data from New South Wales, Australia, suggests that the standard incidence rates (SIR) of HCC are up to four times higher in men and women born in Asia relative to the Australian-born population (73). This mirrors the trends seen in

the United States and the Netherlands, where the HCC rates are disproportionately higher in migrants from Asia and the Pacific Islands compared to the locally-born population (74, 75).

1.3.2 Australian prevalence of hepatitis B related HCC:

In Australia, HCC is the eighteenth most commonly diagnosed cancer (fifteenth in males and twentieth in females) and the eleventh most common cause of cancer related mortality (76). However, there has been a significant increase in the incidence and mortality rates of HCC over the past 3 decades. The HCC incidence almost tripled from 1.8 to 5.2 per 100,000 and the mortality has doubled from 2.3 to 4.9 per 100,000 during this period (76). These registry-based data do not include the suspected cases of HCC diagnosed through non-histological methods, such as imaging, and hence could be an underestimation of the true HCC incidence as was shown by a recent population-based study in Melbourne, which concluded that the HCC incidence was two-fold higher than reported by the state cancer registry, because of incomplete capture of HCC cases (77). HCC is the fastest growing cause of cancer related mortality among Australians (78) and the survival for those with HCC remains the lowest among all cancers (76, 79). In developed countries, the overall 5- year survival following HCC diagnosis is <10% and in developing countries, outcomes are poorer (80). Hence, the prevalence of HCC is low as it is one of the few cancers where the mortality rate often equals or exceeds the incidence rates.

One possible explanation for the rising HCC incidence is the increasing prevalence of chronic HBV infection among immigrants from highly endemic areas (81, 82). Estimated HBV- related HCC cases among Asia-Pacific residents have increased significantly from 12 per year in 1980 to 140 in 2005 and this is expected to increase further until 2025. This projected increase will be seen across all age groups from 30 to 60+ years (10). Other sub-groups, where there has been an increase in the HCC incidence, include; males, residents of socio-economically disadvantaged areas and Aboriginal and Torres Strait Islanders (83, 84).

Using linked HBV notification and cancer registry data, a linkage study in NSW reported that the

HCC incidence doubled from 1.4 to 2.8 per 100,000 person-years between 1990 and 2002, and the majority of this increase was attributed to chronic HBV and HCV infections. During the same time period, the age and sex standardised HCC incidence in those with HBV notifications increased from 8.8 to 69 per 100,000 population (73). The proportion of HCC attributable to those with HBV notifications increased from 13% in 1975-1983 to 21% in 1995-2002 in a hospital-based study from Victoria (85). These data support the assumption that the increased incidence and death rates from HCC over the past few decades are in part due to chronic HBV infection.

A linkage study from Australia in 2007 linked HBV notifications from the notifiable disease database to the HCC from cancer registry reported that 16% of HCC cases could be linked to HBV notifications (73). Another linkage project reported that the risk of HCC in those with HBV notification was 31 fold higher relative to those without HBV notification (86). The HBV- related HCC incidence in Australia in 2005 was 104 per 100,000 person-years in males and 21 per 100,000 person-years in females. The median age for HBV- related HCC diagnosis varied by region of birth and was 57, 63 and 66 years for those born in Asia, Europe and Australia respectively (86). While alcoholic and chronic HCV related cirrhosis are the predominant aetiologies for HCC in Australian-born patients, CHB is the main risk factor for overseas-born patients (85).

1.3.3 Hepatitis B related mortality:

Globally, the mortality from HBV- related cirrhosis and HCC were estimated at 310,000 and 340,000 persons per year respectively (87). The cumulative 5- year survival rate once decompensated cirrhosis ensues is poor at 35% (12). Without proper monitoring and access to anti-viral therapy, the life-time risk of liver related mortality in CHB would be around 15-25% (29). Since there is lack of population-level data regarding the liver-related mortality in CHB, model-derived estimates show that in 2014, 395 Australians died due to CHB- related complications (range: 304-614) (88). In addition, CHB- related end stage liver disease was the underlying reason for 5.6% of liver transplants in 2012 (89). These estimates indicate that there has been a gradual increase in the morbidity and mortality attributable to CHB over recent years.

In a linkage study from NSW where HBV notifications were linked to death records between 1990 and 2002, the overall mortality for those with HBV notification was 46.1 per 10,000 person-years (90). This was 1.4 times higher than the general Australian population. However, the liver-related mortality in the same study was 11.7 per 10,000 person-years which was 12 fold higher than the standard population. HCC was the prime driver of liver-related mortality with a rate of 6.7 per 10,000 person-years (10.6 and 2.3 per 10,000 person-years in males and females respectively). This was 28 fold higher than the standard population. Liver-related mortality rates were low below the age of 40 years but increased exponentially with increasing age.

HCC is associated with extremely poor survival and HBV- related HCC in particular was found to have poorer survival compared to other aetiologies (91-94). Based on less recent studies, the median survival for HBV- related HCC was less than 15 months in most of the studies (70, 91, 95-97) except one study where the median survival was 33 months (98). However, this study looked at the impact of an HCC screening program and hence could be prone to selection bias. The majority of these studies are either from Asia or Italy and there is a paucity of local Australian data on the trends in the incidence and survival of HBV- related HCC. This information would be helpful in formulating health care policies and interventions aimed at improving survival in this cohort.

1.4 ANTI-VIRAL THERAPY IN AUSTRALIA:

The importance of sustained suppression of HBV viral replication using anti-viral therapy, to alter the natural history of CHB and to mitigate the risk of progression to end stage liver disease and HCC development, has been well documented from the REVEAL-HBV study (46, 47). Modelled estimates from Australia have demonstrated that appropriate monitoring and treatment significantly reduces the risk of complications and is also more cost-effective compared to cancer screening alone (99). Risk of CHB- related complications have been predominantly reported in patients with HBV DNA levels persistently more than 20,000 IU/mL (47).

1.4.1 Treatment recommendations:

The main aims of treatment are to achieve normalization of ALT (biochemical response), HBeAg seroconversion and decreased HBV DNA levels (virological response) and improvement in liver histology (histological response). Treatment is indicated whenever the risk of liver related morbidity and mortality over the near future is high and the likelihood of achieving and maintaining viral suppression with continued treatment is high. The table below summarises the recommendations for using anti-viral therapy in CHB [adapted from AASLD practice guidelines (95) **(Table 1.1)**.

1.4.2 Treatment uptake:

Although liver biopsy is not mandatory prior to the initiation of anti-viral therapy in Australia since 2011, the overall treatment uptake, based on dispensing data from pharmaceutical Benefits Scheme (PBS) in 2013, remains very low. Only NSW and Victoria have a treatment uptake that is higher than the national average with Tasmania having the lowest treatment uptake. However, recent trends show that the number of people with CHB receiving anti-viral therapy has increased in recent years, with a larger increase occurring between 2011 and 2012 (88). The overall and state-wide prevalence and treatment uptake in Australia is reported in the table below **(Table 1.2)**:

Table 1.1: Treatment recommendations in chronic hepatitis B

HBeAg	HBV DNA level	ALT	Recommendations
+	>20,000 IU/mL	≤2x ULN	Consider biopsy and treatment if age >40years, ALT high but <2x ULN or with family history of HCC and if the biopsy shows moderate inflammation or significant fibrosis
+	>20,000 IU/mL	>2x ULN	Observe for 3-6 months and treat if there is no spontaneous HBeAg loss
-	>20,000 IU/mL	>2x ULN	Treat
-	>2000 IU/mL	1-2x ULN	Consider liver biopsy and treat if the biopsy shows moderate inflammation or significant fibrosis
-	≤2000 IU/mL	≤ ULN	Observe and treat only if the HBV DNA or ALT increases
+/-	detectable	Any level	If cirrhotic, treat
+/-	undetectable	Any level	If compensated cirrhotic, observe and treat if HBV DNA becomes detectable If decompensated cirrhotic, treat and refer to transplant centre

A major issue in increasing the treatment uptake rates is the number of undiagnosed people with CHB. Currently only 57% of all CHB in Australia have been diagnosed and among them, less than a quarter are receiving any form of annual monitoring or treatment. The remainder of the population (~87%) are not receiving annual HBV DNA monitoring or treatment (83). The high proportion of people who have undiagnosed, and hence untreated, CHB will increase the risk of transmission and contribute to a significant increase in CHB- related complications. Based on these estimates, the second national hepatitis B strategy was released which aimed to increase the treatment target to 15% among the CHB population to prevent adverse outcomes (97). Currently, there are no modelled projections or estimates to assess the cost-effectiveness of this strategy.

The universal HBV infant vaccination program which was introduced in 2000 in Australia has been highly successful with an infant vaccination coverage of >90%. Although this initiative has resulted in reduction of new infections among eligible children and adolescents (84), a major issue remains the management of the already diagnosed, ageing CHB population and those migrating from high HBV endemic areas where the commencement of vaccination programs were delayed, such as China and Vietnam where it was introduced only in 2000 (27).Hence, the second national hepatitis B strategy focuses mainly on increasing the diagnosis and management of those with CHB.

Table 1.2: Prevalence estimates and treatment uptake in Australia:

State/Territory	Prevalence (%)*	Treatment uptake (%)^
Overall Australia	218,567 (1.02%)	11,071 (5.3%)
Northern Territory	3,555 (1.68%)	62 (2.4%)
New South Wales	77,076 (1.11%)	5491 (7.6%)
Victoria	56,730 (1.06%)	3192 (5.8%)
Australian Capital Territory	3,603 (1.01%)	166 (4.6%)
Western Australia	22,055 (0.99%)	594 (3.0%)
South Australia	14,442 (0.90%)	506 (2.9%)
Queensland	37,399 (0.86%)	1,022 (2.6%)
Tasmania	3,513 (0.71%)	38 (1.1%)

*- Modelled estimated prevalence (100); ^- Proportion of people with CHB who were prescribed anti-viral therapy in 2013 (based on PBS script dispensing) (88)

1.5 DISEASE BURDEN AND MONITORING IN HEPATITIS B:

Disease burden for CHB is not only assessed by the costs in managing the disease but also by the loss in quality of life, which is assessed by various parameters. CHB is a relatively costly disease to manage as it requires predominantly life-long care and imposes a disproportionate economic burden on the health care system as shown by a South Korean study (101). Although only a small proportion of the CHB population would require treatment, ongoing monitoring is still required off-treatment to either prevent complications or to diagnose and manage them at an early stage.

1.5.1 Health care costs in hepatitis B management:

The economic burden of the CHB population involves assessing both the direct and indirect costs. Direct costs include drug costs and the monitoring required. A real-life cohort study from Victoria, Australia, in 2001 showed that the direct costs varied significantly based on the phase/stage of CHB. The mean costs per CHB patient per year would vary from AU $1,233 for those with CHB without cirrhosis, AU $11,961 for decompensated cirrhosis and AU $11,753 for HCC (102). This was then extrapolated to 2008 prices in another study, and the mean annual cost per person was AU $6,272 for those in the immune-active phase requiring treatment, AU $18,877 for decompensated cirrhosis and AU $18,979 for HCC management (103). This study used the level of treatment uptake in 2008 and projected modelled estimates until 2017 for managing the CHB population in Australia. This projected an 80% increase in the direct costs of CHB management over the 10- year period, predominantly driven by an increase in the incidence of CHB- related complications.

Indirect costs in CHB management include factors such as loss of workplace productivity, production loss due to hospitalisations, job loss, transportation costs and premature death. These are more difficult to assess and there are few real-life cohort studies with most others based on estimates. A German study following CHB patients for a 6 month period calculated that the indirect costs accounted for 12.8% of the total CHB management costs (104). Another South Korean study, using estimates, calculated that the indirect costs amounted to 20.9% of the total costs (101).

Various parameters have been used to assess the quality of life (QoL) in CHB as it forms an important aspect of disease burden. One of them, Disability-Adjusted Life Years (DALY) uses disability weights as a metric to measure disease burden in various CHB health states. The alternative is Quality-Adjusted Life Years (QALY) where utility weights are used as a metric to measure disease burden. Utility weights (measuring QALY) are a better parameter to assess disease burden as they are commonly derived from surveys of patients or general populations, unlike disability weights (measuring DALY) which are generally derived from expert opinion. Utility weights are a continuous measure and given a score between zero and one, with one assigned to perfect health and zero to death. Levy et al., surveyed more than 500 patients with CHB across six countries and derived the utility weights for each health state in CHB (105). Those with decompensated cirrhosis and HCC had the lowest utility weights, 0.35 and 0.38 respectively, indicating poor QoL in these health states.

1.5.2 Screening and surveillance:

HCC has a prolonged subclinical growth (106, 107) during which, if tumours are diagnosed using screening tests, they are amenable to curative treatment. The main objective of HCC screening is to decrease the HCC- related mortality. Although uncontrolled studies looking at HCC screening have suggested improvement in survival and earlier stage of HCC diagnosis (stage migration), they are prone to lead-time bias (108-111). Currently, there is only one randomized controlled trial (RCT), from China, looking at the benefit of screening (112). This study demonstrated a 37% reduction in HCC- related mortality in the screening arm.

Screening for HCC is primarily based on 6- monthly ultrasound examination of the abdomen in high-risk groups. Traditionally, serum biomarkers like alpha-fetoprotein (AFP) were used along with ultrasound, but since AFP lacks adequate sensitivity and specificity for screening and diagnosis, it has been removed from the current AASLD guidelines (113-115). The recommended screening interval of six months was initially based on tumour doubling time and since then, several large cohort studies have concurred with this interval (116-118).

There have been many risk scores for HCC proposed in CHB population, with a numerical cut-off value for each score associated with a negative predictive value at 10- years **(Table 1.3)**. These include GAG-HCC score, Chinese university score (CU-HCC) and REACH-B score (119-121). Age and HBV-DNA were a common component across all the three scores while other parameters include gender, ALT, albumin, bilirubin, underlying cirrhosis and HBeAg status. Among them, REACH-B score is easy to use and more practical as it does not require knowledge about underlying cirrhosis.

Table 1.3: Risk scores in chronic hepatitis B

Scores	**Variables**	**Cut-off**	**Negative predictive value at 10- years**
GAG-HCC	Age, albumin, bilirubin, HBV-DNA, cirrhosis	5	97%
CU-HCC	Age, gender, cirrhosis, HBV-DNA	101	99%
REACH-B	Age, gender, HBV-DNA, ALT, HBeAg/anti-HBe	8	98%

Another way of assessing the benefit of HCC screening would be to perform cost-efficacy analysis. Screening for HCC in CHB population is deemed to be cost-effective only if the anticipated HCC risk is more than 0.2% per year (high risk groups) (119, 122). The table below explains the incidence rates and the current recommendations for HCC screening in various CHB sub-groups **(Table 1.4)**. These recommendations are regardless of whether or not a patient is being treated with anti-viral therapy. Although these recommendations are cost-effective, currently, there are no Australian studies looking at the survival benefit of a centrally co-ordinated HCC screening process.

Table 1.4: Screening recommendations in chronic hepatitis B

CHB sub-groups	**Incidence estimates**	**Recommendation for screening**
Asian males, age >40 years (Irrespective of fibrosis stage or disease activity)	0.4-0.6%/year	Beneficial
Asian females, age >50 years (irrespective of fibrosis stage or disease activity)	0.3-0.6%/year	Beneficial
Cirrhosis (any phase of CHB)	3-8%/year	Beneficial
CHB patient with family history of HCC	unknown	Recommended screening from a younger age (commencing age not defined)
African/North American blacks with CHB	unknown	Recommended screening from a younger age (commencing at 20 years)
Caucasians with active viral replication (No cirrhosis)	Unknown	Beneficial (No age limit proposed)
Non-Asian CHB (No cirrhosis, Anti-HBe +ve and low/nil viral replication)	Low risk	Benefit uncertain
Asian males <40 and Females <50 years (no cirrhosis)	<0.2%/year	Not cost-effective

1.6 TREATMENT OPTIONS FOR HEPATITIS B RELATED HCC:

Management of HBV- related HCC requires a multidisciplinary approach involving hepatologists, surgeons and interventional radiologists. The type of intervention for HCC depends on various factors including; host factors (liver synthetic function impairment, performance status of the individual, co-morbidities, underlying portal hypertension) and tumour factors (number and size of the tumour nodules, portal vein invasion). Although there are multiple staging systems for HCC, the most widely used is the Barcelona Clinic Liver Cancer (BCLC) staging system (68). This has been externally validated (123) and its main advantage is the linkage of each stage to an appropriate treatment modality and the expected survival for each modality **(Figure 1.7)**.

1.6.1 Curative options:

Although resection, liver transplantation and percutaneous ablation can be curative options for HCC, only 30-40% in the western world and Japan qualify for these treatments on diagnosis. In a real world retrospective cohort study from a tertiary transplant centre in NSW involving 235 consecutive patients referred for HCC management, 116 patients (49.4%) underwent curative treatment (124). As the study involved a single transplant centre, selection bias was a likely factor in the higher proportion of subjects receiving curative treatments. Interestingly, only resection and liver transplantation had a significant impact on the overall survival while percutaneous ablation did not. Median survival in this study was 26 months and there was no aetiology specific difference in survival in univariate analysis.

Surgical resection is the preferred treatment option in those who are non-cirrhotic or with a single small tumour in a cirrhotic liver without underlying portal hypertension. Currently, the overall 5-year survival post resection is more than 50% in appropriately selected candidates [119-121].

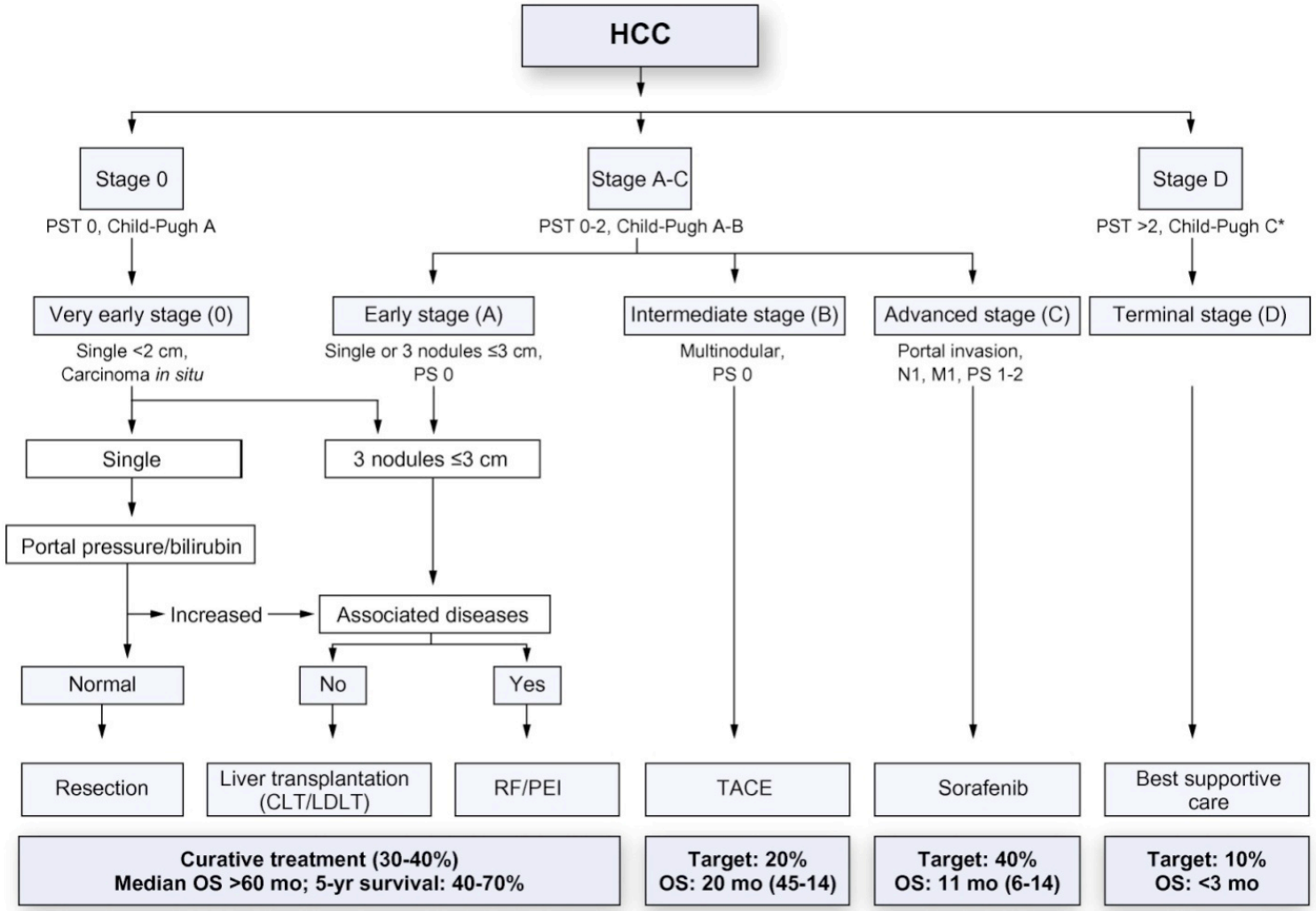

Figure 1.7: BCLC staging system and treatment algorithm in HCC

(Adapted from EASL practice guidelines for the management of HCC (125))

With improvement in surgical techniques, the post-operative mortality is <3% (126-128) however, the post-operative decompensation remains an important cause of morbidity if candidates are not selected properly. Two factors predict the risk of decompensation in the post-operative period; elevated bilirubin and significant portal hypertension – assessed by portal pressure measurement. This is clearly demonstrated by the difference in overall 5- year survival which is >70% in the absence of these factors, <50% with significant portal hypertension alone and <30% in those with both factors (126, 129). The risk of tumour recurrence post resection is up to 70% at 5 years, with microvascular invasion and satellite nodules on the resected specimen being significant predictors of recurrence (130, 131). Tumour recurrence results from either microvascular dissemination or de novo occurrence in the liver remnant (132, 133). Currently, there are no neo-adjuvant or adjuvant therapies recommended to prevent post-operative recurrence.

Liver transplantation is offered to patients within the Milan criteria; solitary HCC <5cm or with up to 3 tumour nodules all ≤3cm, with a 5- year overall survival >70% (134). The Milan criteria have been criticized as too restrictive with various alternative criteria proposed to allow greater expansion. University of California San Francisco (UCSF) criteria (single tumour <6.5cm, up to 3 tumour nodules with none >4.5cm, and cumulative tumour size ≤8cm) have shown similar 5- year overall survival compared to Milan criteria, although in outcome studies UCSF criteria were based on explant pathology rather than pre-transplant radiology (135). In Australia, the majority of transplant centres employ the UCSF criteria for patient selection and 5- year overall survival was 72% in 2014 (136). One of the major issues with using expanded the criteria is the risk of increasing drop-out from the liver transplant waiting list due to tumour progression. The majority of patients require some form of loco-regional therapy to downstage and to prevent tumour progression while on the waitlist.

Percutaneous ablation is the other curative option for those with early stage disease but with underlying portal hypertension and associated co-morbidities, as they are not suitable for resection or transplantation. This is usually achieved by either a chemical (ethanol) or thermal

(radiofrequency) ablation under ultrasound guidance. A multicentre study from Italy concluded that for very early stage HCC (single tumour <2cm) radiofrequency ablation (RFA) achieves comparable 5- year overall survival (70%) to that of surgical resection in optimal candidates (137). However, the recurrence rate is similar to resection. Recurrence can either be along the margins of the ablated zone or intra-hepatic distant recurrence from microsatellite deposits.

Percutaneous ethanol injection (PEI) achieves a complete response rate of >90% for single tumours <2cm but, response drops to 70% for 2-3cm tumours and only 50% for tumours >3cm. Studies comparing RFA and PEI have shown that they have similar efficacy for tumours <2cm but RFA requires fewer treatment sessions, and RFA is better than PEI for tumours >2cm (138-140). This has been confirmed by a cumulative meta-analysis which showed that survival is better with RFA compared to PEI (141). Because of these data, in current clinical practice, PEI is restricted to treating only small HCCs that are not suitable for thermal ablation due to proximity to structures vulnerable to thermal injury. These therapies could potentially be used as a bridge to transplantation but there is a risk of peritoneal seeding, particularly with poorly differentiated tumours (142).

Over the last two decades, various alternative thermal ablation therapies have been assessed in trials including laser, cryotherapy and microwave. Among them, microwave ablation (MWA) has been studied most extensively and has become the preferred percutaneous ablation modality in some centres. Although none of the major international guidelines on HCC management mention MWA as a treatment option (115, 125), it has some theoretical advantages over RFA including a larger ablation zone and faster ablation times secondary to rapid increase and maintenance of intra-tumoural temperatures. Studies comparing these two modalities have been restricted to retrospective observational studies and have shown conflicting results. There are no studies comparing these two techniques for HCC management in an Australian population. A recent study from China showed that the overall survival rates were comparable between MWA and surgical resection for treating tumours within the Milan criteria; however, the disease free survival was lower with MWA compared to resection (143).

1.6.2 Non-curative options:

The majority of patients with HCC (60-70%) will only be eligible for palliative treatment options on diagnosis and their median overall survival varies from <3 to 20 months. Two commonly used modalities in this group are trans-arterial chemo-embolization (TACE) and systemic therapy with sorafenib. A small proportions of this group (~10%) have terminal stage illness at diagnosis and are only suitable for symptomatic management.

TACE is the first line palliative treatment option for those with intermediate stage HCC (without portal vein thrombosis or extra-hepatic spread). It is associated with a median overall survival of 20 months. Multiple sessions are usually required to control the disease, particularly with bilobar HCC. Those with advanced stage disease with or without portal vein invasion and Child-Pugh class A, are candidates for sorafenib therapy based on the landmark SHARP trial (144). In this trial a 31% reduction in the risk of death was observed with a median overall survival of 10.7 months. The median time to tumour progression was 5.5 months. This has been reproduced in another randomized controlled trial mostly in patients with HBV- related HCC from the Asia-Pacific region. In this trial, although there was a 32% reduction in the risk of death, the median overall survival (6.5 months) and the median time to progression (2.8 months) were much less than in the SHARP trial (145).

A recent study from France compared selective internal radiotherapy (SIRT) using Yttrium-90 microspheres to sorafenib for treating advanced stage disease with macrovascular portal invasion. After propensity score matching, there was a 60% reduction in the risk of death with SIRT, with a median overall survival of 26.2 months compared to 8.7 months with sorafenib (146). Another small pilot randomized trial compared SIRT with TACE for treating intermediate stage tumours and this showed that the median overall survival, progression-free survival and time to progression was similar between the two modalities (147). SIRT is currently not used widely in routine clinical practice as more data are awaited from randomized controlled trials.

2. TRENDS IN THE INCIDENCE AND SURVIVAL OF HEPATITIS B RELATED HEPATOCELLULAR CARCINOMA IN SOUTH AUSTRALIA USING LINKED DATA: 1996-2010

2.1 INTRODUCTION

HCC is the sixth most common type of cancer worldwide with an increasing annual incidence (Section 1.3.1) (148). It is also the second and sixth most common cause of cancer related mortality in males and females respectively (149). Furthermore, the incidence and mortality rates of HCC continue to increase globally. Cancer registry based studies in various countries including Canada, France, UK, USA and Australia have reported an increase in HCC incidence over the past two decades (81, 150-153). Even though the absolute number of subjects diagnosed with HCC remains low compared to other tumours in Australia, there has been a significant increase in the incidence and mortality rates of HCC over the past two decades in both genders (154). Local data from South Australia (SA) mirrors the national trends and indicate a significant increase in the incidence and mortality rates of HCC over the last decade (155).

Globally, the majority of patients diagnosed with HCC have underlying chronic hepatitis B virus (HBV) infection (80, 156). Indeed, infections with HBV or chronic hepatitis C virus (HCV) account for more than 80% of HCC cases worldwide (80, 148). In Australia, the increasing HCC incidence has been attributed to the increasing HBV and HCV- linked cases which is projected to increase further among the Asia-Pacific born residents until at least 2025 (10, 73). However, detailed epidemiological studies of trends in HBV-related HCC incidence and outcomes are lacking.

South Australia has a population of approximately 1.6 million. It is typical of other Australian states

and other migrant communities around the world where the majority of the population were derived initially from European migration, with more recent arrivals from Asia-Pacific and African regions, where HBV is endemic. In a 2011 census, 22% of the SA population were born overseas and among these 12.6% were from a non-English speaking background. The largest non-English speaking country of birth in SA was Italy followed by India, China and Vietnam (157). Despite the rising incidence of HCC and high migration rates from HBV endemic areas, there are currently no detailed local data on the incidence and survival of HBV- related HCC. Assessing these trends would therefore be important for both SA and similar communities worldwide and would enable recognition and appropriate health care planning for this disease.

The aims of this chapter were therefore to determine the trends in the incidence rates and survival of HBV- related HCC from 1996 to 2010 in SA, including projections through to 2020 using the assumption that rates of change remain the same until then.

2.2 PATIENTS AND METHODS:

A population-based cohort study of HBV-related HCC was undertaken by linking all chronic HBV cases that were notified to the SA Communicable Disease Control Branch (CDCB) between January 1996 and December 2010, with all HCC cases and deaths recorded in SA cancer registry and death registry. HBV subjects with a chronic HCV or Human Immunodeficiency virus (HIV) co-infection were excluded. Subjects were followed up from the date of HBV notification to either death or 31/10/2014 (end of study period). This is mainly to cover the latency period for HCC development and also to allow adequate follow-up of the last few patients notified with HBV at the end of 2010. Follow-up period to calculate HCC survival was from the date of HCC diagnosis to either death or end of study period. The study protocol was approved by the SA Health Human Research Ethics Committee.

2.2.1 Data sources:

Although HBV infection notification in SA has been made mandatory by the Public and Environmental Health Act 1987, data of chronic HBV were incomplete up to 1995 (158). Hence, we collected the data including age, gender, country of birth and racial origin for those notified with chronic HBV from 1 January 1996 – 31 December 2010 from CDCB. HCC cases were identified using the ICD-O-3 topographical code C22.0 recorded in the SA cancer registry during the same time period. In SA, the cancer registry captures data using the hospital discharge summaries. Thus an ICD code of C22.0 either in the principal or secondary diagnosis is registered as a liver cancer irrespective of the modality used for diagnosis (histology or radiology), thus minimizing the risk of missed HCC cases. Information on deaths including date and cause of death was collected from the SA births, deaths and marriages SA registry (BDM).

2.2.2 Data linkage procedures:

Probabilistic linkage was conducted between the HBV notification dataset and the SA Cancer registry, using a linkage tool for cancer registries; Link Plus (Beta Version 3.0.0). Blocking variables used were patient last name, patient given name and date of birth (DOB), and matching variables used were patient last name, patient first name, patient middle name, DOB and gender. Matches with high cut off values (probability) were linked, and a manual review of uncertain matches was conducted, using additional information from the relevant data source. This data was then deterministically linked with the death registry. Record linkage was performed by the Disease Surveillance and Investigation Section within the department of health, with assistance from the SA Epidemiology Branch. All personal identifiers were removed before the linked data was transferred to the researcher for analysis.

2.2.3 Statistical analysis:

Separate descriptive analyses of all chronic HBV notifications, and of HBV cases with a linked

HCC record was performed. Crude incidence rates of HBV- related HCC were calculated using person-years of follow-up, stratified by age group and sex, and the rates were expressed as the number of HCC cases/100,000 person-years. Person-years for each subject were defined as the number of years from HBV notification to the first of either HCC diagnosis, date of death or 31/10/2014. Age-standardized incidence rates of HBV- related HCC were calculated in Microsoft Excel (Microsoft 2007, Redmond, Washington) using 2001 SA population as the standard (159) and the rates were expressed as the number of HCC cases/100,000 person-years. The rates were compared based on the age group, gender and period of HCC diagnosis using Poisson regression models. Join-point regression models (160) were used to calculate the annual percentage change (APC) in the age-standardized rates of HBV- related HCC and to identify any changes in the trend using the join-point regression program software (version 4.2.0) (161).

Forecasting of the number of HBV- related HCC cases from 2015 to 2020 was performed using the "smoothed-out moving average" function in the time series forecasting analysis in Microsoft Excel. Moving average for a particular year accounts for that year, the preceding 2 years and 2 years that follow (5- years in total). Hence, the moving average was reported from 1998 (2- years after the initial assessment) to 2018 (2- years prior to the final prediction).

Survival rates were calculated and compared for three different time periods (1996-2000, 2001-2005 and 2006-2010) using the Kaplan-Meier method. We also assessed differences in survival rates according to gender, age and region of birth. A sensitivity analysis was performed excluding subjects notified with chronic HBV after HCC diagnosis to exclude any bias (as the HBV notification might have been the result of HCC diagnosis). A two-sided P value of less than 0.05 was considered statistically significant for all analyses. Survival analysis was carried out using IBM SPSS statistics software (version 19.0; IBM Corp., Armonk, New York, USA) for Windows.

2.3 RESULTS:

2.3.1 Baseline characteristics:

There were a total of 3881 chronic HBV notifications to CDCB between 1996 and 2010 with an annual range of 205 to 328 per year **(Figure 2.1)**. The majority of patients were males (58%), born in Asia or Africa (51.3%) with a median (IQR) age of 33.5 (20.3) years at the time of notification **(Table 2.1)**. Of these, 47 (1.2%) had a linked HCC record. Among the HCC cases, the median (IQR) age at diagnosis was 58.9 (13.4) years, the majority (83%) were males. Most (62%) HCC cases were diagnosed between 51-69 years and 38.3% were born in either Asia or Africa.

2.3.2 Crude and age-standardized incidence rates:

The overall HBV- related HCC crude incidence rate was 111.3 per 100,000 person-years. This was significantly higher among men than women, 156.3 vs. 46.3 per 100,000 person-years, $p<0.001$. Incidence rates were also significantly higher for those ≥45 years **(Table 2.2)**. The overall age-standardized HBV- related HCC incidence rate was 189.1 per 100,000 person-years. The rate for men was almost three times higher than for women: 241.7 vs. 88.6 per 100,000 person-years.

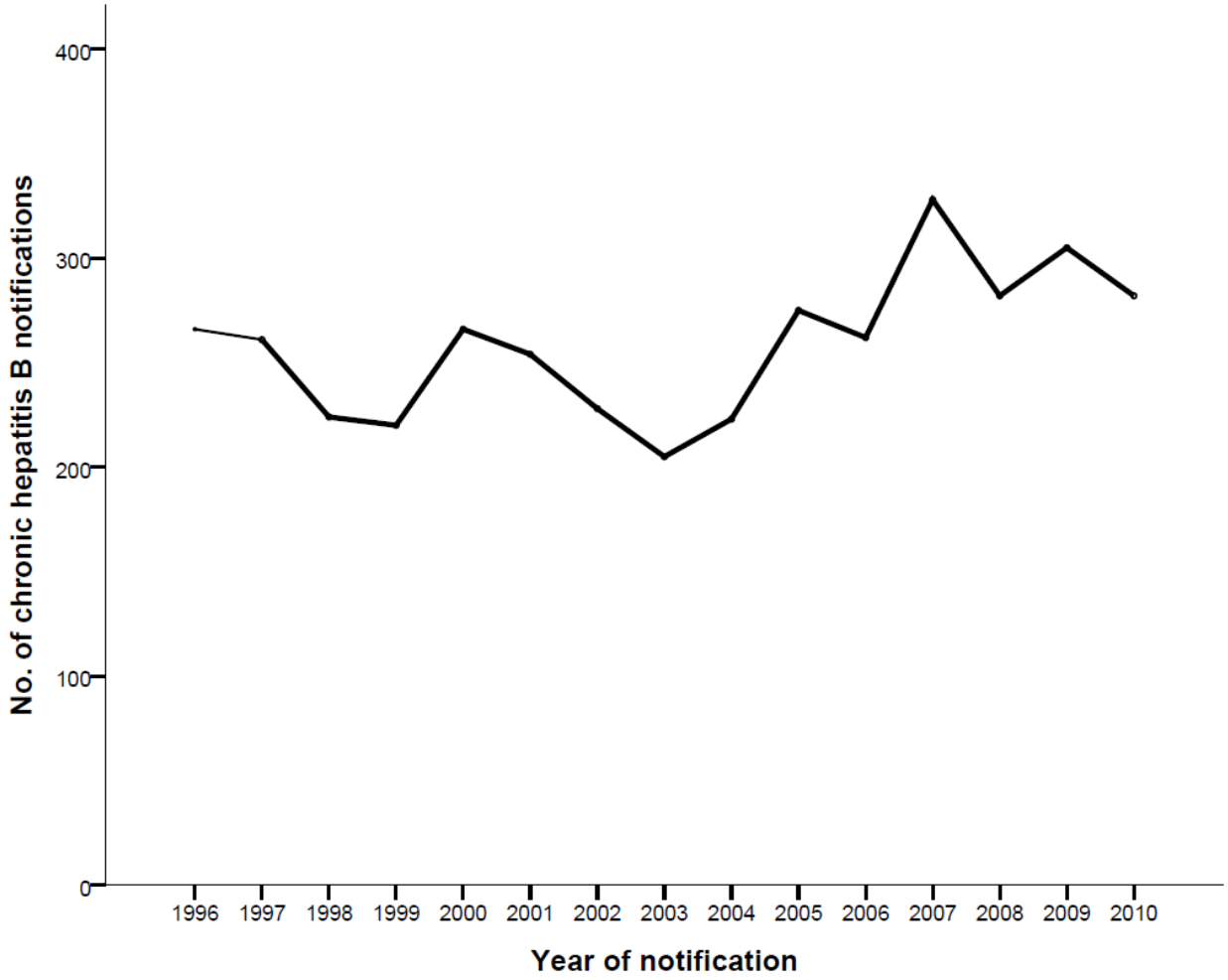

Figure 2.1: Annual chronic hepatitis B notifications in South Australia

Table 2.1: Characteristics of the linked cohort:

Total HBV notifications	3881
Median (IQR) age of notification	33.5 (20.3)
Males, n (%)	2250 (58)
Median (IQR) follow-up in months	126 (91)
Total number of linked HCC cases	47
Median (IQR) age at HCC diagnosis	58.9 (13.4)
Age at HCC diagnosis (years), n (%)	
1-49	9 (19.1)
50-59	15 (31.9)
60-69	14 (29.8)
≥70	9 (19.1)
Males diagnosed with HCC, n (%)	39 (83)
Region of birth among linked HCC cases, n (%)	
Australia & Oceania	5 (10.6)
Europe	9 (19.1)
Africa	5 (10.6)
Asia	13 (27.7)
Americas	1 (2.1)
Unknown	14 (29.8)
Person-years of follow-up, median (IQR)	2.4 (5.9)

HBV – Chronic hepatitis B virus infection; IQR – Inter-quartile range; HCC – Hepatocellular carcinoma

Table 2.2: Crude incidence rates and survival of hepatitis B related hepatocellular carcinoma in South Australia: 1996-2010

	Observed HCC cases	Crude incidence rate/100,000 person-years	No. of deaths, n (%)	Median (95 % CI) survival (months)
Overall	47	111.3	33 (70.2)	12.5 (3.6-21.4)
Age group (years)				
1-44	7	17.9	5 (71.4)	4.9 (0.1-13.8)
45-64	25	346.3	17 (68)	19.2 (3.9-11.5)
≥65	15	699.7	11 (73.3)	4.6 (0.1-11.2)
Gender				
Males	39	156.3	28 (71.8)	11.5 (3.1-19.8)
Females	8	46.3	5 (62.5)	21.9 (0.1-44.1)
Period of HCC diagnosis				
1996-2000	9	45.8	8 (88.9)	9.3 (0.1-22.1)
2001-2005	14	100.6	12 (85.7)	10.2 (0.1-22.8)
2006-2010	24	275.4	13 (54.2)	21.8

HCC – Hepatocellular carcinoma; CI – Confidence Interval

2.3.3 Trends in the incidence rates and projections:

There was more than a 200% increase in the age-standardized incidence rates during the study period: from 139.7 per 100,000 person-years in 1996 to 486.1 per 100,000 person-years in 2010. Join-point regression analysis showed this to be a significant increase with an annual percentage change (APC) (95% CI) of 20.8% (10.1-32.5), p=0.001 **(Figure 2.2)**.

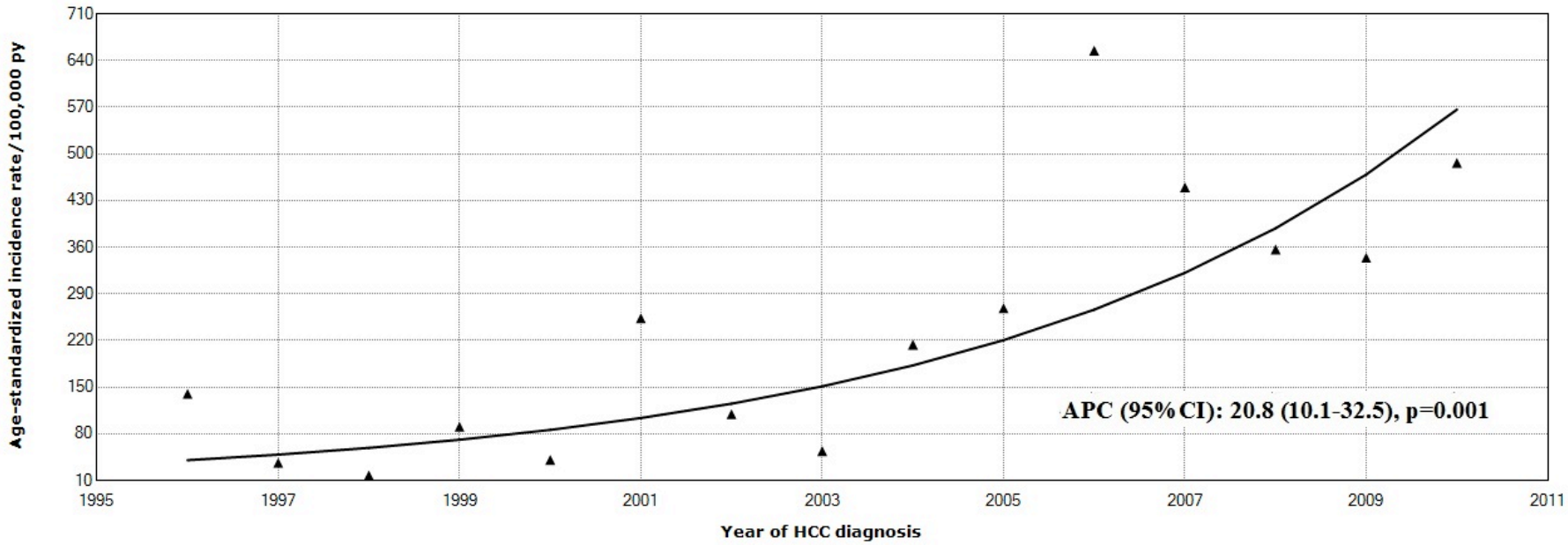

Figure 2.2: Trends in the age-standardized incidence rates of hepatitis B related hepatocellular carcinoma between 1996 and 2010 in South Australia.

Join-point regression plot with the small triangles representing the age-standardized incidence rates/100,000 person-years (py) for each year.

Time-series forecasting analysis projected that the actual number of HCCs diagnosed in HBV population will continue to increase and figure 3 shows the projected number of HCC cases for the next 5 years to 2020. The moving average of 6.3 HCC cases per year in 2010 is projected to increase to approximately 9 HCC cases per year in 2018 **(Figure 2. 3)**.

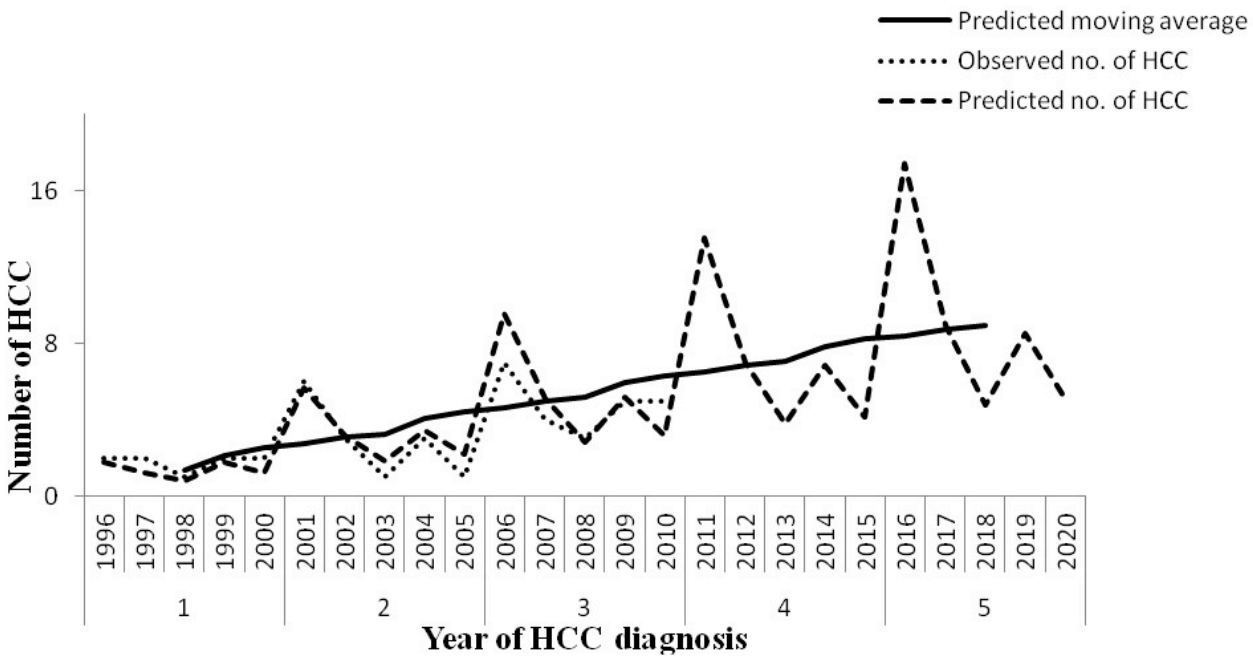

Figure 2.3: Predicted number of hepatitis B related hepatocellular carcinomas until 2020 in South Australia.

Forecasting based on smoothed-out average.

2.3.4 Survival in chronic hepatitis B related HCC:

In the overall HBV cohort, 63 patients (1.6%) died during the follow-up period. In those with HBV-related HCC the median (95% CI) survival was 12.5 (3.6-21.4) months **(Table 2.2)** with 33 of the 47 HCC subjects (70.2%) dying during the follow-up period. The 1-, 2- and 3- year survival was 50%, 34% and 32% respectively. There was a trend towards increasing survival during the 2006-2010 time period (21.8 months) compared to the previous two time periods (1996-2000 and 2001-

2005), 9.2 and 10.2 months respectively, [log-rank: χ^2 =5.8, degrees of freedom (2), p=0.056] **(Figure 2.4)**. There was no difference in survival rates based on gender (p=0.5), region of birth (p=0.6) and age at HCC diagnosis (p=0.4).

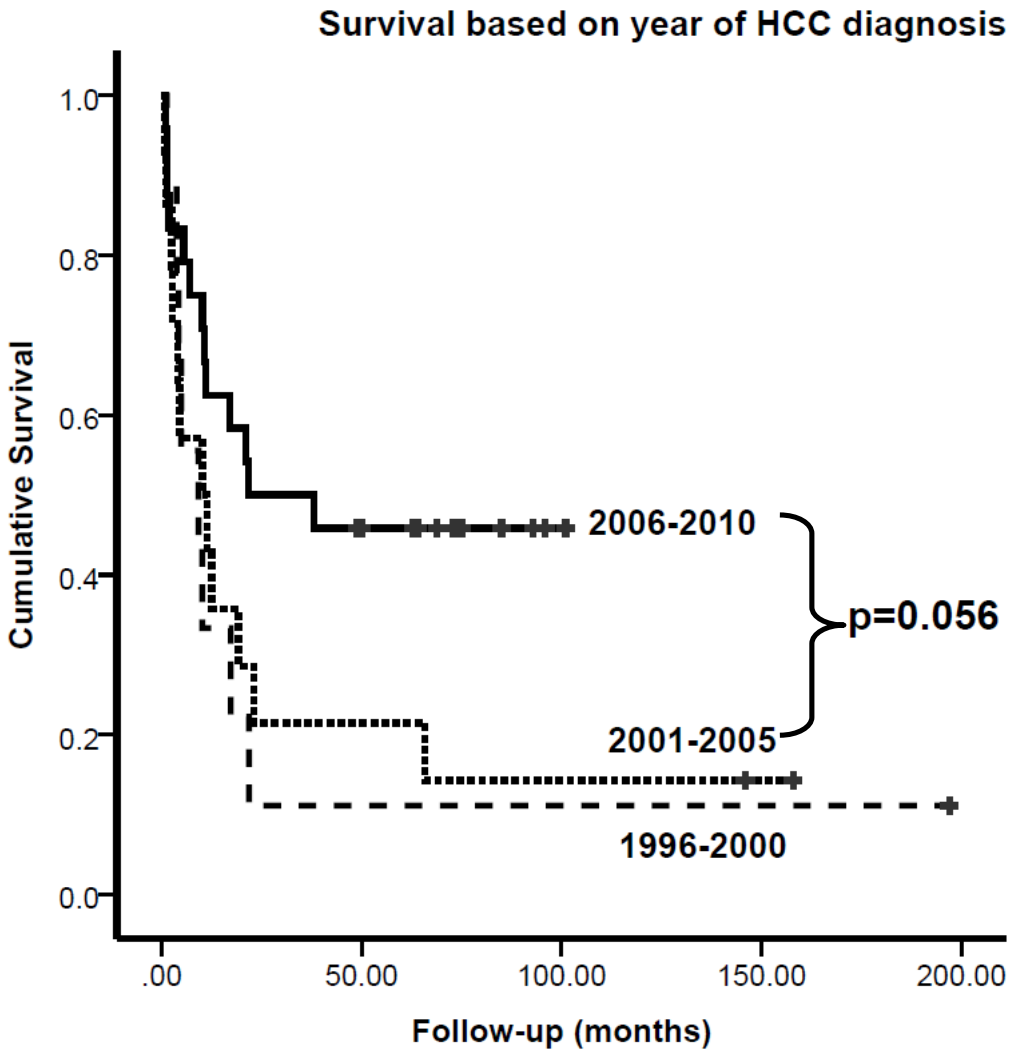

Figure 2.4: Survival in hepatitis B related hepatocellular carcinoma in South Australia – based on year of HCC diagnosis

2.3.5 Sensitivity analysis:

In sensitivity analysis we excluded 6 HCC patients where HBV notification occurred after the HCC diagnosis. In this smaller cohort (n=41), the overall crude incidence rate (97.1/100,000 person-

years) and age-standardized incidence rate (169.7/100,000 person-years) were similar to the primary analysis. Join-point regression analysis in this cohort was similar to the trend observed in primary analysis; APC (±SE): 32.7 (±8.6), p=0.002.

2.4 DISCUSSION:

During the study period, 1996-2010, there was a significant increase in both crude and age-standardized incidence rates of HBV- related HCC in South Australia. This finding was similar to that reported in a study performed from New South Wales (NSW) between 1992 and 2007 which also showed a significant increase in the age, sex and birth cohort adjusted- incidence rates of HBV-related HCC from 1992-1997 to 2004-2007 (162). The results in our study also mirror the results of other studies worldwide which have used the directly age-standardized method to show an increase in the age-adjusted incidence of HCC (73, 150, 163, 164).

The significant increase in the incidence rates of HBV- related HCC in our study is likely to reflect the increasing HBV prevalence in South Australia and the cohort effect of ageing migrants with chronic HBV infection. The estimated chronic HBV prevalence in Australia in 2011 was 1.02% (165) with more than 50% of those infected born in either China or Vietnam (15, 42). The prevalence of HBV is likely to increase further in Australian communities due to factors including (i) increasing net overseas migration (NOM) to Australia (166) (ii) delayed introduction of HBV vaccination programs in some South-East Asian countries (iii) sub-optimal vaccine coverage in other high-risk groups (Indigenous Australians, injection drug users, men who have sex with men) (20, 167, 168) and (iv) an ageing population. While it is possible that the age-standardised rates may be different in Asian and non-Asian populations and/or migrant/non-migrant populations, we could not assess this as the numbers in each sub-group are insufficient to provide meaningful conclusions. In South Australia, the estimated prevalence was slightly less than the national average in 2011, 0.9% (165), but is predicted to increase as NOM is the main component of population

growth in SA (169). Based on forecasting we estimated that the number of HBV- related HCC in SA would increase by at least 50% this decade.

Another potential contributor to the rising incidence of HBV-related HCC may be improved case finding in the later time periods. It is feasible that improved HBV screening practices by the general practitioners, awareness, screening and surveillance processes in those with chronic HBV at the local hepatitis clinic level may have resulted in detection of more cases. The trend towards improved survival in the latter time-period is consistent with increasing identification of earlier HBV related HCC within screening programs.

The findings of this study, namely a 200 % increase in age–standardized incidence of HCC in SA during the study period (equivalent to a 21% annualised increase of HBV-related HCC) is concerning. It identifies an important public health concern and suggests the need for an appropriate public health intervention given chronic HBV is a preventable disease. Interventions which could reduce the burden and rising trend of HBV-related HCC may include; improved HBV screening and vaccination for high risk groups, improved HBV treatment uptake and improved HCC screening for at risk populations. Such measures will require an appropriately resourced and coordinated public health effort.

The median survival in this study (12.5 months) for HBV-related HCC was short but similar to a study from NSW which had a median survival of 15 months (70). There was a temporal trend demonstrating non-significant improvement in survival during the latter time-period in our study. This is consistent with previous reported studies which showed improvement in survival and earlier detection of HCC over the years (94, 170, 171). This finding may reflect improved awareness and implementation of HCC screening for at risk HBV patients together with greater availability of effective therapy within the SA health region over this time period. Our study showed no significant difference in survival based on age and gender consistent with previous published literature (92, 98, 172). The lack of association between age, gender and HBV- related HCC

survival implies that the HCC screening and treatment access are similar across the groups.

The strength of this study is that it represents a robust and detailed epidemiological investigation of a large population. However, there are also several limitations to our study. Firstly, this linkage study was based on notification of chronic HBV infection and HCC diagnosis to the respective registries. We cannot exclude the possibility of under-representation of HCC cases compared to hospital-based data as shown in a recent study in Victoria (77, 173). However, we used standard methodology which has also been employed in other cancer registry based linkage studies (70, 73, 162). Also, the SA cancer registry has a number of overlapping sources of information and a variety of data quality checks are performed on all data. We believe performing these cross-checks at various time-points would minimize the missed rate of unreported cancers to the cancer registry. Secondly, we were unable to test for the influence of underlying liver disease, anti-viral therapy, stage of HCC diagnosis and HCC screening on the overall survival as this information was not recorded in the registries. Thirdly, subjects who were diagnosed with HBV prior to 1996 who then developed HCC during the study period were not included in the analysis. This is because there was no mandatory HBV notification in South Australia until 1995 and hence accessing reliable epidemiological information for this cohort is not possible. Further, this would introduce a selection bias as patients would not be "consecutive subjects" diagnosed with HBV. Finally, the absolute number of HBV- related HCC in each year was small and hence, we could not stratify our analysis to assess gender based trends as there were no women diagnosed in some years.

In conclusion, we report the first population-based study assessing the trends of HBV- related HCC in South Australia. There was a significant rise in both crude and age-standardized incidence rates of HBV- related HCC from 1996-2010 and this is predicted to increase still further at least up to 2020. The steady rise in incidence of this preventable cancer raises concerns within our own health region and similar health care regions worldwide. The findings suggest the urgent need for more effective public health care interventions to reduce health care impacts of this frequently devastating disease.

3. ESTIMATING THE CLINICAL AND ECONOMIC IMPACT OF INCREASING TREATMENT UPTAKE IN CHRONIC HEPATITIS B

3.1 INTRODUCTION

Hepatitis B virus infection is a major public health problem as it affects more than 240 million people worldwide (174). Individuals with HBV infection are at increased risk of morbidity and mortality with up to 780,000 deaths/ year (87, 174, 175) due to decompensated liver disease and hepatocellular carcinoma (HCC). HBV infection is the most important risk factor for HCC worldwide, accounting for 60-80% of HCC cases globally (80). Several large cohort studies have shown the effectiveness of anti-viral therapies in achieving sustained suppression of HBV replication and subsequent reduction in complications (47, 176, 177). Consequently major international guidelines advocate the use of nucleos(t)ide analogues or interferon for HBV viral suppression in patients meeting specific treatment criteria (178-180). The annual direct costs associated with managing and treating HBV infection in Australia were estimated at AU$171.8 million in 2008 and projected to rise to AU$307.9 million in 2017 (36).

In Australia, recent data provide an estimated true prevalence of chronic hepatitis B (CHB) of 1.02% (181). This is likely to be much higher than the actual reported prevalence which is based on notifications, since an estimated 44% of cases remain undiagnosed (13). This problem is shared by other western nations like the United States, European Union (EU) and Canada where there is a high CHB prevalence among the migrant population (182). Migration to EU, North America and

Australia occurs mainly from countries such as China, India and Vietnam where the CHB prevalence is >2%.

Only a proportion of individuals with HBV infection are eligible for treatment and based on international and Australian estimates, this would range from 10-25% (65). However, the treatment uptake in Australia is low with only 5.3% of CHB patients receiving therapy in 2011 and is much lower in South Australia (SA) – 2.9% (88). This rate is similar to an estimate from the United States which examined Food and Drug Administration approved HBV prescriptions. Only 50,000 persons were on treatment, from an estimated 1.4 to 2 million CHB prevalent cases, providing an estimated treatment uptake rate of 2.5-5% (183). The first SA Hepatitis B action plan, released in 2013, aimed to increase treatment uptake to a target rate of 10% among the overall CHB population (184). At the same time, a national treatment uptake target was set at 15% following the 2nd National Hepatitis B Strategy which was aimed at preventing adverse outcomes (65).

Although there is agreement on the need for higher treatment rates amongst eligible CHB patients, no formal cost-effectiveness analysis of these proposed treatment uptake regimes has been performed. Indeed there is a paucity of literature worldwide that describes the cost-effectiveness of increasing treatment uptake using current generation nucleos(t)ide analogues. The aims of this chapter were therefore to compare the long-term cost-effectiveness of the two specified treatment uptake rates with that of current treatment rate. A model-based probabilistic cost-effectiveness analysis was undertaken comparing costs and outcomes associated with the current and proposed treatment rates.

3.2 METHODS:

3.2.1. Development of the cost-effectiveness model

Using a cohort Markov model (185, 186), the cost-effectiveness was estimated for 3 scenarios:

Scenario 1: 2.9% treatment uptake – current levels (88)

Scenario 2: 10% treatment uptake – state target (184)

Scenario 3: 15% treatment uptake – proposed national target (65)

Modelling was based on the most current estimates of prevalence, treatment uptake and outcomes of CHB population available in South Australia (13, 36, 65, 88, 181, 184) **(Table 3.1)**. This population consists of an estimated 2,550 treatment eligible CHB patients (17.7% of the overall CHB population of 14,400) (181). Based upon Australian cross-sectional estimates of outcomes in HBV (36), we calculated that amongst 2550 HBV cases eligible for treatment, 2,051 would have either eAg +ve/-ve chronic hepatitis B with no cirrhosis (CHB); 448 compensated cirrhosis (CC); 15 decompensated cirrhosis (DC) and 36 HCC. In our modelling we *a priori* assigned anyone with DC or HCC to treatment for each of the 3 scenarios **(Table 3.1)**. Therefore, increasing treatment uptake translated into treating a higher proportion of subjects with CHB or CC **(Table 3.2)**.

Table 3.1: Estimates of probabilities & distributions of being in each health state initially used in the reference case and sensitivity analyses

	Tenefovir Treatment Arm		Natural History Arm	
	Estimate[a]	**Distribution[b]**	**Estimate[a]**	**Distribution[b]**
Probability of following either the treatment or natural history arm – all individuals (Scenario 1 - 2.9% uptake[c,] based on current treatment uptake in South Australia)				
All states	0.165 [r = 418, n = 2550]	Dirichlet	0.835 [r = 2132, n = 2550]	Dirichlet
Probability of being in each state initially (Scenario 1 - 2.9% uptake[c,] based on current treatment uptake in South Australia)				
CHB[d]	0.720 [r = 301, n = 418]	Dirichlet	0.818 [r = 1744, n = 2129]	Dirichlet
CC[e]	0.159 [r = 66, n = 418]	Dirichlet	0.182 [r = 388, n =2129]	Dirichlet
DC[f]	0.036 [r = 15, n = 418]	Dirichlet	0	-
HCC[g]	0.086 [r = 36, n = 418]	Dirichlet	0	-
LT[h]	0	-	0	-
sAg loss[i]	0	-	0	-
Probability of total number of individuals in treatment or natural history arm (Scenario 2 - 10% uptake[j,] based on targeted treatment uptake in South Australia)				
All states	0.570 [r = 1440, n = 2550]	Dirichlet	0.430 [r = 1110, n = 2550]	Dirichlet
Probability of being in each state initially (Scenario 2 - 10% uptake[j,] based on targeted treatment uptake in South Australia)				
CHB[d]	0.789 [r = 1137, n = 1440]	Dirichlet	0.819 [r = 908, n = 1110]	Dirichlet
CC[e]	0.175 [r =252, n = 1440]	Dirichlet	0.181 [r = 202, n =1110]	Dirichlet
DC[f]	0.010 [r = 15, n = 1440]	Dirichlet	0	-
HCC[g]	0.025 [r = 36, n = 1440]	Dirichlet	0	-
LT[h]	0	-	0	-
sAg loss[i]	0	-	0	-

	Tenefovir Treatment Arm		Natural History Arm	
	Estimate[a]	**Distribution[b]**	**Estimate[a]**	**Distribution[b]**
Probability of following either the treatment or natural history arm – all individuals (Scenario 3 - 15% uptake[k], based on targeted treatment uptake in Australia)				
All states	0.855 [r = 2160, n = 2550]	Dirichlet	0.145 [r = 390, n = 2550]	Dirichlet
Probability of being in each state initially (Scenario 3 - 15% uptake[k], based on targeted treatment uptake in Australia)				
CHB[d]	0.799 [r = 1722, n = 2160]	Dirichlet	0.819 [r = 313, n = 390]	Dirichlet
CC[e]	0.178 [r =387, n = 2160]	Dirichlet	0.181 [r =77, n =390]	Dirichlet
DC[f]	0.007 [r = 15, n = 2160]	Dirichlet	0	-
HCC[g]	0.017 [r = 36, n = 2160]	Dirichlet	0	-
LT[h]	0	-	0	-
sAg loss[i]	0	-	0	-

[a] Figures in square brackets are occurrences (r) and population size (n);

[b] Distributions used in probabilistic sensitivity analysis;

[c]2.9% uptake means treating only 14.8% of those with Hepatitis B (n = 2550). As everyone with Decompensated cirrhosis (DC) or Hepatocellular carcinoma (HCC) will always get treated, this uptake translates to treating 14.8% of all Chronic Hepatitis B, no cirrhosis - CHB cases (14.8% of 2045 CHB cases in 2011 = 301 cases) and 14.8% of all Compensated cirrhosis - CC cases (14.8% of 454 CC cases in 2011 = 66 cases) and 100% of those in DC and HCC (100% of 15 DC cases in 2011 and 100% of 36 HCC cases in 2011). All persons who are not on treatment (n = 1744 CHB cases and n = 388 CC cases) follow the natural history arm.

[d]CHB = Chronic Hepatitis B, no cirrhosis

[e]CC = Compensated cirrhosis

[f]DC= Decompensated cirrhosis

[g]HCC = Hepatocellular carcinoma

[h]LT = Liver transplant

[i]sAg loss = Spontaneous seroclearance

[j]10% uptake means treating only 56.1% of those with Hepatitis B (n = 2550).

As everyone with DC or HCC will always get treated, this uptake translates to treating 56.1% of all CHB cases (56.1% of 2045 CHB cases in 2011 = 1137 cases) and 56.1% of all CC cases (56.1% of

454 CC cases in 2011 = 252 cases) and 100% of those in DC and HCC (100% of 15 DC cases in 2011 and 100% of 36 HCC cases in 2011). All persons who are not on treatment (n = 908 CHB cases and n = 202 CC cases) follow the natural history arm.

[k]15% uptake means treating 85.2% of those with Hepatitis B (n = 2550). As everyone with DC or HCC will always get treated, this uptake translates to treating 85.2% of all CHB cases (85.2% of 2045 CHB cases in 2011 = 1722 cases) and 85.2% of all CC cases (85.2% of 454 CC cases in 2011 = 387 cases) and 100% of those in DC and HCC (100% of 15 DC cases in 2011 and 100% of 36 HCC cases in 2011). All persons who are not on treatment (n = 313 CHB cases and n = 77 CC cases) follow the natural history arm.

Table 3.2: Starting distributions for each health state in each of the 3 scenarios

Scenarios	Treatment uptake [overall HBV cohort: n=14400]	Meeting criteria for treatment:				
		n=2550 (%)	CHB: n=2051 (%)	CC: n=448 (%)	DC: n=15 (%)[†]	HCC: n=36 (%)[†]
1	418 (2.9%)	418 (16.4%)	301 (14.7%)	66 (14.7%)	15 (100%)	36 (100%)
2	1440 (10%)	1440 (56.5%)	1137 (55.4%)	252 (56.3%)	15 (100%)	36 (100%)
3	2160 (15%)	2160 (84.7%)	1722 (84%)	387 (86.4%)	15 (100%)	36 (100%)

CHB – chronic hepatitis B, no cirrhosis; CC – compensated cirrhosis; DC – decompensated cirrhosis; HCC – hepatocellular carcinoma. [†] - Assumption that everyone in DC and HCC were treated across all 3 scenarios.

To estimate the cost-effectiveness of different treatment uptakes, a cohort Markov model (179-180) was built in TreeAge Pro 2009 software (181). Briefly, this entails dividing a patient's possible course of disease progression into a number of health states with prior transition probabilities assigned for the movement between these states over a discrete time period (Markov cycle). For each scenario, individuals assigned to treatment were assigned transition probabilities derived from known probability distributions following treatment with tenofovir, chosen because of the

availability of comprehensive long term histological data with serial liver biopsies on the therapy **(Table 3.3)**.

Individuals who were not assigned to treatment were assumed to follow transition probabilities associated with the natural history of HBV infection. Long-term costs and health outcomes were assessed by attaching estimates of resource use and health outcomes to each of the 6 states in the model. Model-based predictions of costs and outcomes were compared between each scenario in a cost-utility analysis (CUA) from a health payer (Australian Medicare) perspective.

Table 3.3: Estimates of transition probabilities & distributions used in the reference case and sensitivity analyses

	Tenofovir Treatment Arm			Natural History Arm		
	Estimate[a]	**Distribution[b]**	**Source**	**Estimate[a]**	**Distribution[b]**	**Source**
Probability of moving between health states						
Probability of moving from CHB[c] to CC[d]	0.002	Beta	Marcellin (187)	0.044	Beta	Butler (36)
Probability of moving from CHB[c] to HCC[e]	0.003	Beta	Marcellin (187)	0.006	Beta	Butler (36)
Probability of moving from CHB[c] to sAg loss[f]	0.008	Beta	Marcellin (187)	0.012	Beta	Liaw (188)
Probability of moving from CC[d] to CHB[c]	0.236	Beta	Marcellin (187)	0.000	Beta	Expert opinion
Probability of moving from CC[d] to DC[g]	0.020	Beta	Kanwal (189)	0.073	Beta	Kanwal (189)
Probability of moving from CC[d] to HCC[e]	0.010	Beta	Marcellin (187)	0.034	Beta	Kanwal (189)
Probability of moving from DC[g] to CC[d]	0.350	Beta	Kanwal (189)	0.080	Beta	Kanwal (189)

	Tenofovir Treatment Arm			Natural History Arm		
	Estimate[a]	**Distribution[b]**	**Source**	**Estimate[a]**	**Distribution[b]**	**Source**
Probability of moving from DC[g] to LT[h]	0.020	Beta	Lim (190)	0.250	Beta	Kanwal (189)
Probability of moving from HCC[e] to LT[h]	0.300	Beta	Expert opinion	0.300	Beta	Kanwal (189)
Probability of death for those who have suffered an event						
Probability of death from CC[d]	0.003	Beta	Marcellin (187)	0.049	Beta	Kanwal (189)
Probability of death from DC[g]	0.034	Beta	Lim (190)	0.190	Beta	Kanwal (189)
Probability of death from HCC[e]	0.400	Beta	Expert opinion	0.400	Beta	Butler (36)
Probability of death from LT[h] (Year 1)	0.090	Beta	Lynch (145)	0.090	Beta	Lynch (145)
Probability of death from LT[h] (Year 2 +)	0.048	Beta	Lynch (145)	0.048	Beta	Lynch (145)

	Tenofovir Treatment Arm			Natural History Arm		
	Estimate[a]	**Distribution[b]**	**Source**	**Estimate[a]**	**Distribution[b]**	**Source**
Probability of death for all causes						
Probability of death	0.020	Beta	Australian Bureau of Statistics (2015)	0.020	Beta	Australian Bureau of Statistics (2015)

[a] Five and three year probabilities were converted into annual probabilities using the ProbToProb function in TreeAge; [b] Distributions used in probabilistic sensitivity analysis; [c]CHB = Chronic Hepatitis B, no cirrhosis; [d]CC = Compensated cirrhosis; [e]HCC = Hepatocellular carcinoma; [f]sAg loss = Spontaneous seroclearance; [g]DC= Decompensated cirr hosis; [h]LT = Liver transplant

3.2.2 Model structure and inputs:

The structure of the Markov model is shown in **Figure 3.1**

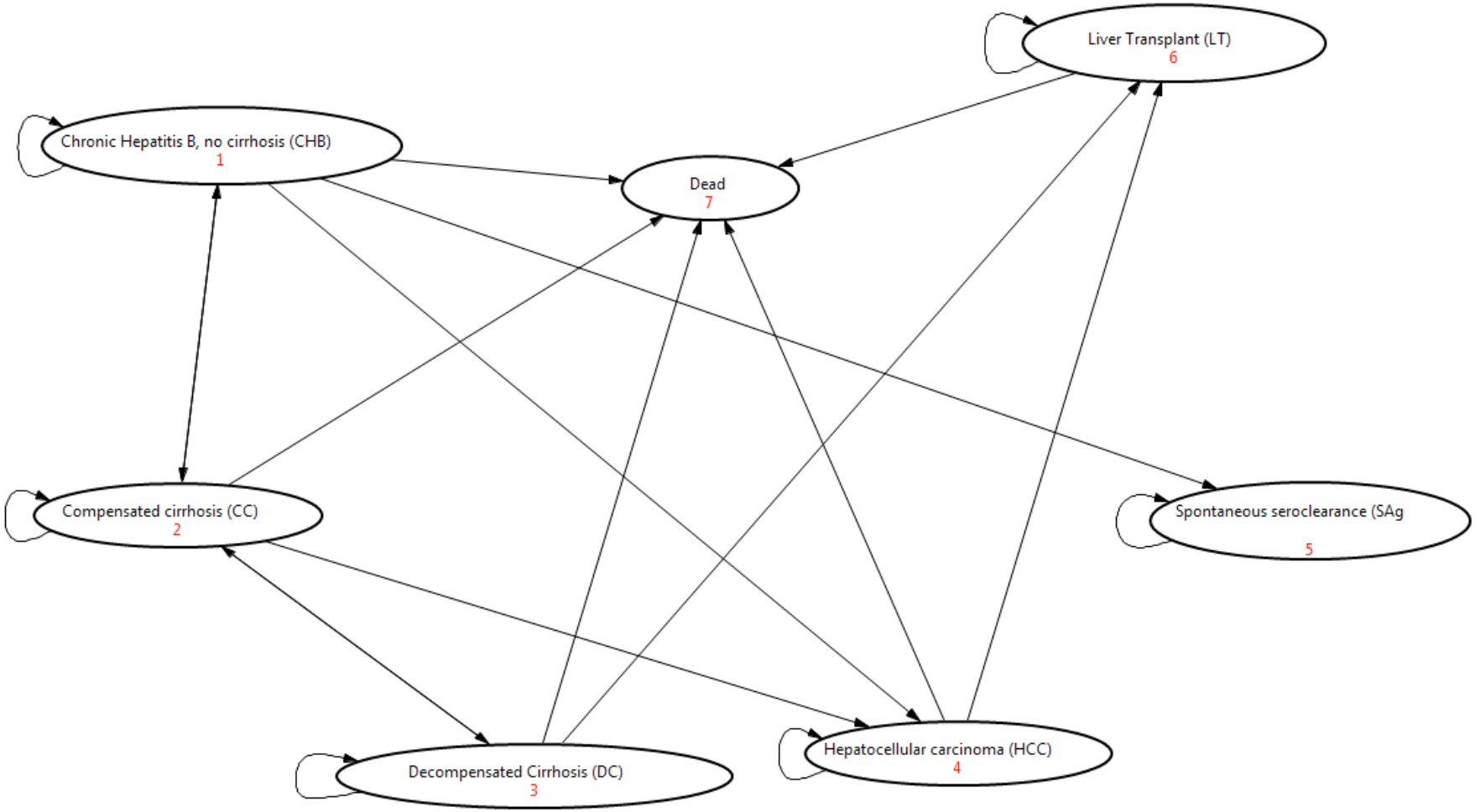

Figure 3.1: Markov structure showing 7 possible states. Each arrow has an associated transition probability.

The time horizon for the model was 10 years and a cycle length of one year (deemed appropriate in models similar to ours) (191-193) was used. Model parameters were based on the best available estimates from published data (36, 145, 187-190) **(Table 3.3)**. The risks of adverse effects were not incorporated into the model as these are generally considered mild and assumed to have no effect on costs, mortality, or quality of life (191). The Markov process for each arm began by identifying the initial distribution of patients within any of the six states based on the estimated 2011 CHB prevalence (181). The six health states were CHB, CC, DC, HCC, Spontaneous seroclearance (sAg loss) and liver transplant (LT). Patients could remain in any state or move to one of the other five possible health states unless they died before the end of the time horizon for the model. In the initial patient distribution (existing CHB treatable population), there were no sAg loss or LT cases and so the initial probability assigned to these two health states was 0. The transition probabilities governing movement between the six states for both the natural history and treatment arms are shown in **table 3.3**. Known 5 and 3-year transition probabilities were converted into the respective annual probabilities using the 'ProbToProb' function in TreeAge.

3.2.3 Direct costs and Utility values:

Average total direct costs for each health state were obtained from Butler et al (102) and inflated to 2014/15 prices. All costs are reported in Australian dollars and, where appropriate, were discounted at 5% as recommended by the Australian Pharmaceutical Benefits Advisory Committee (194). Total costs for individuals assigned to a natural history progression included costs of outpatient visits, lab tests and imaging, and inpatient admissions (except the drug costs). Total costs for the treated individuals included all costs associated with a natural history progression plus the cost of anti-viral therapy (tenofovir). To reflect the accurate cost of treatment with tenofovir, the current 2014 cost per person per year of the drug (AU $5,878) was used in calculating total costs and this was then weighted across the health states based on the cost distributions for health states, similar to previous modelling (36). Drug costs for LT states were not reported in Butler et al (102). On average, drug

costs in Butler et al., made up 9% of all total costs and this figure was used to estimate drug costs for the LT states. All cost data are shown in **table 3.4**.

Table 3.4: Utility estimates and costs for various health states:

Health states	Utilities	Direct costs (AU $)*	
		Natural history	With treatment
CHB	0.68 (0.66 - 0.70)	$2,267	$3,592
CC	0.69 (0.66 - 0.71)	$2,027	$2,793
DC	0.35 (0.32 - 0.37)	$21,923	$23,574
HCC	0.38 (0.36 - 0.41)	$21,993	$23,126
sAg loss‡	0.79 (0.77 – 0.80)	$0	$0
LT (year 1)¶	0.57 (0.54 - 0.60)	$285,083	$285,083
LT (year 2+)¶	0.67 (0.64 - 0.69)	$45,726	$45,726

CHB – chronic hepatitis B, no cirrhosis; CC – compensated cirrhosis; DC – decompensated cirrhosis; HCC – hepatocellular carcinoma; LT – liver transplant.

‡ - Individuals achieving sAg loss were discharged and hence their cost is $0.

¶ - Assumption that everyone post liver transplant will be on anti-viral therapy hence, no difference in costs between the natural history and treatment arm.

*As only point estimates were obtained for these costs, the standard error was assumed to be equal to the mean as has been done elsewhere (195)

Gamma distributions were used for calculating all costs in this model.

All utility scores, which reflect the health-related quality of life associated with each health state in the model were obtained from the literature (100) and are shown in **table 3.4**. The starting quality of life (QoL) values for individuals in the model were obtained from Australian age-specific QoL estimates (190). Utility scores for health states occurring thereafter were applied mid-way through each one-year cycle and those for the subsequent health states at the start of the next cycle. Future

health state utility scores were modelled as multiplicative values of the Australian age-specific utility estimate (190) and the utility score of each particular health state.

3.2.4 Analysis:

The analysis was undertaken from a Australian health system (Medicare) perspective with the primary outcome being the incremental cost per quality adjusted life year (QALY) gained (196). Clinical outcomes (number of deaths, liver transplants and HCC cases) were also estimated. Probabilistic analyses were used based on 50,000 Monte Carlo simulations, with cost-effectiveness planes (CEPs) and cost-effectiveness acceptability curves (CEACs) reported (197, 198). Dirichlet distributions were applied to the probability of following the natural history or the treatment arm and to probabilities of being in each state at the start of the Markov process. Beta distributions were used to model the probability of dying, the probability of transitioning between different health states as well as the uncertainty around the utility values. Gamma distributions were fitted to all costs used in the model for consistency. The parameters used for these distributions are shown in Tables 1, 2 and 3.

In sensitivity analyses we relaxed the assumption that all individuals with DC or HCC will always get treated and allowed the same treatment uptake to be applied uniformly across all health states. We also varied the time horizon for each model from 10 years to between 1 and 7 years. This time horizon was chosen to represent a plausible range within which the cost-effectiveness of each scenario could be assessed against the cost-effectiveness threshold of $50,000/QALY gained, which is the implicit criterion used in Australian studies (199).

3.3 RESULTS:

3.3.1 Health economic outcomes:

The mean long-term (10 year) costs and QALYs gained per patient are presented in **table 3.5**. Scenario 3 was associated with the lowest mean costs (AU $60,133) followed by scenario 2 (AU $61,964) and then scenario 1 (AU $64,597). Further, scenario 3 was again associated with the highest QALY gains (8.196) followed by scenario 2 (7.985) and then scenario 1 (7.684) meaning that scenario 3 was both cheaper and more effective (dominates) than either scenario 1 or 2 while scenario 2 was also cheaper and more effective than scenario 1.

The CEPs **(Figure 3.2)** show the joint distribution of the mean incremental costs and mean QALYs gained with all results in the north-east and south-east quadrants indicating some uncertainty in the results. The discounted costs to the QALYs gained per patient are shown in **figure 3.3**.

Table 3.5: Economic and clinical outcomes assuming a 10-year horizon for each scenario:

Time Horizon	Costs/QALYs & Clinical outcomes	Scenario 1	Scenario 2	Scenario 3
10 years	Mean total health care costs	AU $64,597	AU $61,964	AU $60,133
	Mean QALYs gained	7.684	7.985	8.196
	Total number of liver transplants	869	563	348
	Number of liver transplants avoided (compared to Scenario 1)	-	306	522
	Total number of HCC cases	320	225	159
	Number of HCC cases prevented (compared to Scenario 1)	-	95	161
	Total number of deaths	779	635	534
	Number of deaths prevented (compared to Scenario 1)	-	144	245

QALY – quality adjusted life years; HCC – hepatocellular carcinoma.

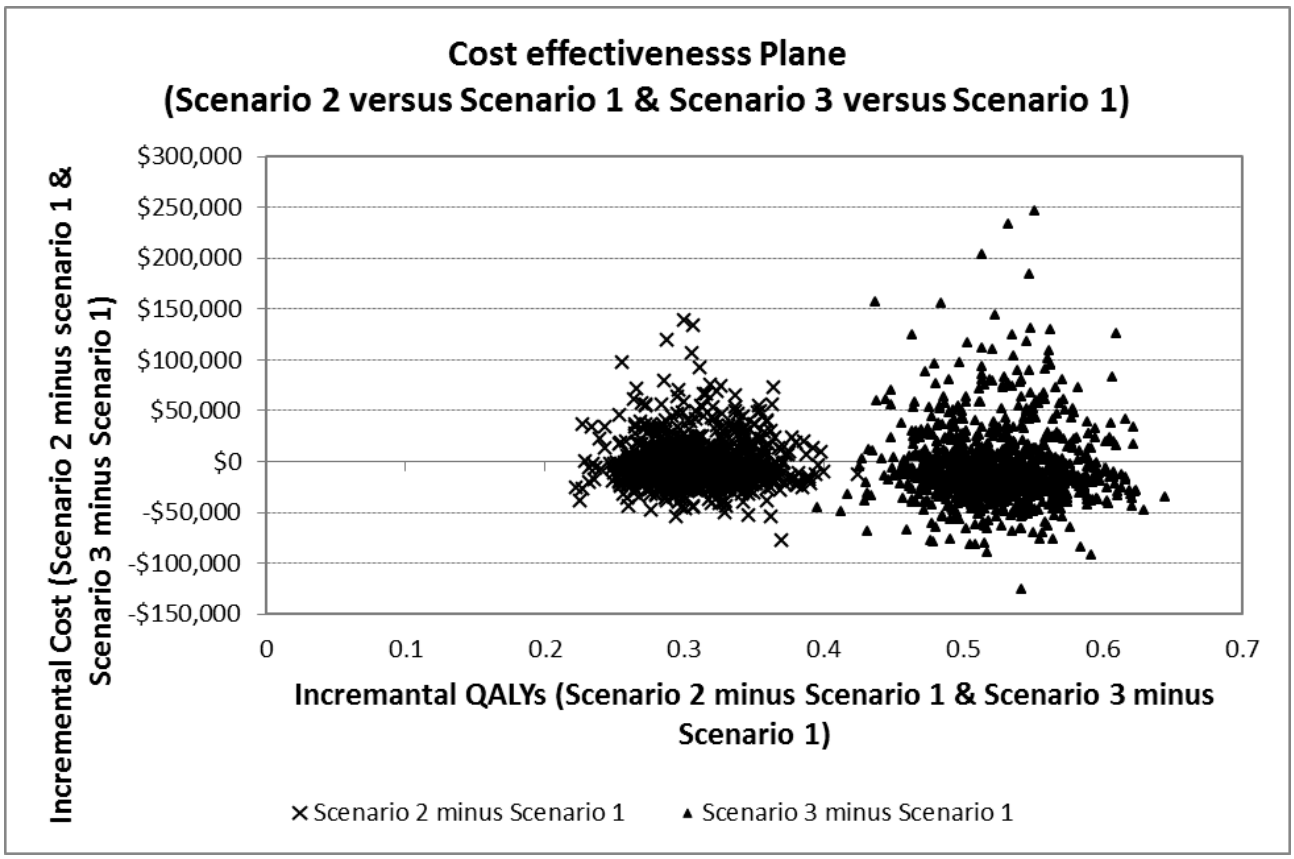

Figure 3.2: Cost effectiveness plane assessing the incremental cost and QALY while comparing various scenarios: Each point represents a simulation estimate.

QALY – quality adjusted life years

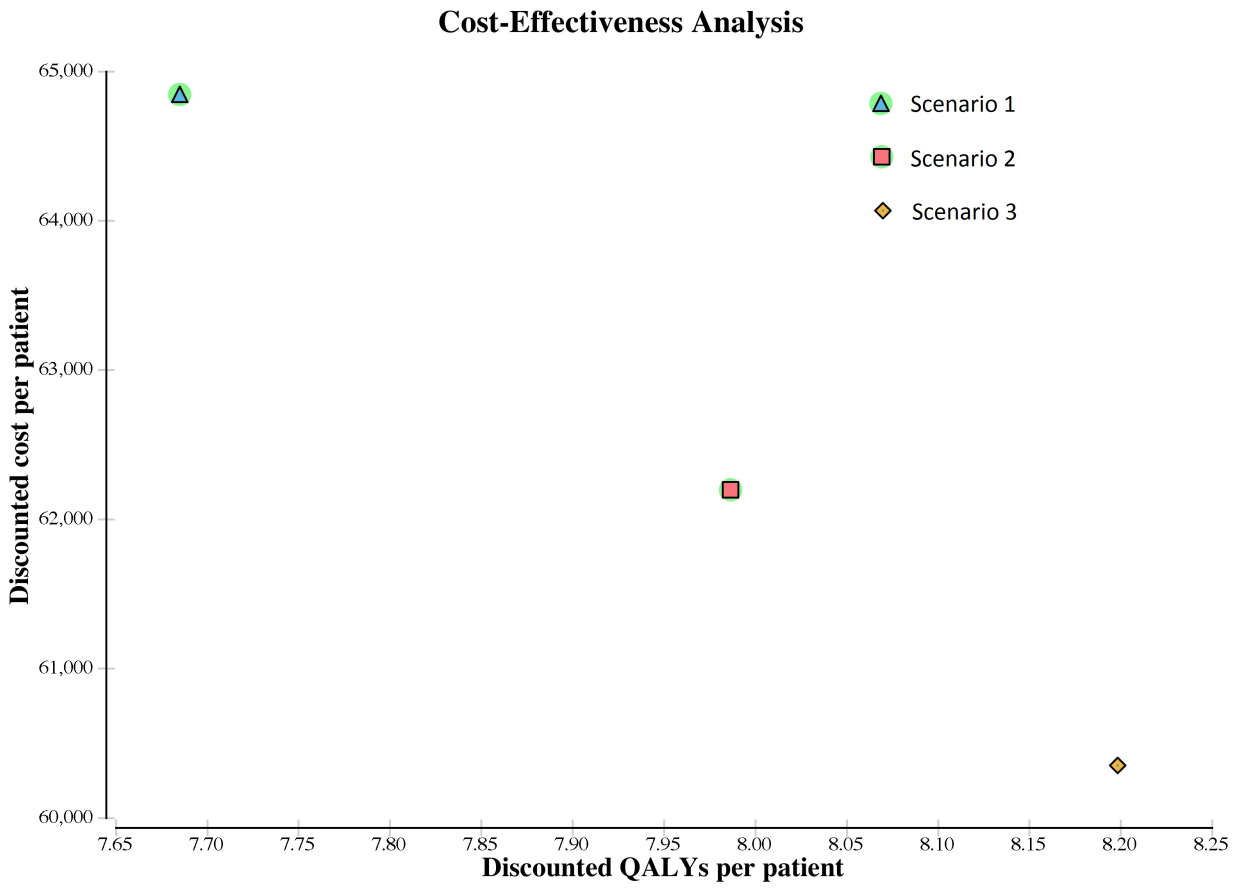

Figure 3.3: Cost-effective analysis assessing the cost and QALY while comparing various scenarios:

QALY – quality adjusted life years

The cost-effectiveness acceptability curves (CEACs) **(Figure 3.4)** show that assuming a value per QALY-gained of at least AU $50,000, the probability of scenario 2 being cost-effective compared to scenario 1 was at least 86% while the corresponding probabilities of scenario 3 being cost-effective compared to scenario 1 and then to scenario 2 were at least 85% and 84%, respectively (**Figures 3.4 A, B and C**). At lower QALY thresholds, the probability of the intervention being cost-effective compared to the control was lower, dropping to 70% at around AU $20,000 per QALY-gained for all three comparisons.

(A)

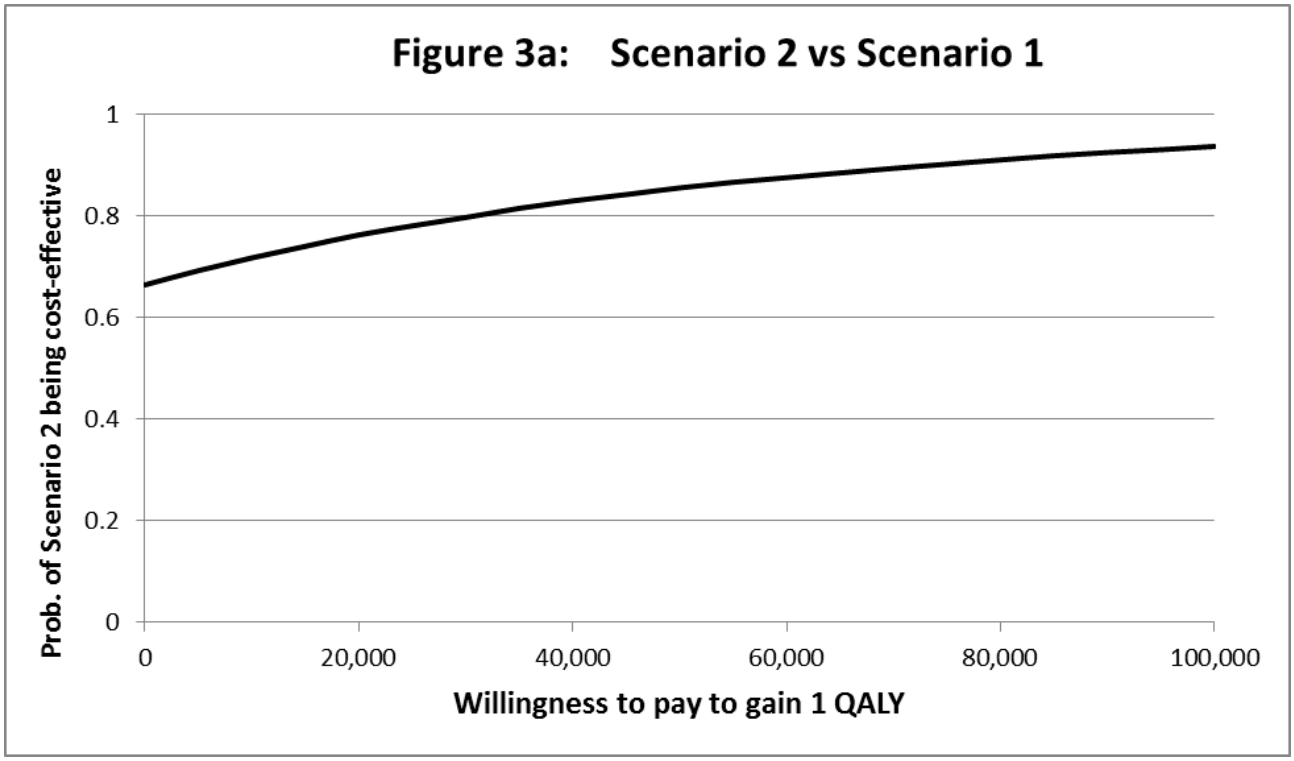
Figure 3a: Scenario 2 vs Scenario 1
Prob. of Scenario 2 being cost-effective
1
0.8
0.6
0.4
0.2
0
0
20,000
40,000
60,000
80,000
100,000
Willingness to pay to gain 1 QALY

(B)

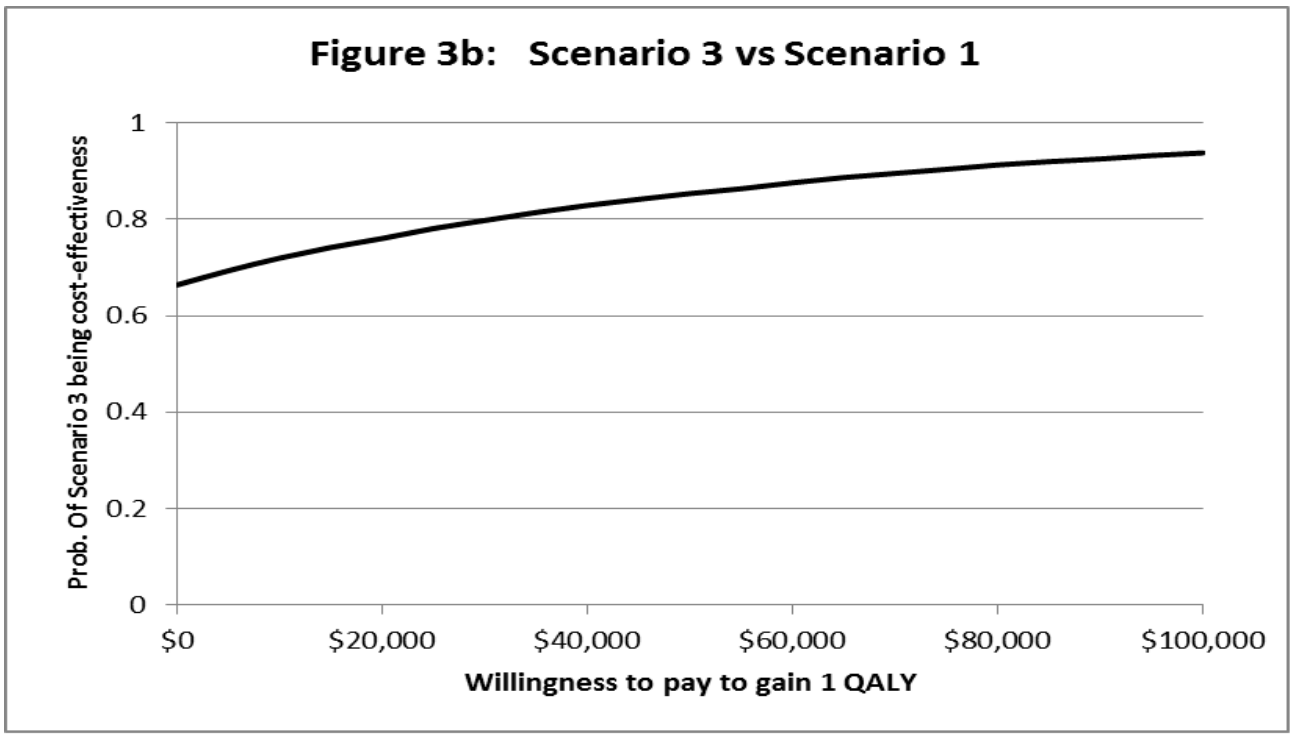
Figure 3b: Scenario 3 vs Scenario 1
Prob. Of Scenario 3 being cost-effectiveness
1
0.8
0.6
0.4
0.2
0
$0
$20,000
$40,000
$60,000
$80,000
$100,000
Willingness to pay to gain 1 QALY

(C)

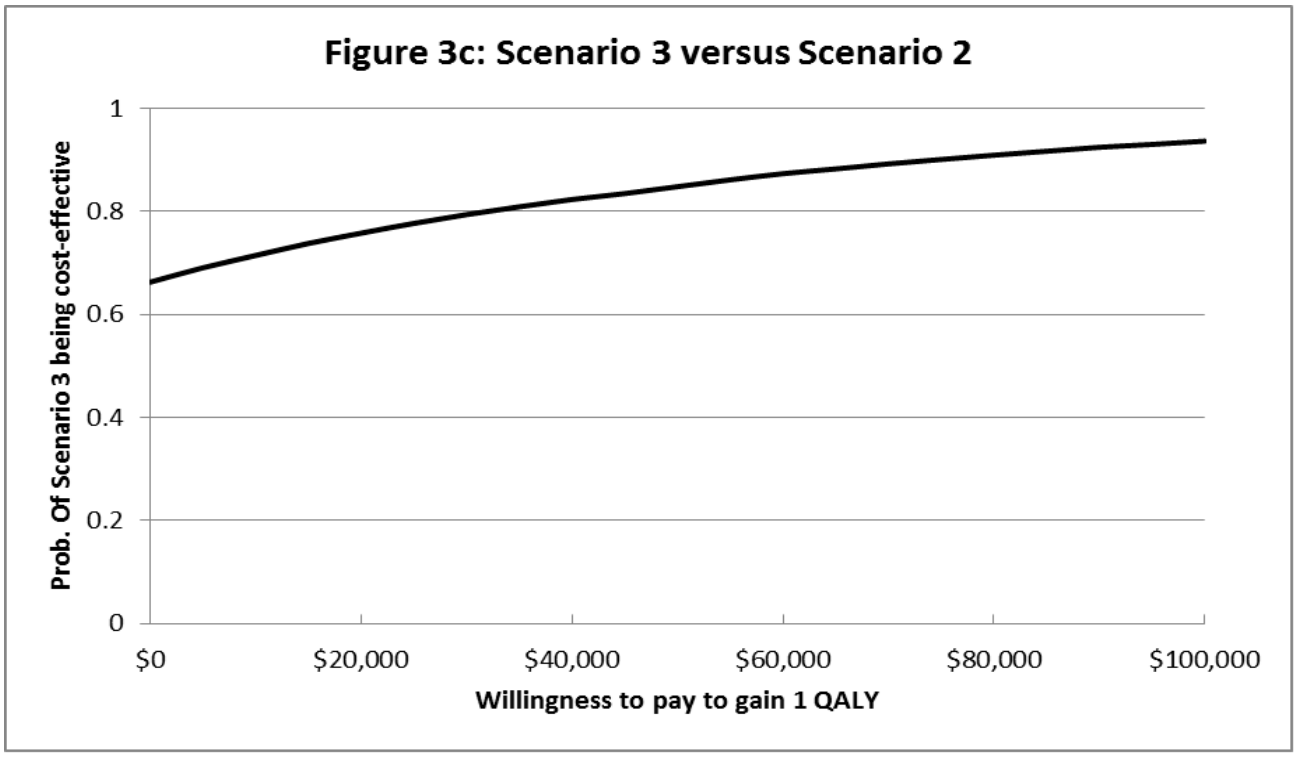

Figure 3.4: Cost-effectiveness acceptability curves comparing:

A) Scenario 2 v Scenario 1

B) Scenario 3 v Scenario 1

C) Scenario 3 v Scenario 2

3.3.2 Clinical outcomes:

Compared to scenario 1, scenario 3 would result in a 50% reduction in cumulative HCC incidence and a 30% reduction in HBV related mortality over a 10- year period **(Table 3.5)**. However, the greatest benefit with increasing treatment uptake would be seen in the number of liver transplants avoided with a reduction of 60% for scenario 3 compared to scenario 1. Scenario 2 also resulted in reduction in HCC incidence, mortality rates and liver transplantation compared to scenario 1, but the magnitude of the benefits were slightly lower.

3.3.3 Sensitivity analysis:

Figure 3.5 shows the results obtained when: (i) time horizons were varied **(Table 3.6)** (ii) time horizons were varied and the same treatment uptake applied uniformly across all health states **(Table 3.7)** and (iii) time horizons were varied and higher values for utilities of the modelled health states were applied **(Table 3.8)**. A similar pattern was observed in all scenarios comparing higher to lower treatment uptake. For the sake of brevity, only results for the comparison between scenarios 1 and 3 are shown in **Figure 3.5**. In all sensitivity analyses, the ICERs for higher treatment uptake (scenario 3) compared to lower treatment uptake (scenario 1) were all below AU $50,000 per QALY gained provided the time horizon was at least 2 years, with higher treatment uptake dominating lower treatment uptake (i.e. cheaper and more effective) for all time horizons greater than 4 years (sensitivity analysis ii), 5 years (sensitivity analysis iii) and 6 years (sensitivity analysis i).

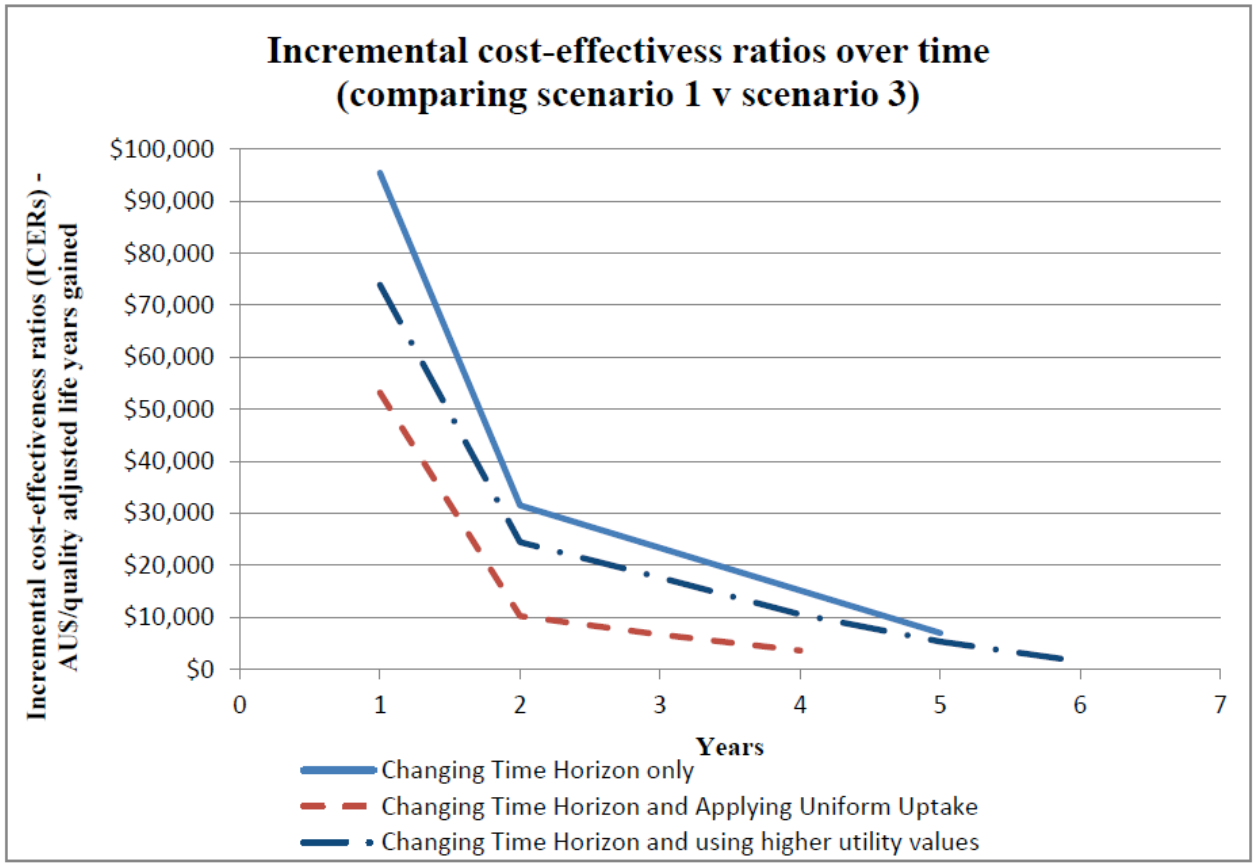

Figure 3.5: Incremental cost-effectiveness ratio with varying time horizons while comparing various scenarios

ICER – Incremental cost-effectiveness ratio

Table 3.6: Cost-effectiveness results (Based on probabilistic analysis and sensitivity analysis involving changing time horizons)

Time Horizon	Costs/QALYs outcomes	Scenario 1	Scenario 2	Scenario 3	ICER 1 Scenario 1 vs Scenario 2	ICER 2 Scenario 1 vs Scenario 3	ICER 3 Scenario 2 vs Scenario 3
7 years	Mean total health care costs	$46,086	$45,728	$45,496	Scenario 1 is dominated	Scenario 1 is dominated	Scenario 2 is dominated
	Mean QALYs gained	5.943	6.108	6.224			
6 years	Mean total health care costs	$39,612	$39,816	$39,979	$1,624	$1,717	$1,850
	Mean QALYs gained	5.247	5.373	5.461			
5 years	Mean total health care costs	$33,070	$33,681	$34,130	$6,746	$6,874	$7,055
	Mean QALYs gained	4.485	4.576	4.639			
4 years	Mean total health care costs	$26,466	$27,367	$28,017	$14,928	$15,108	$15,365
	Mean QALYs gained	3.651	3.712	3.754			
3 years	Mean total health care costs	$20,004	$20,862	$21,479	$28,600	$24,583	$20,567
	Mean QALYs gained	2.740	2.770	2.800			

2 years	Mean total health care costs	$13,686	$14,224	$14,612	$33,167	$32,414	$31,424
	Mean QALYs gained	1.741	1.757	1.770			
1 year	Mean total health care costs	$4,108	$4,493	$4,767	$94,322	$95,136	$96,299
	Mean QALYs gained	0.653	0.657	0.660			

ICER – Incremental cost-effectiveness ratio; QALY – quality adjusted life years

Table 3.7: Changing the time horizon and allowing treatment uptake for HCC and DC to vary in the same line as uptake for CHB and CC

Time Horizon	Costs/QALYs outcomes	Scenario 1	Scenario 2	Scenario 3	ICER 1 Scenario 1 vs Scenario 2	ICER 2 Scenario 1 vs Scenario 3	ICER 3 Scenario 2 vs Scenario 3
5 years	Mean total health care costs	$41,256	$40,713	$40,445	Scenario 1 is dominated	Scenario 1 is dominated	Scenario 2 is dominated
	Mean QALYs gained	5.239	5.370	5.462			
4 years	Mean total health care costs	$34,596	$34,504	$28,305	$2,667	$3,602	$4,943
	Mean QALYs gained	4.479	4.573	4.639			
3 years	Mean total health care costs	$27,921	$28,089	$28,305	$5,232	$6,699	$8,804
	Mean QALYs gained	3.646	3.709	3.753			
2 years	Mean total health care costs	$13,796	$14,505	$14,974	$33,663	$32,842	$31,674
	Mean QALYs gained	2.346	2.367	2.382			
1 year	Mean total health care costs	$14,829	$14,771	$14,811	$49,497	$53,184	$58,504
	Mean QALYs gained	1.739	1.756	1.768			

In the base case analysis, we assumed that 100% of everyone with hepatocellular cirrhosis (HCC) or decompensated cirrhosis (DC) will always be treated. In this sensitivity analysis, we have relaxed this assumption and allowed treatment uptake for those in these two health states to vary in the same line as uptake for chronic hepatitis B (CHB) and compensated cirrhosis (CC)

Table 3.8: Changing the time horizon and using higher utilities

Time Horizon	Costs/QALYs outcomes	Scenario 1	Scenario 2	Scenario 3	ICER 1 Scenario 1 vs Scenario 2	ICER 2 Scenario 1 vs Scenario 3	ICER 3 Scenario 2 vs Scenario 3
7 years	Mean total health care costs	$46,086	$45,728	$45,496	Scenario 1 is dominated	Scenario 1 is dominated	Scenario 2 is dominated
	Mean QALYs gained	5.943	6.108	6.224			
6 years	Mean total health care costs	$39,832	$40,088	$40,279	$1,471	$1,508	$1,561
	Mean QALYs gained	7.050	7.224	7.346			
5 years	Mean total health care costs	$33,260	$33,915	$34,386	$5,265	$5,320	$5,397
	Mean QALYs gained	6.031	6.155	6.243			
4 years	Mean total health care costs	$26,682	$27,539	$28,153	$10,490	$10,575	$10,695
	Mean QALYs gained	4.913	4.994	5.052			
3 years	Mean total health care costs	$20,170	$20,990	$21,579	$17,509	$17,657	$17,867
	Mean QALYs gained	3.687	3.734	3.767			

2 years	Mean total health care costs	$13,796	$14,305	$14,674	$24,173	$24,481	$24,918
	Mean QALYs gained	2.346	2.367	2.382			
1 year	Mean total health care costs	$4,136	$4,526	$4,804	$73,421	$73,926	$74,644
	Mean QALYs gained	0.880	0.886	0.889			

In the base case analysis, utilities for the health states in the model were obtained from Levy et al. 2008 (105), a study of 1,134 individuals drawn from the United States, Canada, United Kingdom, Spain, Hong Kong, and mainland China . In this sensitivity analysis, we used higher values of these utilities reported in Woo et al. 2012 (200), a study of 433 Canadians. The mean values (95% confidence intervals) were 0.92 (0.91-0.94) for CHB, 0.88 (0.85-0.92) for CC, 0.73 (0.39-1.00) for DC, 0.81 (0.67-0.94) for HCC, and 0.84 (0.77-0.91) for post liver transplant (LT).

3.4 DISCUSSION:

This study showed that increasing treatment uptake in CHB population, in those eligible, to either 10% or 15% from the current 2.9% was cheaper and also cost-effective, primarily due to a reduction in the estimated number of clinical events, particularly HCC and liver transplant.

To our knowledge, this is the first economic analysis comparing different treatment uptake rates in CHB with a modern, high-barrier to resistance drug. Two cost-utility analyses of lamivudine, a low-barrier to resistant drug, for the treatment of CHB have been conducted in Australia (201, 202)**.** Both studies concluded that lamivudine was associated with a favourable cost-effectiveness ratio when compared against other treatment scenarios but none of the scenarios included tenofovir or a comparison of different treatment uptake rates. The reductions seen in the lifetime risk of developing CC, DC and HCC (5, 11 and 11%, respectively) were however similar to the ones obtained in our study. The findings from our study are likely to be applicable to many other western health regions due to similar CHB prevalence, high proportion of unreported cases and low treatment uptake rates.

Butler and colleagues (36) also used Markov mathematical simulation to model the current and projected burden of CHB in Australia over a 10 year period but based their analysis on a representative cohort of people with CHB in 2008. In their study, they compared natural history, 2008 treatment and management practices (treatment rate) and enhanced treatment and management practices. Outcomes were not expressed in terms of costs per QALYs gained but as incremental cost per CHB-related death averted and incremental cost per life-year saved. Similar to our study, they also projected a reduction in CHB-related deaths (39%) due to an increase in treatment effect (28.04%). The lower ratio between treatment effect and number of deaths may have been due to differences in baseline estimates of CHB prevalence assumed in the two studies.

While increasing uptake of therapy appears cost-effective and is likely to reduce important clinical events, this remains a challenging goal as a large percentage of the CHB cohort remains

undiagnosed. As outlined in the current Australian hepatitis B strategy (65), the most important step will be to increase the screening rates in priority at risk populations – people from culturally and linguistic diverse backgrounds, indigenous Australians, injecting drug users and men having sex with men. This will require a concerted, targeted effort with appropriate education and public health awareness initiatives.

Varying the time horizons of the model from the 10 years period used in the base case analysis and assuming a threshold of AU $50,000/QALY (199) showed that increased treatment uptake only became cost-effective when the time horizon was at least 2 years. This was because of the lag time between increased treatment uptakes and reduction in clinical events (liver transplants, HCC cases and deaths). Applying a uniform treatment uptake to all health states did not change the base case: strategies that involved a higher treatment uptake still dominated those that were based on a lower uptake. This is because most of reduction in clinical events was from the treating those with compensated cirrhosis.

This study has several strengths. It is the first to model the benefits of increased treatment uptake with tenofovir – a potent nucleotide analogue with a high barrier to resistance. Our estimated annual transition probabilities between states were reliably based using data from a large cohort of tenofovir patients who underwent serial liver biopsies (187). Also, the HBV population used for primary analysis was based on the published estimated prevalence of HBV in South Australia (184) and their corresponding known distribution of states, rather than hypothetical prevalence estimates. Thirdly, sensitivity analysis was performed to: (i) assess the cost-effectiveness of this strategy with varying time-horizons and (ii) vary the treatment uptakes in each health state to assess the robustness of the model.

There are several limitations to this study. Firstly, only tenofovir was assessed in calculating annual treatment transition probabilities. This was mainly because of the availability of comprehensive long-term data on tenofovir therapy. This may not reflect the real life practice as various

nucleos(t)ide analogues are used, however, the other commonly used oral anti-viral, Entecavir, has similar potency and high barrier to resistance. Furthermore, the transition probabilities used in this study were obtained from a controlled trial setting and we acknowledge that this might not entirely reflect the real-world practices because of compliance issues. Secondly, the transition probabilities used in this study were derived from studies in a different patient population as no local data were available. However, the majority of these cohorts had a significant proportion of Asian individuals, similar to the current South Australian CHB population. Thirdly, as mentioned in the methods section, we assessed only the direct costs involved from a health payer perspective and did not include the indirect costs such as loss of productivity. Lastly, since there was no recent SA data for the cost of managing these patients, we used data obtained more than a decade ago and extrapolated to its current value.

In conclusion, our analysis demonstrated that increasing treatment uptake in a CHB population is cost-effective. Varying the time horizons of the model from the 10-year period used in the base case analysis and assuming a threshold of AU $50,000 showed that strategies involving higher treatment uptakes were still more cost-effective provided the time horizon was at least 2 years.

4. SURVIVAL OF HEPATOCELLULAR CARCINOMA PATIENTS DIAGNOSED WITHIN A CENTRALLY COORDINATED SCREENING PROGRAM

4.1 INTRODUCTION:

Hepatocellular Carcinoma HCC results in more than 300,000 deaths globally each year. The highest regions of HCC incidence appear to be in Sub-Saharan Africa and China, with rates of greater than 15 per 100,000 population (149), compared to Western counties where the HCC incidence is relatively low, 6 per 100,000 population (203). According to the Australian Institute for Health and Welfare, the age standardized rate (ASR) for HCC incidence was 5.9 per 100,000 population in 2011 (204). Although the HCC incidence rate in Australia is relatively lower, the mortality is increasing and has equalled the incidence rates, 5.9 per 100,000 population in 2012. HCC therefore has a poor survival with a relative 1- and 5-year survival of 40% and 16% respectively in Australia (204).

Current recommendation for HCC screening is to use 6-monthly abdominal ultrasound in high risk patients (115). However, mortality reduction with this screening strategy is equivocal as there is only limited prospective data. A large Chinese study used a cluster randomization process to evaluate mortality benefits of a screening program (112). The study evaluated more than 19,000 patients with HCC and found that there was a 37% reduction in mortality in the screening group. It would be impossible to undertake another randomized controlled trial (RCT) of screening vs no screening because of ethical concerns.

Prospective cohort studies, the next level of evidence to RCT, of screened patients developing HCC compared to unscreened patients are prone to lead-time bias due to the reduced lead time in those screened. Researchers have tried to correct for this bias by calculating the lead-time to diagnosis,

which is dependent on tumour growth rate (205). Another way of assessment is examining survival and the stage of tumour diagnosis (206-208). Although diagnosing tumours at an earlier stage does not necessarily translate into a direct survival benefit, given the influence for lead-time bias, detecting disease at an early stage is still an essential requirement for an effective screening test, in order to be able to influence survival.

There is a paucity of local Australian data that evaluates the benefit of regular screening programs; given the differences in demographics in the Chinese study versus a heterogeneous Western population, it is important therefore to evaluate the impact of screening/ surveillance programs in an Australian population. Adherence to screening is relatively poor in real world environments, and this may also limit the effectiveness of an HCC screening program (209).

Our aim in this chapter was therefore to compare the overall survival between HCC patients diagnosed within a centrally co-ordinated screening program versus those diagnosed outside this group. We also evaluated tumour stage at diagnosis as well as the number of patients offered curative treatment in the two groups. A further aim was to examine the performance of the screening program with respect to adherence to the 6-monthly screening ultrasound.

4.2 METHODS:

4.2.1 Study Design and participants:

The study was a retrospective cohort analysis of consecutive patients diagnosed with HCC from 01/01/2004 to 31/12/2013 within the Southern Adelaide Local Health Network (SALHN) catchment area (estimated population ~350,000, one tertiary referral hospital with a liver transplantation centre and two smaller secondary hospitals). Patients were excluded if their primary address did not fall within SALHN postcodes or if they were diagnosed at another facility and subsequently referred to our Liver Transplant Unit or Palliative Care Hospice for ongoing

management. Patients were not included in the screening group if they were diagnosed with HCC within 3 months of screening program entry.

Patients were identified using the ICD-10 Code for HCC (C22.0) from all three hospitals and cross-referenced with South Australian Cancer Registry to ensure maximal case finding. Diagnosis was confirmed either histologically or with characteristic radiological appearance as per the current guidelines (115). Although the dedicated, centrally co-ordinated HCC screening program, run by non-medical clinical staff, was only established within our network in 2009, we evaluated 5- years prior to this to assess any era effect. The study protocol was approved by the Southern Adelaide Clinical Human Research Ethics Committee (SAC HREC).

4.2.2 HCC screening program:

An audit performed in 2007 within this local health network identified that individuals at high risk of developing HCC were having inadequate screening ultrasounds (209). One of the major barriers for this was the tertiary care practice, and this required system redesign for quality improvement. Based on this audit finding, a dedicated, centrally co-ordinated HCC screening program was established in 2009 along with an easy-to-use patient database with automated recall function. Booking process for ultrasounds, blood tests and medical reviews were centralised and monitored by an HCC co-ordinator. Patients received written reminders about ultrasound appointments prior to their visits which also included the contact details for the HCC co-ordinator. Patients who failed to attend their appointments were contacted and re-educated about the importance of this screening program, and a subsequent ultrasound appointment was made.

4.2.3 Data Collection:

Baseline demographics including age at diagnosis, gender, indigenous status, aetiology of liver disease and stage of liver disease based on Child Pugh and MELD score were obtained. Number of AFP measurements and HCC screening ultrasound scans (USS) were recorded for 2 years prior to

diagnosis. Those who had at least 2 screening scans in a 12- month period prior to diagnosis were deemed to have adequate screening. Those with suspicious tumour nodules or with elevated AFP were then evaluated with cross-sectional imaging (either multi-phase CT or contrast enhanced MRI) to confirm the diagnosis. Tumour characteristics were obtained from radiologic and histologic data including number, size and location of tumours, the presence or absence of portal vein thrombosis or invasion and alpha feto-protein (AFP) level on diagnosis. Based on the above parameters, Barcelona Clinic Liver Cancer (BCLC) staging was assessed and tumours were classified as early (stage O and A) or late (stage B, C and D).

Treatment intent, either curative (resection, liver transplantation or percutaneous ablation therapies) or palliative (trans-arterial chemo-embolization, oral chemotherapy or symptomatic management) was also recorded. Duration of follow up was from the date of diagnosis (confirmatory scan) until date of death or date of last follow up (30/04/2015).

4.2.4 Statistical Analysis:

Baseline characteristics were expressed either as median (IQR) for continuous variables or as number (%) for categorical variables. Primary outcome in this study was overall survival (OS), which was calculated using the Kaplan-Meier method and compared between those diagnosed within and outside the screening program. Secondary outcomes like BCLC stage, size of the largest tumour and treatment intent on diagnosis were also compared between the above two groups using chi-squared tests and Fisher's Exact tests as appropriate.

The OS between those diagnosed between 2004 and 2008 (era 1) to those diagnosed between 2009 and 2013 (era 2) was also compared to assess any era effect. Logistic regression analysis was performed to determine the predictors of mortality with a 2- sided p value of <0.05 being considered statistically significant. We used propensity score (PS) analysis to create an estimated probability (propensity) of being in the screening program based on several possible predictors of the screening program. This allowed adjustment for possible selection bias. The PS analysis

consisted of a probit regression model with the screening program as the binary outcome variable, and age, sex and the year of diagnosis as covariates. The estimated effect of the screening program on survival was then assessed using Cox regression with the screening program being the exposure of interest, and the PS, AFP and MELD as covariates. All statistical analysis was performed using IBM SPSS Statistics software for windows, Version 19.0. Armonk, NY: IBM Corp. and Stata (MP Version 14.0, Stata Corp, Texas, USA).

4.3 RESULTS:

4.3.1 Baseline characteristics:

During the study period, 130 subjects were diagnosed with HCC and met inclusion criteria. Among them, 107 (82.3%) were males with a mean (±SD) age of 63.2 (±12.3) years at diagnosis and were followed up for a mean (±SD) duration of 20 (±23.5) months (**Table 4.1**).

Chronic hepatitis C (CHC) related cirrhosis was the predominant underlying aetiology followed by alcohol and Non-alcoholic steato-hepatitis (NASH) related cirrhosis. The majority of patients (56.2%) were well compensated Child-Pugh A at the time of HCC diagnosis.

4.3.2 Overall survival:

Ninety-six patients (73.8%) died during the follow-up period and the median (95% CI) overall survival (OS) was 15.7 (9.7-21.8) months. There was no survival difference between the HCC diagnosed in the two eras [12.9 (5.7-20.2) v 16.3 (7.5-24.9), p=0.6]. However, those diagnosed within the dedicated screening program had a better OS compared to those who were diagnosed outside this program (26.8 v 11.5 months, p=0.01). The 1-, 2- and 3- year survival was also better in those diagnosed within the program (**Table 4.2**). Even after adjusting for the era of HCC diagnosis, a survival benefit was still seen for those diagnosed within the program (**Figure 4.1**).

Table 4.1: Baseline characteristics

Variables	**Results**
Age at diagnosis [median (IQR)], years	62 (19)
Males [n (%)]	107 (82.3)
Aetiology [n (%)]*	
Chronic hepatitis C (CHC)	25 (19.2)
Alcohol	23 (17.7)
Non-alcoholic steatohepatitis	22 (16.9)
Alcohol + CHC	21 (16.2)
Diagnosed 2009-2013 (Era 2) [n (%)]	81 (62.3)
Diagnosed within the program [n (%)]	24 (18.5)
Child-Pugh score [n (%)]$^{\eta}$	
A	73 (56.2)
B	39 (30)
C	13 (10)
BCLC stage [n (%)]	
Early (stage O and A)	39 (30)
Late (stage B, C and D)	91 (70)
Follow-up [median (IQR)], months	11.3 (23.3)

*-Only four common aetiologies mentioned; $^{\eta}$-Child-Pugh score could not be calculated in 5 (3.8%) patients; IQR – Inter-quartile range

Table 4.2: Overall survival in HCC

Groups	Median survival (95%CI), months	1- year (%)	2- year (%)	3- year (%)
2004-2008; outside the program	12.9 (5.7-20.2)	53.1	29.6	22.4
2009-2013; outside the program	10.4 (3.9-16.8)	45.0	34.5	20.6
2009-2013; within the program	26.8	76.0	61.4	46.0

4.3.3 Stage of disease, treatments offered and proportion with adequate screening:

Overall, only 39 (30%) patients had a very early or early BCLC stage at diagnosis. Within the screening program, 14/24 had an earlier stage of diagnosis compared to 25/106 outside the program [(58.3% v 23.6%), χ^2 =11.3, p=0.001]. Further, the majority (95.2%) of those within the screening program had a tumour <5cm (largest tumour nodule in case of multiple nodules) on diagnosis compared to only 46.3% outside the program, p<0.001.

There were 48 patients (36.9%) who were treated with a curative intent. Again, 15/24 (62.5%) within the screening group had a treatment with curative intent compared to only 33/106 (31.1%) outside this group, χ^2 = 8.3, p=0.004.

Overall, 20% (26 out of the 130 patients) had adequate screening (as described in the methods section). Within the screening group, 19 out of 24 patients had adequate screening compared to 7 out of 106 patients diagnosed outside the program [(79.2% v 6.6%), χ2 = 64.4, p<0.001].

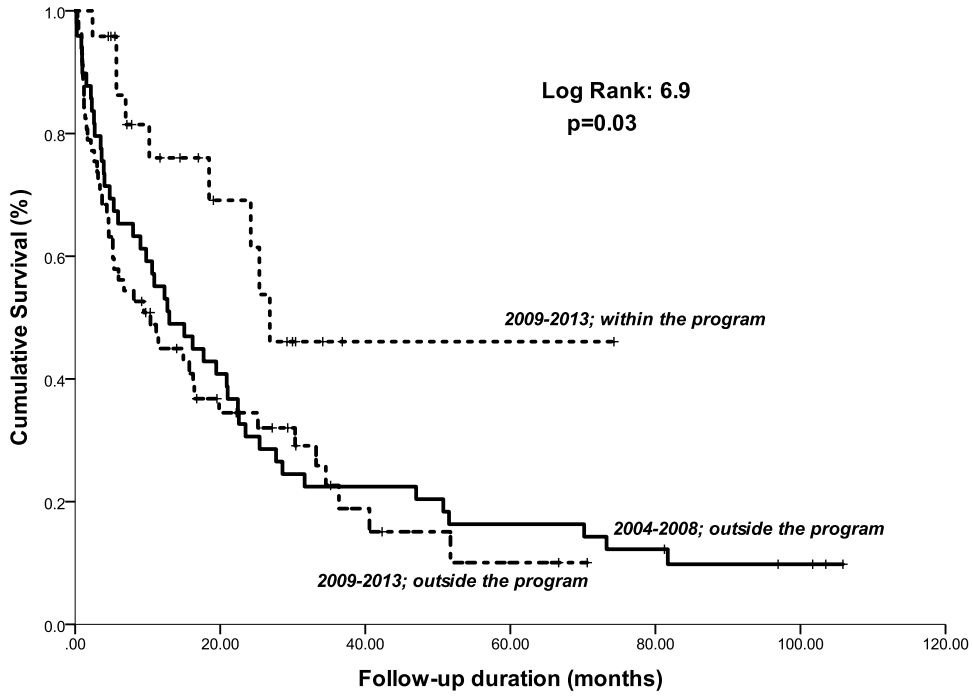

Figure 4.1: Overall survival of HCC diagnosed within and outside the program (unadjusted)

4.3.4 Predictors of mortality:

On univariate analysis, increasing age, HCC diagnosed outside the screening program, AFP>400, later BCLC stage at diagnosis and non-curative treatment intent were predictors of increased mortality.

Table 4.3: Predictors of mortality (n=130)

Variables	**Univariate analysis**		**Multivariate analysis**	
	HR (95%CI)	**P value**	**HR (95%CI)**	**P value**
Age (per year)	1.02 (1.00-1.03)	0.03	1.0 (0.9-1.0)	0.2
Diagnosed outside the program	2.4 (1.2-4.7)	0.01	1.9 (0.9-3.9)	0.09
AFP >400	3.2 (2.0-5.0)	<0.001	3.0 (1.8-4.9)	<0.001
Late BCLC stage	2.3 (1.5-3.8)	<0.001	2.0 (1.2-3.2)	0.007
Non-curative treatment intent	4.7 (2.9-7.7)	<0.001	4.5 (2.6-7.8)	<0.001

In multivariate analysis, after adjustment for gender and era of HCC diagnosis in addition to the above factors, later stages of BCLC, AFP >400 and non-curative treatment intent were independent predictors of increased mortality. There was a trend towards increasing mortality in those diagnosed outside the screening program but this was not statistically significant **(Table 4.3)**.

4.3.5 Propensity score adjustment:

After propensity score adjustment, those diagnosed within the screening program had a 58% reduction in mortality compared to those diagnosed outside the program [HR (95% CI): 0.42 (0.20-0.89), p=0.02] (**Figure 4.2**). This remained significant even after adjusting for the stage of liver disease (based on MELD score) and AFP levels [0.46 (0.22-0.97), p=0.04]. However, the screening program lost its significance when it was adjusted for MELD score, the stage of HCC on diagnosis and AFP levels (**Table 4.4**).

Table 4.4: Predictors of mortality after propensity score adjustment

Variables	**HR (95% CI)**	**P value**
Screening program	0.63 (0.28-1.42)	0.3
AFP >400	2.02 (1.26-3.24)	0.003
MELD score (per 10 units)	1.07 (0.61-1.89)	0.8
Late BCLC stage	1.45 (1.02-2.07)	0.04

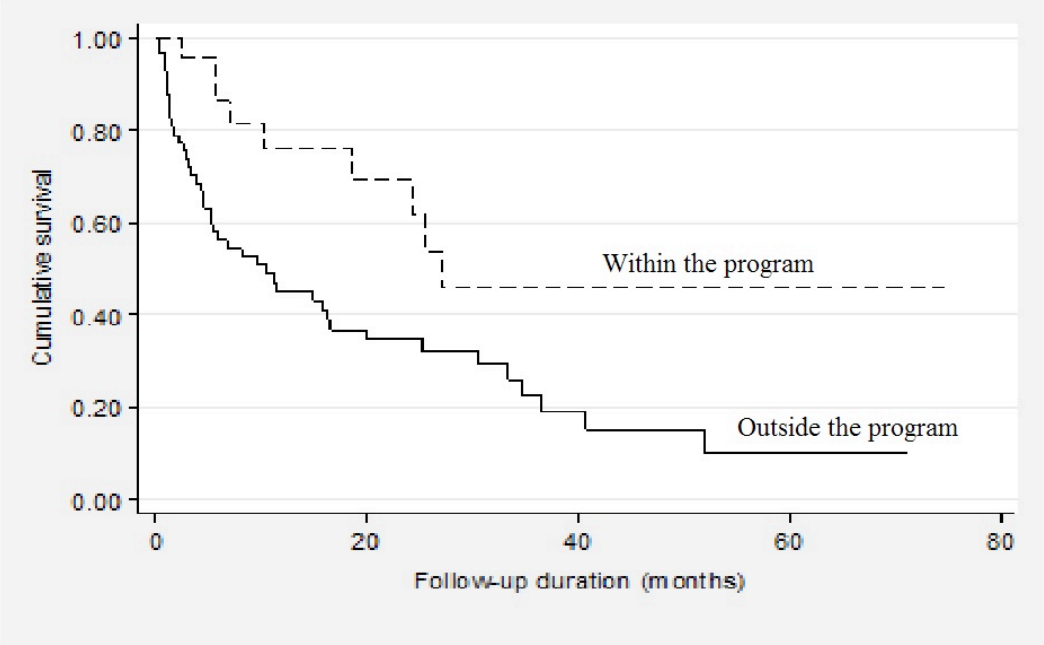

Figure 4.2: Overall survival of HCC diagnosed within and outside the program after propensity score adjustment

4.4 DISCUSSION:

Hepatocellular carcinoma is a rapidly progressive cancer which has a poor prognosis unless it is diagnosed in the subclinical growth period during which curative interventions are possible. This study shows that the survival is improved in HCC patients diagnosed within a dedicated, centrally co-ordinated screening program targeting a high risk population.

Cohort studies reporting survival benefits in the screened population who develop HCC are prone to lead-time bias. One way to correct for this bias is to calculate and adjust for the lead-time. Unfortunately, this is dependent on the tumour growth rate/ doubling time which is not constant. The tumour doubling time, in turn, depends on the tumour differentiation. Hence, the noted survival benefit might vary depending on the calculated lead-time as shown in a study where, the longer the lead-time, the true survival benefit was less likely to be significant (210). The alternative to this is to adjust for clinical differences in the screened and unscreened population using propensity scores

which adjusts for clinical differences between subjects based on their propensity for treatment. In this study, there was a significant reduction in mortality in the screened population even after propensity score adjustment. The screening benefit also remained significant after adjusting for the underlying liver disease severity but lost its significance when adjusted for the stage of HCC.

In addition to survival, there are various other surrogate end points to prove effectiveness of screening/surveillance programs. One such end point is stage migration: the ability of screening programs to find earlier stage disease. Stage migration alone cannot be used to prove efficacy of a screening program as those with early stage disease have the possibility of curative treatment to reduce mortality. In this study, there were more patients within the screening program who had an early stage disease and had curative treatments contributing to increased survival. This in fact, reiterates the importance of stage migration with screening programs resulting in improved survival.

Another controversial issue is that of using biannual AFP measurements in addition to USS for screening. The current AASLD and EASL guidelines on HCC management do not recommend use of AFP for screening mainly because of the low sensitivity (~60% overall) and a higher false positive rate leading to over-investigations (115, 125). However, the Asian Pacific Association for the Study of Liver (APASL) recommends the combination of AFP and USS as it increases the detection rate by 6-8% (211). This has been replicated by an Australian study where the detection rate increased to 97% using the combination screening compared to 92% with USS alone (212). In this study, we used the combination screening, and higher AFP level was one of the strongest predictors of mortality in multivariate analysis. In addition to being a screening tool, it could also be used as a prognostic marker as shown in this study.

One of the major strengths of this study is the detailed epidemiological and clinical data available for all the patients. This enabled us to adjust the survival benefit seen with the screening program to various confounding factors. There are several limitations to this study. Firstly, it is a single centre study performed in a tertiary, liver transplant centre limiting the generalizability of the conclusions

from this study. Secondly, HCC treatments continually evolved during the study period, particularly the percutaneous ablation therapies, and this may have influenced survival. Finally, only a small proportion (<20%) of patients in the overall cohort were diagnosed within the program. This small sample size could explain why the survival benefit in this group did not reach statistical significance on multivariate analysis, even though there was a trend.

Positive outcomes in terms of stage of diagnosis, proportion offered curative therapy and survival were reassuring, given the known beneficial effects of HCC screening from a randomized controlled trial and health care costs associated with screening. Findings suggested that the SALHN program was likely to have high adherence to screening protocols to achieve these outcomes. This was confirmed by data showing that patients within the program had an overall adherence rate of 79%. This adherence rate is likely to be an important quality indicator and process measure of an effective HCC screening program. Achieving acceptable adherence rates is likely to be a significant challenge for many programs and methods to overcome barriers have been previously described (209). The design of the screening program used in this study with components of central coordination, was likely to be an important contributor to its good adherence rate and positive outcomes.

In conclusion, this study showed that HCC diagnosed through a dedicated screening program was associated with improved overall survival. The detection of smaller tumours at an earlier stage suggests that screening reduced the lead time to HCC diagnosis enabling more patients to have curative therapies. High AFP, late BCLC stage and non-curative treatment intent were independent predictors of mortality. Unfortunately, this study also demonstrated that the majority of HCC diagnosed in the health region was at clinical presentation and occurred outside a screening program. This finding highlights the need for improved detection of high risk patients and improved uptake of HCC screening uptake in that population.

5. LOCAL RECURRENCE RATES OF EARLY STAGE HEPATOCELLULAR CARCINOMA POST PERCUTANEOUS THERMAL ABLATION IN ROUTINE CLINICAL PRACTICE: A MULTI-CENTRE RETROSPECTIVE COHORT STUDY

5.1 INTRODUCTION

The worldwide incidence and mortality rates of HCC continue to increase. It is a tumour with poor prognosis as it often presents late and without treatment the 5- year survival is less than 5% (213). Treatment of HCC depends on the stage of tumour, underlying Child-Pugh class and performance status of the patient. Radiofrequency ablation (RFA) has been used as a curative option in subjects with very early or early stage (BCLC stage O - A) HCC who are either Child-Pugh status A/B and a performance status score of 0 (115).

Some randomized controlled trials have shown that RFA is as effective as surgical resection for treating small HCC (214, 215). However, even after complete ablation of tumours with percutaneous thermal ablation (PTA), the risk of tumour recurrence is high because of multicentric carcinogenesis (216). In real world practice, larger and multiple tumours are frequently treated with PTA. Hence, in these real world settings the local and overall intrahepatic recurrence are likely to be higher than expected but have not been well studied. Therefore assessing tumour recurrence rates following PTA, particularly local site recurrence, in a large, non-trial setting would be informative. Assessing factors predicting recurrence post PTA for early stage HCC, enabling identification of high risk subjects, would also be of clinical importance.

Most of the published studies evaluating the local tumour progression (LTP) rates post PTA are from Asian countries where the predominant aetiology and the age at diagnosis may be different compared to western populations. A recently published study which had the largest sample size from a western population showed a LTP rate of 20.5% (217). However, this study included only treatment naïve subjects with single HCC nodule ≤3cm. An improved understanding of the LTP rates in routine clinical practice and associated risk factors is required to help evaluate and then stimulate the potential for improvements in techniques and patient outcomes in this setting. In this chapter, we assessed the LTP rates post PTA and the factors predicting HCC recurrence.

5.2 MATERIALS AND METHODS:

5.2.1 Patient cohort:

Consecutive patients who had PTA as the initial treatment modality for primary HCC between January 2006 – December 2012 across 3 tertiary centres in Australia (Flinders Medical Centre, Royal Adelaide Hospital, Sir Charles Gairdner Hospital) were examined retrospectively. HCC was diagnosed using contrast enhanced cross-sectional imaging features or biopsy according to AASLD guidelines (115). The decision to offer PTA to patients was made by a multi-disciplinary team consisting of hepatologists, hepato-biliary surgeons and interventional radiologists. During the study period, there was a transition from RFA to Microwave ablation (MWA) as the preferred PTA technique for HCC management in some Australian centres. Two centres in our study adopted MWA in 2011 and the third centre adopted it in early 2012 as the preferred modality.

Subjects were included if they had a single nodule ≤5 cm in the largest dimension or up to 3 nodules with each nodule measuring ≤3 cm, and where PTA was carried out with a curative intent. Patients were excluded from the study if they had; any prior loco-regional therapy, PTA for local

tumour control on a liver transplant waiting list, known extra-hepatic metastasis or macrovascular invasion. The study protocol was approved by all local Hospital Research Ethics Committees.

5.2.2 RFA procedure:

All procedures were carried out by one of three interventional radiologists. Patients were anaesthetised with antibiotic cover. The Radionics cool tip system (Radionics, Burlington, MA) was used with a disposable l7- gauge straight single electrode with a 3cm active tip. Grounding pads were applied to the patient's thighs. The single electrode was positioned under either CT or ultrasound guidance. The automated generator program produced power to a peak of 200W. Power was maintained until tissue impedance rose more than 20Ω, then power reduced to 10W for 15 seconds. Power was increased to maximum until impedance rose above 20Ω. This cycle was repeated for a total of 12 minutes. The number of burns was tailored to each lesion with the maximal individual burn radius of 3cm. Post treatment CT was performed to assess for adequate lesion ablation.

5.2.3 MWA procedure:

All procedures were performed by one of 3 interventional radiologists under general anaesthesia with patients paralysed to perform breath holds if required. Prophylactic antibiotics were administered. The Acculis Microwave Tissue Ablation (MTA) system (Microsulis Medical Ltd, Hampshire, UK) operating at 2.45 GHz with a maximum power output of 140W was used for all treatments. The Accu2i pMTA applicator (Microsulis Medical Ltd), with a 16-mm active tip, 1.8-mm diameter and 14 or 19 cm length disposable microwave antenna, was used for all treatments. The single antenna was positioned into the target lesion under CT/ultrasound guidance, the duration and power were determined by the treating interventional radiologist. This was based on manufacturer's recommendations of treatment radius allowing for at least 5mm circumferential margin beyond tumour size, to achieve technically successful ablations. Post treatment CT scan was performed to ensure complete ablation.

5.2.4 Data collection and follow-up:

Baseline demographic details, aetiology of underlying liver disease, tumour characteristics and number of sessions required to achieve complete ablation were collected retrospectively. Adverse events that delayed discharge or required re-hospitalization (≤30 days post procedure) related to the procedure, and procedure related mortality were also collected.

Contrast enhanced cross-sectional imaging was done 6-8 weeks post procedure to assess the response to PTA. Subjects who had contrast enhancement during the initial follow-up study were considered to have had an inadequate initial treatment and had a repeat PTA. Subjects were included in the study only after achieving complete radiological ablation. Further follow-up imaging was done 3-6 monthly after discussion in the multi-disciplinary meeting.

5.2.5 End points and statistical analysis:

The primary endpoint was LTP, as this was felt to be the endpoint most relevant to PTA therapy aiming to provide local tumour control. Patients were censored at the time of diagnosis of recurrence on follow-up imaging. Other relevant measures of tumour recurrence including overall intrahepatic recurrence (IHR) which is composed of both LTP and intrahepatic distant recurrence (IDR – new HCC nodule remote from the ablative lesion) were also assessed and described according to the standardization of terminology and reporting criteria by the international working group of image-guided tumour ablation (218).

A multivariate cox-regression analysis was performed to identify the independent predictors of IHR, LTP and IDR. A further secondary endpoint was procedure related adverse events. A two sided p value of <0.05 was considered statistically significant for all analyses. Statistical analysis was performed using IBM SPSS Statistics software for windows, Version 19.0. Armonk, NY: IBM Corp.

5.3 RESULTS:

5.3.1 Baseline characteristics:

During the study period, 180 nodules were treated with a curative intent in 156 subjects. Among them, 30 subjects (35 nodules) were excluded as they had either prior loco-regional therapies (n=23) or had incomplete follow-up (n=7). Hence, 145 nodules treated in 126 subjects [77.8% males, mean (±SD) age: 62.1 (±10.4) years] **(Table 5.1)** were included in the final analysis.

Table 5.1: Baseline characteristics at inclusion (n=126):

Characteristics	**Number (%)**
Gender	
Males	98 (77.8)
Aetiology*	
CHC	42 (33.3)
CHB	23 (18.3)
Alcohol	19 (15.1)
NAFLD	11 (8.7)
Alcohol and CHC	19 (7.9)
Cirrhosis	
Present	117 (92.9)
Histopathology	60 (47.6)
Well differentiated	35 (27.8)
Moderately Differentiated	18 (14.3)
Poorly differentiated	7 (5.5)

Child-pugh class	117 (92.9)
A	92 (73)
B	23 (18.3)
C	2 (1.6)
PTA method	
RFA	101 (80.2)
MWA	25 (19.8)

Characteristics	**Mean (±SD)**
Age (years)	62.1 (±10.4)
Bilirubin (μmol/L)	20.8 (±16.5)
Albumin (g/L)	35.6 (±5.3)
Creatinine (μmol/L)	83.3 (±55.7)
INR	1.2 (±0.2)
Pre-treatment AFP (kIU/L)	317 (±1497)
Tumour size (mm)	21.5 (±8.2)
Follow-up (months)	13.5 (±12.9)

*Only the 5 most common aetiologies mentioned.

CHC – Chronic Hepatitis C; CHB – Chronic Hepatitis B; NAFLD – Non-alcoholic fatty liver disease; PTA – Percutaneous Thermal Ablation; RFA – Radiofrequency Ablation; MWA – Microwave Ablation; INR – International Normalized Ratio; AFP – Alpha feto-protein

Equivalent numbers of subjects were treated across the three centres and the majority (93%) had underlying cirrhosis. Chronic Hepatitis C (CHC), Chronic Hepatitis B (CHB) and alcohol were the predominant aetiologies for the underlying liver disease contributing 33.3%, 18.3% and 15.1% respectively. The majority of subjects (73%) had Child-Pugh class A cirrhosis and the mean (±SD)

follow up duration was 13.5 (±12.9) months. The majority (85.7%) of subjects had a single nodule with a mean (±SD) tumour diameter of 21.5 (±8.2) mm and 23.4% of nodules were located in segment 8. Fifteen nodules (10.3%) required >1 treatment session to achieve complete ablation. Mean (±SD) tumour diameter in this particular cohort was 21.1 (±10.2) mm which was not statistically different from the overall cohort.

5.3.2 Recurrence rates and recurrence free survival:

During the follow up period, the overall IHR rate (including patients with LTP and IDR) was 57.2%. The LTP rate and IDR rate were 23.4% and 42.8% respectively and 9% of subjects had both LTP and IDR. Mean (±SD) recurrence free survival was 46.9 (±3.6) months for LTP, 28.9 (±3.1) months for IDR and 23.4 (±2.5) months for overall IHR. The one, two and three- year recurrence free survival rates are shown in **table 5.2**. There was no statistically significant difference in the recurrence rates across the 3 centres ($p>0.05$).

Table 5.2: Recurrence free survival rates:

	1- year	**2- year**	**3- year**
Overall recurrence free survival	57.3%	29.6%	25.7%
LTP free survival	77.4%	62.5%	58.9%
IDR free survival	67.6%	42%	36.5%

LTP – Local tumour progression; IDR – Intrahepatic distant recurrence.

For tumour nodules ≤20mm in this cohort, the LTP rate was lower at 15.9% (11/69) during the follow-up period. The mean (±SD) LTP free survival in this group was similar at 48.8 (±4.2) months compared to the overall cohort. The one , two and three- year LTP free survival rates for tumour nodules ≤ 20mm were 86.2%, 70% & 70% respectively. Tumour nodules requiring >1

treatment session had a shorter mean time to LTP compared to those who achieved complete ablation with one treatment session (13.3 months v 50.3 months).

5.3.3 Predictors of recurrence:

In univariate analysis, histopathology (poorly differentiated), pre-treatment AFP >50 kIU/L and requirement of >1 treatment session were predictive of LTP **(Table 5.3)**. However, requirement of >1 treatment session lost its significance on multivariate cox-regression analysis (p=0.5) and only poorly differentiated HCC and pre-treatment AFP >50 kIU/L independently predicted LTP **(Figures 5.1 & 5.2)**. There was a trend towards higher LTP with tumour nodules >20mm (p=0.057) and in females (p=0.07) but these were not statistically significant.

Pre-ablation AFP >50 kIU/L was the only predictor of overall IHR. There was a non-statistically significant trend towards higher IHR in those with cirrhosis (p=0.07).

5.3.4 Comparison of RFA and MWA:

During the study period, 80.2% were treated with RFA and 19.8% had MWA. There was a higher proportion of patients with poorly differentiated HCC in the MWA group compared to the RFA group [29.4% v 11.1%, p=0.03]. There were no other statistically significant differences in the baseline characteristics between the two groups including age, cirrhosis status, Child-Pugh class, AFP level and mean tumour diameter (p>0.05 for all).

LTP rates were not significantly different between RFA and MWA groups [22.8% v 25.8%, p=0.7]. The LTP rates in the RFA and MWA groups for tumours ≤20mm were also similar (17% v 10%, p=0.5). Finally, the procedure related adverse events requiring hospitalisation were similar between the two groups (5% v 4%, p=0.8).

Table 5.3: Predictors of local tumour progression:

Variables	Univariate		Multivariate	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
Age	0.9 (0.9-1.01)	0.9		
Gender - Females	1.9 (0.9-4.0)	0.07		
Cirrhosis	1.6 (0.4-6.8)	0.5		
Child-Pugh A	0.9 (0.4-2.3)	0.9		
Histopathology				
Well differentiated	1		1	
Mod. Differentiated	1.3 (0.4-4.3)	0.7	0.4 (0.09-1.7)	0.2
Poorly differentiated	3.2 (1.1-10.3)	0.048	4.8 (1.1-20.4)	0.032
AFP >50 kIU/L	2.3 (1.1-4.8)	0.02	8.2 (1.7-39.0)	0.008
More than 1 session	3.1 (1.4-6.8)	0.006	1.9 (0.3-13.2)	0.5
Tumour >2cm	2 (0.9-4.2)	0.057		
RFA	0.7 (0.3-1.5)	0.3		

HR – Hazard Ratio; CI – Confidence Interval; AFP - α-feto protein; RFA – Radiofrequency Ablation.

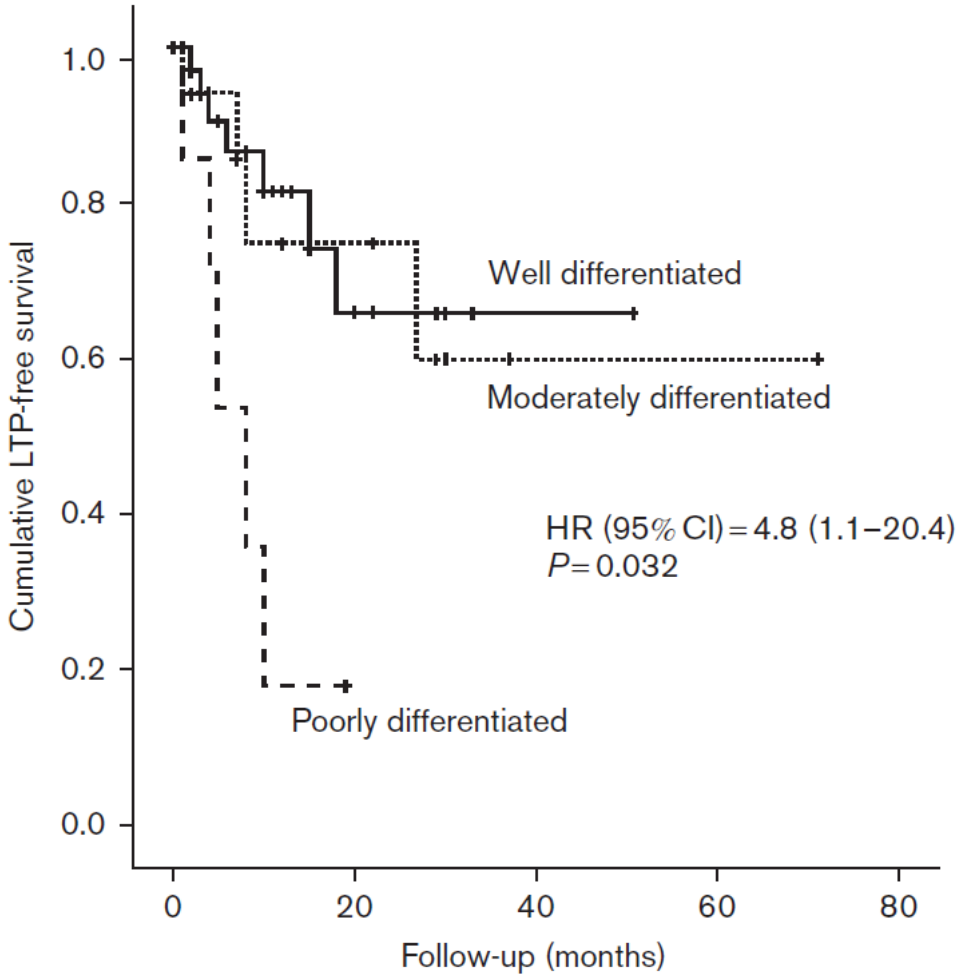

Figure 5.1: Histopathology as a predictor of local tumour progression.

LTP – Local tumour progression; HR – Hazard ratio; CI – Confidence interval

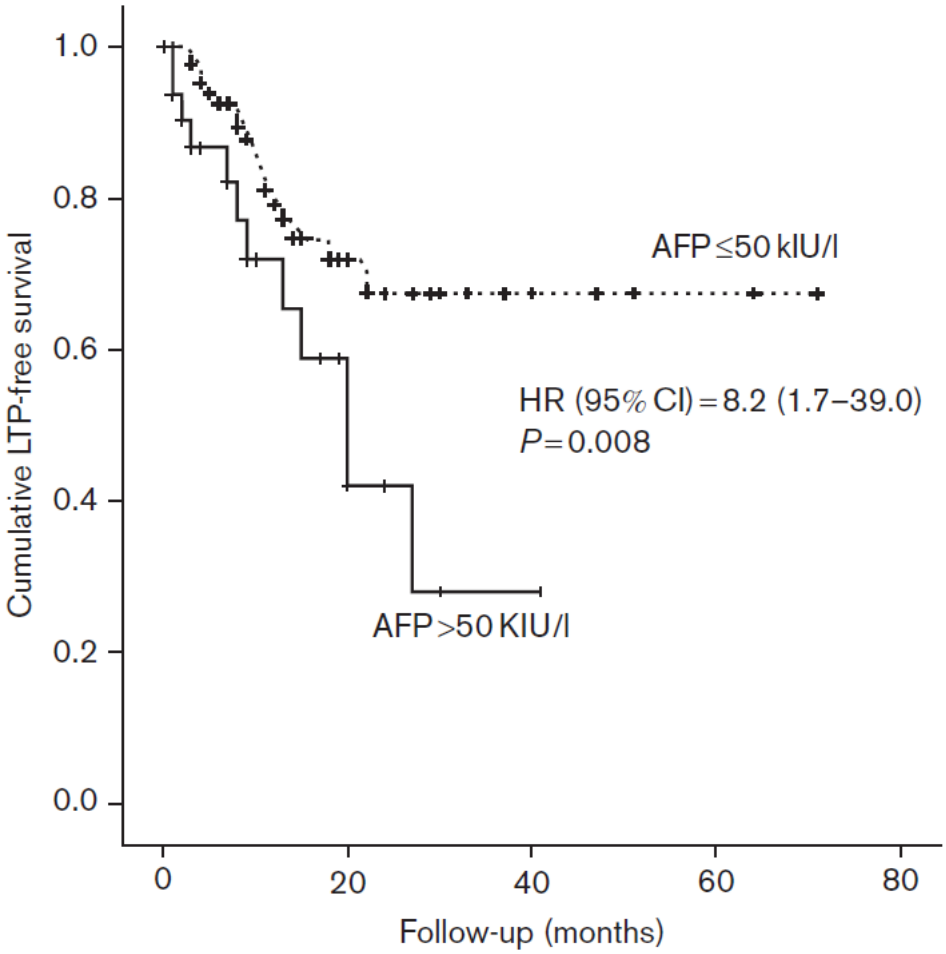

Figure 5.2: Pre-treatment AFP as a predictor of local tumour progression.
AFP – Alpha feto-protein; LTP – local tumour progression; HR – hazard ratio; CI – confidence interval

5.3.5 *Adverse Events*:

Overall, there were 6 (4.8%) procedure related adverse events requiring re-hospitalization/delayed discharge. These were decompensation with intra-abdominal collection (n=2), small pneumothorax (n=2), massive hepatic infarction (n=1) and skin burn from the ablation probe (n=1). All patients recovered with supportive care and were subsequently discharged. There were no procedure related deaths in this cohort. In addition, there were 5 patients re-admitted ≤30 days from procedure with pneumonia (n=3) and non-ST elevation acute coronary syndrome (n=2).

5.4 DISCUSSION:

This multicentre study is one of the largest investigations of PTA performance in a real world setting in Australia and highlights the relatively high, 23.4%, LTP rates of early stage HCC treated with curative intent by PTA techniques. Various randomized (139, 219) and non-randomized (220, 221) studies have shown that the LTP post RFA varies widely from 2% to 34% depending on the tumour size and the follow-up duration. Studies looking at the LTP rates post MWA have shown similar results and vary between 10.5% and 24% (222, 223). The majority of HCC in our study were treated by RFA and only one-fifth were treated by MWA. All subjects were analysed together, irrespective of the treatment modality, as previous comparative studies have shown no difference in LTP rates and major adverse events between the two techniques (222-225). LTP rates and recurrence free survival post PTA in our study are consistent with previously published studies.

The study's findings should alert centres performing these procedures about the need for local audit of LTP rates following PTA. Such information is important for clinicians and patients when making informed decision making about treatment alternatives such as surgical resection. Meta-analysis comparing PTA and surgical resection for early stage HCC have recently suggested that the long term overall and disease free survival is better with surgical resection (226-229) but with increased complication rates and longer hospital stays. In addition, a simulation study for very early stage HCC showed that LTP rates post RFA should be <9% for it to be comparable with resection with a 3% operative mortality (230). Data from our study, showing high local recurrence rates post PTA also provide support for resection as first line therapy for early stage HCC in centres with similarly high LTP rates post PTA, where surgical resection can be performed with low mortality rates.

The relatively high risk of LTP post curative RFA in this and other studies, suggests the need for adjuvant therapies in combination with PTA to improve outcomes. The combination of PTA and trans-arterial chemoembolization (TACE) has been extensively studied and a recently published meta-analysis showed that this combination (RFA and TACE) had a superior 1, 3 and 5- year

overall survival compared to RFA alone for early stage HCC (231). A further potential candidate for adjuvant therapy with PTA in the setting of early stage HCC is radiotherapy (either conventional 3-dimensionsional conformal external beam or stereotactic techniques). Stereotactic ablative body radiotherapy for solitary HCC has shown good local control and overall survival (232, 233). Local recurrence rates with stereotactic radiotherapy using CyberKnife® for solitary early stage HCC were comparable to RFA (234). Such radiotherapy techniques have a sound theoretical basis (235) but there have been no studies investigating the use of radiotherapy as an adjuvant therapy post PTA for early stage HCC. In our view, these studies are an urgent clinical priority.

Previous studies have shown that the tumour size, pre-ablation AFP, proximity to vessels, Child-Pugh score, age, multiple nodules and tumour differentiation (236-238) to be important predictors of LTP. In our study, within the variables available for analysis, we have confirmed the importance of poorly differentiated HCC and pre-treatment AFP >50 kIU/L as independent predictors of LTP, with tumours >2cm of borderline significance. Given the importance of tumour differentiation as a predictor of LTP, routine biopsy of the lesion at the time of PTA should be considered, particularly given the relatively low risk of tumour seeding (0.95%) with combined PTA and biopsy (239) and the potential of this information to alter surveillance strategy post PTA. These poorly differentiated tumours can also be targeted with adjuvant therapies to reduce LTP but more prospective studies are required before this can be a standard practice.

This study was not designed as a comparative study between MWA and RFA. As MWA was adopted only late in the study period, the number of subjects who underwent MWA were small and more subjects in this cohort had poorly differentiated tumours. This was incidental as the biopsies were performed just prior to MWA and the histological characteristics were unknown at the time of ablation.

Adverse events requiring rehospitalisation or delayed discharge post procedure in this study were low (4.8%) and similar to previously reported studies (223, 224, 240). Two patients in the MWA

cohort developed pneumothorax which was treated conservatively. The tumour location in these patients required a trans-pleural approach for complete ablation resulting in small pneumothorax which delayed their discharge post procedure. Unfortunately, the proportion of patients who developed procedure related pain couldn't be assessed because of the retrospective nature of the study. The low rate of adverse events and lack of procedure related deaths found in this study confirms the safety of PTA techniques in routine clinical practice settings.

One of the major strengths of this study was the inclusion of subjects only when a complete response to thermal ablation was confirmed on follow-up imaging. Hence, the baseline tumour load in our population was homogenous which made the assessment of LTP more meaningful. A limitation of this study was its retrospective nature, but the large size, multicentre nature and detailed information collected, do allow high generalizability of findings to typical centres where these techniques are being used in routine clinical practice. Further study limitations included a lack of complete data such as tumour histopathology (available in only 48% of subjects) and tumour proximity to blood vessels, and availability of such data may have improved our analysis of predictors for tumour recurrence.

In conclusion, the LTP rates post PTA for early stage HCC in routine clinical practice was high and the LTP free survival is only modest. Poorly differentiated HCC and pre-treatment AFP are important, independent predictors of LTP. PTA techniques were well tolerated with few serious adverse events associated with treating early stage HCC. Further appropriately powered and designed studies investigating the use of adjuvant therapies combined with PTA to decrease LTP rates appear warranted.

6. PERCUTANEOUS THERMAL ABLATION FOR EARLY STAGE HEPATOCELLULAR CARCINOMA: A SYSTEMATIC REVIEW AND META-ANALYSIS COMPARING RFA AND MWA

6.1 INTRODUCTION:

Hepatocellular carcinoma is the second and sixth most frequent cause of cancer related mortality in men and women respectively (149). Among available treatments, liver transplantation within established criteria achieves the best overall survival (5- year survival >70%) (115) for HCC but relatively few patients are eligible for transplant at diagnosis and its availability is also limited by donor shortages. While curative surgical resection offers the next best overall survival (5- year survival >50%) (115), less than 30% of cases are eligible for resection at diagnosis because of poor hepatic reserve (68). Hence loco-regional therapies are frequently required for HCC management (241).

A variety of techniques including RFA, MWA, transarterial chemoembolization (TACE) and radioembolization with yttrium-90 are currently used for treatment of HCC. The American Association for Study of Liver Disease (AASLD) guidelines recommends the use of RFA as a bridge to transplantation or in subjects with early stage (BCLC-A) HCC who are either Child-Pugh status A or B and with a performance status score of 0 (115).

The most commonly available alternative to RFA, MWA, uses electromagnetic waves with frequencies ≥900 MHz to induce cellular death via coagulation necrosis (242). This technique was first described in 1994 (243) and has emerged as a potential alternative to RFA in treating small HCC. Over the past two decades, considerable improvements in percutaneous/ laparoscopic MWA

techniques have resulted in improved outcomes (244-246). MWA has been predominantly used in China and Japan (247-249), but the technique is now gaining popularity in the West.

MWA technology has theoretical advantages over the RFA methods. These are related to technical factors including reduced "heat-sink" effect (loss of temperature in the peripheries of tumour nodules close to blood vessels), rapid increase and maintenance of higher intra-tumoural temperatures, deeper penetration, faster ablation times and the ability to achieve larger tumour ablation volumes (242). To date, a single randomized controlled trial (RCT) showed equivalent therapeutic effects and complication rates (223). However, this study was undertaken during the initial development of MWA. With further evolution of the technique, comparisons of MWA and RFA in a number of observational studies have produced conflicting results (222, 240, 250). This lack of agreement may relate to changes in generators/antennas used in the studies. For example, a prospective non-randomized study using the recently available cooled-shaft antenna for MWA reported significantly larger ablation volumes than RFA (250).

However, despite the theoretical advantages from these improvements in MWA, it remains unclear if these are associated with clinical benefits. We therefore performed a systematic review and meta-analysis of all available observational studies and RCTs to compare the effectiveness and safety of RFA and MWA in treating HCC.

6.2 METHODS:

The study was pre-registered with the PROSPERO register (251) (Reg.no.: CRD42014009312) and followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines (252).

6.2.1 *Eligibility criteria*:

Inclusion criteria were: (i) Participants: adults with either very early stage (single tumour ≤2cm), early stage (single tumour or up to 3 nodules with each measuring ≤3cm) or multifocal/large HCC outside Milan criteria (134) but without vascular invasion or extra-hepatic metastasis, (ii) Clinical interventions: percutaneous RFA or MWA for treatment of HCC, (iii) Comparators: effectiveness and safety of RFA versus MWA, (iv) Outcome measures: the primary outcome was the risk of local tumour progression (LTP) and secondary outcomes were complete ablation (CA) rates, overall survival and major adverse events (AE), (v) Study designs: RCTs, prospective or retrospective cohort studies.

6.2.2 *Search strategy*:

An electronic search was performed of Medline, EMBASE and the Cochrane central register of controlled trials databases from Jan 1980 to May 2014 using the following MeSH terms or free text: "catheter ablation", "radiofrequency ablation* or therap*", "microwave ablation* or therap*" and "hepatocellular carcinoma or HCC" **(Figure 6.1)**. The search was limited to studies in humans but there were no language restrictions. Manual searches were carried out by searching the reference lists for all the included studies. Abstracts from the AASLD and European Association for Study of Liver (EASL) meetings for the past 2 years (2012 & 2013) were also reviewed. Two reviewers (MC and AC) independently performed the initial literature search and selected relevant studies based on the inclusion criteria. Consensus for the inclusion of selected studies was achieved via discussion.

6.2.3 *Data collection and study quality assessment*:

The following data were extracted: first author, publication year & journal, study design, baseline characteristics of the participants, tumour characteristics and generators/antennas used for ablation, mean follow-up and details about the primary and secondary outcome measures. Attempts were

made to contact the corresponding author of articles by email for missing data. Data were extracted by two investigators independently and a consensus of the data was achieved by discussion.

Study quality was assessed using a modified version of the Newcastle-Ottawa quality assessment scale (253). Included studies were assessed based on 3 criteria: participant selection (max 2 points), comparability of groups (max 2 points) and measurement of the outcome (max 3 points) with a total possible score of 7 **(Table 6.1)**. Studies with a score of 5-7 were considered to be of high quality and of low quality if the score was ≤4.

Search Strategy: Database: Ovid MEDLINE(R) <1946 to May Week 4 2014>

---

1 exp Catheter Ablation/ (21145)

2 ((radiofrequenc* or radio-frequenc* or radio frequenc*) and (ablation* or therap* or treat*)).mp. (16834)

3 (RFTA or RFA or RFT or RFCA).mp. (3771)

4 ((microwav* or micro-wav* or micro wav*) and (ablation* or therap* or treat*)).mp. (5222)

5 (MWA or MWAT or MWT or PMCT).mp. (945)

6 1 or 2 or 3 or 4 or 5 (32535)

7 exp Carcinoma, Hepatocellular/ (58518)

8 exp Liver Neoplasms/ (125439)

9 ((hepat* or liver) and (carcinom* or tumour* or neoplasm* or malign* or cancer*)).mp. (215140)

10 HCC.mp. (24414)

11 7 or 8 or 9 or 10 (215943)

12 6 and 11 (4384)

13 limit 12 to (humans and yr="1980 -Current") (4133)

Figure 6.1: Search strategy used in MEDLINE

Table 6.1: Modified Newcastle-Ottawa quality assessment scale*

Selection:

1. Subjects treated are truly/somewhat representative of the total HCC population:
   a. Yes (*)
   b. No
2. Details of criteria for assignment of subjects to different treatment groups provided:
   a. Yes (*)
   b. No

Comparability:

1. Were the 2 groups comparable? (Four factors were assessed: Age, Gender distribution, number of nodules treated and mean follow-up duration)
   a. All 4 factors described and similar between 2 groups (**)
   b. Up to 2 factors differed/not compared/not reported (*)
   c. 3 or more factors differed/not compared/not reported

Outcome:

1. Assessment of outcome:
   a. Confirmation of outcome by secure records (follow-up radiology report) (*)
   b. No description
2. Follow-up long enough for outcomes to occur (at least 24 months post thermal ablation in both groups):

a. Yes (*)

b. No

3. Adequacy of follow-up of treatment groups:
   a. Complete follow-up or <20% lost to follow-up (*)
   b. No description/Unclear

*High quality: 5-7 stars; Low quality: 1-4 stars

Although the most common adverse events reported were transient post-procedural pain and mild fever, we assessed only major complications requiring intervention or delaying discharge. These included hepatic infarction, liver abscess, bile duct damage & biliary fistula, skin burns, subcapsular hematoma, peritoneal haemorrhage, biliary peritonitis, significant liver decompensation, puncture wound infection, haemothorax and pneumothorax.

6.2.4 *Data synthesis and statistical analysis*:

All the analyses were performed using Review Manager (version 5.2 for Windows; Cochrane collaboration, Oxford, UK). A random-effects model using the method of DerSimonian and Laird was used for each outcome. Meta-regression analysis was performed to adjust for the difference in follow-up period between the studies. Inter-study heterogeneity was assessed using the I^2 statistic and p-value for the chi-squared test of heterogeneity. I^2 >50% and $p<0.1$ were considered to represent significant statistical heterogeneity (254). Outcomes were reported using a pooled odds ratio (OR) with 95% confidence intervals (CI). Subgroup analyses based on study quality and on tumour stage was performed only for the primary outcome. Publication bias was assessed visually using funnel plots.

6.3 RESULTS

6.3.1 *Study selection and inclusion*:

The search strategy initially identified 4133 studies, of which 14 full-text articles met inclusion criteria **(Figure 6.2)**. Three studies conducted by Ohmoto et al., in the same institution and published between 2006 and 2009 (240, 255, 256) showed significant overlap in the enrolment period. Since the last study published in 2009 (240) had the most comprehensive information, the other 2 studies were excluded. As the analysis was focussed on percutaneous approach, two studies that compared laparoscopic RFA and laparoscopic MWA (257, 258) were also excluded. A study

comparing MWA and multipolar RFA in an ex vivo porcine liver was excluded as it was not performed in humans (259). A search of international liver meeting abstracts revealed one additional abstract which met the inclusion criteria. This has since been published as a full-text article (260). Thus, a total of 10 studies were included in the final meta- analysis.

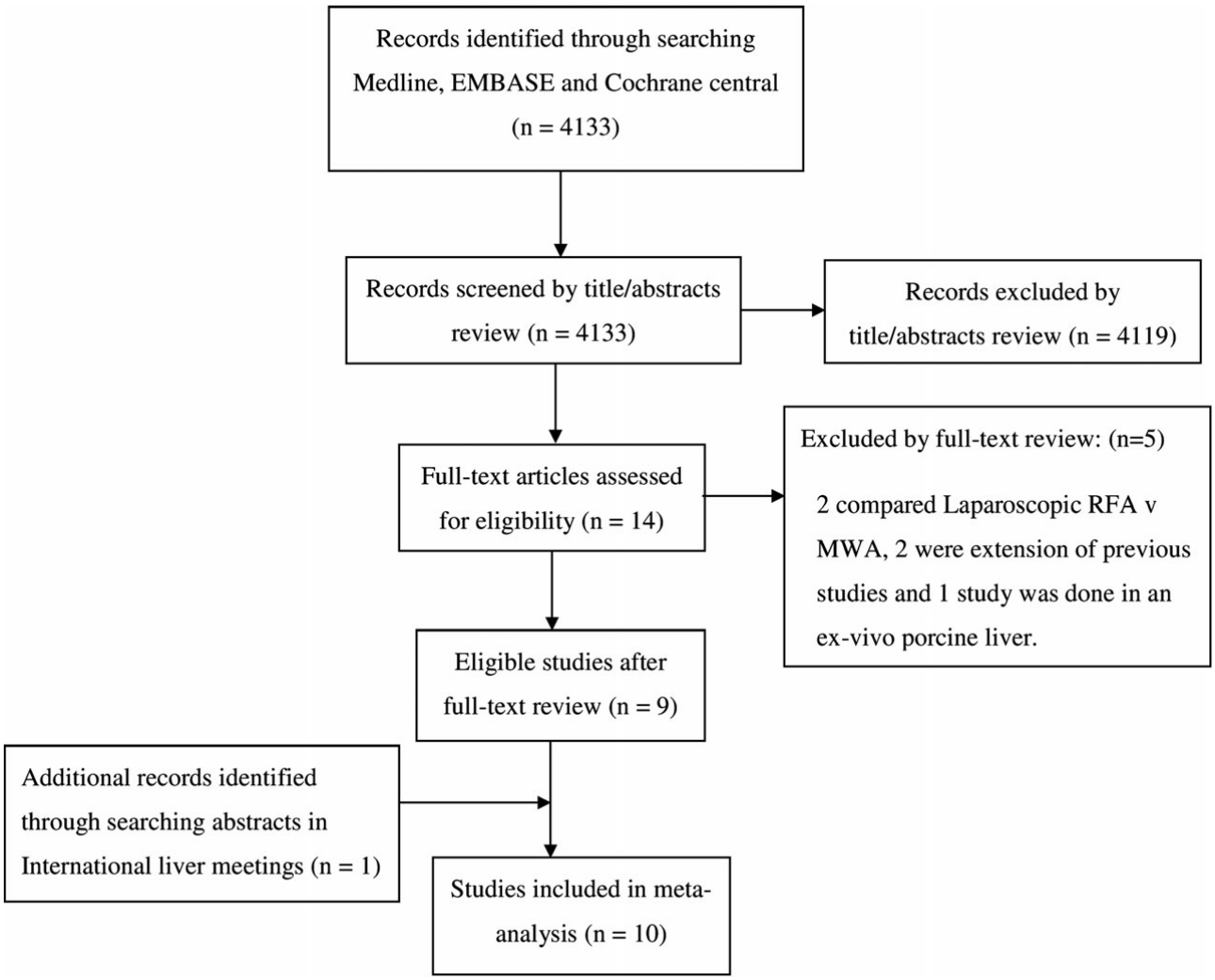

Figure 6.2: Flow chart of study selection

RFA – Radiofrequency ablation; MWA – Microwave Ablation

6.3.2 *Characteristics and quality of included studies*:

The 10 included studies comprised one RCT (223), eight retrospective observational studies (222, 224, 225, 240, 261-264) and one non-randomised prospective comparison trial (250). Study characteristics are detailed in **Table 6.2**.

Apart from a single multi-centre study performed in Australia (264) others were single centre studies from either China or Japan (222-225, 240, 250, 261-263). Ablative energy was delivered by a variety of generators and antennas with the most common being Cool-tip RF ablation system and MTC-3 microwave generator. The sample sizes in individual studies ranged from 42 to 198 subjects, with the total number of patients being 1298 (RFA =638, MWA =660). The mean tumour diameter in the majority of studies was between 2 and 3cm. The mean follow-up period was between 5 and 45 months **(Table 6.3)**. Based on the modified Newcastle-Ottawa quality assessment scale, 5 of the 10 included studies were considered to be of high quality (222-224, 250, 261) **(Table 6.4)**.

Table 6.2: Baseline characteristics of included studies:

Author, Year, Journal	**Design**	**Country**	**No. of subjects**	**RFA (subjects/ nodules)**	**MWA (Subjects/ nodules)**	**Criteria**	**RFA system**	**MWA system**
Zhang, 2013 PLOS one (222)	Retrospective	China	155	78/97	77/105	Within Milan criteria	HiTT ablation system	MTC-3 microwave (FORSEA^{TM}) generator
Ohmoto, 2009 JGH (240)	Retrospective	Japan	83	34/37	49/56	≤2cm	Radionics generator	Microtaze coagulator
Lu, 2005 J Gastroent (224)	Retrospective	China	102	53/72	49/98	Single <8cm, Max 5 nodules	WE-7568 RF delivery system	UMC-I MW generator
Shibata, 2002 Radiology (223)	RCT	Japan	72	36/48	36/46	Within Milan criteria	RF 2000 generator	Microtaze generator
Xu, 2004 Clin Rad (225)	Retrospective	China	97	43/78	54/112	Maximum 5 nodules	WE-7568 RF delivery system	UMC-I MW generator
Qian, 2012 Eur Radiol (250)	Prospective	China	42	20/20	22/22	Single & <3cm	Cool-tip RF ablation system	MTC-3 microwave (FORSEA^{TM}) generator

Chinnaratha, 2013 AASLD (264)	Retrospective	Australia	126	101/114	25/31	Within Milan criteria	Radionics cool-tip system	Acculis Microwave Tissue Ablation system
Ding, 2013 Eur Jour Rad (262)	Retrospective	China	198	85/98	113/131	Within Milan criteria	Cool-tip RF ablation system	MTC-3 microwave therapy instrument
Kuang, 2011 J Gast Surg (261)	Retrospective	China	83	31/31	19/19	Single & ≤2cm	WE-7568 RF delivery system, Cool-tip RFA system	UMC-I MW generator or MTC-3 microwave generator
Yin, 2009 Cancer (263)	Retrospective	China	108	59	49	Up to 3 nodules, One nodule: 3-7cm	WE-7568 RF delivery system, Cool-tip RFA system	UMC-I MW or MTC-3 (FORSEA™) generator

RCT – Randomized Controlled Trial; AASLD – American Association for the Study of Liver Disease.

6.3.3 *Local tumour progression*:

All 10 studies evaluated local recurrence and provided data on LTP. There was no significant inter-study heterogeneity (I^2 = 23%, p=0.23). The pooled OR (95%CI) using a random-effects model was 1.01 (0.67-1.50), p=0.98 indicating no difference in the LTP rates for RFA and MWA **(Figure 6.3)**. Meta-regression analysis performed to adjust for the difference in follow-up period showed a similar effect size [OR (95%CI): 1.02 (0.94-1.11), p=0.55]. The Funnel plot analysis using visual inspection indicated a lack of publication bias with studies distributed symmetrically around the overall effect size **(Figure 6.4)**.

In a subgroup analysis based on tumour stage, 2 studies (143 subjects) comparing RFA and MWA to treat very early stage HCC (single tumour ≤2cm) (240, 261) had pooled OR (95%CI) of 0.48 (0.15-1.57), p=0.22. In 5 studies (705 subjects) that evaluated tumours confined to the Milan criteria (single tumour ≤5cm or up to 3 tumours with each measuring ≤3cm) (222, 223, 250, 262, 264), the pooled OR (95%CI) was 0.73 (0.45-1.19), p=0.21. A further three studies (450 subjects) that looked at the use of RFA and MWA in treating HCC beyond the Milan criteria (single tumour >5cm or >3 nodules) (224, 225, 263), the pooled OR (95%CI) was 1.88 (1.10-3.23), p=0.02 indicating a benefit for MWA **(Figure 6.5)**.

Table 6.3: Patient characteristics and follow-up:

Studies	Gender (M:F)		Age (years) Mean ± SD		Tumour size (cm) Mean ± SD		Follow-up (months) Mean ± SD	
	RFA	**MWA**	**RFA**	**MWA**	**RFA**	**MWA**	**RFA**	**MWA**
Zhang, 2013 PLOS one (222)	64:14	67:10	54±10.5	54±9.5	2.3±0.4	2.2±0.4	26.3±11.5	24.5±12.9
Ohmoto 2009, JGH (240)	25:9	41:8	67	64	1.6	1.7	26±11.5	33.9±24
Lu, 2005 J Gastroent (224)	43:10	44:5	54.5±11.7	50.1±13.7	2.6±1.2	2.5±1.2	24.8±14.6	25.1±12.7
Shibata, 2002 Radiology (223)	26:10	24:12	63.6	62.5	2.3	2.2	18	18
Xu, 2004 Clin Rad (225)	84:13		53.4		2.6±4	2.5±1.1	27.4	
Qian, 2012 Eur Radiol (250)	19:1	20:2	56±11	52±12	2.0±0.5	2.1±0.4	5.1±1.3	

Chinnaratha 2013, AASLD (264)	80:21	18:7	62.1±10.7	61.9±8.9	2.2±8.9	2.5±9.1	14.8±13.8	8.3±5.9
Ding, 2013 Eur Jour Rad (262)	68:17	85:28	58.6±8.5	59.1±11.7	2.4±0.8	2.6±0.9	27.7±15.3	18.3±9.3
Kuang, 2011 J Gast Surg (261)	78:5		55		1.7		45±27	
Yin, 2009 Cancer (263)	94:14		53±12		3.9±0.8		22±18.5	

Table 6.4: Quality of included studies:

Studies	Modified Newcastle-Ottawa Scale			
	Selection (Max 2 pts)	**Comparability (Max 2 pts)**	**Outcome (Max 3 pts)**	**Total (Max 7 pts)**
Zhang, 2013, PLOS one (222)	**	*	**	*****
Ohmoto, 2009, JGH (240)	**		**	****
Lu, 2005, J Gastroent (224)	**	*	**	*****
Shibata, 2002, Radiology (223)	**	**	*	*****
Xu, 2004, Clin Rad (225)	**		**	****
Qian, 2012, Eur Radiol (250)	**	**	**	******
Chinnaratha, 2013, AASLD (264)	*	*	**	****
Ding, 2013, Eur Jour Rad (262)	**	*	*	****
Kuang, 2011, J Gast Surg (261)	**		***	*****
Yin, 2009, Cancer (263)	*		**	***

Seven studies (848 subjects) reported LTP rates for tumours ≤5cm (222, 223, 240, 250, 261, 262, 264). There was no significant inter-study heterogeneity (I^2=0%, p=0.71). The pooled OR (95%CI) using a random-effects model was 0.69 (0.44-1.08), p=0.010 indicating a favourable trend towards RFA **(Figure 6.6)**.

The pooled OR (95%CI) for the 5 high quality studies (222-224, 250, 261) was 1.15 (0.69-1.92), p=0.60 and for the 5 low quality studies (225, 240, 262-264) was 0.92 (0.49-1.73), p=0.79 **(Figure 6.7)**. There was no significant inter-study heterogeneity in any of the sub-group analyses (I^2 <50% and p>0.1 for all).

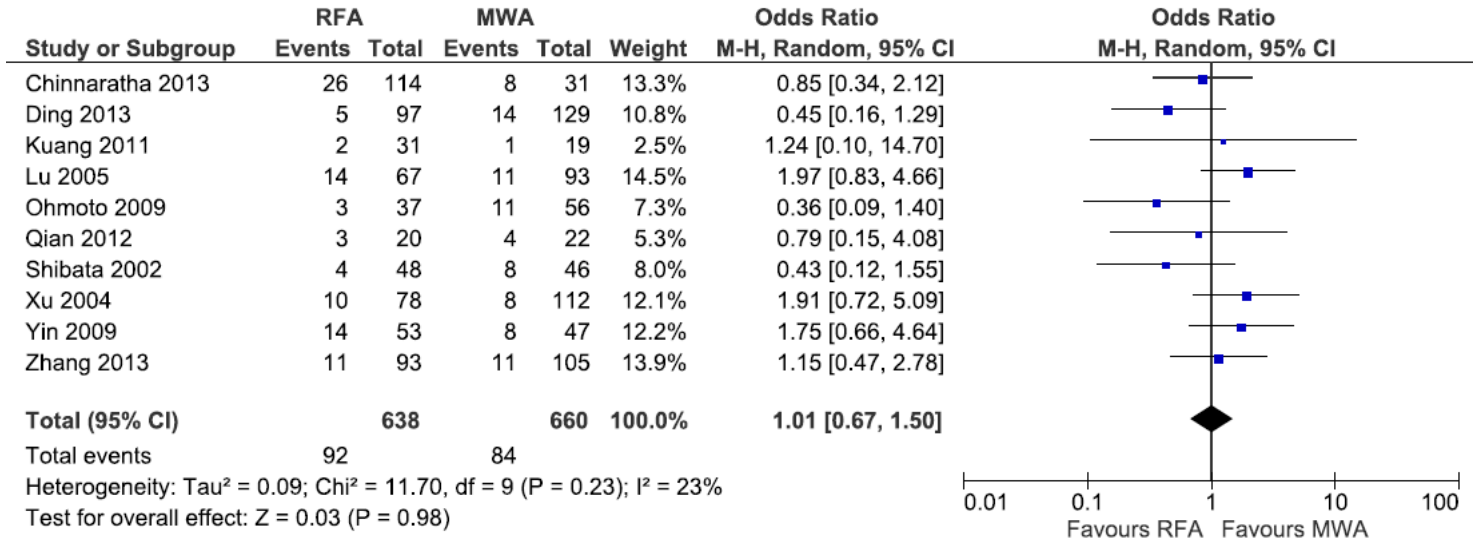

Figure 6.3: Forest plot of meta-analysis comparing local tumour progression (LTP) between radiofrequency ablation (RFA) and microwave ablation (MWA); CI – Confidence Interval.

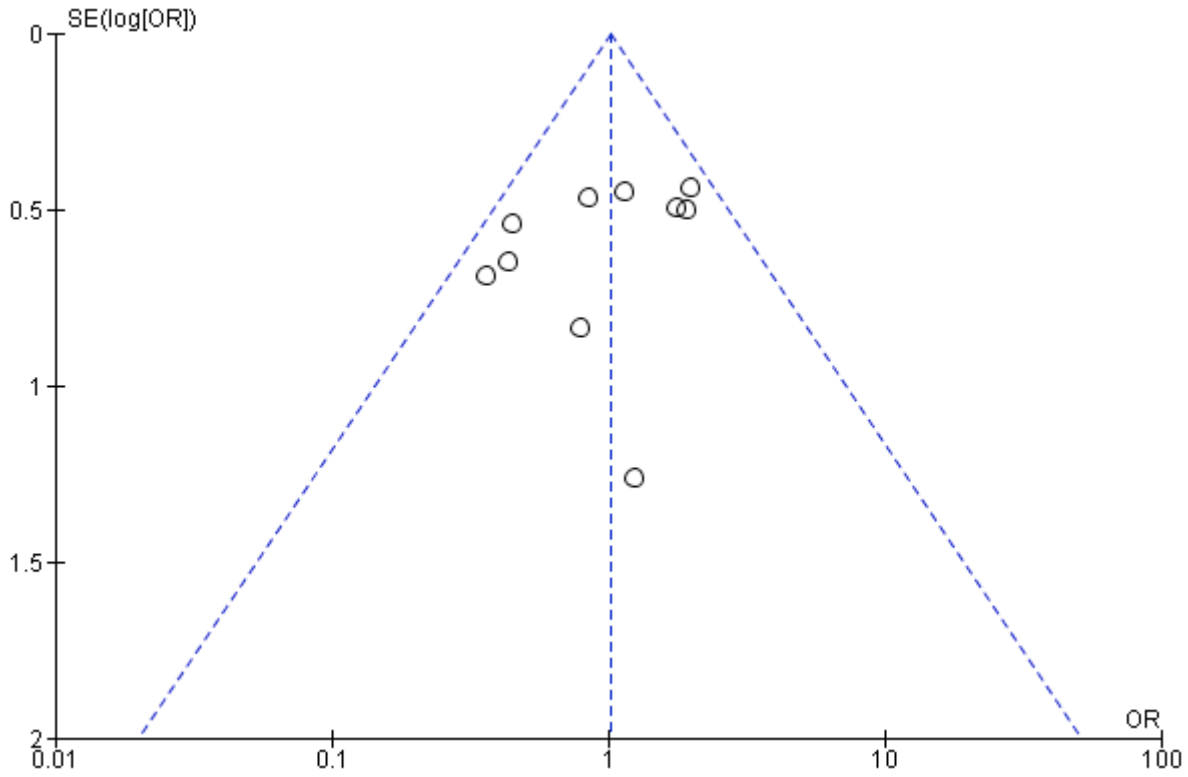

Figure 6.4: Funnel plot to assess for possible publication bias in the meta-analysis regarding the local tumour progression

6.3.4 *Complete ablation and overall survival*:

Eight studies (1081 subjects) reported on complete ablation rates (222-225, 250, 261-263). There was no significant inter-study heterogeneity (I^2 =0%, p=0.64). The pooled OR (95%CI) using a random-effects model was 1.03 (0.63-1.69), p=0.89 indicating no difference between the two modalities **(Figure 6.8)**. There was no evidence of publication bias **(Figure 6.9 (A))**.

Four studies (538 subjects) estimated overall survival (222, 224, 240, 262). No significant heterogeneity was found among studies reporting the 1- year overall survival (I^2 =32%, p=0.2). The random-effects model pooled OR (95%CI) was 1.18 (0.46-3.03), p=0.73 **(Figure 6.10)**. There was significant heterogeneity in the studies reporting on 3-year overall survival (I^2 =53%, p=0.09). A random-effects model pooled OR (95%CI) was 0.76 (0.44-1.32), p=0.33 **(Figure 6.11)**. There was no evidence of publication bias with regard to overall survival **(Figure 6.9 (B))**.

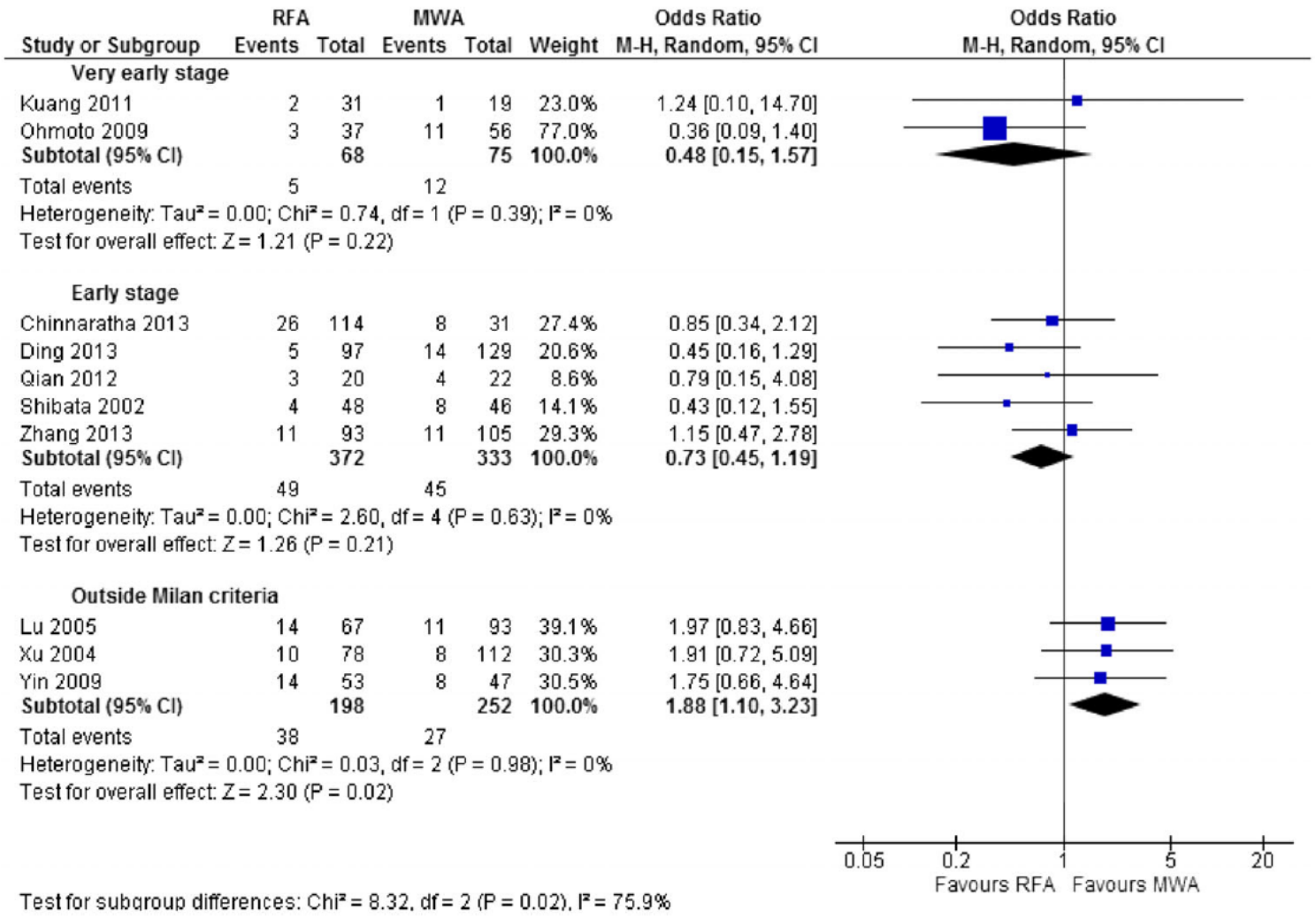

Figure 6.5: Forest plot of subgroup meta-analysis comparing local tumour progression between radiofrequency ablation (RFA) and microwave ablation (MWA) based on the stage of tumour.

CI – Confidence Interval.

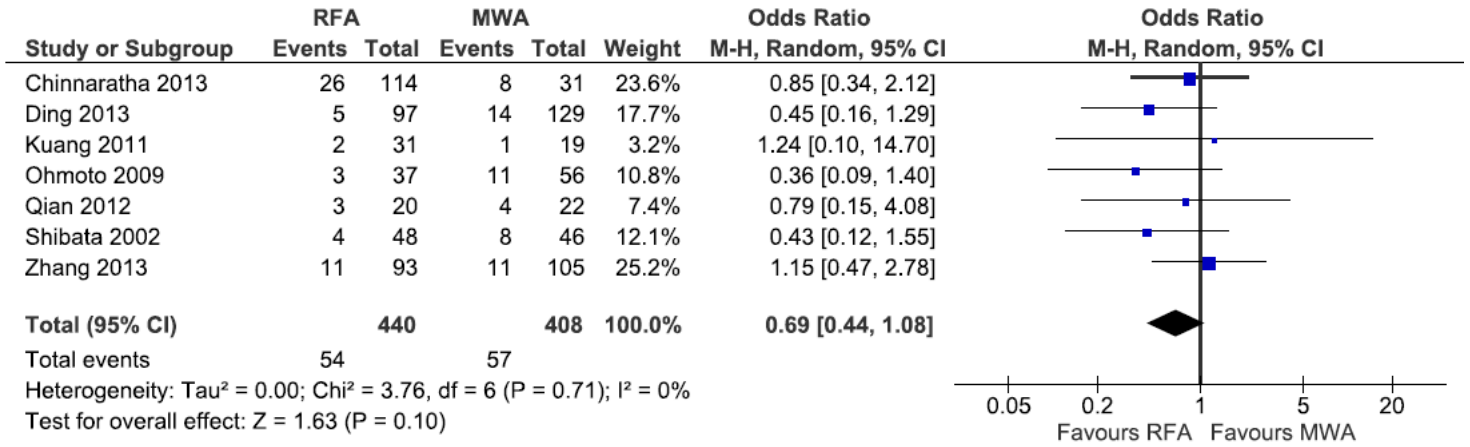

Figure 6.6: Forest plot of meta-analysis comparing local tumour progression (LTP) between radiofrequency ablation (RFA) and microwave ablation (MWA) for tumours ≤ 5cm.

CI – Confidence Interval.

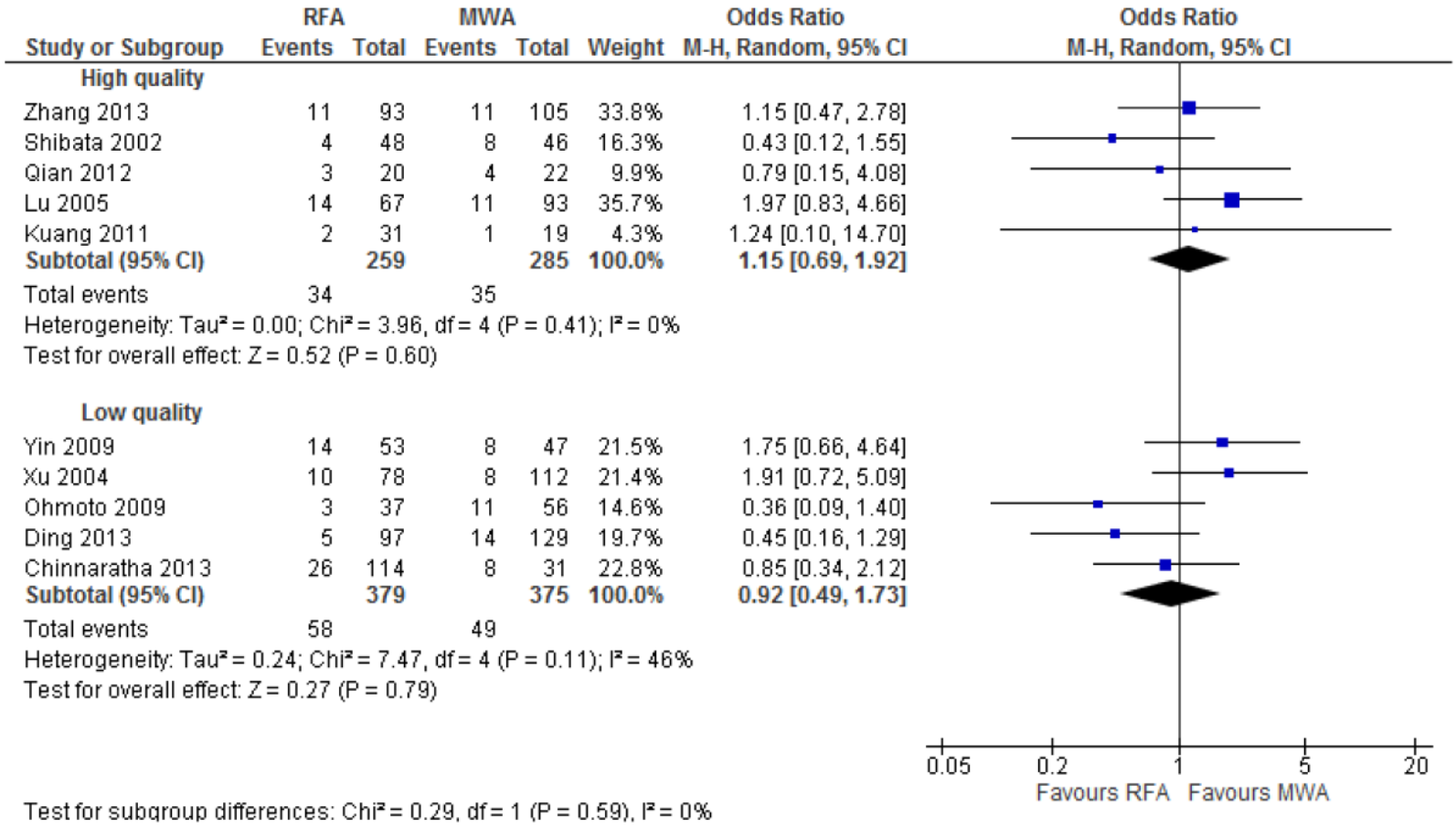

Figure 6.7: Forest plot of subgroup meta-analysis comparing local tumour progression between radiofrequency ablation (RFA) and microwave ablation (MWA) based on the quality of studies

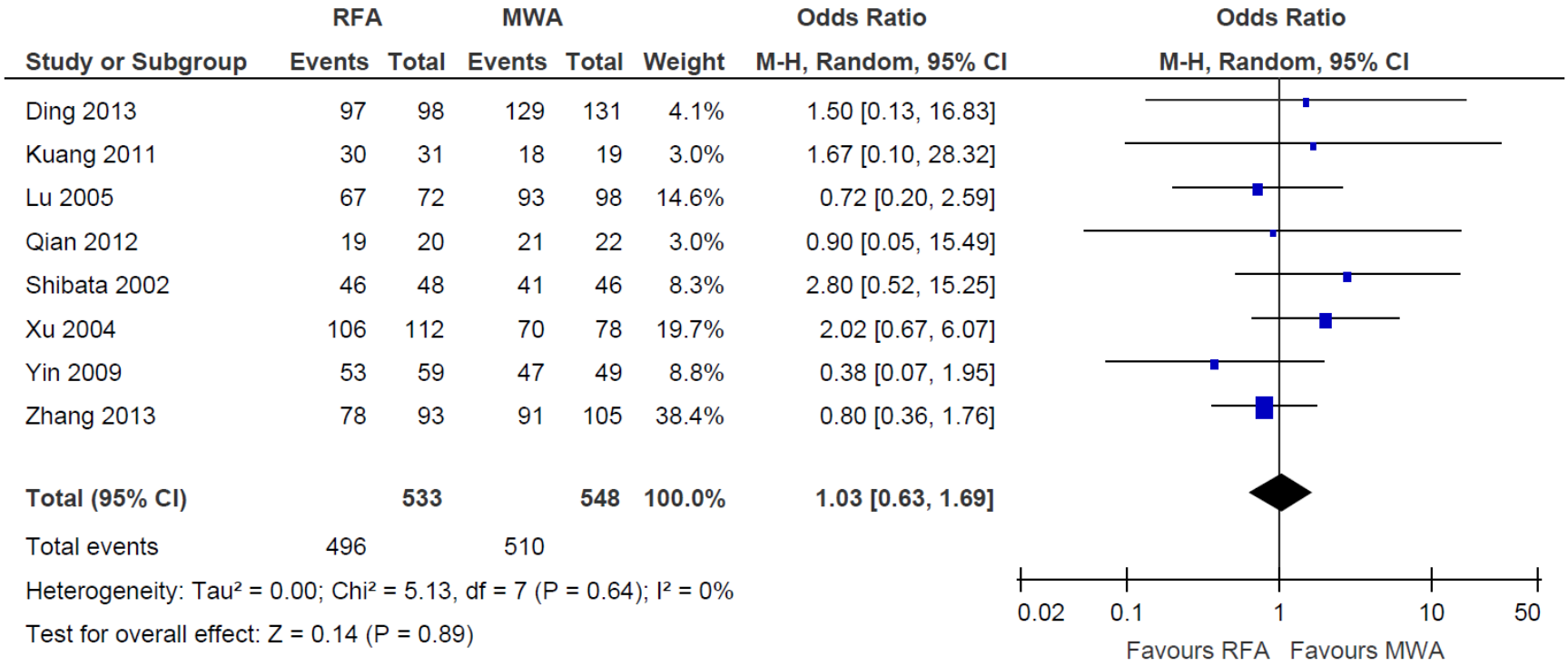

Figure 6.8: Forest plot of meta-analysis comparing the complete ablation rates between radiofrequency ablation (RFA) and microwave ablation (MWA).

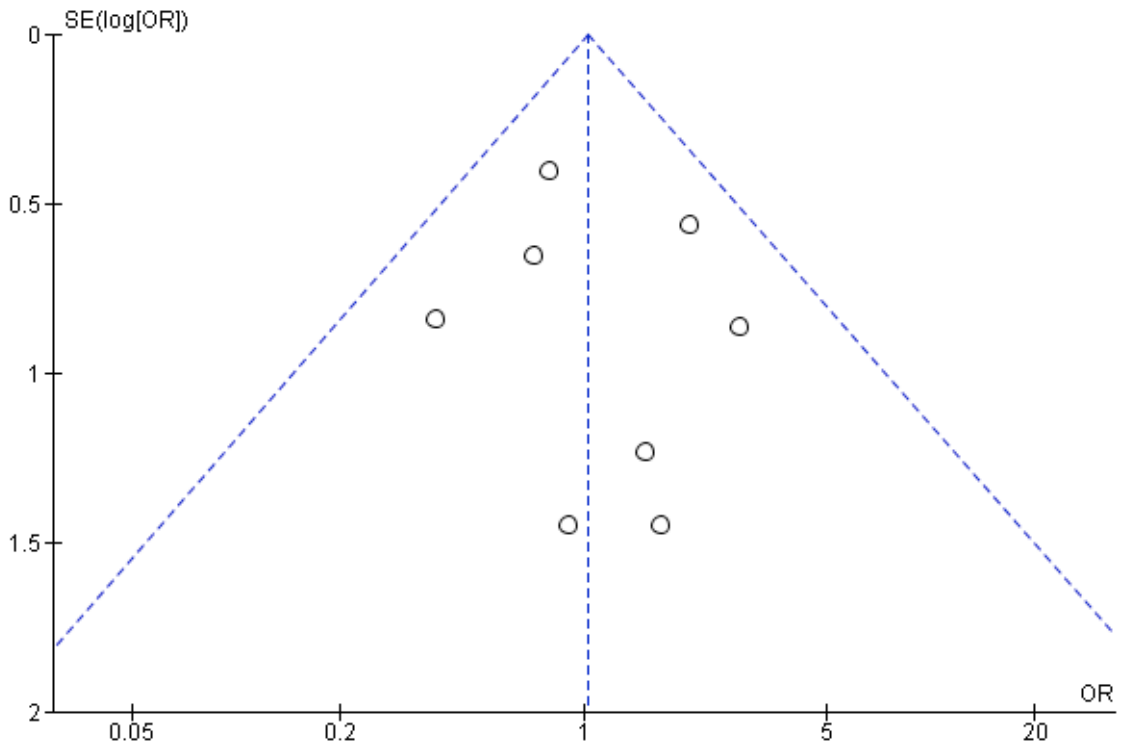

Figure 6.9 (A): Funnel plot to assess for possible publication bias in the meta-analysis regarding complete ablation rates

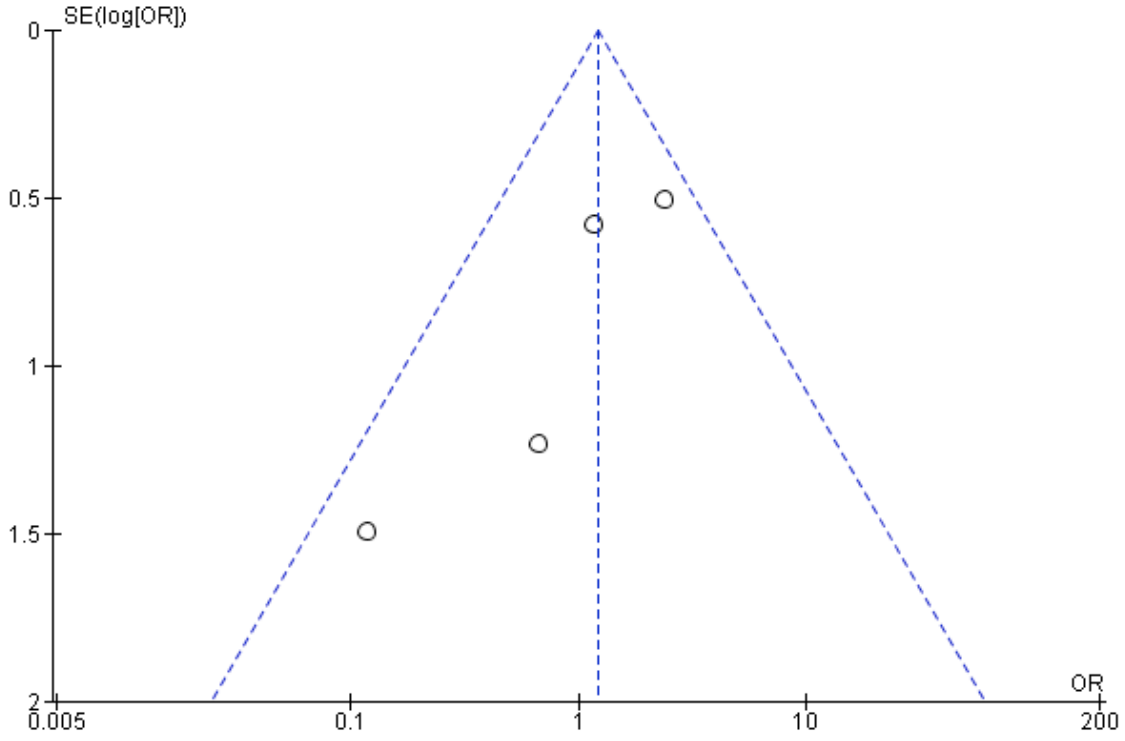

Figure 6.9 (B): Funnel plot to assess for possible publication bias in the meta-analysis regarding the 1- year overall survival

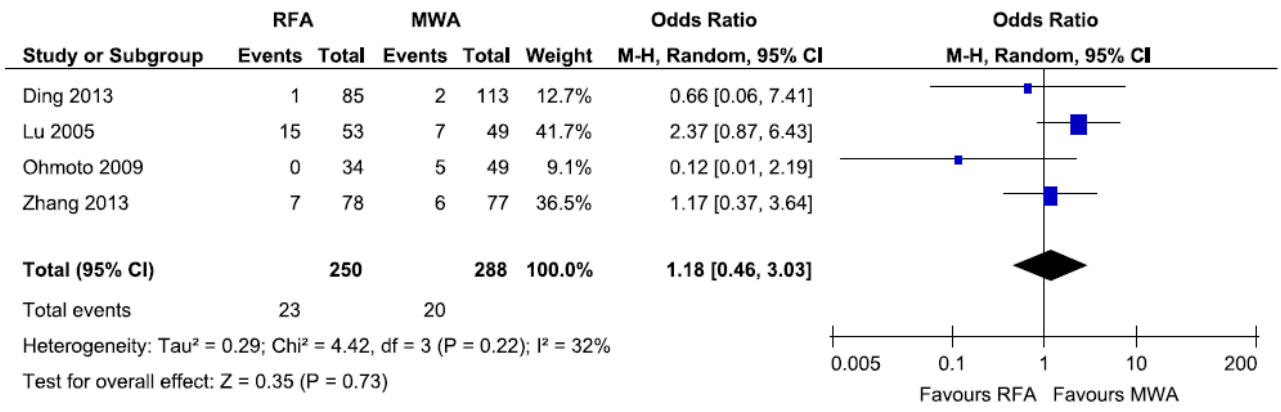

Figure 6.10: Forest plot of meta-analysis comparing the 1- year survival between radiofrequency ablation (RFA) and microwave ablation (MWA)

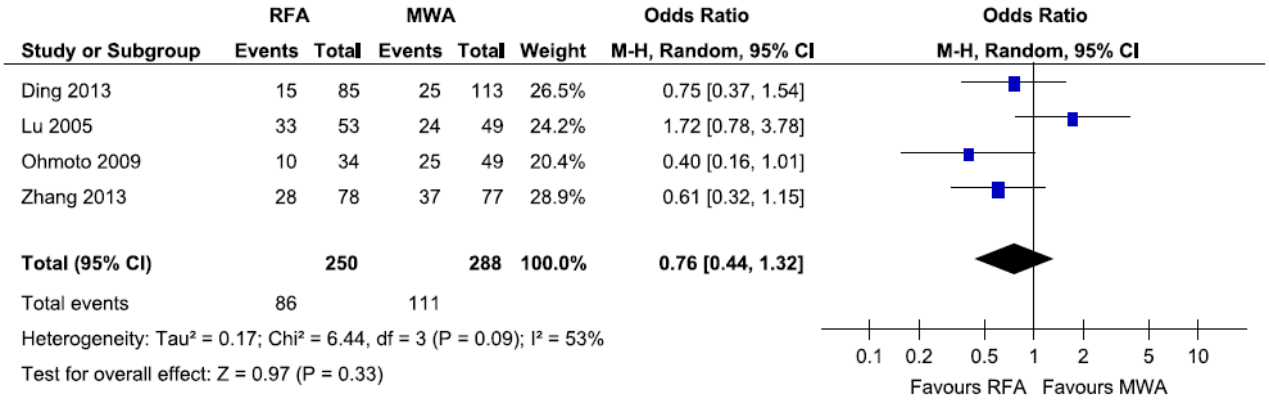

Figure 6.11: Forest plot of meta-analysis comparing the 3- year survival between radiofrequency ablation (RFA) and microwave ablation (MWA)

6.3.5 *Major complications*:

Seven studies (1043 subjects) reported the data on major complications (222-224, 240, 261, 262, 264). There was no significant heterogeneity among the studies (I^2 =0%, p=0.8). The random-effects model pooled OR (95%CI) was 0.63 (0.29-1.38), p=0.25 suggesting no statistically significant difference in major complication rates between the 2 techniques **(Figure 6.12)**. There were no reported incidences of tumour seeding in these studies. Overall, there was only one treatment related death amongst the 7 studies suggesting a mortality risk of 1:1000 for percutaneous thermal ablation techniques in treating HCC. There was no evidence of publication bias **(Figure 6.13)**.

6.4 DISCUSSION:

Percutaneous thermal ablation techniques are a well-established treatment option for the management of hepatocellular carcinoma. This is the first meta-analysis comparing the effectiveness and safety of the two commonly used modalities, RFA and MWA. The results indicate that MWA is as effective as RFA in terms of local control, complete ablation rates and overall survival, with a similar safety profile in treating HCC of various sizes. For tumours ≤5cm, there was a marginal trend favouring RFA for local tumour control but not statistically significant. However, our subgroup analysis suggests MWA may be more effective compared to RFA in preventing LTP when treating large tumours.

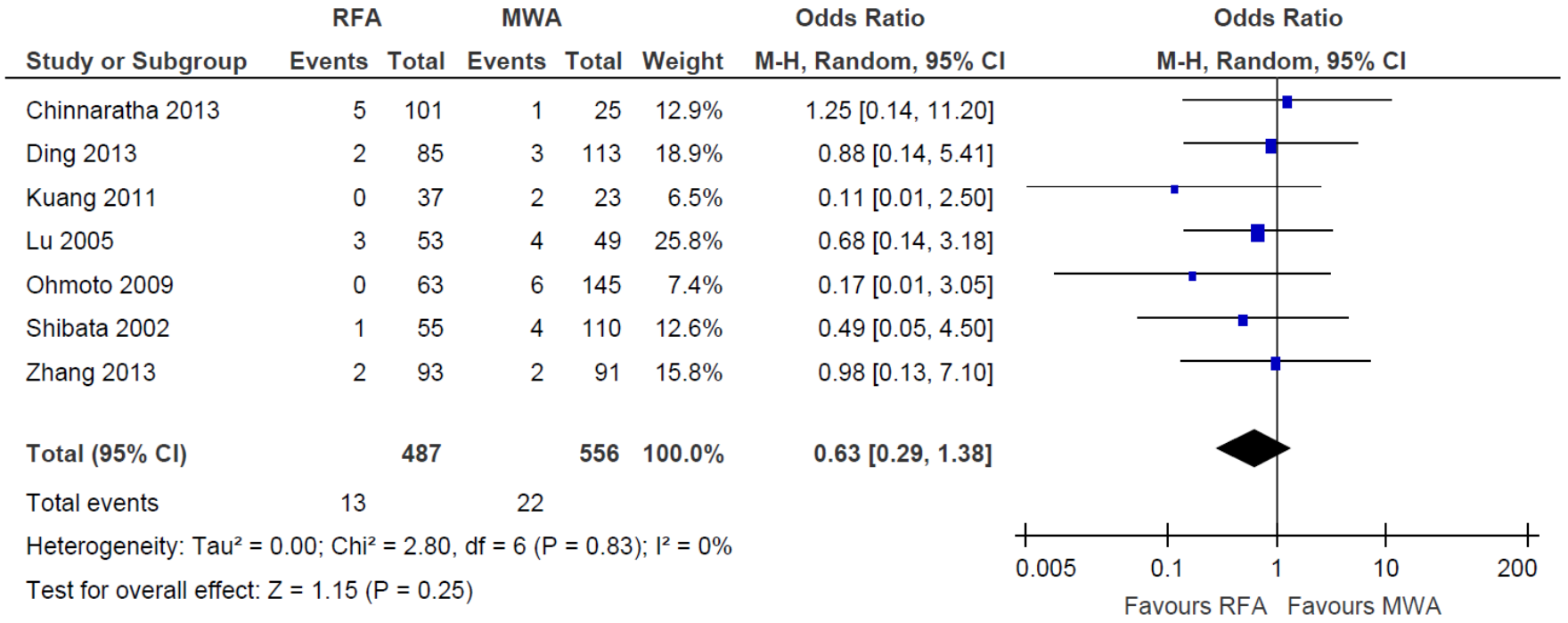

Figure 6.12: Forest plot of meta-analysis comparing the major adverse events between radiofrequency ablation (RFA) and microwave ablation (MWA)

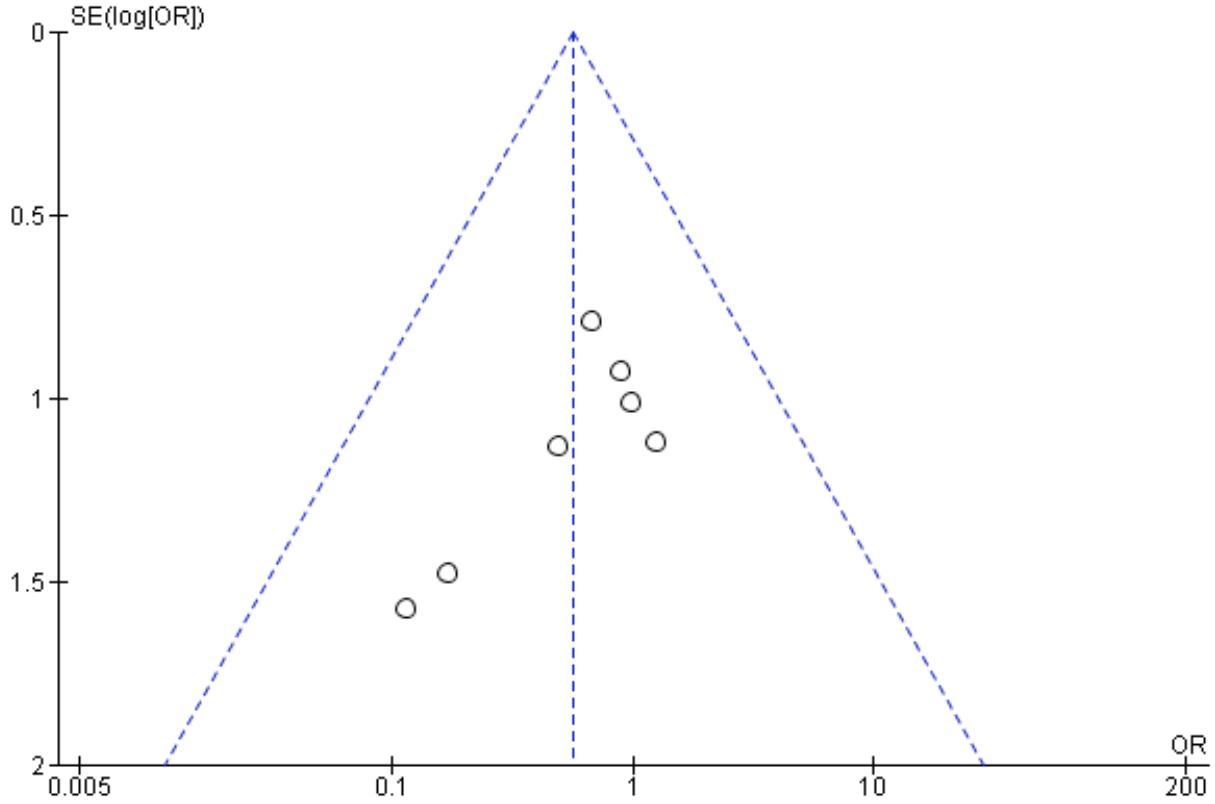

Figure 6.13: Funnel plot to assess for possible publication bias in the meta-analysis regarding major adverse event reporting

This is consistent with previous experimental and clinical studies demonstrating larger ablation zones with MWA resulting in superior local tumour control (246, 250). Thus, for tumours measuring 3.0-8.0cm, complete ablation rates with MWA varied between 91%-100% (246, 265, 266). One of the major reasons for larger ablation zones with MWA is its ability to overcome the heat-sink effect. Indeed, complete ablation rate, LTP rate, overall survival and major complications have recently been shown to be similar whether HCC is located ≤5mm or >5mm from a vessel (267). However, despite the larger volume of tissue destruction, the complication rate with MWA while treating tumours up to 8.0cm remains acceptable, between 2.6%-7.5% (268, 269). Although MWA performed better than RFA for treating tumours outside Milan criteria in this study, this might not be the preferred treatment option for this cohort. Yi et.al. showed that combination of TACE with either MWA/RFA improved the overall survival by 58% and the recurrence free

survival by 52%, compared to RFA or MWA alone in tumours up to 7cm (270). A recently published meta-analysis showed significant improvement in overall survival with combination of TACE and RFA compared to RFA alone for tumours >5cm, but no difference in survival for smaller tumours (271).

In addition to consideration of tumour size, the choice between the two techniques is also influenced by the time involved. A theoretical advantage with MWA is the ability to produce a rapid rise and sustain higher intra-tumoural temperatures thereby reducing the ablation time. In the only reported RCT comparing the two modalities, the mean time required (per session) for MWA was consistently shorter compared to RFA [Mean (±SD): 33 ±11 minutes v 53 ±16 minutes] (223). Two further studies comparing RFA and MWA using a laparoscopic approach showed similar results with shorter operative time with MWA (257, 258).

Guidelines from major international associations like AASLD, EASL and Asian Pacific Association for the Study of the Liver (APASL) were reviewed for their consensus statements on percutaneous thermal ablation techniques in the management of HCC (115, 125, 211). Both the AASLD and EASL guidelines recommend the use of RFA as a bridge to transplantation or in early stage HCC in subjects with Child-Pugh A or B cirrhosis and with good performance status. However, APASL guidelines includes a broader term, “Percutaneous ablation therapies” including percutaneous ethanol injection (PEI), MWA and RFA as a first-line treatment of unresectable small HCC with ≤3 nodules (each ≤3cm) in Child-Pugh A or B cirrhosis. In view of our findings, we suggest the authors of future guidelines also consider broadening the options and include MWA as an alternative to RFA.

There are a number of limitations to the study. First, the lack of standardization of generators and antennas used for ablation restricts direct comparison of the studies included in meta-analysis **(Table 6.2)** and a subgroup analysis based on equipment was not possible due to the small numbers within each treatment group. Secondly, LTP was analysed as a binary endpoint as only four studies reported this as a censored outcome. However, meta-regression to adjust for the difference in

follow-up periods showed no difference in the overall effect size. Finally, as majority of the studies were observational cohort reports from single centres, there is a possibility of patient selection bias.

In conclusion, this meta-analysis suggests that MWA is as effective and as safe as RFA for the overall treatment of HCC and may be more effective compared to RFA for treating larger tumours. However, given the different types of generators and antennas in the included studies, the results need confirmation by a well-designed, large, multicentre RCT using currently available generators before implementation.

7. CONCLUSIONS

New notifications of hepatitis B virus infection have remained stable in South Australia at between 200 and 330 cases/ year over the past two decades. However, both the crude and age-standardized incidence rates of HCC in those with CHB have increased dramatically over the same time period. Projections, based on the current trend, have demonstrated that the incidence of HCC is likely to increase for the next 5 years in this cohort. As expected in any study with HCC, crude incidence increased with increasing age and the incidence rate in males was more than three times that of females. Survival of those diagnosed with HCC during the latter time-period, between 2006 and 2010 was improved compared to the earlier time-periods. The reasons behind this improved survival were not assessed in this thesis but possibilities include increased awareness about appropriate HCC screening resulting in earlier diagnosis and improvement in therapeutic techniques.

One option to decrease the HCC incidence rates in those with CHB is to increase the treatment uptake in this cohort, as HBV viral replication (higher viral load) is one of the strongest risk factors for HCC development (7, 47, 122). Using a Markov model, this thesis demonstrates that differential treatment uptake rates have significant impacts on clinical outcomes. The highly ambitious but achievable current national treatment uptake target of 15% showed significant cost-effectiveness compared to the current treatment uptake rate (2.9%) resulting in lower mean cost/ person and increased QALY over a 10- year period. This was mainly secondary to a significant reduction in adverse clinical outcomes including HCC, liver transplantation and mortality. The results were not seen immediately as there was a time lag of 2- years between achieving the target and the appearance of cost-effectiveness.

Another strategy to improve survival in CHB and cirrhosis is to increase the screening rates in high risk individuals. An earlier study from the candidates health region showed that the screening

uptake was poor (209). This prompted the setting up of a dedicated, centrally coordinated, screening program as part of a system re-design effort in 2009. This study showed that those diagnosed within this screening program had a significantly better survival compared to those diagnosed outside this program during the same time-period and also prior to 2009. Rather than adjusting for lead-time, propensity scores (calculated using age, gender and year of diagnosis) were used to adjust the two groups in this thesis. The survival benefit remained even after adjustment for the stage of liver disease and the AFP level on diagnosis. However, the survival benefit lost its statistical significance when adjusted for the HCC stage at diagnosis. This showed that the survival benefit seen within the screening program is likely secondary to HCC stage migration. There was an 11- fold increased chance of detecting HCC at an earlier stage and an 8- fold increased chance of having treatment with a curative intent for those within the screening program.

The majority of HCC's diagnosed at an earlier stage will be amenable to treatment with a curative intent. Percutaneous thermal ablation therapy is one of the curative treatments but the multicentre real world retrospective cohort study of this thesis demonstrated a relatively high local recurrence rate around the margins of the treated zone. This finding suggests the need for further improvements in non-surgical local therapies for early stage HCC.

There have been conflicting results on the clinical outcomes achieved with the two most commonly used percutaneous thermal ablation techniques, RFA and MWA. The data in the systematic review and meta-analysis included in this thesis shows the overall risk of local tumour progression and adverse events to be similar between the two techniques but, MWA is superior relative to RFA for treatment of larger tumours.

7.1 RECOMMENDATIONS:

A number of recommendations follow from the five clinical studies of this thesis relating to improving clinical outcomes of patients with HCC.

7.1.1 Improving HBV management via increased disease detection and treatment uptake:

Chapter 2 of this thesis demonstrated the rising incidence rate of HBV-related HCC in SA. It is likely that other end stage complications of HBV, such as cirrhosis, are also increasing in incidence. A major driver of morbidity in HBV is the high rates of undiagnosed infection. Based on the current modelled estimates, approximately 46% of those with CHB are undiagnosed in Australia. To reduce complications from HBV a number of public health strategies must address this high rate of undiagnosed infection with improved efforts at disease detection. Improved implementation of the *National Hepatitis B testing policy* amongst general practitioners (GP) and primary health care workers will be pivotal using strategies such as "opportunistic screening" of high risk individuals. Examples of the high-risk individuals to be targeted for disease screening include:

- Migrants - both humanitarian and non-humanitarian migrants from areas with HBV prevalence of more than 2% (intermediate and high prevalence areas) to be screened on arrival. Since 2006, only humanitarian migrants and asylum seekers are targeted for HBV screening.
- Indigenous Australians - opportunistic HBV screening among Indigenous Australians while presenting with non-liver related issues (after informed consent).
- Patients undergoing chemotherapy - Implement policies and protocols for mandatory HBV screening in all patients undergoing chemotherapy or other immune-suppressive therapy.
- Other high risk individuals to be opportunistically screened and vaccinated include:
    - People who inject drugs (PWID)
    - Men having sex with men (MSM)
    - Sex workers

- Those with chronic diseases such as cirrhosis, inflammatory bowel disease etc.,
- Those diagnosed with HIV or HCV infection, particularly those on treatment
- Sexual and house-hold contacts of those with chronic HBV
- Those in custodial settings

Another important component of reducing the disease burden from HCC is facilitating improved treatment uptake with current antiviral therapy for eligible patients. Chapter 3 of the thesis demonstrated the clinical benefits and cost effectiveness of increasing treatment uptake beyond current low levels. Achieving this however will be a complex public health challenge. Improving GP education in high prevalence areas and improving access to specialist care are likely to be key components of this strategy. Expanding the eligibility criteria for prescribers via accreditation of GPs, as part of the *SA s100 hepatitis B prescriber policy may be beneficial*, in partnership with more specialist HBV physicians.

7.1.2 Improving uptake and performance of HCC screening:

Another important recommendation, arising from Chapter 4, is the need for greater uptake of high quality HCC screening programs in cirrhotic and at risk patients. HCC is one of the common causes of liver related mortality in those with cirrhosis. Chapter 4 demonstrated good outcomes for patients within such a screening program but very low HCC screening rates for high risk individuals in our health region. Centrally co-ordinated HCC screening should be considered in busy tertiary centres where there is a risk of inadequate screening due to frequent failure to attend scheduled out-patients visits. Knowledge of local adherence rates to HCC screening protocols is a critical first step to understanding the need for redesigning more robust processes around care for this patient group. Ideally far more centralized systems, equivalent to other national screening programs, are likely to be more effective in reducing the mortality from HCC than ad hoc local programs.

7.1.3 Reducing the local recurrence rate from percutaneous therapy for early HCC:

Chapter 5 of this thesis, which provided real world multicentre data, highlighted the underappreciated problem of high local recurrence rates associated with the current percutaneous therapies for early HCC. Local recurrence rates approached 25 % and strongly suggest the need for improved/ adjuvant therapy. Trials investigating combined therapies with percutaneous ablation or improved single modality therapies such as stereotactic radiotherapy should be encouraged on the basis of results from this thesis.

7.2 LIMITATIONS:

This thesis was primarily designed to look at the impact of CHB- related HCC in South Australia. However, chapters 4, 5 and 6 assessing the screening program and percutaneous interventions looked at the overall HCC population (irrespective of underlying aetiology) as the number was limited in terms of CHB- related HCC patients. It is likely that results from this thesis could be extrapolated to the CHB- related HCC population as aetiology has not been identified as an independent predictor of survival in prior studies of HCC surveillance programs (109, 111). Furthermore, no aetiology specific differences in survival of early stage HCC patients treated with percutaneous ablative therapies have been noted (216, 272, 273).

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