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Objective: To assess and provide in-depth analysis of appropriate delivery of care in patients with hepatocellular carcinoma (HCC) based on time of diagnosis within Americans in the United States.

Design: Meta-analysis of retrospective cohort studies describing receipt of appropriate treatment utilization and delivery of care for HCC.

Results: Among all twenty-three included studies, a total of 7,986 of 17,286 (44.4%, 95% CI 43.7-45.1%) patients received overall treatment. Of 48,200 patients with HCC, only 10,518 (21.8%, 95% CI 21.5-22.2%) patients received curative treatment and 6,810 of 11,776 (57.8%, 95% CI 56.9-58.7%) patients who were within early stage HCC received curative treatment.

Conclusion: HCC treatment is underutilized in the United States. Although the pooled treatment rate for early HCC patients receiving curative treatment is somewhat better, only about four-sevenths receive appropriate care. There are significant socio-demographic disparities with the lowest treatment rates in non-Caucasians and non-private insurance patients.

APPROPRIATE DELIVERY OF CARE IN AMERICAN PATIENTS WITH  
HEPATOCELLULAR CARCINOMA: A SYSTEMATIC REVIEW

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APPROPRIATE DELIVERY OF CARE IN AMERICAN PATIENTS WITH  
HEPATOCELLULAR CARCINOMA: A SYSTEMATIC REVIEW

THESIS

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School of Public Health  
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By

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I lovingly dedicate my thesis to my father, Pheng Bun Tan, who has taught me to work hard and to always follow my dreams.

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# CHAPTER 1

## INTRODUCTION

### *Background*

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide and one of the leading causes of death among patients with cirrhosis (El-Serag & Rudolph, 2007). Unfortunately, the incidence of HCC is increasing rapidly in the United States and is expected to skyrocket over the next 20 years (Singal et al., 2012). Age-adjusted incidence rates of HCC have tripled over the last 30 years, escalating from 1.6 to 4.9 per 100,000 (Singal et al., 2012). The current epidemics of hepatitis C virus (HCV) cirrhosis and advanced nonalcoholic fatty liver disease (NAFLD) are large factors contributing to the rising occurrence of HCC (Singal et al., 2012).

### *Public Health Importance of Hepatocellular Carcinoma*

In 2007, HCC had the thirteenth highest incidence rate among tumors in United States (Singal & Marrero, 2008). In addition, HCC had the largest increase in incidence of all solid tumors from 1995 to 2004 (Singal & Marrero, 2008). HCC alone results in over 500,000 deaths per year and is the eighth most common cause of cancer-related death in the United States (Singal & Marrero, 2008). The five-year survival rate in 1996 showed a minor 1% improvement from the five-year survival rate in 1985 (5% vs. 4% respectively) (Singal & Marrero, 2008).

HCC has significant associated morbidity and mortality rates (Singal & Marrero, 2008). Despite efficacious screening tests, advances in technology and available treatments, prognosis for patients diagnosed with HCC is very poor (Singal, Chan, Getachew, Guerrero, Reisch, & Cuthbert, 2012). Prognosis for HCC patients is highly

contingent on the tumor stage at the time of diagnosis (Singal, Yopp, Gupta, & et al., 2012). Curative treatment options are only available for patients who are diagnosed at an early stage (Singal et al., 2012). Early stage HCC is often defined using the Milan criteria, i.e, one nodule less than 5 cm or three nodules each less than 3 cm in diameter without vascular invasion or distant metastases (Singal et al., 2012). Patients with early HCC can be treated with surgical resection or liver transplantation and achieve five-year survival rates near 70% (Singal et al., 2012). In contrast, patients diagnosed with advanced HCC only have palliative measures available and have a median survival of less than one year (Singal et al., 2012).

### *Gaps In Knowledge*

The effectiveness of HCC treatment is highly conditional upon tumor stage at the time of diagnosis. The Barcelona Clinic Liver Cancer (BCLC) staging system has been implemented as the principal determinant of prognosis and the treatment guide for patients with HCC (Singal & Marrero, 2008).

Studies have proved that despite surveillance efforts, nearly all patients with HCC are diagnosed beyond early stages, so curative options are no longer available (Singal & Marrero, 2010). Moreover, although there have been advances in treatment options throughout the past couple years, appropriate delivery of care must be individualized so the patient can benefit optimally with local treatments (Singal & Marrero, 2010). Furthermore, elderly, African Americans and patients of low socioeconomic status (SES) have poor survival rates due to multiple factors (Artinyan et al., 2010). These multiple factors include medical, financial, and social factors (Artinyan et al., 2010).

This systematic review will evaluate the process of appropriate delivery of care for HCC patients within the United States. In addition, the purpose of this study is to quantify utilization rates for HCC treatment among patients in the United States and to summarize patterns of association between treatment utilization rates and patient socio-demographic characteristics.

### *Relevance In The History of Health Services Research*

The history of health services research (HSR) began roughly in the 1950s and 1960s with first funding of grants for HSR focused on the impact of hospital organizations (Steinwachs & Hughes, 2008). Then in 1989, the federal role in health services research took place when Congress created the Agency for Health Care Policy and Research, later known as the Agency for Healthcare Research and Quality (Steinwachs & Hughes, 2008). The Agency's mission was to focus on improving medical practice, patient healthcare outcomes, as well as investing in methods for quality measurement, patient safety and health information technology (Steinwachs & Hughes, 2008). Today AHRQ provides leadership for the field by investing in HSR (Steinwachs & Hughes, 2008). Furthermore, the U.S. Department of Veterans Affairs, Centers for Disease Control and Prevention, the National Institutes of Health, CMS and other Federal agencies fund HSR. Private funding from the Robert Wood Johnson Foundation, Commonwealth Fund, Kaiser Family Foundation, and other private funding sources has also grown recognizing that HSR is important in improving the management of health care systems (Steinwachs & Hughes, 2008). Hepatocellular carcinoma is a complex and burdensome disease and comprehensive control requires use of multiple strategies across

patient care. Priorities for hepatocellular carcinoma in the health services research field are vital in reducing rates and improving health outcomes for Americans.

## CHAPTER 2

### PROCESSES OF CANCER CARE

It is infamously known that there are many gaps in health care within the United

States. The United States leads in cutting-edge advances in medicine, yet the United States ranks among the lowest in many measures of health care (Taplin & Rodgers, 2010). The IOM reports on cancer make it well known that the United States is fragmented and uncoordinated in the processes of cancer care and delivery due to affects by numerous levels of influence (Taplin & Rodgers, 2010). Moreover, the IOM reports *Crossing the Quality Chasm* and *Ensuring Quality Cancer Care* identify six principles to improve care. These six principles are safety, effectiveness, patient-centeredness, timeliness, efficiency and equity (Taplin & Rodgers, 2010).

In the article by Taplin and colleague, “process of cancer care” is defined as the sum of the types of care, transitions, steps, and interfaces that must be traversed to receive health care across the cancer continuum (Table 1) (Taplin & Rodgers, 2010). Taplin and colleague additionally defined, “system of care” as one that develops an infrastructure for communication that facilitates care delivery consistent with the IOM’s six principles (Taplin & Rodgers, 2010). Care across the cancer continuum encompasses multiple variables, including risk assessment, detection, diagnosis, primary treatment, survivorship and surveillance, and palliative care (Figure 1) (Taplin & Rodgers, 2010).

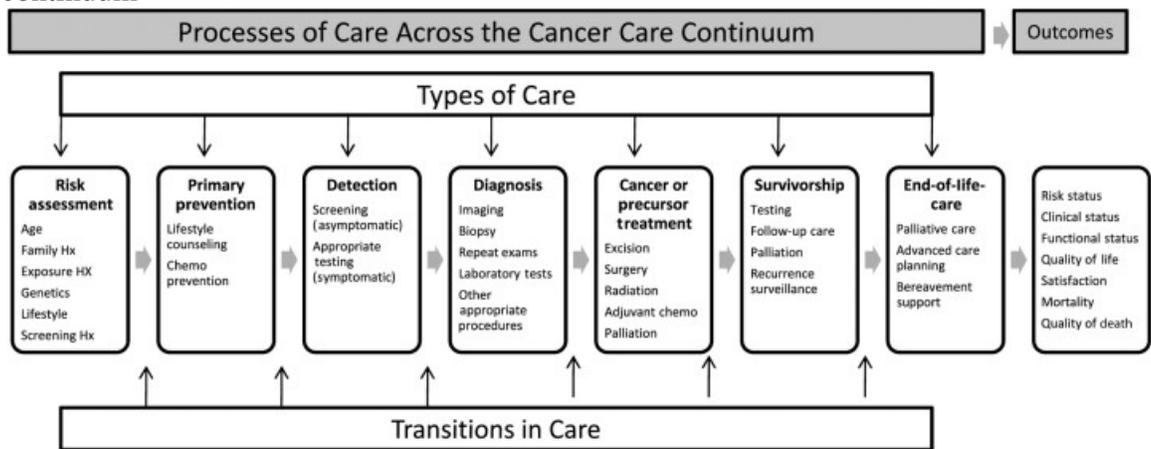
Table 1. The process of cancer care

Term	Definition
Type of care	The care delivered to accomplish a specific goal, such as detection, diagnosis, and treatment
Transition	The set of interactions necessary to go from one type of care to another. The

Step	transition from detection to diagnosis is one example
Interface	The series of medical encounters or actions within a type or transition in care The interactions that link steps in care and involve transferring information and/or responsibility between providers, patients, and/or their respective organizations. These interfaces are critical to creating an entire process that achieves the goal of each step or type of care.

Taplin & Rodgers, 2010

Figure 1. Types and transitions in care that constitute the process of care across the cancer continuum



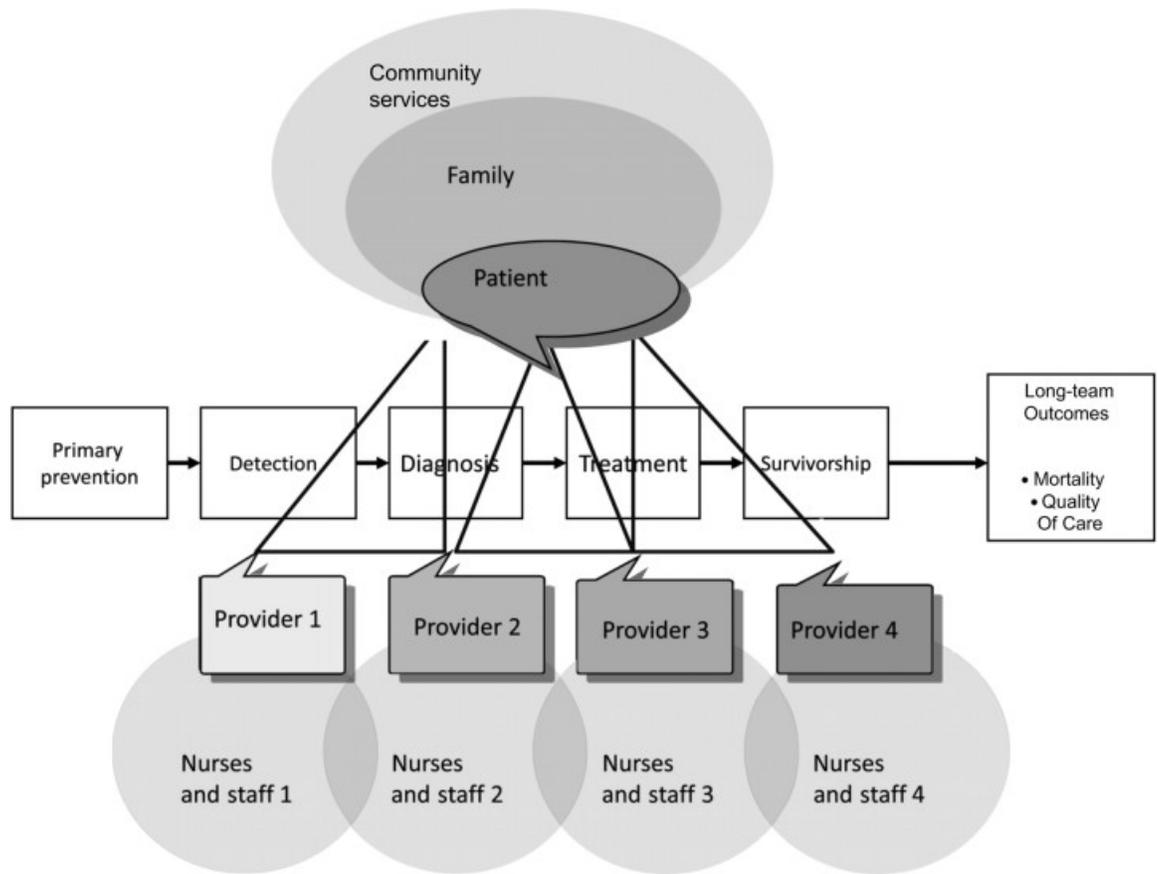
Taplin & Rodgers, 2010, Adapted from Zapka et al. 2003

Each types of care and transitions between care in Figure 1 presents varying challenges to the individual patients, families, and physicians. For example, a diagnosis of hepatocellular carcinoma may involve multiple steps, such as referral to hepatology for management of the cirrhosis and evaluation of a liver mass, referral to radiology for further imaging, referral to oncology for chemotherapy or surgeon for resection. Each visit to see a health care provider is a step in the processes of care across the cancer continuum, which involves multitudinous steps and interfaces. Moreover, the plurality of

providers and institutions involved in cancer care add to the complexity of the system of care. The transfer of information and responsibility from one physician to another, from physicians to staff, from providers to patients and families, and from one institution to another is essential to the process of care across the continuum (Taplin & Rodgers, 2010). Patients and providers must share an understanding of the disease, the therapy, and its consequences, as well as know who must do what and when (Taplin & Rodgers, 2010). Furthermore, the exchange of information and responsibility is significant during transitions in care when new providers or care organizations become involved and new care decisions become necessary (Taplin & Rodgers, 2010). Thus, the interfaces of care and coordination among providers and institutions are of great importance to the successful process of cancer care.

Figure 2 displays the triangles of communication established among cancer patients and their health care providers. The communication triangle shows multiple challenges that are critical to care for patients and physicians, as well as community service providers, patients' families, and physicians' staff regarding coordinating care (Taplin & Rodgers, 2010).

Figure 2. The triangles of communication across the cancer continuum



Adapted from Taplin et al. 2009 (16)

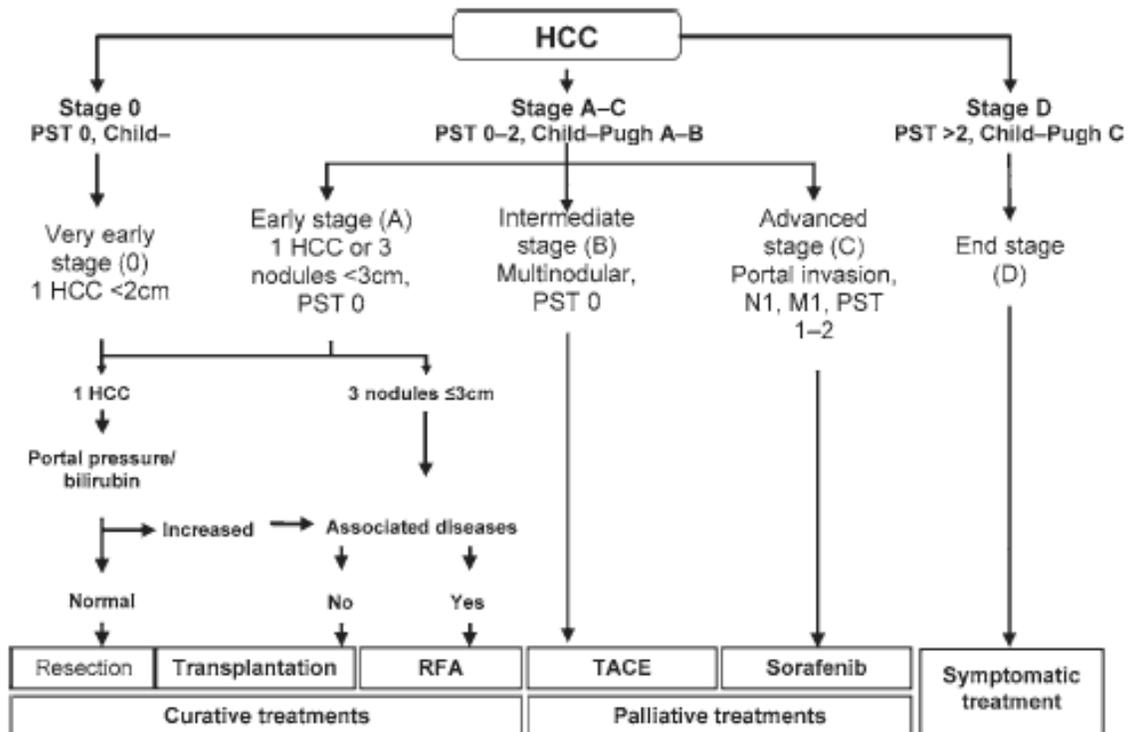
## CHAPTER 3

## TREATMENT OF HEPATOCELLULAR CARCINOMA

### *Staging Systems of Hepatocellular Carcinoma*

Staging systems are often used in cancers to predict the prognosis of patients and to guide therapeutic approaches. Currently, there is no universally accepted staging system for HCC. Accurate staging for patients diagnosed with HCC is extremely vital in providing patients with appropriate treatment options. There are multiple staging systems proposed for HCC, including the 1) TNM Staging System 2) Okuda 3) Japanese Integrated Staging (JIS) Score 4) Cancer of the Liver Italian Program (CLIP) and 5) Barcelona Clinic Liver Cancer (BCLC) Staging System. Although the Barcelona Clinic Liver Cancer Staging System is not universally accepted, it is the only staging system authenticated in more than one country. Moreover, the Barcelona Clinic Liver Cancer Staging System provides the most information for prognosis and treatment guide for patients with HCC (Singal & Marrero, 2010). Literature suggests that treatment decisions for the patient should be made based on tumor burden, degree of liver dysfunction and performance status of patients. The BCLC is advantageous since it combines tumor burden, liver function, and performance status with an evidence-based treatment guideline.

Figure 3. Treatment algorithm for patients with hepatocellular carcinoma using the Barcelona Clinic Liver Cancer Staging System



### *Surgical Resection*

Surgical resection, which is surgical removal of the tumor, is the best choice for treatment in patients with noncirrhotic HCC (Singal & Marrero, 2010). The patient selection process for surgical resection in patients with cirrhosis is extremely narrow, given that a sufficient liver remnant must be left behind. Resection is primarily used in patients with unifocal tumors and good underlying liver function (i.e. Child Pugh A cirrhosis). Five-year survival rates are only 25% in patients with significant portal hypertension and bilirubin levels more than 1 md/dl in comparison to 74% five-year survival rates in patients without hypertension and normal bilirubin levels. Furthermore, surgical resection is associated with a high risk of tumor recurrence, approximately 50% after five years (Singal & Marrero, 2010).

### *Liver Transplantation*

Liver transplantation is a distinctive treatment since it removes the tumor and underlying liver disease. Patients are only selected for liver transplantation in the United States if they meet ‘Milan criteria’, where the patient’s tumor is less than 5 cm or three tumors less than 3 cm each without vascular invasion or extrahepatic spread (Singal & Marrero, 2010) 20. Recurrence rates are approximately less than 15% and there is a 68% 5 year survival rate (Singal & Marrero, 2010).

### *Percutaneous Ablation*

Percutaneous ablation is the best form of therapy for patients with early stage HCC who are not otherwise eligible for surgical resection or liver transplantation (Singal & Marrero, 2010). There are two forms of percutaneous ablation, percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA). RFA is preferred over PEI as it delivers higher rates of complete response with fewer sessions (Singal & Marrero, 2010). RFA can achieve complete response in tumors smaller than 4 cm in 90% to 95% of cases. Further, RFA has significantly better 3-year survival rates than those of PEI (Singal & Marrero, 2010).

### *Transarterial Chemoembolization*

In patients who are diagnosed with intermediate stage HCC, transarterial chemoembolization (TACE) is typically the primary form of therapy. TACE requires selective and intricate delivery of intra-arterial chemotherapy into the tumor to promote

cell death (Singal & Marrero, 2010). Transarterial chemoembolization also provides prolonged survival, 2-year survival rate of 63%, compared to 27% in those who do not receive therapy (Singal & Marrero, 2010).

#### *Yttrium-90 Radioembolization (TheraSphere)*

Radioembolization using Yttrium-90 microspheres is a new form of treatment that has been recently introduced to treat patients with intermediate or advanced stage HCC. Radioembolization using Yttrium-90 is a process where Yttrium-90 particles are injected through the hepatic artery via a catheter directly to the tumor in the liver and internal radiation is emitted (Singal & Marrero, 2010). This method is a way to target the tumor directly using radiation without harming surrounding healthy, functional tissues of the organs (Singal & Marrero, 2010).

#### *Systemic Targeted Therapy*

Systemic targeted therapy or targeted cancer therapy, also known as molecularly targeted therapies, refers to drug therapies or other substances that interfere with cancer cell division (proliferation) and spread of cancer. Systemic targeted therapy may be effective for the patient by interfering with tumor growth and progression (National Cancer Institute, 2012). Sorafenib, also referenced by the brand name Nexavar, is an enduring chemotherapy drug that has recently been introduced to treat patients with advanced stage HCC. Presently, Sorafenib is now considered a standard of care for most patients with advanced HCC. Moreover, there have been trial studies assessing whether combining Sorafenib and other treatment modalities such as resection or TACE will be beneficial for the patient (Singal & Marrero, 2010) 44.

## CHAPTER 4

### METHODS

#### *Literature Search*

The medical literature was searched on March 18<sup>th</sup>, 2013 via a computer-assisted search using the Ovid interface to Medline. We identified all relevant published articles that examined the course of utilization of treatment and delivery in patients diagnosed

with HCC. Ovid Medline was searched from January 1<sup>st</sup>, 1989 through March 18<sup>th</sup>, 2013 with the following keyword combinations:

1. [liver ca\$ or hepatocellular ca\$ or HCC]

AND

2. [treat\$ or therap\$ or resect\$ or transplant\$ or surg\$ or chemo\$ or emboliz\$ or TACE or ablat\$ or RFA or Nexavar or Sorafenib].

These keywords: [treat\$ or therap\$ or resect\$ or transplant\$ or surg\$ or chemo\$ or emboliz\$ or TACE or ablat\$ or RFA or Nexavar or Sorafenib] were used in the search since they are various treatment options for HCC, depending on tumor stage. Given our emphasis on current delivery of care in HCC patients within the United States, our search was limited to human studies published in English. With the denotation of HSR emergence in 1989, we thus searched articles published after January 1<sup>st</sup>, 1989. Manual searches of references from relevant articles were performed to identify studies that were missed by our computer-assisted search.

### *Study Selection*

One investigator reviewed all publication titles of citations identified by the search strategy. Potentially relevant articles were also selected and selection criteria were applied. Articles were then manually and independently checked for inclusion criteria and disagreements were resolved through coming to consensus.

*Inclusion criteria included:* (i) cohort studies that described receipt of appropriate delivery of care for HCC

(ii) studies from the United States after 1989 so as to be representative of the field of health services research and current delivery of care

(iii) available data regarding information for patients who did and did not receive appropriate delivery of care for HCC

*Exclusion criteria included:*

- i) studies performed outside the United States
- ii) non-English language
- iii) non-human data
- iv) secondary data such as systematic reviews, meta-analyses and secondary treatments for recurrent HCC and/or metastases
- v) case reviews and clinical trials or pilot studies with a treatment protocol (as they do not evaluate appropriate delivery of care in a real-world clinical setting)

#### *Data Extraction*

Two investigators independently extracted required information from eligible studies using standardized forms. Data was collected on age, gender, and race/ethnicity, data regarding the population of interest, number of patients with early stage HCC, and early stage definition (Milan criteria vs. UCSF criteria). Data was also collected on number of patients eligible for curative treatment, number of patients that received curative treatment, number of patients eligible for treatment and number of patients that

received treatment. Finally, data was collected on study design, geographic location and date of the study, and number of patients in each study.

#### *Clinical End Point and Statistical Analysis*

Our primary study outcomes were receipt of any treatment among patients with HCC, receipt of curative therapies among all patients with HCC, and receipt of curative therapies among patients with early stage HCC. These outcomes were derived for each study, and 95% confidence intervals were calculated using the adjusted Wald method. Weighted pooled estimates were computed by multiplying the point estimate for each study by the proportion of individuals in that study relative to the number of individuals in all included studies.

## CHAPTER 5

### RESULTS

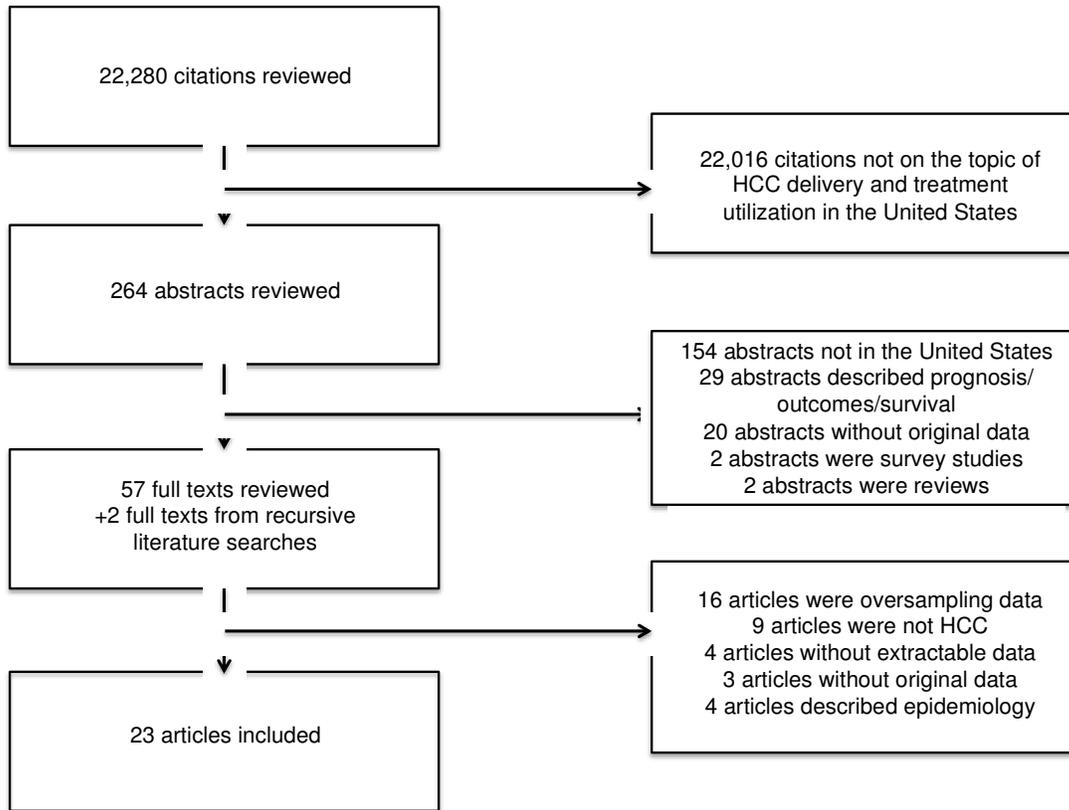
#### *Literature Search*

The computer-assisted search yielded 22,280 potentially relevant articles based on the keywords. After initial review, 264 titles were potentially appropriate, and these abstracts were reviewed. Fifty-seven publications underwent full-text review. An additional two publications were added from recursive literature search to undergo full-text review. A total of fifty-nine articles were entered into a chart and data on author,

year, study years, study setting, study type, mean age, gender, race, percent cirrhotic, percent Child Pugh A, number of patients with HCC, number of patients with early HCC, definition of early stage HCC, number of patients that received curative HCC treatment, and number of patients that received any form of treatment for HCC was extracted and organized.

A total of thirty-six articles were excluded. Sixteen articles were classified as repeat analyses using the same dataset as other studies; of these sixteen studies, twelve were from multi-center SEER databases, two articles were from the California Cancer Registry, one article was from Hawaii and one was from Deaconess. Thirteen articles were not related to HCC treatment receipt, four articles did not have extractable HCC data, and three were without original data. The remaining articles met all inclusion criteria, denoting a total of twenty-three studies for inclusion in this meta-analysis (Figure 4).

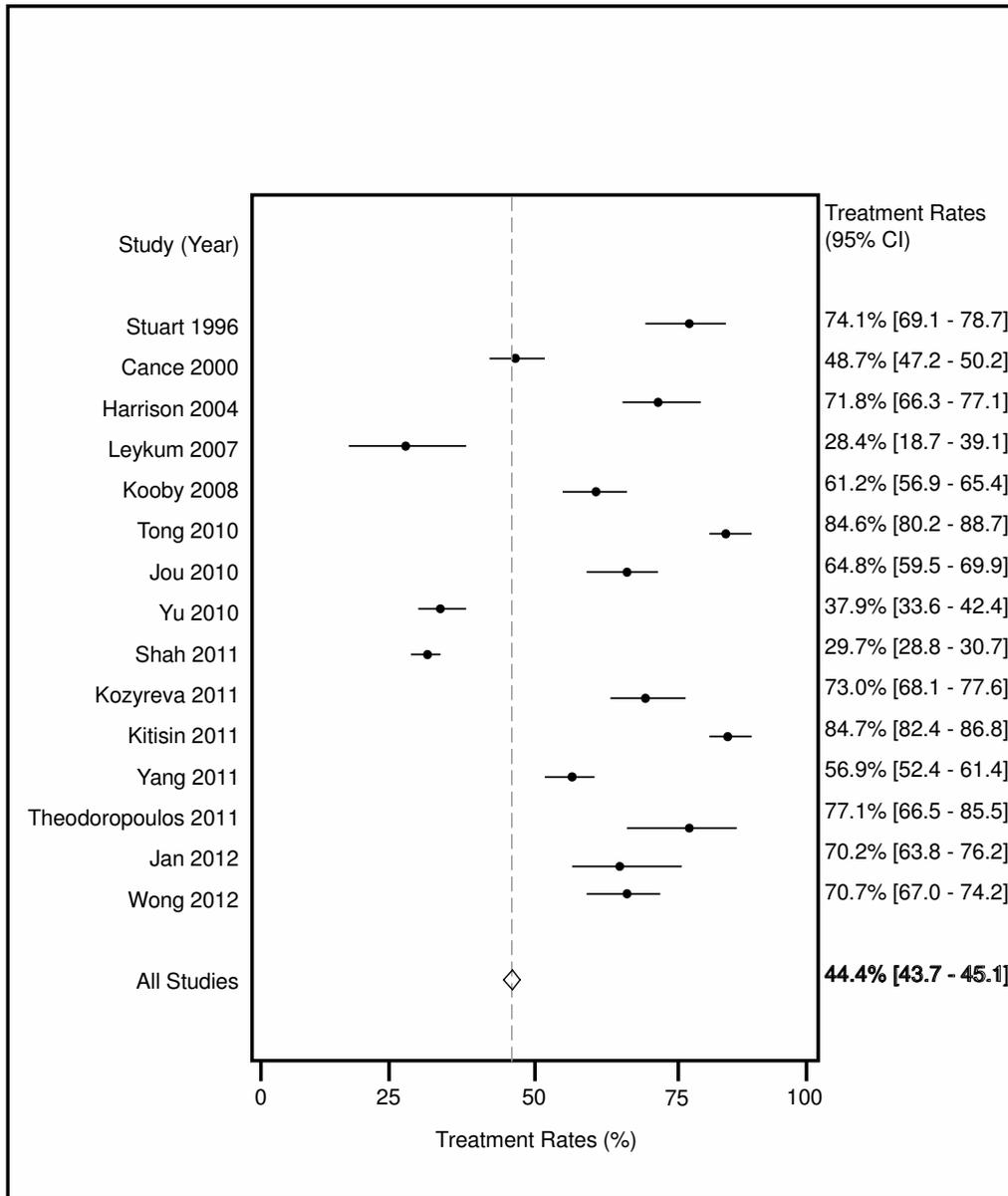
Figure 4. Flow diagram search map



### *Hepatocellular Carcinoma Treatment Utilization*

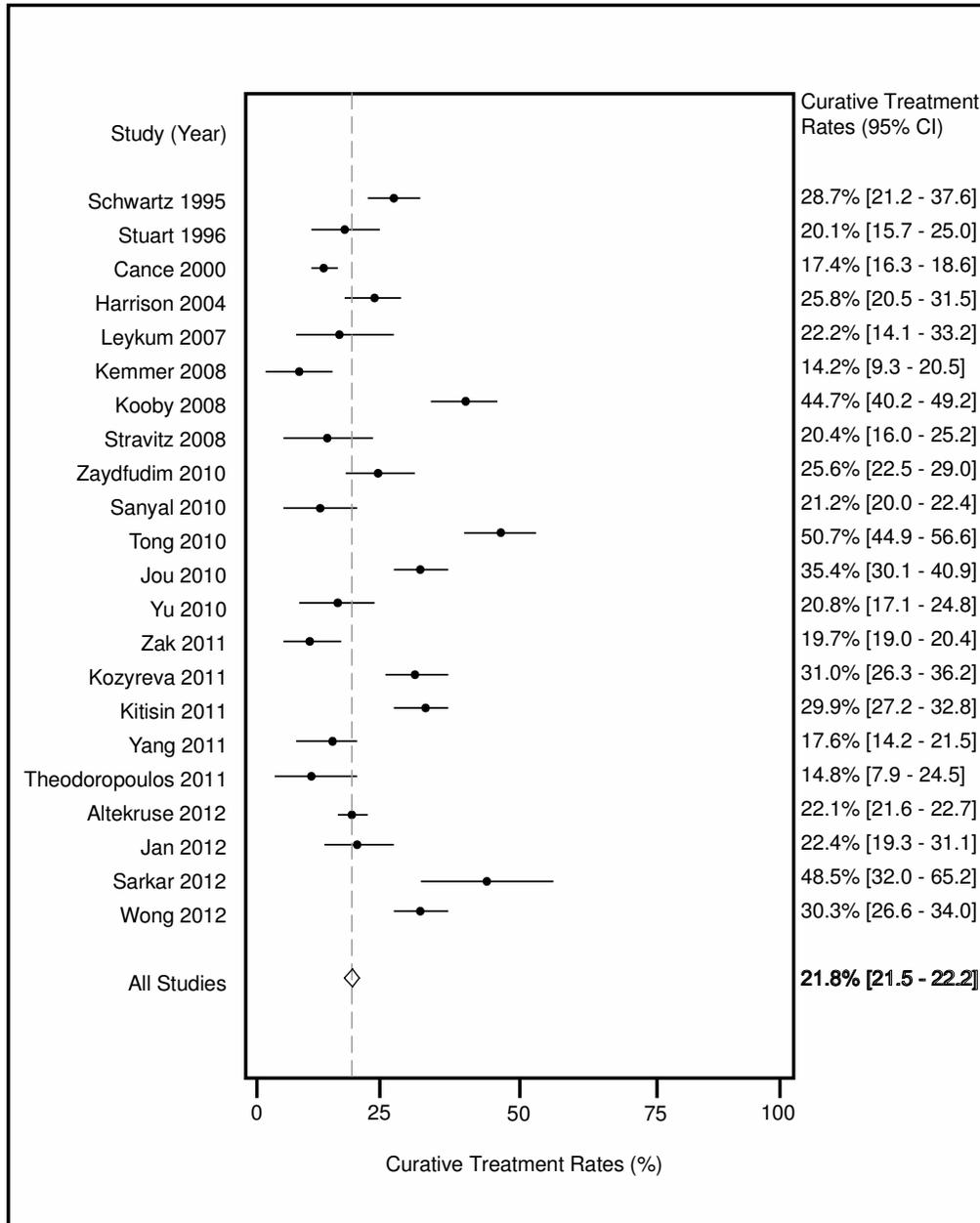
Among all twenty-three included studies, a total of 7,986 of 17,286 (44.4%, 95% CI 43.7-45.1%) patients received overall treatment. Overall treatment rates among the twenty-three studies ranged from 28.4% to 84.6% (Figure 5).

Figure 5. Treatment utilization rates



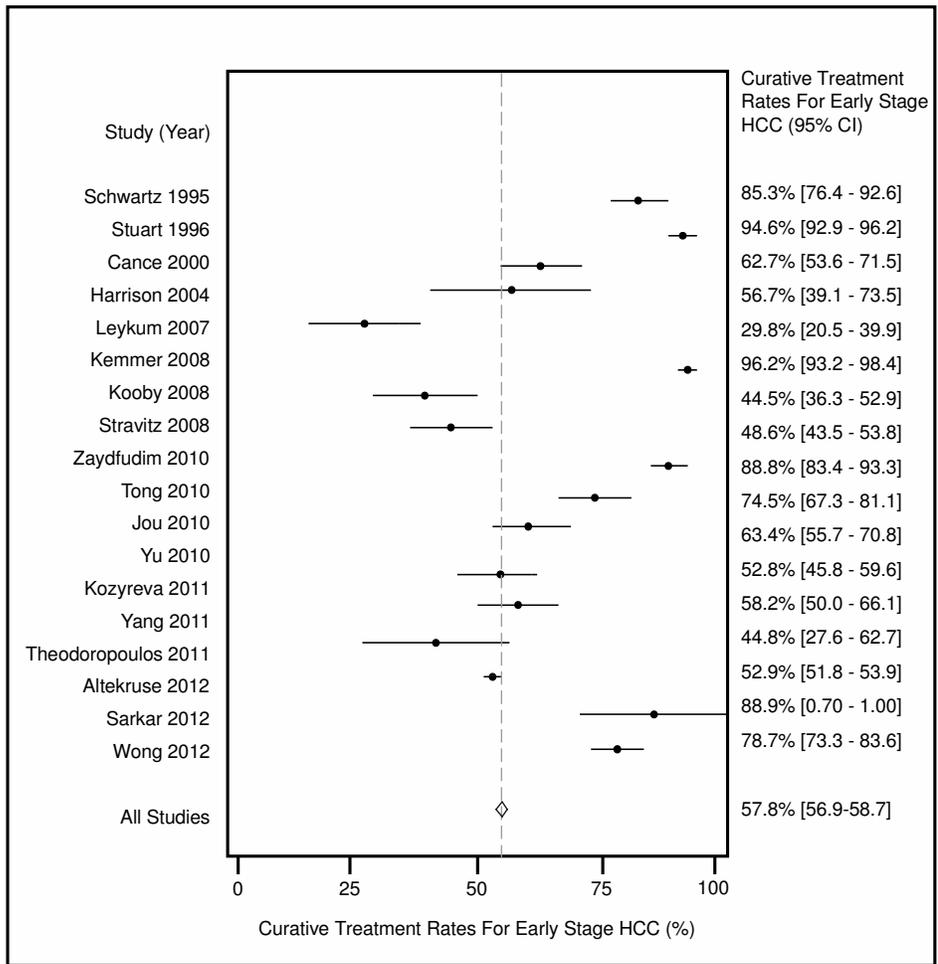
Among all twenty-three included articles, 10,518 out of 48,200 (21.8%, 95% CI 21.5-22.2%) patients received curative treatment. These studies ranged from 14.2% to 50.7% (Figure 6).

Figure 6. Curative treatment utilization rates



However, when we calculated curative treatment rates for patients who were within early stage HCC and eligible to receive curative treatment, we found that 6,810 of 11,776 (57.8%, 95% CI 56.9-58.7%) patients received curative treatment. These studies ranged from 29.8% to 96.2% for patients with early HCC receiving appropriate curative treatment (Figure 7).

Figure 7. Curative treatment utilization rates for early stage hepatocellular carcinoma patients



### *Clinical Setting*

A majority, 70% of patients with hepatocellular received care from academic centers. There were sixteen studies where patients received treatment from academic centers (Table 2). Two studies used the Surveillance, Epidemiology, and End Results Database, one used the National Cancer Database, and two used Cancer State Registries (Table 3).

Table 2. Characteristics of twenty-three retrospective cohort studies assessing hepatocellular carcinoma treatment

<b>Author, Year</b>	<b>Study Setting</b>	<b>Mean Age (Years)</b>	<b>Gender (% Male)</b>	<b>Race (% Caucasian)</b>	<b>Cirrhotic (%)</b>
Schwartz 1995	Mt. Sinai	NR	NR	NR	14
Stuart 1996	Deaconess	NR	78	NR	68
Cance 2000	National Cancer Database	64.6	70.3*	58.7	NR
Harrison 2004	Newark	NR	79	61	NR
Leykum 2007	South Texas VA	56.4	100	38.9	57
Kemmer 2008	Cincinnati	NR	80	64	100
Kooby 2008	Emory	59.5	72	71	82
Stravitz 2008	VCU	57	86	63	100
Zaydfudim 2010	Tennessee Cancer Registry	56.3	73.8	78.4	NR
Sanyal 2010	MarketScan Thomas Reuters	63.7	65.6	NR	48.5
Tong 2010	UCLA	61.5	78.1	42	72.7
Jou 2010	Duke	NR	79.6	67.7	NR
Yu 2010	Columbia	NR	79.5	40.4	NR
Shah 2011	SEER-Medicare	NR	66.7	73.6	50.6
Zak 2011	California Cancer Registry Data	45-74	71	36.5	NR
Kozyreva 2011	Tufts and MGH	66.1	79.1	77.3	NR
Kitisin 2011	Pittsburg	62	75.3	87.3	83.7
Yang 2011	Mayo	62	72	83	83
Theodoropoulos 2011	Hahnemann	NR	80	47	83
Altekruse 2012	SEER	NR	NR	NR	NR
Jan 2012	Tulane	63.5	74.8	66.9	94.4
Sarkar 2012	UCSF	NR	78	25	61
Wong 2012	Hawaii	61.5	74.9	18.4	73.8

NR-Not Reported; SEER-Surveillance, Epidemiology, and End Results; VA-Veterans Administration; \*-Averaged Across Years

*Definition of Early Stage Among Included Studies*

There were a variety of definitions for early stage hepatocellular carcinoma among the twenty-three included studies. Eight studies determined early stage hepatocellular carcinoma via the Milan Criteria, five studies determined early stage hepatocellular carcinoma using the American Joint Committee on Cancer Staging System, two studies used the Barcelona Clinic Liver Cancer Staging System, one study used TNM Staging, one study used localized, and one study used CLIP classification, which combines Child-Pugh staging with tumor criteria (Levy & Sherman, 2002) (Table 3).

**Table 3. Hepatocellular carcinoma early stage definition and treatment rates**

<b>Author, Year</b>	<b>Study Years</b>	<b># of Early Stage HCC Patients</b>	<b>Early HCC Patients (%)</b>	<b>Definition of Early Stage HCC</b>	<b>Curative Treatment</b>
Schwartz 1995	1988-1994	NR	NA	NR	OLT or Resection
Stuart 1996	1986-1995	73	23.2	TNM Stage I-II	Surgery or OLT
Cance 2000	1985-1996	744	18.4	AJCC Stage I or II	Surgery
Harrison 2004	1997-2003	108	40.9	AJCC Stage I or II	OLT and Resection
Leykum 2007	2000-2005	28	38.9	Milan	OLT, Resection, RFA
Kemmer 2008	2000-2005	82	48.5	Milan	OLT
Kooby 2008	1990-2004	232	46.3	Milan	OLT, Resection, RFA
Stravitz 2008	1990-2004	135	45.5	Milan	OLT
Zaydfudim 2010	2004-2006	358	52.6	AJCC Stage I or II	OLT, Resection, RFA
Sanyal 2010	2002-2008	NR	NA	NR	OLT, Resection, RFA
Tong 2010	2000-2007	158	56.8	Milan	OLT, Resection, RFA
Jou 2010	2002-2008	151	47.3	BCLC A	OLT, Resection, RFA
Yu 2010	2002-2008	151	32.7	AJCC Stage I or II	OLT
Shah 2011	1991-2005	3197	36.6	AJCC Stage I or II	OLT, Resection, RFA
Zak 2011	1996-2006	NR	NA	NR	OLT, Resection, RFA
Kozyreva 2011	1998-2008	197	58.8	CLIP Stage I or II	OLT and Resection
Kitison 2011	2000-2009	NR	NA	NR	OLT, Resection, RFA

Yang 2011	2007-2009	139	30.2	Milan	OLT, Resection, RFA
Theodoropoulos 2011	2001-2007	27	33.3	BCLC A	OLT or Resection
Altekruse 2012	1992-2008	8940	41.8	Localized	OLT, Resection, RFA
Jan 2012	2003-2011	NR	NA	NR	OLT
Sarkar 2012	1997-2008	16	51.6	Milan	OLT, Resection, RFA
Wong 2012	1992-2009	237	38.3	Milan	OLT and Resection

*NR-Not Reported; NA-Not Applicable; AJCC-American Joint Committee On Cancer; BCLC-Barcelona Clinic Liver Cancer; OLT-Orthotopic Liver Transplantation; RFA-Radiofrequency Ablation*

### *Correlates of Hepatocellular Carcinoma Treatment*

*Age.* Older age has been demonstrated to be a negative predictor in HCC treatment. Lower treatment rates have been observed in patients older than 65 years. Sanyal and colleagues found that patients less than 65 years received significantly more transplant (11.1% vs. 2.0%;  $p < 0.05$ ), any chemotherapy excluding Sorafenib (36.3% vs. 29.2%;  $p < 0.05$ ), and TACE (19.7% vs 7.4%;  $p < 0.05$ ) compared to those equal to or older than 65 years (Sanyal et al., 2010). Yu and colleagues similarly found that patients less than or equal to 60 years of age received more transplants (Yu et al., 2010). Those in the age group between 53-60 years were less likely to receive transplant (OR 0.09, 95% CI 0.01-0.54) (Yu et al., 2010). Moreover, age groups 61-67 years (OR 0.49, 95% CI 0.09-2.69) and age groups equal to or older than 68 years (OR 0.01, 95% CI 0.00-0.14) were also less likely to receive transplant (Yu et al., 2010). Adding to this, Kozyreva and colleagues discovered elderly patients, age equal to or greater than 70 years, received transplant less frequently compared with younger patients (19.6% vs. 5.3%,  $p = .0002$ ) (Kozyreva et al., 2011). However, the elderly were more likely to receive supportive care (22.9% vs. 36.8%,  $p = .01$ ) (Kozyreva et al., 2011).

*Gender.* Although, Zaydfudim and colleagues noted that females were more likely to receive surgical treatment (OR 1.78, 95% CI 1.15-2.76) (Zaydfudim et al., 2010), gender is not a patient factor associated with higher or lower HCC treatment utilization.

*Race/Ethnicity.* Six studies noted racial disparities in HCC treatment. Of the six studies, four demonstrated significantly lower treatment rates in non-Caucasian races. African American patients were significantly less likely than Caucasian patients to receive transplant (OR 0.03, 95% CI 0.0-0.37) (Yu et al., 2010). Similarly, African American and Hispanic patients were less likely than Caucasian patients to undergo transplant ( $P < .05$ ) (Zak et al., 2011). Hispanics and Asians were also less likely to be in receipt of a transplant (OR 0.42 vs. OR 0.33, 95% CI respectively) (Yu et al., 2010). African American and Hispanic patients were less likely than Caucasian and Asian/Pacific Islander patients to have hepatectomy or ablation ( $P < .05$ ) (Zak et al., 2011). Wong and colleagues found that Pacific Islanders and Filipinos had less liver transplantation procedures, fewer met Milan criteria, and a smaller proportion of those who met Milan criteria actually received transplantation (Wong et al., 2012). As well, Zaydfudim and colleagues found that other races were less likely to receive surgical treatment than Caucasian races (OR 0.56, 95% CI 0.19-1.68) (Zaydfudim et al., 2010).

Moreover, African American and Hispanic patients had more progressed HCC (Yu et al., 2010). African Americans and Hispanics were more likely to be diagnosed with late-stage HCC, tumors not within the Milan criteria, high Child-Pugh scores, and high AFP levels (Yu et al., 2010). Compared to Caucasians, African American patients

are much less likely to be referred for evaluation and placed on a waiting list for transplant (Ayanian et al., 1999).

*Insurance and Socioeconomic Status.* Insurance status is strongly correlated with receipt of transplantation (Yu et al., 2010). Patients with private insurance were significantly more likely to receive a transplant, compared to those with Medicaid (OR 22.07, 95% CI, 2.67-182.34) (Yu et al., 2010). Likewise, Zaydfudim and colleagues found that privately insured patients were more likely to undergo resection or transplantation than those with Medicaid or no insurance ( $P < 0.001$ ) (Zaydfudim et al., 2010). Medicaid and uninsured patients were less likely to receive surgical treatment ( $P < 0.01$  for both) (Zaydfudim et al., 2010). Moreover, Medicaid recipients presented with more advanced HCC than privately insured patients, and had poorer survival (Yu et al., 2010). Uninsured patients with HCC are more likely to present with late-stage HCC ( $P = 0.005$ ) (Zaydfudim et al., 2010). Medicaid insurance is also an indicator of socioeconomic status. Medicaid patients had a lower median household income in comparison to privately insurance patients (Yu et al., 2010).

Surgical treatment is a curative option for patients with HCC, yet none of the uninsured patients with stage I HCC received surgery compared with 49% of the privately insured, 39% of the government insured, and 24% insured via Medicaid (Zaydfudim et al., 2010). Only 25% uninsured patients with stage II HCC received surgery in comparison to 61% of the privately insured, 60% of the government insured, and 30% Medicaid insured (Zaydfudim et al., 2010). In the Medicare population, only 43.1% of patients with early stage HCC underwent therapy (Shah et al., 2011).

## CHAPTER 6

### DISCUSSION

Any level of treatment, especially curative treatment, is highly recommended for patients diagnosed with HCC. If HCC is not diagnosed at an early stage, prognosis is extremely poor. Yu and colleagues noted that among patients who received transplants, patients who are within the Milan criteria have better survival than those who do not (Yu et al., 2010). Our meta-analysis highlights significant underutilization of appropriate treatment delivery in clinical practice. Low treatment rates were reported in several studies, including two analyses from multi-center databases (Shah et al., 2011 & Altekruse et al., 2012). Our systematic review is the first in literature to critically summarize these studies and document socio-demographic disparities in HCC treatment utilization. There were noteworthy socio-demographic disparities with the lowest treatment utilization rates in non-Caucasians and patients with non-private insurance.

In regards to racial disparities in African Americans receiving curative treatment, a study found patient-related barriers like personal and cultural beliefs about transplantation, lower socioeconomic status and levels of education (Navaneethan & Singh, 2006). Furthermore, barriers such as physician perceptions, insufficient transplant workup, delayed referrals and immunologic mis-matching based on the human leukocyte antigen (HLA) status are all healthcare-related barriers to treatment (Navaneethan & Singh, 2006). Physicians also believed that African Americans were less likely to be evaluated for transplant because of patients' preferences, availability of donors, failure to complete evaluations, comorbid illnesses, patient-physician mistrust or physician bias (Ayanian et al., 2004). Provider-recorded rationales for recommended HCC treatment strategies indicate that a minority of patients had medical contraindications, refused

therapy, or died before treatment (Zaydfudim et al., 2010). Population studies have stressed geographic disparities associated with racial and socioeconomic variations (Sonnenday et al., 2007). Different geographic regions provide varying levels of surgical care for patients of different races (Sonnenday et al., 2007).

In regards to insurance and socioeconomic status, Guidry and colleagues found that African American individuals were more inclined to reach their insurance spending limits more frequently in comparison to Caucasian individuals, and subsequently more likely to lose medical insurance coverage after being diagnosed with cancer (Yu, Sloane, Guo, & Howell, 2006). African American HCC patients are also more likely to have an annual household income of less than \$25,000, and less likely to have Medicare and private health insurance (Yu et al., 2006). Thus, these factors may limit access to more appropriate HCC treatments. Furthermore, previous research has demonstrated that hospitals with a high proportion of Medicaid patients are less likely to achieve a high-performance status (Werner, Goldman, & Dudley, 2008). Medicaid patients are also more likely to not be well educated and have language barriers. Consequently, health literacy may play a vital role in HCC treatment disparities.

Many studies in literature describe racial and socioeconomic disparities in relation to survival of patients with HCC (Artinyan et al., 2010). Patients who are elderly, non-Caucasian, and do not have private insurance suffer from significantly lower rates of HCC treatment when compared to their counterparts. The roles of patient attitudes, co-morbid conditions, and barriers to assessing appropriate HCC treatment have not been clearly evaluated. It is important to note that current studies were all performed in highly-uniform populations, with the majority of patients being male, Caucasian, and insured.

Thus, studies in racially and socioeconomically diverse patient populations are imperative for validation.

### *Limitations*

The primary limitation of our meta-analysis was the incapability to identify causality due to the nature of a retrospective analysis of secondary data. Current studies did not provide explanations as to why early stage HCC patients did not receive appropriate curative treatment. Particular rationales as to why there is significant underutilization of treatment in HCC patients who are diagnosed at an early stage are necessary to identify intervention targets that can increase curative treatment rates and prolong survival. Moreover, all studies have evaluated homogenous populations, and it is important to stress that HCC treatment studies must be done on racially and socioeconomically diverse populations.

One other limitation is that many current studies of HCC treatment patterns are limited since they utilize multi-center databases. For instance, many HCC treatment studies used the multi-center SEER database, which includes only specific geographic regions and limited socio-demographic data and may not be an accurate portrayal of HCC treatment underutilization in the United States (Zak, Rhoads, & Visser, 2011). Many HCC treatment studies also used Medicare data, which only tracks patients aged 65 years and older and thus excludes younger patients receiving surgical treatment for HCC (Zak, Rhoads, & Visser, 2011). Moreover, these analyses commonly do not distinguish racial groups, SES, expected source of payment or the type of admitting hospital (Zak, Rhoads, & Visser, 2011). These socio-demographic factors may potentially play a vital role in affecting utilization of HCC treatment.

### *Future Practice and Policy Implications*

Disparities in cancer care, especially hepatocellular carcinoma, are the subject of great concern in health care. Countless studies have documented that individuals with specific racial and ethnic minorities, as well as individuals from lower SES groups have greater cancer risk and worse outcomes (Ward et al., 2004). Policy implications regarding surveillance programs for patients at risk of developing hepatocellular carcinoma are highly recommended so patients can be diagnosed at an early stage and curative options are available. Moreover, surveillance practice and policy implications for hepatocellular carcinoma targeting non-Caucasians is highly recommended, as utilization rates for screening and treatment are extremely low (Singal et al., 2012).

## CHAPTER 7

## CONCLUSION

HCC treatment is a complex process, with multiple steps that are prone to failure (Taplin & Rodgers, 2010). Providers must be able to identify and diagnosis HCC patients at an early stage, be able to refer patients for appropriate curative treatment, the healthcare system must schedule the procedure(s), and patients must comply with treatment recommendations. Current studies in literature fail to address in-depth analysis as to what factors mediate or moderate underutilization of HCC treatment. Improved access to care for non-Caucasian patients and Medicaid and uninsured patients may be beneficial and prolong survival. Future research should investigate correlates to identify appropriate intervention strategies.

In summary, HCC treatment is underutilized in the United States, with a pooled treatment rate of only 44.4%. Further, only 21.8% of HCC patients received curative treatment, but 57.8% of early stage HCC patients received appropriate curative treatment. Although the pooled treatment rate for early HCC patients receiving curative treatment is somewhat better, only about four-sevenths receive appropriate care. There are significant socio-demographic disparities with the lowest treatment rates in non-Caucasians and non-private insurance patients. Further studies are needed to explore reasons for treatment underutilization, particularly in these disadvantaged subgroups. These studies will be the first essential step in identifying appropriate intervention targets to increase appropriate HCC treatment and curative treatment rates and reduce socio-demographic disparities.

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