Published in final edited form as:
Aliment Pharmacol Ther. 2013 October ; 38(7): 703–712. doi:10.1111/apt.12450.

Meta analysis: underutilization and disparities of treatment among patients with hepatocellular carcinoma in the united states

Debra Tan, MPH[1], **Adam Yopp, MD**[2,3], **Muhammad S Beg**[3,4], **Purva Gopal**[5], and **Amit G. Singal, MD MS**[3,4,6]

[1]School of Public Health, UNT Health Science Center, Fort Worth, TX

[2]Department of Surgery, University of Texas Southwestern, Dallas, TX

[3]Harold C. Simmons Cancer Center, UT Southwestern Medical Center, Dallas, TX

[4]Department of Internal Medicine, UT Southwestern Medical Center, Dallas, TX

[5]Department of Pathology, University of Texas Southwestern, Dallas, TX

[6]Department of Clinical Sciences, University of Texas Southwestern, Dallas, TX

Abstract

Background—Despite wide availability of treatment options for hepatocellular carcinoma (HCC), several studies have suggested underutilization in clinical practice.

Aims—To quantify utilization rates for HCC treatment among patients with HCC in the United States and summarize patterns of association between utilization rates and patient socio-demographic characteristics.

Methods—We performed a systematic literature review using the Medline database from January 1989 through March 2013. Two investigators independently extracted data on patient populations, study methods, and results using standardized forms. Pooled treatment rates for any treatment and curative treatment, with 95% confidence intervals, were calculated. Pre-specified subgroup analysis was performed to identify patient-level correlates of treatment utilization.

Results—We identified 24 studies that met inclusion criteria. The pooled rates of any treatment and curative treatment were 52.8% (95%CI 52.2-53.4%) and 21.8% (95%CI 21.4-22.1%) respectively. Among patients diagnosed at an early stage, the pooled curative treatment rate was

Correspondence: Amit G. Singal, M.D., M.S. Dedman Scholar of Clinical Care Division of Digestive and Liver Diseases University of Texas Southwestern 5959 Harry Hines Blvd, POB 1, Suite 420 Dallas TX 75390-8887 Tel: 214-645-6029 Fax: 214-645-6294 amit.singal@utsouthwestern.edu.

Author Contributions

Debra Tan involved in acquisition of data, interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content.

Adam Yopp involved in study concept and design, interpretation of data, and critical revision of the manuscript for important intellectual content.

Muhammad Beg involved in critical revision of the manuscript for important intellectual content.

Purva Gopal involved in critical revision of the manuscript for important intellectual content.

Amit Singal involved in study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, statistical analysis, and study supervision. Amit Singal is the guarantor of the article.

All authors approved the final version of the manuscript.

Conflicts of Interest: Amit Singal and Adam Yopp are on the Speaker Bureau for Bayer and Onyx Pharmaceuticals. None of the other authors have any conflicts of interest relevant to this manuscript to disclose.

59.0% (95%CI 58.1-59.9%). Elderly, non-Caucasians and patients of low socioeconomic status had lower treatment rates than their counterparts.

Conclusions—Rates of HCC treatment in the United States, including curative treatment rates among patients detected at an early stage, are disappointingly low. Future efforts should focus on identifying appropriate intervention targets to increase treatment rates and reduce socio-demographic disparities.

Keywords

Hepatocellular carcinoma; treatment; socio-demographic disparities; United States

INTRODUCTION

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide and is one of the leading causes of death among patients with cirrhosis[1]. Its incidence in the United States is increasing due to the current epidemic of non-alcoholic fatty liver disease and hepatitis C virus (HCV) infection[1]. Prognosis for patients with HCC depends on tumor stage, degree of underlying liver dysfunction, and patient performance status, with curative therapies only available for patients detected at an early stage. Patients detected at an early stage can achieve 5-year survival rates of 70% with transplant or resection, whereas those with advanced HCC are only eligible for palliative treatments and have a median survival of less than one year[2, 3].

HCC disproportionately affects disadvantaged populations, with the highest age-specific incidence occurring among minorities. HCC rates are two times higher in Asian Americans than African Americans, whose rates are two times higher than those in Caucasians[1]. Elderly, African Americans and patients of low socioeconomic status (SES) have poorer survival rates than their counterparts[4, 5]. The reasons for differences in survival are likely multi-factorial, involving a combination of medical, financial, and social factors. Several studies have reported lower rates of surveillance, whereas others have postulated biologic differences in tumor behavior, and others have reported differential rates of HCC treatment [4, 6-8]. The aims of our study were to 1) quantify utilization rates for any treatment and curative treatment among patients with HCC in the United States and 2) to summarize patterns of association between utilization rates and patient socio-demographic characteristics.

METHODS

Literature Search

We conducted a computer-assisted search with the Ovid interface to Medline to identify relevant published articles. We searched the Medline database from January 1, 1989 through March 1, 2013 with the following keyword combinations: [treat$ OR therap$ OR transplant $ OR resect$ OR surg$ OR ablat$ OR RFA OR chemo$ OR emboliz$ OR TACE OR nexavar OR sorafenib] AND [hepatocellular ca$ OR liver ca$ or HCC]. Given our focus on current utilization of treatment within the United States, our search was limited to human studies published in English after 1989. Manual searches of references from relevant articles were performed to identify studies that were missed by our computer-assisted search. Finally, consultation with expert hepatologists was performed to identify additional references or unpublished data.

Study Selection

One investigator (D.T.) reviewed all publication titles of citations identified by the search strategy. Potentially relevant studies were retrieved, and selection criteria were applied. The articles were independently checked for inclusion (D.T. and A.S.) and disagreements were resolved through consensus. Inclusion criteria included: (i) cohort studies that described receipt of HCC treatment in patients with HCC, ii) studies from the United States after 1989 so as to be representative of current delivery of care, and (iii) available data regarding socio-demographic information for patients who did and did not receive treatment. We excluded: i) clinical trials with a protocol and/or extra nursing support as they do not evaluate delivery of care in a real-world clinical setting, ii) studies conducted outside the United States, and iii) survey studies because of high rates of over-reporting by physicians. Additional exclusion criteria included non-English language, non-human data, and lack of original data. If publications used the same patient cohort, data from the most recent manuscript were included.

Data Extraction

Two reviewers (D.T. and A.S.) independently extracted required information from eligible studies using standardized forms. A third investigator (A.Y.) was available to resolve any discrepancies. Data were collected on study design, geographic location and date of the study, number of patients with cirrhosis, number of HCC patients, and number of patients with early stage HCC in each study. We recorded definitions of any treatment, curative treatment, and early stage HCC for each study. Finally, data were collected on age, gender, race/ethnicity, and SES (insurance status and income) for those who received treatment and those who failed to receive treatment. Authors were contacted as necessary for missing information.

Clinical End Point and Statistical Analysis

Our primary study outcomes were rates of any treatment and rates of curative treatment among patients with HCC. Rates of any treatment included curative treatments (transplant, resection, or radiofrequency ablation) and non-curative treatments (chemoembolization, radiation-based therapy, or systemic therapy). Studies that only reported rates of transplantation, resection, and/or radiofrequency ablation were included in analyses for receipt of curative treatment but not those for receipt of any treatment.

The proportion of patients who received treatment was derived for each study, and 95% confidence intervals were calculated using the adjusted Wald method. A weighed pooled estimate of treatment rates was 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. Sensitivity analyses were planned for the following predefined variables: 1) the study cohort (single-center vs. multi-center administrative database), 2) the proportion of patients with early stage HCC, 3) the definition of curative treatment, and 4) introduction of the Milan criteria for liver transplantation in 1996. All data analysis was performed using Stata 11 (StataCorp, College Station, TX).

RESULTS

Literature Search

The computer-assisted search yielded 22280 potentially relevant articles. After initial review, 264 titles were potentially appropriate, and these abstracts were reviewed. Fifty-seven publications underwent full-text review, and 34 were excluded. Sixteen of these articles were excluded as they were repeat analyses using the same cohort as other studies,

eleven were not related to receipt of HCC treatment, four did not have extractable data, and three did not have any original data. One additional relevant article was identified through recursive literature searches. The remaining twenty-four studies met all inclusion criteria[9-32] (Supplemental Figure, Table 1).

Treatment Utilization

There were 16 studies, with a total of 24237 patients, which assessed receipt of any treatment, including both curative and non-curative treatments, among patients with HCC. Rates of treatment ranged from 28% to 85% among studies, with a pooled treatment rate of 52.8% (95%CI 52.2-53.4%) (Figure 1). We evaluated potential sources of heterogeneity through pre-planned subgroup analysis. The pooled treatment rate was 49.1% (95%CI 48.4 – 49.8%) among the 19489 patients in the three multi-center studies, which was significantly lower than the 72.0% (95%CI 70.7 – 73.3%) treatment rate among the 13 single-center studies, which contained a total of 4748 HCC patients ($p<0.001$). Among the multi-center studies, the study by Sanyal and colleagues reported substantially higher treatment rates than the other two studies. Given this study used insurance claims data, untreated patients who did not receive hospice may not have been fully captured. If this study was removed, the pooled treatment rate of the two remaining multi-center studies was only 38.5% (95%CI 37.7-39.3%).

Utilization of Curative Treatment

There were 23 studies, with a total of 50769 patients, which assessed receipt of curative treatment among patients with HCC. Rates of curative treatment ranged from 14% to 51% among studies, with a pooled treatment rate of 21.8% (95%CI 21.4-22.1%) (Figure 2). Once again, we found substantial heterogeneity between studies, which was explored though sensitivity and subgroup analyses. We first performed a sensitivity analysis based on introduction of the Milan criteria for liver transplantation. When excluding the studies by Stuart and Cance, which both exclusively included cohorts prior to 1996, the pooled treatment rate was 22.5% (95%CI 22.1-22.9%). We next explored heterogeneity through subgroup analyses. The pooled curative treatment rate was 20.8% (95%CI 20.5 – 21.2%) among 45244 patients in the six multi-center studies, which was significantly lower than the 29.4% (95%CI 28.2 – 30.7%) curative treatment rate among the 17 single-center studies, which contained a total of 5525 HCC patients ($p<0.001$). We also performed a subset analysis, based on the definition of curative treatment. Studies that included transplant, resection, and RFA as curative treatments had a pooled curative treatment rate of 22.2% (95%CI 21.8-22.6%) compared to a pooled rate of 19.8% (95%CI 19.0-20.6%) among studies that only included surgical treatment (liver transplantation and/or resection) ($p<0.001$).

Eighteen of the studies reported the number of patients with early HCC. Of the 32884 HCC patients in these studies, 12455 (37.9%) had early stage HCC. The pooled curative treatment rate among patients with early stage HCC was 59.0% (95%CI 58.1-59.9%) (Figure 3). When excluding the two studies by Stuart and Cance, the pooled treatment rate was 54.9% (95%CI 54.0-55.9%). Only three studies defined early stage with the Barcelona Clinic Liver Cancer (BCLC) staging system, while an additional 8 studies used Milan criteria. The other seven studies used a variety of definitions including the American Joint Committee on Cancer (AJCC) or Tumor Node Metastases (TNM) staging systems. The pooled curative treatment rate among studies using the BCLC or Milan criteria was 72.4% (95%CI 69.9-74.8%), which was significantly higher than the pooled curative treatment rate of 56.7% (95%CI 55.8-57.6%) among studies using other definitions ($p<0.001$).

Correlates of HCC Treatment

Several patient factors are associated with higher utilization rates for HCC treatment, but heterogeneity in the reporting of these associations precluded pooling of the data.

Age—Older age was a consistent negative predictor of HCC treatment, with five studies reporting higher treatment rates in younger patients[17, 19, 22, 29, 30]. Most studies lacked sufficient data to adjust for potential differences in tumor stage at presentation[19, 22, 30]. However, Kozyreva and colleagues found patients older than 70 years were significantly less likely to receive any treatment than younger patients (36.8% vs. 22.9%, p=0.01) despite having similar tumor stage (p=0.95) and liver function as younger patients (Child A 57.9% vs. 56.7%)[17].

Gender—The majority of studies that evaluated the impact of gender found no difference in treatment rates between males and females[16, 22, 29, 30]. The study by Zaydfudim and colleagues was the only that suggested differential treatment rates by gender[31]. They found that females had a 1.78-odds (95%CI 1.15-2.76) of undergoing surgical treatment, after adjusting for age, race, insurance status, and tumor stage.

Race/Ethnicity—Five included studies demonstrated disparities in HCC treatment utilization, particularly that of curative treatments, according to race[11, 22, 27, 29, 30]. Studies by Zak and Harrison reported lower treatment rates among African American patients but lacked sufficient data to adjust for differences in tumor stage and/or liver function[11, 30]. Similarly, Shah and colleagues found higher treatment rates among Asian patients using the SEER-Medicare database, but it is unknown if this is related to differential rates of underlying cirrhosis[22]. Yu and colleagues found African Americans were significantly less likely to receive a transplant than Caucasian patients (OR 0.03, 95%CI 0.00 – 0.37) after adjusting for confounders including age, insurance status, and tumor stage but did not find a significant association with Hispanic ethnicity (OR 0.42, 95%CI 0.09 – 2.08)[29]. Similarly, Wong and colleagues found that Pacific Islanders and Filipinos who were detected at an early stage were significantly less likely to undergo liver transplant than Caucasians (10.0% vs. 38.0%)[27].

Socioeconomic Status—The impact of SES on HCC treatment utilization has only been evaluated in four studies[22, 29-31]. Several other studies evaluated patients with insurance or easy access to health care and therefore were unable to determine the impact of SES on treatment utilization[9, 18, 19]. There was a consistent effect of higher treatment rates among patients with private insurance compared to patients without insurance or those with Medicare/Medicaid. In the Tennessee Cancer Registry, both uninsured patients (OR 0.05, 95%CI 0.01-0.37) and those with Medicaid (OR 0.32, 95%CI 0.15-0.69) were significantly less likely to receive surgical therapy than those with private insurance, after adjusting for age, gender, race, and tumor stage[31]. Yu and colleagues reported similar results, with privately insured patients significantly more likely to receive liver transplantation (OR 22.07, 95%CI 2.67-182.34), independent of tumor stage[29].

DISCUSSION

Despite strong evidence demonstrating HCC treatment significantly improves survival, our meta-analysis highlights that many patients with HCC fail to receive treatment in clinical practice. We found less than one-fourth of patients with HCC undergo curative treatment, and nearly 50% do not receive any treatment. The low rates of curative treatment are in part related to diagnoses at an advanced stage; however, more than one-third of patients diagnosed at an early stage do not receive curative treatment. Our study also highlights the

presence of significant socio-demographic disparities, with the lowest treatment rates among non-Caucasians and patients of low SES.

The transition from diagnosis to treatment is a complex process, involving several steps and interfaces with multiple new providers[33]. Providers must be aware of the cancer diagnosis, complete the staging work-up, determine the optimal treatment, and finally refer patients to the appropriate consultants[34]. The complex array of potential treatment options, each delivered by a different type of provider, may make this process even more difficult for HCC. These treatment decisions for HCC have become increasingly complex with the availability of novel therapies and the growing use of multimodal and multi-provider treatments. Patients may be asked to make multiple transitions between several providers as various treatment options are considered. A breakdown at any step can result in treatment underutilization and/or treatment delays. Even in the setting of optimal processes, patients may choose to forgo therapy given disinterest, other barriers to care, or perceived excess risk from the treatment. Current studies fail to provide an in-depth analysis to clarify which factors mediate or moderate underutilization of HCC treatment. A multidisciplinary approach involving a team of hepatologists, surgeons, interventional radiologists, radiation oncologists, medical oncologists, and radiologists may improve communication and allow better delivery of optimal treatment[35]. Further research is needed to evaluate the benefits of multidisciplinary care and identify other potential intervention strategies to increase appropriate HCC treatment[36].

Therapeutic choices for HCC are dependent on tumor stage, liver function and performance status[2]. Although there is not one universally accepted staging system, the BCLC staging system has been incorporated into guidelines and is the most widely used, given that it combines all three features[37, 38]. However, it is important to note that most studies, particularly those from large administrative databases, provide limited data regarding liver function or patient performance status. This lack of data precludes an accurate assessment of the appropriateness of lack of treatment. For example, it would be appropriate to not treat a patient with poor functional status, but this would be regarded as treatment underutilization in several studies included in this meta-analysis. Automated data has been demonstrated to underestimate quality of care in other areas, such as HCV-related care, for similar reasons[39]. It is crucial that future studies provide data regarding liver function and patient performance status to better interpret treatment utilization rates.

The low curative treatment rates appear to be related to high rates of late stage diagnosis, as only 40% of patients are diagnosed at an early stage despite the availability of efficacious surveillance tools[40]. When examining the subgroup of patients detected at an early stage, curative treatment rates are closer to 57-73%, depending on the definition of early stage HCC. The low rates of early tumor detection are multi-factorial, with surveillance underuse and suboptimal effectiveness of surveillance tools in clinical practice both playing a large role[41-44]. Patients diagnosed incidentally or symptomatically are significantly more likely to be diagnosed at an advanced stage, when curative options are no longer an option[23, 45]. Interventions are needed to improve surveillance rates, which can increase early tumor detection, facilitate higher rates of curative treatment, and thereby improve overall survival[36, 46].

Racial and socioeconomic disparities have been well described in the survival of patients with HCC[4]. Although prior studies have suggested difference in tumor biology and/or surveillance rates, our meta-analysis highlights the importance of socio-demographic disparities in treatment utilization. Patients who are elderly, non-Caucasian, and of low SES suffer from significantly lower HCC treatment rates than their counterparts. While current studies suggest an association between socio-demographic factors and HCC treatment, none

have explored why treatment is not being performed in these subgroups. The roles of patient attitudes, co-morbid conditions, and barriers to accessing care have not been clearly evaluated. For example, elderly patients and patients of low SES may have lower treatment rates due to difficulty accessing medical care or a higher rate of co-morbid conditions. Similarly, race and SES are often highly correlated so independent causal effects can be difficult to identify.

The primary limitation of our meta-analysis was our inability to identify specific reasons for underutilization of HCC treatment. Current studies did not distinguish cases in which physicians failed to order treatment, cases in which treatment was not appropriate (e.g., patients with significant co-morbidities or those with Child C cirrhosis who were not transplant candidates), and those in which patients were non-adherent after treatment was recommended. Studies evaluating the reasons behind treatment under-utilization are necessary to identify intervention targets that can increase treatment rates.

Our meta-analysis was also limited by clinical heterogeneity among studies, such as the different operational definitions used for early stage disease and/or curative treatment. This variability in definitions makes it difficult to compare treatment rates across studies. Clear consistent definitions and measures are necessary to better quantify and interpret HCC treatment rates[47]. This clinical heterogeneity may also relate to other etiologies such as inter-center variation in treatment rates, similar to what has been reported for HCC surveillance[43]. Inter-center variation in treatment rates may be even larger given the selected availability of some treatments, such as liver transplantation. Another possible explanation for clinical heterogeneity is changes in treatment expertise over time; however, we did not see any evidence of a time trend on subgroup analysis.

In summary, HCC treatment is underutilized nationally, with nearly 50% failing to receive any treatment and less than 25% receiving curative treatment. Even among patients diagnosed at an early stage, more than 1 in 3 fail to receive curative treatment. There are also significant socio-demographic disparities with the lowest treatment rates in non-Caucasians and patients of low SES. Further studies are needed to explore reasons for the underutilization of treatment, particularly in these disadvantaged subgroups. These studies will be the first crucial step in identifying appropriate intervention targets to increase HCC treatment rates and reduce socio-demographic disparities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support: This work was conducted with support from Center for Translational Medicine, NIH/NCATS Grant Number KL2TR000453 and an ACG Junior Faculty Development Award. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Center for Translational Medicine, UT Southwestern Medical Center and its affiliated academic and health care centers, the National Center for Advancing Translational Sciences, or the National Institutes of Health.

REFERENCES

1. El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. Gastroenterology. 2007; 132:2557–76. [PubMed: 17570226]
2. Bruix J, Sherman M. Management of Hepatocellular Carcinoma: An Update. Hepatology. 2010; 53:1–35.

3. Lopez PM, Villanueva A, Llovet JM. Systematic review: evidence-based management of hepatocellular carcinoma--an updated analysis of randomized controlled trials. Aliment Pharmacol Ther. 2006; 23:1535–47. [PubMed: 16696801]
4. Artinyan A, Mailey B, Sanchez-Luege N, Khalili J, Sun CL, Bhatia S, Wagman LD, Nissen N, Colquhoun SD, Kim J. Race, ethnicity, and socioeconomic status influence the survival of patients with hepatocellular carcinoma in the United States. Cancer. 2010; 116:1367–77. [PubMed: 20101732]
5. Decker KM, Harrison M, Chateau D. Influence of direct referrals on time to diagnosis after an abnormal breast screening result. Cancer Detect Prev. 2004; 28:361–7. [PubMed: 15542262]
6. Sloane D, Chen H, Howell C. Racial disparity in primary hepatocellular carcinoma: tumor stage at presentation, surgical treatment and survival. J Natl Med Assoc. 2006; 98:1934–9. [PubMed: 17225837]
7. Davila JA, El-Serag HB. Racial differences in survival of hepatocellular carcinoma in the United States: a population-based study. Clin Gastroenterol Hepatol. 2006; 4:104–10. quiz 4-5. [PubMed: 16431312]
8. Siegel AB, McBride RB, El-Serag HB, Hershman DL, Brown RS Jr. Renz JF, Emond J, Neugut AI. Racial disparities in utilization of liver transplantation for hepatocellular carcinoma in the United States, 1998-2002. Am J Gastroenterol. 2008; 103:120–7. [PubMed: 18005365]
9. Altekruse SF, McGlynn KA, Dickie LA, Kleiner DE. Hepatocellular carcinoma confirmation, treatment, and survival in surveillance, epidemiology, and end results registries, 1992-2008. Hepatology. 2012; 55:476–82. [PubMed: 21953588]
10. Cance WG, Stewart AK, Menck HR. The National Cancer Data Base Report on treatment patterns for hepatocellular carcinomas: improved survival of surgically resected patients, 1985-1996. Cancer. 2000; 88:912–20. [PubMed: 10679662]
11. Harrison LE, Reichman T, Koneru B, Fisher A, Wilson D, Dela Torre A, Samanta A, Korogodsky M. Racial discrepancies in the outcome of patients with hepatocellular carcinoma. Arch Surg. 2004; 139:992–6. [PubMed: 15381619]
12. Jan T, Medvedev S, Cannon RM, Saggi B, McGee J, Paramesh A, Killackey M, Shores NJ, Slakey DP, Balart L, Buell JF. Racial disparity and their impact on hepatocellular cancer outcomes in inner-city New Orleans. Surgery. 2012; 152:661–6. discussion 666-7. [PubMed: 22935095]
13. Jou JH, Chen PH, Jazwinski A, Bouneva I, Smith AD, Muir AJ. Rates of surveillance and management of hepatocellular carcinoma in patients evaluated at a liver transplant center. Dig Dis Sci. 2010; 55:3591–6. [PubMed: 20683659]
14. Kemmer N, Neff G, Secic M, Zacharias V, Kaiser T, Buell J. Ethnic differences in hepatocellular carcinoma: implications for liver transplantation. Dig Dis Sci. 2008; 53:551–5. [PubMed: 17562173]
15. Kitisin K, Packiam V, Steel J, Humar A, Gamblin TC, Geller DA, Marsh JW, Tsung A. Presentation and outcomes of hepatocellular carcinoma patients at a western centre. HPB (Oxford). 2011; 13:712–22. [PubMed: 21929672]
16. Kooby DA, Egnatashvili V, Graiser M, Delman KA, Kauh J, Wood WC, Staley Iii CA. Changing management and outcome of hepatocellular carcinoma: evaluation of 501 patients treated at a single comprehensive center. J Surg Oncol. 2008; 98:81–8. [PubMed: 18623039]
17. Kozyreva ON, Chi D, Clark JW, Wang H, Theall KP, Ryan DP, Zhu AX. A multicenter retrospective study on clinical characteristics, treatment patterns, and outcome in elderly patients with hepatocellular carcinoma. Oncologist. 2011; 16:310–8. [PubMed: 21349948]
18. Leykum LK, El-Serag HB, Cornell J, Papadopoulos KP. Screening for hepatocellular carcinoma among veterans with hepatitis C on disease stage, treatment received, and survival. Clin Gastroenterol Hepatol. 2007; 5:508–12. [PubMed: 17382601]
19. Sanyal A, Poklepovic A, Moyneur E, Barghout V. Population-based risk factors and resource utilization for HCC: US perspective. Curr Med Res Opin. 2010; 26:2183–91. [PubMed: 20666689]
20. Sarkar M, Stewart S, Yu A, Chen MS, Nguyen TT, Khalili M. Hepatocellular carcinoma screening practices and impact on survival among hepatitis B-infected Asian Americans. J Viral Hepat. 2012; 19:594–600. [PubMed: 22762144]

21. Schwartz ME, Sung M, Mor E, Fisher A, Popescu I, Fiel I, Sheiner P, Emre S, Guy S, Miller CM. A multidisciplinary approach to hepatocellular carcinoma in patients with cirrhosis. J Am Coll Surg. 1995; 180:596–603. [PubMed: 7749537]
22. Shah SA, Smith JK, Li Y, Ng SC, Carroll JE, Tseng JF. Underutilization of therapy for hepatocellular carcinoma in the medicare population. Cancer. 2011; 117:1019–26. [PubMed: 20945363]
23. Stravitz RT, Heuman DM, Chand N, Sterling RK, Shiffman ML, Luketic VA, Sanyal AJ, Habib A, Mihas AA, Giles HC, Maluf DG, Cotterell AH, Posner MP, Fisher RA. Surveillance for hepatocellular carcinoma in patients with cirrhosis improves outcome. Am J Med. 2008; 121:119–26. [PubMed: 18261500]
24. Stuart KE, Anand AJ, Jenkins RL. Hepatocellular carcinoma in the United States. Prognostic features, treatment outcome, and survival. Cancer. 1996; 77:2217–22. [PubMed: 8635087]
25. Theodoropoulos J, Brooks A. Inconsistency in the management of patients with hepatocellular carcinoma: the need for a strict protocol. Am Surg. 2011; 77:207–14. [PubMed: 21337882]
26. Tong MJ, Chavalitdhamrong D, Lu DS, Raman SS, Gomes A, Duffy JP, Hong JC, Busuttil RW. Survival in Asian Americans after treatments for hepatocellular carcinoma: a seven-year experience at UCLA. J Clin Gastroenterol. 2010; 44:e63–70. [PubMed: 19745756]
27. Wong LL, Hernandez B, Kwee S, Albright CL, Okimoto G, Tsai N. Healthcare disparities in Asians and Pacific Islanders with hepatocellular cancer. Am J Surg. 2012; 203:726–32. [PubMed: 22227170]
28. Yang JD, Harmsen WS, Slettedahl SW, Chaiteerakij R, Enders FT, Therneau TM, Orsini L, Kim WR, Roberts LR. Factors that affect risk for hepatocellular carcinoma and effects of surveillance. Clin Gastroenterol Hepatol. 2011; 9:617–23. e1. [PubMed: 21459158]
29. Yu JC, Neugut AI, Wang S, Jacobson JS, Ferrante L, Khungar V, Lim E, Hershman DL, Brown RS Jr. Siegel AB. Racial and insurance disparities in the receipt of transplant among patients with hepatocellular carcinoma. Cancer. 2010; 116:1801–9. [PubMed: 20143441]
30. Zak Y, Rhoads KF, Visser BC. Predictors of surgical intervention for hepatocellular carcinoma: race, socioeconomic status, and hospital type. Arch Surg. 2011; 146:778–84. [PubMed: 21422327]
31. Zaydfudim V, Whiteside MA, Griffin MR, Feurer ID, Wright JK, Pinson CW. Health insurance status affects staging and influences treatment strategies in patients with hepatocellular carcinoma. Ann Surg Oncol. 2010; 17:3104–11. [PubMed: 20585872]
32. Kanwal F, Befeler A, Chari RS, Marrero J, Kahn J, Afdhal N, Morgan T, Roberts L, Mohanty SR, Schwartz J, VanThiel D, Li J, Zeringue A, Di'Bisceglie A. Potentially curative treatment in patients with hepatocellular cancer--results from the liver cancer research network. Aliment Pharmacol Ther. 2012; 36:257–65. [PubMed: 22670798]
33. Taplin SH, Clauser S, Rodgers AB, Breslau E, Rayson D. Interfaces across the cancer continuum offer opportunities to improve the process of care. J Natl Cancer Inst Monogr. 2010; 2010:104–10. [PubMed: 20386059]
34. Sussman J, Baldwin LM. The interface of primary and oncology specialty care: from diagnosis through primary treatment. J Natl Cancer Inst Monogr. 2010; 2010:18–24. [PubMed: 20386050]
35. Taplin SH, Rodgers AB. Toward improving the quality of cancer care: addressing the interfaces of primary and oncology-related subspecialty care. J Natl Cancer Inst Monogr. 2010; 2010:3–10. [PubMed: 20386048]
36. Singal AG, Yopp AC, Gupta S, Skinner CS, Halm EA, Okolo E, Nehra M, Lee WM, Marrero JA, Tiro JA. Failure Rates in the Hepatocellular Carcinoma Surveillance Process. Cancer Prev Res (Phila). 2012; 5:1124–1130. [PubMed: 22846843]
37. Camma C, Di Marco V, Cabibbo G, Latteri F, Sandonato L, Parisi P, Enea M, Attanasio M, Galia M, Alessi N, Licata A, Latteri MA, Craxi A. Survival of patients with hepatocellular carcinoma in cirrhosis: a comparison of BCLC, CLIP and GRETCH staging systems. Aliment Pharmacol Ther. 2008; 28:62–75. [PubMed: 18373636]
38. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology. 2011; 53:1020–2. [PubMed: 21374666]
39. Kanwal F, Hoang T, Kramer J, Chrusciel T, El-Serag H, Dominitz JA, Asch SM. The performance of process measures in hepatitis C. Am J Gastroenterol. 2012; 107:1512–21. [PubMed: 22777337]

40. Singal A, Volk ML, Waljee A, Salgia R, Higgins P, Rogers MA, Marrero JA. Meta-analysis: surveillance with ultrasound for early-stage hepatocellular carcinoma in patients with cirrhosis. Aliment Pharmacol Ther. 2009; 30:37–47. [PubMed: 19392863]

41. Singal AG, Conjeevaram HS, Volk ML, Fu S, Fontana RJ, Askari F, Su GL, Lok AS, Marrero JA. Effectiveness of Hepatocellular Carcinoma Surveillance in Patients with Cirrhosis. Cancer Epidemiol Biomarkers Prev. 2012; 21:793–9. [PubMed: 22374994]

42. Davila JA, Morgan RO, Richardson PA, Du XL, McGlynn KA, El-Serag HB. Use of surveillance for hepatocellular carcinoma among patients with cirrhosis in the United States. Hepatology. 2010; 52:132–41. [PubMed: 20578139]

43. Singal AG, Nehra M, Adams-Huet B, Yopp AC, Tiro JA, Marrero JA, Lok AS, Lee WM. Detection of hepatocellular carcinoma at advanced stages among patients in the HALT-C trial: where did surveillance fail? Am J Gastroenterol. 2013; 108:425–32. [PubMed: 23337478]

44. Singal AG, Yopp A, C SS, Packer M, Lee WM, Tiro JA. Utilization of hepatocellular carcinoma surveillance among American patients: a systematic review. J Gen Intern Med. 2012; 27:861–7. [PubMed: 22215266]

45. Trevisani F, De NS, Rapaccini G, Farinati F, Benvegnu L, Zoli M, Grazi GL, Del PP, Di N, Bernardi M. Semiannual and annual surveillance of cirrhotic patients for hepatocellular carcinoma: effects on cancer stage and patient survival (Italian experience). Am J Gastroenterol. 2002; 97:734–44. [PubMed: 11922571]

46. Singal AG, Tiro JA, Gupta S. Improving hepatocellular carcinoma screening: applying lessons from colorectal cancer screening. Clin Gastroenterol Hepatol. 2013; 11:472–7. [PubMed: 23200983]

47. Vernon SW, Briss PA, Tiro JA, Warnecke RB. Some methodologic lessons learned from cancer screening research. Cancer. 2004; 101:1131–45. [PubMed: 15316907]

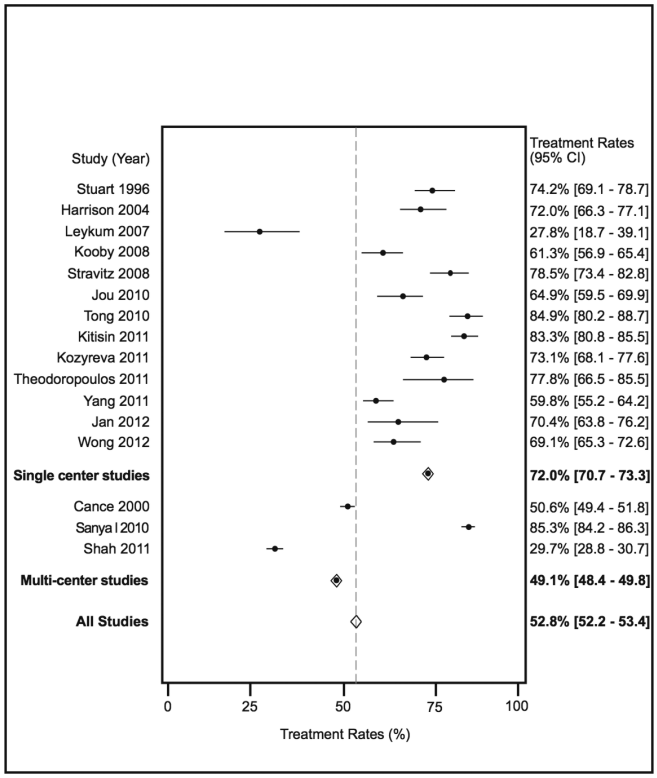

Figure 1.
Treatment Rates for Hepatocellular Carcinoma

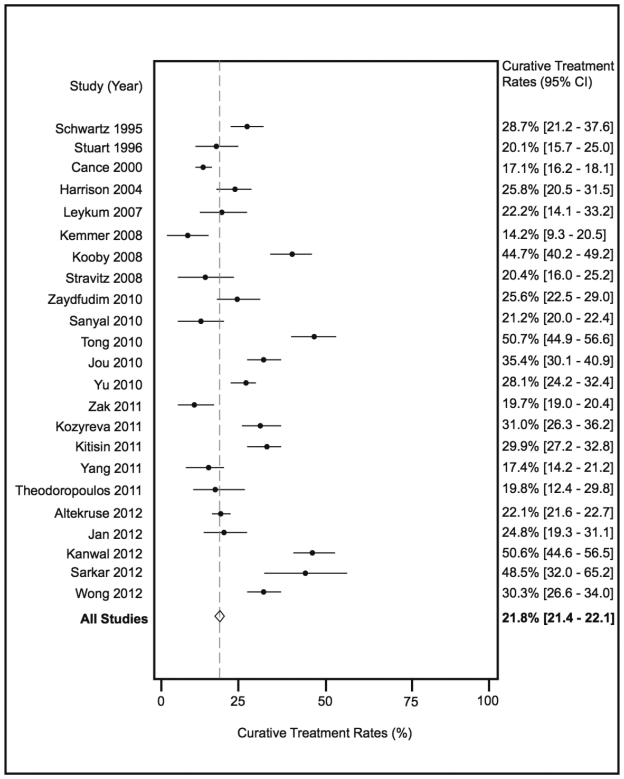

Figure 2.
Rates of Curative Treatment for Hepatocellular Carcinoma

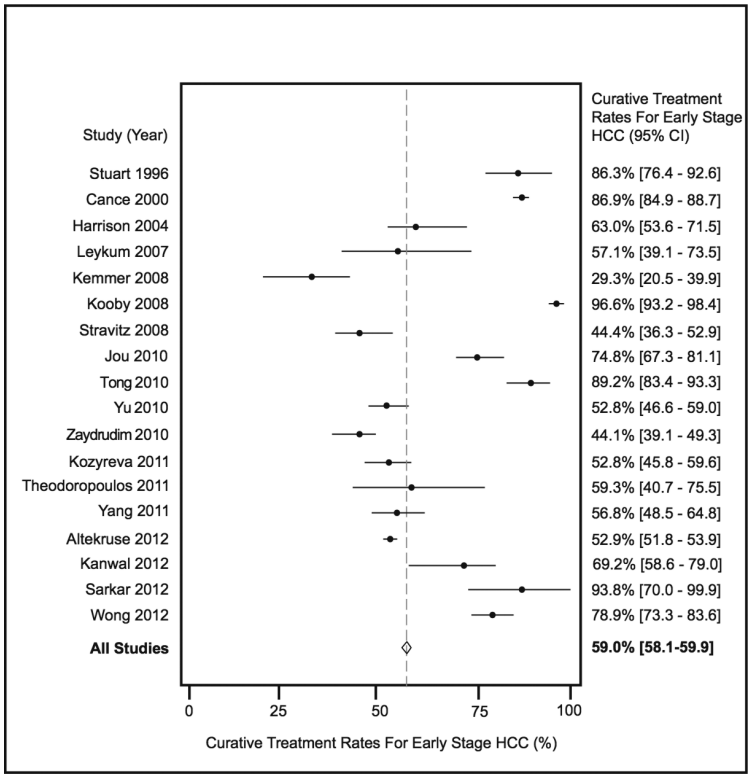

Figure 3.
Curative Treatment Rates among Patients with Early Stage Hepatocellular Carcinoma

Table 1

Characteristics of Studies Assessing Hepatocellular Carcinoma Treatment Utilization

Author, Year	Study Setting	Mean Age (Years)	Gender (% Male)	Race (% Caucasian)	Cirrhosis (%)
Altekruse 2012[9]	SEER-Medicare Database	NR	74	49	NR
Cance 2000[10]	National Cancer Database	60-69	71	60	NR
Harrison 2004[11]	University of Medicine and Dentistry, New Jersey	59	80	61	93
Jan 2012[12]	Tulane University	64	76	67	94
Jou 2010[13]	Duke University	NR	80	68	100
Kanwal 2012[32]	Liver Cancer Research Network	59	76	77	100
Kemmer 2008[14]	University of Cincinnati	57	80	64	100
Kitisin 2011[15]	University of Pittsburgh	62	75	87	84
Kooby 2008[16]	Emory University	60	72	71	82
Kozyreva 2011[17]	Tufts University and Massachusetts General Hospital	62	79	77	90
Leykum 2007[18]	South Texas VA hospitals	55	100	40	79
Sanyal 2010[19]	Marketscan Claims Research Database	63	66	NR	NR
Sarkar 2012[20]	University of California, San Francisco	50-64	78	0	100
Schwartz 1995[21]	Mount Sinai Medical Center	NR	NR	NR	100
Shah 2011[22]	SEER-Medicare Database	75	67	74	55
Stravitz 2008[23]	Virginia Commonwealth University	57	86	63	100
Stuart 1996[24]	Deaconess Health System	64	78	NR	68
Theodoropoulos 2011[25]	Hahnemann University	55	80	47	83
Tong 2010[26]	University of California, Los Angeles	62	78	0	73
Wong 2012[27]	Hawaii Medical Center	62	75	19	74
Yang 2011[28]	Mayo Clinic	62	72	83	83
Yu 2010[29]	Columbia University	60	80	40	NR
Zak 2011[30]	California Cancer Registry	55-64	71	37	NR
Zaydfudim 2010[31]	Tennessee Cancer Registry	61	74	78	NR

NR-Not Reported; SEER- Surveillance, Epidemiology, and End Results; VA-Veterans Administration

Table 2

Treatment Utilization Rates for Hepatocellular Carcinoma

Author, Year	Study Years	Number of HCC Patients	Rates of any HCC Treatment (%)
Altekruse 2012[9]	1998 – 2008	21390	NR
Cance 2000[10]	1985 – 1996	6353	3213 (50.6%)
Harrison 2004[11]	1997 – 2003	264	190 (72.0%)
Jan 2012[12]	2003 – 2011	206	145 (70.4%)
Jou 2010[13]	2002 – 2008	319	207 (64.9%)
Kanwal 2012[32]	2001 – 2007	267	NR
Kemmer 2008[14]	2000 – 2005	169	NR
Kitisin 2011[15]	2000 – 2009	1010	841 (83.3%)
Kooby 2008[16]	1990 – 2004	501	307 (61.3%)
Kozyreva 2011[17]	1998 – 2008	335	245 (73.1%)
Leykum 2007[18]	2000 – 2005	72	20 (27.8%)
Sanyal 2010[19]	2002 – 2008	4406	3757 (85.3%)
Sarkar 2012[20]	1997 – 2008	31*	NR
Schwartz 1995[21]	1998 – 1994	115	NR
Shah 2011[22]	1991 – 2005	8730	2595 (29.7%)
Stravitz 2008[23]	1997 – 2005	297	233 (78.5%)
Stuart 1996[24]	1986 – 1995	314	233 (74.2%)
Theodoropoulos 2011[25]	2001 – 2007	81	63 (77.8%)
Tong 2010[26]	2000 – 2007	278	236 (84.9%)
Wong 2012[27]	1992 – 2009	618	427 (69.1%)
Yang 2011[28]	2007 – 2009	453	271 (55.2%)
Yu 2010[29]	2002 – 2008	462	NR
Zak 2011[30]	1996 – 2006	12148	NR
Zaydfudim 2010[31]	2004 – 2006	680	NR

NR-Not Reported

*Subset of total population with cirrhosis

Table 3

Rates of Curative Treatment for Hepatocellular Carcinoma

Author, Year	Number of Early HCC	Definition of Early HCC	Curative Treatment (%)	Definition Curative Treatment
Altekruse 2012[9]	8940 (41.8%)	Localized	4727 (22.1%)	Resection, OLT and RFA
Cance 2000[10]	1252 (19.7%)	AJCC Stage I-II	1088 (17.1%)	Surgery
Harrison 2004[11]	108 (40.9%)	AJCC Stage I-II	68 (25.8%)	Resection and OLT
Jan 2012[12]	NR	NR	51 (24.8%)	OLT
Jou 2010[13]	151 (47.3%)	BCLC Stage A	113 (35.4%)	Resection, OLT and RFA
Kanwal 2012[32]	76 (28.5%)	BCLC Stage A	135 (50.6%)	Resection, OLT and RFA
Kemmer 2008[14]	82 (48.5%)	Milan Criteria	24 (14.2%)	OLT
Kitisin 2011[15]	NR	NR	302 (29.9%)	Resection, OLT and RFA
Kooby 2008[16]	232 (46.3%)	Milan Criteria	224 (44.7%)	Resection, OLT and RFA
Kozyreva 2011[17]	197 (58.8%)	CLIP Stage I-II	104 (31.0%)	Resection and OLT
Leykum 2007[18]	28 (38.9%)	Milan Criteria	16 (22.2%)	Resection, OLT and RFA
Sanyal 2010[19]	NR	NR	932 (21.2%)	Resection, OLT and RFA
Sarkar 2012[20]	16 (51.6%)	Milan Criteria	15 (48.5%)	Resection, OLT and RFA
Schwartz 1995[21]	NR	NR	33 (28.7%)	Resection and OLT
Shah 2011[22]	3197(36.6%)	AJCC Stage I-II	NR	Resection, OLT and RFA
Stravitz 2008[23]	135 (45.5%)	Milan Criteria	60 (20.4%)	OLT
Stuart 1996[24]	73 (23.2%)	TNM Stage I-II	63 (20.1%)	Resection and OLT
Theodoropoulos 2011[25]	27 (33.3%)	BCLC Stage A	16 (19.8%)	Resection and OLT
Tong 2010[26]	158 (56.8%)	Milan Criteria	141 (50.7%)	Resection, OLT and RFA
Wong 2012[27]	237 (38.3%)	Milan Criteria	187 (30.3%)	Resection and OLT
Yang 2011[28]	139 (30.7%)	Milan Criteria	79 (17.4%)	Resection, OLT and RFA
Yu 2010[29]	246 (53.2%)	AJCC Stage I-II	130 (28.1%)	OLT
Zak 2011[30]	NR	NR	2390 (19.7%)	Resection, OLT and RFA
Zaydfudim 2010[31]	358 (52.6%)	AJCC Stage I-II	158 (23.2%)	Resection, OLT and RFA

AJCC – American Joint Committee on Cancer; BCLC – Barcelona Clinic Liver Cancer; HCC – hepatocellular carcinoma; NR-Not Reported; OLT – Orthotopic liver transplantation; RFA – radiofrequency ablation; TNM – Tumor, Node, Metastases