Published in final edited form as:

J Clin Gastroenterol. 2012 January ; 46(1): . doi:10.1097/MCG.0b013e318224d669.

Utilization and outcomes of palliative therapy for hepatocellular carcinoma: A population-based study in the United States

Jessica A. Davila, PhD, Zhigang Duan, MD, MS, Katherine A. McGlynn, PhD, and Hashem B. El-Serag, MD, MPH

Sections of Health Services Research (Davila, Duan and El-Serag) and Gastroenterology (El-Serag) at the Houston Veterans Affairs Medical Center and Baylor College of Medicine, Houston, Texas; and the Division of Cancer Epidemiology and Genetics (McGlynn), NCI/DHHS

Abstract

Goals—To evaluate the utilization and determinants of receiving palliative treatment for HCC, and its effect on survival.

Background—Palliative treatment for hepatocellular carcinoma (HCC), including transarterial chemoembolization (TACE) and systemic chemotherapy, is available for patients who do not receive potentially curative therapy. The utilization and outcomes of these therapies in clinical practice are unknown.

Study—We conducted a population-based cohort study using Surveillance, Epidemiology, and End-Results registry data linked to Medicare claims of HCC patients >65 years diagnosed during 2000–2005 who did not receive liver transplant, resection, or ablation. The proportions of patients who received TACE or systemic chemotherapy were calculated by tumor stage, liver disease status, and non-HCC co-morbidity. Determinants of receiving palliative therapy were examined in logistic regression models and propensity scores were calculated. Cox proportional hazards models were used to evaluate mortality risk.

Results—We identified 3,163 HCC patients (median age: 75 yrs, 67% men) who did not receive potentially curative treatment. Approximately 12.5% received TACE and 11.0% chemotherapy. In patients with early or intermediate stage HCC, no liver decompensation, and little or no co-morbidity, only 22.8% received TACE and 13.8% chemotherapy. Median survival was significantly higher among patients who received TACE (14.0 months) compared to chemotherapy (5.0 months) or no therapy (2.0 months). A significant reduction in overall mortality was observed for TACE (54%) and chemotherapy (33%).

Conclusions—Utilization of palliative treatment for HCC is low, which could not be explained by clinical features. However, misclassification could have occurred due to the data source. Receipt of TACE or systemic chemotherapy was associated with a reduction in mortality.

Keywords

Hepatocellular carcinoma; palliative treatment; chemotherapy

Corresponding Author: Jessica A. Davila, Ph.D., The Michael E. DeBakey VA Medical Center, 2002 Holcombe Blvd. (152), Houston, TX 77030, Phone (713) 794-8699, Fax (713) 748-7359, jdavila@bcm.tmc.edu.

Conflicts of Interest: No conflicts of interest exist for Drs. Davila, Duan, McGlynn, or El-Serag.

INTRODUCTION

The incidence of hepatocellular carcinoma (HCC) in the United States has tripled during the past 20 years [1–2]. It is estimated that more than 15,000 cases occur annually; approximately 60% of which occur in persons 65 and older [3]. Most of the increase in HCC is attributed to hepatitis C virus (HCV) infection acquired several decades earlier and a continued rise in the number of HCC cases is expected [4]. Potentially curative treatments for HCC including surgical resection, liver transplant, and local ablation can be applied to less than 20% of all HCC cases, specifically those who have early stage disease, compensated liver disease and little co-morbidity [5].

The majority of patients currently diagnosed with HCC have intermediate or advanced stage disease. For these patients, palliative treatment options include transarterial chemoembolization (TACE) and systemic chemotherapy. TACE has been shown in some randomized controlled trials to be associated with a moderate short-term survival benefit compared to no treatment or 5-fluorouracil alone, and it has been accepted and recommended as a palliative therapy for HCC [6]. Multiple systemic chemotherapy agents have also been evaluated in patients with advanced HCC, but until sorafenib was introduced in 2006, there was little consistent evidence to support the efficacy of single or combination chemotherapy.

In the United States, the degree to which palliative therapies are used in clinical practice is unclear. The increasing incidence of HCC combined with several recent developments in the diagnosis and treatment of HCC may lead to gaps in clinical care. To evaluate the utilization of palliative therapies in a large, representative sample of patients with HCC, we have used data obtained from the linked Surveillance, Epidemiology, and End-Results (SEER)-Medicare program to examine the utilization and determinants of receiving palliative therapy for HCC and its effect on survival.

METHODS

Data source

The SEER-Medicare dataset is SEER registry data linked with Medicare claims. Since 2000, the SEER-Medicare data files have contained information on incident cancer cases from 16 cancer registries in eight states (Connecticut, Hawaii, Iowa, Kentucky, Louisiana, New Jersey, New Mexico, and Utah) and nine metropolitan areas (Atlanta, Greater California, Detroit, Los Angeles, San Francisco/Oakland, San Jose-Monterey, Seattle-Puget Sound, and Rural Georgia). The catchment area for the SEER registries included in the SEER-Medicare linkage currently accounts for over 25% of the population in the United States [7].

We used several data files from the SEER-Medicare program, including the Patient Entitlement and Diagnosis Summary (PEDSF), Medicare Provider Analysis and Review (MedPAR), Physician/Supplier File, and the Outpatient Standard Analytic File (SAF). PEDSF contains information on patient demographics, tumor features, and Medicare enrollment. MEDPAR contains inpatient hospital and skilled nursing facility stay records for services reimbursed through Medicare Part A benefits; information available from this file includes hospital admission and discharge dates, up to 10 diagnosis and procedure codes, and dates of each diagnosis and procedure. Physician/Supplier File and SAF are subsets of the National Claims History (NCH) file for services reimbursed through Medicare Part B benefits; these files contain information on outpatient care including dates of service, diagnoses, procedures, and place of service. The study data ended on December 31, 2007.

Study population

We identified all patients age 66 years and older diagnosed with HCC in any of the 16 SEER registries during 2000–2005 who did not receive potentially curative therapy, namely liver transplant, surgical resection, or ablation. *International Classification of Diseases-Oncology* (ICD-O) morphology code 8170 was used to identify patients with possible HCC. Among those with ICD-O code 8170, we selected those with diagnostically confirmed HCC (positive histology, cytology, laboratory test/marker, direct visualization or positive radiology tests). Only patients with continuous enrollment in Medicare Parts A and B for 1-year prior to and following their HCC diagnosis were eligible for inclusion in the study cohort. We excluded patients enrolled in health maintenance organizations (HMOs) 1-year prior to and following their HCC diagnosis because HMO plans are not required to submit individual claims to the Centers for Medicare and Medicaid Services [7]. Patients were also excluded if they had a previous cancer diagnosis or were diagnosed at autopsy.

HCC treatment

TACE and systemic chemotherapy were identified by the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) and Current Procedure Terminology (CPT) codes in the Medicare claims files. (see Appendix) TACE was defined by the presence of at least one ICD-9-CM or CPT code for embolization with an ICD-9-CM or CPT code indicative of chemotherapy within 30-days. Systemic chemotherapy was identified by the presence of an ICD-9-CM or CPT code for chemotherapy in the absence of an embolization code within 30-days. Specific systemic chemotherapy agents were also identified using CPT codes.

Patient characteristics

We collected information on year of HCC diagnosis (2000–2005), age, gender, and race as well as education and income using data obtained from the US Census files that correspond to patient residence at the zip-code level. We also collected information on the presence of cirrhosis, HCV, hepatitis B virus (HBV), and alcoholic liver disease, as well as identified medical conditions used to calculate the Klabunde co-morbidity index score [8]. Several indicators of liver disease severity, including the presence of ascites, varices, and encephalopathy were captured. This information was collected during the 1-year prior to and 1-year following the HCC diagnosis date. Laboratory results are not available from this data source.

Stage of HCC at diagnosis was categorized as early, intermediate or advanced based on two distinct variables available in the SEER database, namely tumor size and historic stage (localized, regional, distant, unknown). Early stage included patients with (1) tumor size 0–3cm and historic stage localized, regional, or unknown; or (2) localized historic stage and missing tumor size. Intermediate HCC included patients with tumor size 3–5cm and historic stage localized, regional, or unknown. Advanced HCC included patients with (1) any tumor size and distant historic stage or (2) tumor size >5cm and any historic stage.

Statistical analysis

Patient treatment status was categorized based on the most aggressive treatment received within the 12-months following the HCC diagnosis date (TACE>systemic chemotherapy>no therapy). Treatment categories were mutually exclusive. We examined several demographic and clinical features as potential determinants of receiving TACE, systemic chemotherapy, or no HCC specific palliative therapy. Multinomial logistic regression analyses were used to examine these associations. Outcomes of this model were receipt of TACE or systemic chemotherapy vs. no therapy.

The survival time was calculated from the date of HCC diagnosis to the date of death or end of the follow-up period (December 31, 2007). We calculated 1- and 3-year survival rates stratified by HCC therapy using a Kaplan-Meier analysis. Cox proportional hazards models were used to examine the effect of therapy type, while adjusting for year of diagnosis, age, gender, race, geographic region, income, HCC risk factors, co-morbidity, indicators of liver disease severity, and HCC stage at diagnosis. The proportional hazards assumption was tested and satisfied. To minimize potential selection bias, two propensity scores (receipt of TACE, receipt of systemic chemotherapy) were calculated using the previously described multivariate logistic regression models. Both scores were adjusted for in the Cox proportional hazards models.

Odds ratios (or hazards ratios for Cox regressions) and 95% confidence intervals were calculated for each parameter estimate [9]. All data manipulation and statistical analyses were performed using SAS 9.1 (SAS Institute Inc., Cary, NC).

The study protocol was approved by the Institutional Review Board of Baylor College of Medicine and the office of Human Subjects Research of the National Institutes of Health.

RESULTS

We identified 3,163 patients diagnosed with HCC during 2000–2005 who did not receive potentially curative treatment and fulfilled the inclusion and exclusion criteria for the study. The median age at HCC diagnosis was 75 years. Approximately two-thirds of the patients were men (66.7%). The racial distribution was 61.4% white, 16.9% Asian, 12.3% Hispanic, 8.3% black and 1.2% other. Approximately 21.9% had alcoholic liver disease, 27.1% HCV, and 8.3% HBV. Approximately 53.4% had a cirrhosis diagnosis recorded within the 12-months prior to HCC diagnosis. Although most patients (65.8%) had advanced stage HCC, 15.1% had early HCC, 6.3% had intermediate HCC, and 12.9% had an unknown HCC stage. (Table 1)

Only 23.5% of patients received any HCC specific palliative therapy. Approximately 12.5% received TACE and 11.0% systemic chemotherapy. For all analyses, patients who received both TACE and systemic chemotherapy (1.6%) were categorized as receiving TACE. Compared to those who received chemotherapy or no therapy, patients who received TACE were more likely to have early or intermediate HCC stage and a low co-morbidity score. They were also more likely to be recently diagnosed with HCC, had HBV, or lived in the western United States. Asians were the most likely (19.2%) to receive TACE while blacks were least likely (5.0%) compared to all other races, although the greatest proportion of Asians patients (73.6%) were diagnosed with advanced HCC.

However, after adjusting for several patient and clinical factors (Table 2), there were no significant differences in receipt of TACE between patients with intermediate versus early stage HCC, while patients with late stage or unknown stage HCC were 35% and 76%, respectively, less likely to receive TACE compared to patients with early HCC. Blacks remained significantly less likely to receive TACE (adjusted OR=0.33; 95% CI: 0.18–0.61) compared to whites, although no significant differences by race were observed. In the multivariate analysis, differences in receipt of TACE also persisted by year of HCC diagnosis, etiology, presence of cirrhosis, co-morbidity and geographic region.

In the group of 167 patients with the most favorable prognostic criteria (early or intermediate stage, no liver decompensation, and no or few co-morbidities), the highest utilization of any HCC specific palliative therapy was observed; however, only 22.8% of patients received TACE and 13.8% received chemotherapy. (Table 3) The lowest utilization of any HCC specific palliative therapy was observed in patients with unknown stage.

Among the 349 patients who received systemic chemotherapy, the specific chemotherapy drugs could be ascertained in 258 patients through Common Procedural Terminology J codes in the SEER-Medicare files. The agents most commonly prescribed were doxorubicin (36.1%), 5-fluorouracil (34.1%) and gemcitabine (23.3%). (Table 4) Few patients were prescribed less common chemotherapies for HCC, including interferon, goserelin, and bevacizumab. Patients receiving single chemotherapy agents or combinations of agents were also examined. Approximately 20.3% (n=52) received doxorubicin alone, 18.2% (n=47) 5-fluorouracil alone, and 12.0% (n=31) gemcitabine alone. The most common combination of agents observed was doxorubicin plus 5-fluorouracil (n=15, 5.8%). (data not shown)

The median survival following HCC diagnosis was significantly higher in patients who received TACE (14.0 months) compared to systemic chemotherapy (5.0 months) or no therapy (2.0 months). The 1- and 3-year survival rates were 53.2% and 14.9%, respectively, in patients who received TACE, 20.9% and 3.7% in patients who received chemotherapy, and 13.9% and 3.6% in the group that received neither. In the unadjusted Cox regression model, receipt of TACE, as well as systemic chemotherapy, was significantly associated with significantly lower overall mortality (54% and 33% reduction, respectively) compared to no therapy (Table 5). Adjusting for significant patient and clinical factors, TACE and chemotherapy remained significantly associated with lower mortality (a 55% and 36% reduction, respectively) compared to no therapy.

DISCUSSION

In this study, HCC-specific palliative treatment was received in less than 25% of HCC patients 66 years and older who had no curative therapy. Only 12.5% of patients received TACE and 11.0% received systemic chemotherapy. Significant racial differences in receipt of palliative therapies were observed, with 20% of Asians receiving TACE as compared with only 5% of blacks, however in the multivariate model, only significant differences in receipt of TACE persisted between whites and blacks. Surprisingly, Asians were more likely to be diagnosed with advanced stage HCC compared to all other races. As expected, patients with late stage or unstaged HCC were significantly less likely to receive TACE compared to patients with early disease, however even in the subgroup with early stage HCC, no liver decompensation, and little or no co-morbidity, only 17.8% received TACE and 16.1% received chemotherapy. The 1- and 3-year survival rates were significantly longer in patients who received TACE or systemic chemotherapy, which could not be explained by other patient or clinical factors. These findings indicate a need for diagnosing HCC at an earlier stage, increasing the utilization of currently available therapies, and for developing new therapeutic options for patients with advanced HCC.

TACE is the preferred palliative treatment option for patients with early and intermediate stage HCC [10–11]. In 2002, two randomized controlled trials, one conducted in Italy and one conducted in China, reported that TACE was associated with a significant increase in survival in patients with early HCC compared to no therapy [12–13]. A significant increase in TACE utilization was reported, from 62% in 1999–2002 to 73% in 2003–2006, among 2,042 Italian patients with Child-Pugh class A identified from the Italian Liver Cancer database [11]. We observed a significant increase over time in the utilization of TACE from 9.3% in 2000–2002 to 15.6% in 2003–2005. However, the utilization of TACE in this United States population-based study is substantially lower than the rate observed in the Italian population.

In this study, which predated the introduction of sorafenib in 2006, doxorubicine was the most commonly used chemotherapeutic agent [14]. A randomized controlled trial found that doxorubicine was not significantly more effective than no therapy [15]. Other frequently

used chemotherapeutic agents in this study included 5-fluorouracil, gemcitabine, and cisplatin. Combinations of these agents have been shown to be more effective than single agents in the treatment of advanced HCC, although minimal improvements in survival have been observed [14–17]. One study reported a significant increase in survival time among patients treated with cisplatin plus 5-fluorouracil compared to those treated with cisplatin alone (12 months vs. 7.5 months, respectively) [16]. Phase II studies of gemcitabine alone have also reported minimal effectiveness in patients with advanced HCC [17], however a higher response rate and longer survival has been observed when gemcitabine was used in combination with cisplatin, doxorubicin, or 5-fluorouracil [14].

The reasons for the observed low utilization of palliative therapy are unclear but could be broadly categorized as appropriate or inappropriate underutilization. Appropriate underutilization would occur among patients with advanced stage HCC at diagnosis, decompensated liver disease, or co-morbid illnesses, as well as those who refuse or are non-adherent to treatment. Inappropriate underutilization could be related to the providers' lack of information on appropriate treatments or biases associated with age, sex, race, or education. Further studies are needed to examine these potential reasons.

Significant differences in the receipt of palliative therapies were observed by demographic features, including race. Approximately 20% of Asians received TACE, compared to 14% of Hispanics, 11% of whites, and 5% of blacks. These findings are consistent with our previous study in HCC patients diagnosed during 1992–1999 [18]. Explanations for the observed racial differences in receipt of HCC treatment may include limited access or referral to healthcare among patients with low education or socioeconomic status, and differences in patient treatment preference [19].

We found a significant increase in survival among patients who received systemic chemotherapy compared to no therapy. Given the observational non-randomized nature of this study, treatment selection bias may have affected the results; patients with less co-morbidity are more likely to receive more aggressive treatment. To account for these differences, a co-morbidity summary score was included in all models. However, residual confounding cannot be excluded.

Our study cohort included only Medicare-enrolled patients who were 66 years and older, and therefore, these findings may not be generalizable to younger patients. However, this limitation is outweighed by the large numbers of patients identified with HCC from the 16 community-based regions across the country as well as the highly valid and complete cancer data in the SEER-Medicare database. In addition, data from SEER cancer registries indicated that approximately 60% of all HCC patients are age 65 and older, thus, our study cohort is representative of a large and relevant segment of patients with HCC. Patient treatment preferences could not be captured using the SEER-Medicare data. Lastly, all clinical information was obtained from administrative data. It is possible that misclassification of clinical factors, including the presence of cirrhosis and liver disease severity, could have occurred and impacted our study results.

In conclusion, we found that the utilization of palliative therapy is lower than 25% among older patients with advanced HCC. HCC at stage of diagnosis is a strong predictor of receiving TACE, but utilization is low even in patients with early stage HCC, no liver decompensation, and little or no co-morbidity. However, some survival benefit was observed among patients who received TACE as well as systemic chemotherapy. Further work is needed to increase the utilization of these palliative therapies in clinical practice.

Acknowledgments

Financial Support: This work was supported in part by Onyx Pharmaceuticals and the Houston VA HSR&D Center of Excellence (HFP90-020).

Abbreviations

HCC	Hepatocellular carcinoma
TACE	Transarterial chemoembolization

References

1. Surveillance, Epidemiology, and End Results (SEER) Program. National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch; (www.seer.cancer.gov) Research Data (1973–2007) released April 2010, based on the November 2009 submission
2. El Serag HB, Davila JA, Petersen NJ, et al. The continuing increase in the incidence of hepatocellular carcinoma in the United States: an update. *Ann Intern Med*. 2003; 139:817–823. [PubMed: 14623619]
3. Altekruse, SF.; Kosary, CL.; Krapcho, M., et al. SEER Cancer Statistics Review, 1975–2007. National Cancer Institute; Bethesda, MD: 2010. http://seer.cancer.gov/csr/1975_2007/, based on November 2009 SEER data submission, posted to the SEER web site
4. Davis GL, Alter MJ, El-Serag HB, et al. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. *Gastroenterology*. 2010; 138:513–521. [PubMed: 19861128]
5. Liu JH, Chen PW, Asch SM, et al. Surgery for hepatocellular carcinoma: does it improve survival? *Ann Surg Oncol*. 2004; 11:298–303. [PubMed: 14993025]
6. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. *Hepatology*. 2003; 37:429–442. [PubMed: 12540794]
7. Warren JL, Klabunde CN, Schrag D, et al. Overview of the SEER-Medicare data: content, research applications, and generalizability to the United States elderly population. *Med Care*. 2002; 40:IV–18.
8. Klabunde CN, Warren JL, Legler JM. Assessing comorbidity using claims data: an overview. *Med Care*. 2002; 40:IV–35.
9. Hosmer, DW.; Lemeshow, S. Applied Logistic Regression. New York: John Wiley & Sons; 1989.
10. Bruix J, Llovet JM. Two decades of advances in hepatocellular carcinoma research. *Semin Liver Dis*. 2010; 30:1–2. [PubMed: 20175028]
11. Giannini EG, Bodini G, Corbo M, et al. Impact of evidence-based medicine on the treatment of patients with unresectable hepatocellular carcinoma. *Aliment Pharmacol Ther*. 2010; 31:493–501. [PubMed: 19912152]
12. Llovet JM, Real MI, Montana X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet*. 2002; 359:1734–1739. [PubMed: 12049862]
13. Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology*. 2002; 35:1164–1171. [PubMed: 11981766]
14. Yeo W, Mok TS, Zee B, et al. A randomized phase III study of doxorubicin versus cisplatin/interferon alpha-2b/doxorubicin/fluorouracil (PIAF) combination chemotherapy for unresectable hepatocellular carcinoma. *J Natl Cancer Inst*. 2005; 97:1532–1538. [PubMed: 16234567]
15. Lai CL, Wu PC, Chan GC, et al. Doxorubicin versus no antitumor therapy in inoperable hepatocellular carcinoma. A prospective randomized trial. *Cancer*. 1988; 62:479–483. [PubMed: 2839280]

16. Kim BK, Park JY, Choi HJ, et al. Long-term clinical outcomes of hepatic arterial infusion chemotherapy with cisplatin with or without 5-fluorouracil in locally advanced hepatocellular carcinoma. *J Cancer Res Clin Oncol*. 2010; 137:659–667. [PubMed: 20552225]
17. Yang TS, Lin YC, Chen JS, et al. Phase II study of gemcitabine in patients with advanced hepatocellular carcinoma. *Cancer*. 2000; 89:750–756. [PubMed: 10951336]
18. El Serag HB, Siegel AB, Davila JA, et al. Treatment and outcomes of treating of hepatocellular carcinoma among Medicare recipients in the United States: a population-based study. *J Hepatol*. 2006; 44:158–166. [PubMed: 16290309]
19. Eckhoff DE, McGuire BM, Young CJ, et al. Race: a critical factor in organ donation, patient referral and selection, and orthotopic liver transplantation? *Liver Transpl Surg*. 1998; 4:499–505. [PubMed: 9791161]

A comparison of patient demographics and clinical factors by receipt of palliative therapy among patients diagnosed with HCC during 2000–2005.

Table 1

	Overall	TACE	Systemic chemotherapy	No HCC specific therapy	P Value *
Total (%)	3,163	395 (12.5)	349 (11.0)	2,419 (76.5)	
Mean age at HCC diagnosis (s.d.)	75.3 (5.3)	74.2 (4.9)	74.3 (5.0)	75.7 (5.4)	<0.01 **
Sex					0.04
Female	1,054 (33.3)	134 (12.7)	95 (9.0)	825 (78.3)	
Male	2,109 (66.7)	261 (12.4)	254 (12.0)	1,594 (75.6)	
Race					<0.01
White	1,942 (61.4)	218 (11.2)	223 (11.5)	1,501 (77.3)	
Black	261 (8.3)	13 (5.0)	26 (10.0)	222 (85.1)	
Hispanic	388 (12.3)	54 (13.9)	43 (11.1)	291 (75.0)	
Asian	572 (18.0)	110 (19.2)	57 (10.0)	405 (70.8)	
Year of HCC diagnosis					<0.01
2000–2002	1,556 (49.2)	144 (9.3)	185 (11.9)	1,227 (78.9)	
2003–2005	1,607 (50.8)	251 (15.6)	164 (10.2)	1,192 (74.2)	
Stage at HCC diagnosis ***					<0.01
Early	476 (15.1)	86 (18.1)	46 (9.7)	344 (72.3)	
Intermediate	199 (6.3)	49 (24.6)	11 (5.5)	139 (69.9)	
Advanced	2,080 (65.8)	241 (11.6)	241 (11.6)	1,598 (76.8)	
Unknown	408 (12.9)	19 (4.7)	51 (12.5)	338 (82.8)	
Income					<0.01
\$24,508	728 (23.0)	69 (9.5)	72 (9.9)	587 (80.6)	
\$24,509–31,961	729 (23.1)	89 (12.2)	63 (8.6)	577 (77.2)	
\$31,962–41,542	727 (23.0)	82 (11.3)	84 (11.6)	561 (77.2)	
>\$41,542	726 (22.9)	123 (16.9)	101 (13.9)	502 (69.2)	
Missing	253 (8.0)	32 (12.7)	29 (11.5)	192 (75.9)	
High school degree by zip code (%)					0.54
0 – 25	726 (22.9)	79 (10.9)	77 (10.6)	570 (78.5)	
26 – 50	729 (23.1)	87 (11.9)	71 (9.7)	571 (78.3)	
51 – 75	717 (22.7)	95 (13.3)	81 (11.3)	541 (75.5)	

	Overall	TACE	Systemic chemotherapy	No HCC specific therapy	P Value*
>76	738 (23.3)	102 (13.8)	91 (12.3)	545 (73.9)	
Missing	253 (8.0)	32 (12.7)	29 (11.5)	192 (75.9)	
Geographic region					<0.01
Central	834 (26.4)	58 (7.0)	89 (10.8)	687 (82.4)	
East	720 (22.8)	87 (12.1)	101 (14.0)	532 (73.9)	
West	1,609 (50.9)	250 (15.5)	159 (9.9)	1200 (74.6)	
HCC risk factors****					
Cirrhosis					
Yes	1,688 (53.4)	285 (16.9)	165 (9.8)	1238 (73.3)	<0.01
No	1475 (46.6)	110 (7.5)	184 (12.5)	1181 (80.1)	
HCV					
Yes	857 (27.0)	183 (21.4)	97 (11.4)	575 (67.3)	<0.01
No	2308 (73.0)	212 (9.2)	252 (10.9)	1844 (79.9)	
HBV					
Yes	261 (8.3)	65 (24.9)	27 (10.3)	169 (64.8)	<0.01
No	2902 (91.7)	330 (11.4)	322 (11.1)	2250 (77.5)	
Alcoholic liver disease					
Yes	693 (21.9)	105 (15.2)	57 (8.2)	531 (76.6)	<0.01
No	2470 (78.1)	290 (11.7)	292 (11.8)	1888 (76.4)	
Indicators of liver disease severity****					
Ascites					
Yes	1,032 (32.6)	87 (8.4)	80 (7.8)	865 (83.8)	<0.01
No	2131 (67.4)	308 (14.5)	269 (12.6)	1554 (72.9)	
Varices					
Yes	523 (16.5)	65 (12.4)	42 (8.0)	416 (79.5)	0.05
No	2640 (83.5)	330 (12.5)	307 (11.63)	2003 (75.9)	
Encephalopathy					
Yes	286 (9.0)	23 (8.0)	20 (7.0)	244 (85.0)	<0.01
No	2876 (90.9)	372 (12.9)	329 (11.4)	2175 (75.6)	
Co-morbidity score					
0-1	1,107 (35.0)	147 (13.2)	166 (15.0)	797 (71.8)	<0.01

	Overall	TACE	Systemic chemotherapy	No HCC specific therapy	P Value*
2-3	1,024 (32.4)	128 (12.5)	101 (9.8)	797 (77.7)	
4-5	603 (19.1)	79 (13.1)	54 (9.0)	470 (77.9)	
6+	429 (13.5)	41 (9.7)	28 (6.6)	355 (83.7)	

* P-value from the Pearson chi-square test
** P-value from ANOVA F-test
*** See methods for definition
**** Not mutually exclusive

Table 2

Results from multinomial logistic regression analyses examining the effect of HCC stage at diagnosis on receipt of therapy.

	Unadjusted Odds Ratios (95%CI)			Adjusted Odds Ratios* (95%CI)		
	TACE	Systematic Chemotherapy	No therapy	TACE	Systematic Chemotherapy	No therapy
Intermediate (vs. early)	1.41 (0.94 – 2.11)	0.59 (0.30 – 1.18)	Reference	1.17 (0.76 – 1.82)	0.60 (0.30 – 1.21)	Reference
Late (vs. early)	0.60 (0.46 – 0.79)	1.13 (0.81 – 1.58)	Reference	0.65 (0.48 – 0.87)	1.11 (0.78 – 1.56)	Reference
Unknown (vs. early)	0.23 (0.13 – 0.38)	1.13 (0.74 – 1.73)	Reference	0.24 (0.14 – 0.41)	1.01 (0.65 – 1.56)	Reference

* Adjusted for significant factors at p<0.10, including year of HCC diagnosis, age, gender, race, SEER region, HCC risk factors (HCV, HBV, alcoholic liver disease), indicators of liver disease severity (ascites, encephalopathy), co-morbidity score, and HCC stage at diagnosis.

Table 3

Receipt of palliative therapies among patients diagnosed with HCC stratified by co-morbidity index score, liver disease severity, and HCC stage.

Co-morbidity score	Liver Disease Severity	Therapy	Early or intermediate stage	Late stage
0-1	Presence of ascites or encephalopathy (n=238)		n=31	n=171
		TACE	*	14 (8.2%)
		Chemotherapy	*	22 (12.9%)
0-1	Absence of ascites or encephalopathy (n=872)		n=167	n=601
		TACE	38 (22.8%)	83 (13.8%)
		Chemotherapy	23 (13.8%)	98 (16.3%)
2-3	Presence of ascites or encephalopathy (n=346)		n=89	n=218
		TACE	*	22 (10.1%)
		Chemotherapy	*	19 (8.7%)
2-3	Absence of ascites or encephalopathy (n=680)		n=133	n=452
		TACE	36 (27.1%)	53 (11.7%)
		Chemotherapy	*	52 (11.5%)
4+	Presence of ascites or encephalopathy (n=544)		n=138	n=333
		TACE	16 (11.6%)	23 (6.9%)
		Chemotherapy	11 (8.0%)	15 (4.5%)
4+	Absence of ascites or encephalopathy (n=483)		n=117	n=305
		TACE	30 (25.6%)	46 (15.1%)
		Chemotherapy	*	35 (11.5%)

* Indicates cell size less than 10

Table 4

Utilization of standard and experimental systemic chemotherapy agents among patients diagnosed with HCC in Medicare claims during 2000–2005 (n=258). These categories are not mutually exclusive, as patients could have received multiple chemotherapy agents.

Frequency (%)	
Standard Chemotherapy	
Doxorubicine	93 (36.1)
5-Fluorouracil	88 (34.1)
Gemcitabine	60 (23.3)
Cisplatin	44 (17.1)
Carboplatin	20 (7.8)
Docetaxel	14 (5.4)
Motomycin	13 (5.0)
Irinotecan	11 (4.3)
Paclitaxel	*
Fluxuridine	*
Epirubicin	*
Etoposide	*
Mitoxantrone	*
Vincristine	*
Experimental Chemotherapy	
Interferon	13 (5.0)
Aldesleukin	*
Arsenic Trioxide	*
Bevacizumab	*
Goserelin	*
Cetuximab	*

* Indicates cell size less than 10

Table 5

Results from Cox proportional hazards models examining the effect of HCC therapy on the risk of 1- and 3-year mortality.

	1-year survival	3-year survival	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio* (95% CI)
TACE	53.2%	14.9%	0.46 (0.38–0.56)	0.45 (0.37–0.55)
Systemic Chemotherapy	20.9%	3.7%	0.67 (0.50–0.88)	0.64 (0.48–0.85)
No therapy	13.9%	3.6%	1.00 (reference)	1.00 (reference)

* Adjusted for significant factors at $p < 0.10$, including for year of HCC diagnosis, age, gender, race, SEER registry, HCC risk factors (HBV, HCV, alcoholic liver disease), co-morbidity score, indicators of liver disease severity (ascites, encephalopathy), and HCC stage at diagnosis.

Appendix

ICD-9-CM and CPT procedure codes to identify receipt of TACE and systemic chemotherapy.

<u>Therapy</u>	<u>ICD-9 codes</u>	<u>CPT codes</u>
Transarterial chemoembolization (TACE)	Embolization: 38.80, 38.86 Chemotherapy: 99.25	Embolization: 37204, 75894 Chemotherapy: J9000, J9280, J9060, 96405, 96408, 96420, 96422, 96423, 96425, 96440, 96445, 96545, 96549, 0331, 0335
Systemic chemotherapy	99.25	J9000, J9010, J9190, J9200, J9201, J9217, J9265, J9060, J9062, J9170, J9178, J9181, J9182, J9280, J9293, J9370, J9015, J9017, J9035, J9202, J9055, 90782, 96400, 96408, 96410, 96412, 96414, 96545, 0331, 0332, 0335
Systemic chemotherapy agents		
Doxorubicine	-	J9000
Carboplatin	-	J9010
Fluorouracil	-	J9190
Fluxuridine	-	J9200
Gemcitabine	-	J9201
Irinotecan	-	J9217
Paclitaxel	-	J9265
Cisplatin	-	J9060, J9062
Docetaxel	-	J9170
Epirubicin	-	J9178
Etoposide	-	J9181, J9182
Mitomycin	-	J9280
Mitoxantrone	-	J9293
Vincristine	-	J9370
Aldesleukin	-	J9015
Arsenic Trioxide	-	J9017
Bevacizumab	-	J9035
Goserelin	-	J9202
Interferon	-	90782, 96400
Cetuximab	-	J9055