Published in final edited form as:

J Am Coll Surg. 2013 November ; 217(5): 896–906. doi:10.1016/j.jamcollsurg.2013.07.007.

Referral Patterns and Treatment Choices for Patients with Hepatocellular Carcinoma: A United States Population-Based Study

Omar Hyder, MD, Rebecca M Dodson, MD, Hari Nathan, MD, Joseph M Herman, MD, MSc, David Cosgrove, MD, Ihab Kamel, MD, Jean-Francois H Geschwind, MD, and Timothy M Pawlik, MD, MPH, PhD, FACS

Departments of Surgery (Hyder, Dodson, Nathan, Pawlik), Radiation Oncology (Herman), Medical Oncology (Cosgrove), Radiology (Kamel), and Interventional Radiology (Geschwind), The Johns Hopkins University School of Medicine, Baltimore, MD.

Abstract

BACKGROUND—Patterns of care of physician specialists may differ for patients with hepatocellular carcinoma (HCC). Reasons underlying variations are poorly understood. One source of variation may be disparate referral rates to specialists, leading to differences in cancer-directed treatments.

STUDY DESIGN—Surveillance, Epidemiology, and End Results (SEER)-linked Medicare database was queried for patients with HCC, diagnosed between 1998 and 2007, who consulted 1 or more physicians after diagnosis. Visit and procedure records were abstracted from Medicare billing records. Factors associated with specialist consult and subsequent treatment were examined.

RESULTS—There were 6,752 patients with HCC identified; 1,379 (20%) patients had early-stage disease. Median age was 73 years; the majority were male (66%), white (60%), and from the West region (56%). After diagnosis, referral to a specialist varied considerably (hepatology/gastroenterology, 60%; medical oncology, 62%; surgery, 56%; interventional radiology [IR], 33%; radiation oncology, 9%). Twenty-two percent of patients saw 1 specialist; 39% saw 3 or more specialists. Time between diagnosis and visitation with a specialist varied (surgery, 37 days vs IR, 55 days; $p = 0.04$). Factors associated with referral to a specialist included younger age (odds ratio [OR] 2.16), Asian race (OR 1.49), geographic region (Northeast OR 2.10), and presence of early-stage disease (OR 2.21) (all $p < 0.05$). Among patients with early-stage disease,

© 2013 by the American College of Surgeons Published by Elsevier Inc.

Correspondence address: Timothy M Pawlik, MD, MPH, PhD, FACS, Department of Surgery, Johns Hopkins Hospital, 600 N Wolfe St, Blalock 688, Baltimore, MD 21287. tpawlik1@jhmi.edu.

Disclosure Information: Nothing to disclose.

Abstract presented at the annual meeting of the Society of Surgical Oncology, Washington, DC, March 2013.

Author Contributions

Study conception and design: Hyder, Pawlik

Acquisition of data: Hyder, Pawlik

Analysis and interpretation of data: Hyder, Dodson, Nathan, Herman, Cosgrove, Kamel, Geschwind, Pawlik

Drafting of manuscript: Hyder, Pawlik

Critical revision: Hyder, Dodson, Nathan, Herman, Cosgrove, Kamel, Geschwind, Pawlik

77% saw a surgeon, while 50% had a consultation with medical oncologist. Receipt of therapy among patients with early-stage disease varied (no therapy, 30%; surgery, 39%; IR, 9%; chemotherapy, 23%). Factors associated with receipt of therapy included younger age (OR 2.48) and early-stage disease (OR 2.20).

CONCLUSIONS—After HCC diagnosis, referral to a specialist varied considerably. Both clinical and nonclinical factors were associated with consultation. Disparities in referral to a specialist and subsequent therapy need to be better understood to ensure all HCC patients receive appropriate care.

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and is the third leading cause of cancer mortality.^{1,2} In the United States, the incidence is 4.9 per 100,000 and has been steadily rising at a rate of 4.5% per year for the last 3 decades.² In men, HCC is the fastest growing cause of cancer-related death. Most patients with HCC are over age 65, and the highest age-specific rates occur among persons aged 75 and older.³ Surgery is the only curative treatment for HCC. However, most patients are not surgical candidates due to advanced disease at presentation or prohibitive comorbidities. Therefore, treatment often presents a challenge and entails a multidisciplinary approach. Nonsurgical therapeutic options for patients include chemotherapy, ablation, and interventional radiologic (IR) procedures such as transarterial chemoembolization (TACE) or bland embolization (TAE). Although the treatment options for patients with advanced HCC have increased over the last couple of decades, the overall survival of patients with HCC remains dismal, with a cause-specific survival of less than 50% at 1 year.²

The use of cancer-directed treatments is multifactorial and is related to both clinical and nonclinical factors. Variation in treatment recommendations have been associated with race, age, socioeconomic status (SES), health insurance status, type of institution, and geographic region, which, in turn, may account for differences in survival.⁴⁻¹⁰ Disparities in access to treatment for HCC have been noted in the literature, but involved relatively small sample sizes, single institutions,^{11,12} regional experiences,¹³ and primarily focused on 1 treatment modality (ie, transplantation or hepatectomy). Recently, our group reported survey-based data that demonstrated how both clinical and nonclinical factors affect physician decision-making in the treatment of patients with HCC.¹⁴⁻¹⁶ These data suggested that a subset of patients with early-stage HCC may not be offered curative intent treatment.¹⁴⁻¹⁶ Earle and colleagues⁴ proposed studying disparities in the receipt of treatment as a 2-step process that involves studying patterns of referral to a specialist and subsequent treatment of referred patients. This model has been used in lung, esophageal, and ovarian cancers.^{4,17,18} Due to the paucity of comprehensive information on factors affecting referral and receipt of treatment for HCC, we used the 2-step process proposed by Earle and associates⁴ to explore disparities in referral patterns, treatment choices, and outcomes in a population-based sample of patients with HCC, using the SEER-linked Medicare database.

METHODS

Patients

We queried the SEER-linked Medicare database for patients with a diagnosis of pathologically confirmed HCC between January 1, 1998 and December 31, 2007. Details of the SEER-Medicare database and linkage techniques have been described.¹⁹⁻²¹ Exclusion criteria included patients with less than 1 year of Medicare coverage in parts A and B, enrollment in an HMO plan in the 12 months preceding the diagnosis, diagnosis of a primary cancer other than HCC within 5 years of HCC diagnosis, enrollment in Medicare due to disability or end-stage renal disease, and patients who survived less than 30 days after HCC diagnosis. The final cohort consisted of 6,752 patients.

Physician consultation information in the 180 days around the time of diagnosis was obtained from Medicare provider files. Physicians were categorized as primary care physicians (general practitioner, family practice, internal medicine, geriatric medicine), gastroenterologists, surgeons (general surgeon, surgical oncologist, transplant surgeon), medical oncologists (hematologist, medical oncologist), radiation oncologists, and interventional radiologists.²² In order to reduce variability of specialty designation in the billing records, we attributed 1 specialty designation to each physician identifier (UPIN). Gastroenterologists and medical oncologists billing elsewhere under a primary care specialty designation were given their specialty designation for all bills. Patients who received surgery, TACE/TAE, or chemotherapy were, by definition, seen by a surgeon, interventional radiologist, or medical oncologist, respectively.¹⁷ We reviewed the billing records of patients not undergoing surgery to determine if they had ever been seen by a physician who had billed for a liver resection or transplantation, to ensure that surgeons with and without specialty designation in Medicare would be captured.^{4,17}

Treatment-related information was obtained from inpatient, outpatient, and provider files. Patients undergoing transplantation or resection on the liver were considered to have had curative intent surgery for HCC. Information on surgery not recorded in the Medicare database was abstracted from the SEER “surgery of primary site” variable. Information on IR procedures (TACE/TAE) and chemotherapy was extracted only from the Medicare database in the 6 months after diagnosis of HCC.

The Elixhauser comorbidity score was used to quantify comorbidity burden.²³ Comorbidities were extracted using standard procedures from the inpatient and outpatient claims for each patient. A numerical comorbidity score was calculated²⁴ and categorized as “high” if the score was ≥ 7 (corresponds to the 75th percentile cutoff in this cohort). Information on liver-related conditions relevant to the etiology, treatment, and prognosis of HCC including hepatitis C virus status, hepatitis B status, nonalcoholic cirrhosis, portal hypertension, and alcoholic liver disease was abstracted from the Medicare files based on ICD-9 codes.¹⁵

Demographic characteristics include age at diagnosis, sex, race (non-Hispanic white, black, Asian, Hispanic white, other), census region (Northeast, West, Midwest, South), and SES.

We classified SES into quintiles of income using established techniques,²⁰ and further classified into top 3 or bottom 2 quintiles.

We analyzed the entire cohort and then performed a subset analysis of patients who were deemed to have early-stage or potentially curable disease (ie, tumor size < 5 cm, 3 or fewer lesions, localized disease) as previously described.¹⁵

Statistical analysis

Data were presented as means and standard deviation for continuous variables and frequency distributions for categorical variables. Logistic regression was used to calculate odds ratios (OR) for the effect of patient and disease characteristics on physician seen and subsequent treatment. Multivariate models included age, sex, race, SES, geographic area, comorbidity burden, and stage of disease. Survival curves were constructed from the Kaplan-Meier method. Cox regression analysis was used to evaluate the effect of patient characteristics on survival. Hazard ratios (HR) and 95% confidence intervals were calculated; a p value < 0.05 was considered statistically significant. Two different multivariate models were used. The first multivariate model included age, sex, race, SES, geographic area, comorbidity burden, and stage of disease. The second included treatment received in addition to the previously mentioned variables. Analysis was performed with SAS version 9.3 (SAS Institute).

RESULTS

Patient characteristics

There were 6,752 patients with histologically confirmed HCC who comprised the cohort. Most patients were male (66.2%) and white (59.6%) (Table 1). Mean age was 75.7 years old and a majority of patients (56.4%) had 1 or more comorbidities. Among the cohort, 3,573 (52.9%) patients had nonalcoholic cirrhosis and 917 (13.6%) had portal hypertension; 42.6% patients had multifocal disease, 60.7% had tumors $\geq$ 5 cm, and 1,379 (20.4%) patients had early-stage disease.

Referral and consultation patterns

Data on referral patterns for the full cohort, as well as for patients with early-stage disease are presented in Table 2. After diagnosis, referral to a specialist varied considerably. Specifically, among all patients with HCC, consultation involved hepatology/gastroenterology (60%), medical oncology (62%), surgery (56%), IR (33%), or radiation oncology (9%). Overall, 22% of patients saw 1 specialist, 32% saw 2 specialists, and 39% saw 3 or more specialists. Among patients who saw multiple specialists, the most common combination was medical oncology and surgery (52%). The time between diagnosis and the initial consultation varied depending on the specialist seen. Median times from diagnosis to first consultation were 28 days for gastroenterologists, 37 days for surgeons, 41 days for medical oncologists, 49 days for radiation oncologists, and 55 days for interventional radiologists. For patients who saw multiple specialists, the average time between the first and second consultation with any specialist was 13 days (range 0 to 176 days).

Several factors were associated referral patterns and consultation (Fig. 1). In particular, factors associated with referral to a cancer specialist included younger age (OR 2.16, 95% CI 1.55 to 3.02), Asian race (OR 1.49, 95% CI 1.07 to 2.01), residence in the Northeast region (OR 2.10, 95% CI 1.50 to 2.95), and earlier disease stage (OR 2.21, 95% CI 1.72 to 2.83) (all $p < 0.05$). Black patients generally had lower rates of consultation compared with whites or Asian/Pacific Islanders. In contrast, patients initially treated at teaching hospitals were slightly more likely to see a specialist compared with those initially treated at a nonteaching hospital (96.9% vs 94.6%; $p < 0.001$). When examining referral patterns to specific specialists, patients seen at teaching hospitals were more likely to be seen by a surgeon (66.2%) compared with patients seen at a nonteaching hospital (46.4%) ($p < 0.001$). Surgical consultation was also more common among younger patients (age 66 to 75 years old, OR 1.88, 95% CI 1.65 to 2.13 vs >80 years) ($p < 0.001$). Although younger age was also associated with a higher likelihood of referral to IR, there was no association between age and medical oncology consultation. Geographic location similarly affected the likelihood of surgical consultation. Patients in the Northeast were the most likely to see a surgeon (OR 1.72, 95% CI 1.49 to 1.99); the odds of surgery consultation were lower for the Midwest or the South; patients in the West were least likely to have a surgical consultation (Table 3). Patients from the Northeast region were also more likely to be referred to IR therapy (OR 1.20, 95% CI 1.04 to 1.39) and medical oncology (OR 1.19, 95% CI 1.03 to 1.38). One of the factors most strongly associated with referral pattern was extent of disease. Patients with early-stage disease were more than 2.5 times more likely to be seen by a surgeon than patients with more advanced disease (OR 2.65, 95% CI 2.37 to 2.96) ($p < 0.001$). In analysis of SEER historic staging, 67.0% of patients with localized disease were seen by a surgeon (Table 4). Among patients with advanced disease, 38.7% saw a surgeon, while 24.5% saw an interventional radiologist and 72.5% saw a medical oncologist. Among the 1,379 patients categorized with early-stage disease, a higher proportion saw a surgeon (76.7%) and a lower proportion were seen by either an interventional radiologist (42.6%) or a medical oncologist (50.4%). Among patients with early-stage disease, factors associated with surgical consultation included younger age (OR lowest vs highest age category 2.34, 95% CI 1.78 to 3.92), living in the Northeast (OR 1.50, 95% CI 1.02 to 2.26), and disease localized to the liver (OR 1.40, 95% CI 1.01 to 1.94) (all $p < 0.05$).

Treatment and long-term outcomes

Among all patients with HCC, the majority of patients received nonsurgical therapy (55.7%), and 27.3% underwent curative intent surgery. Among patients with early-stage disease ($n = 1,379$), 39.2% ($n = 541$) underwent surgery as the first course of treatment, while fewer ($n = 409$; 29.7%) received nonsurgical therapy (Table 4). In analyzing the entire cohort, the median time from diagnosis to first procedure was 61 days (surgery, 47 days; ablation, 73 days; TACE/TAE, 76 days).

A number of factors were associated with receipt of therapy. Younger patients had more surgery, with the odds of surgery decreasing with increasing age (Table 3). Although 36.5% of patients between 66 and 69 years of age had surgery, only 21.9% of patients 75 years or older underwent a surgical procedure. Similar differences in receipt of surgery were noted among patients with early-stage disease (66 to 69 years, 68.0% vs 75 years, 47.5%; $p <$

0.001). Lower consultation rates partly explained the lower rate of surgery among older patients. On multivariate analyses of the full cohort, patients in the 66 to 69 age group had a 148% higher odds of undergoing surgery after consultation with a surgeon as compared with the 80 years and older age group (OR 2.48, 95% CI 1.04 to 3.07); on subset analysis of patients with early-stage disease this difference remained (OR 2.63, 95% CI 1.68 to 4.12). Race also affected receipt of surgical therapy; black patients had lower rates and Asians had higher rates of surgery compared with whites on multivariate analysis ($p = 0.01$). Patients in the top 3 SES quintiles were also more likely to receive surgery after consultation with a surgeon (OR 1.21, 95% CI 1.05 to 1.41 vs patients in the lower 2 quintiles). Age and SES had similar effects on likelihood of receipt of TACE/TAE after consultation with IR. Although there was no association between age and medical oncology consultation, patients in the youngest vs oldest category were twice as likely to receive chemotherapy after consultation (OR 2.19, 95% CI 1.79 to 2.68) ($p < 0.001$).

Patients in the Northeast had higher rates of surgery overall (32.4%), seeing a surgeon (61.2%), and subsequently undergoing surgery (53.1%), as compared with patients in the West (26.3%, 53.2%, and 49.4%, respectively), Midwest (25.4%, 57.3%, and 44.2%, respectively), and South (26.5%, 60.2%, and 44.0%, respectively) (all $p < 0.05$). Similar relationships were noted in the early-stage disease stage cohort, albeit with higher rates of surgery overall, surgical consultation, and surgery after consultation. After adjustment for the effect of other covariates, the differences between the Northeast and the West geographic region remained remarkable (overall surgery: OR 1.82, 95% CI 1.54 to 2.14; surgeon consultation: OR 1.72, 95% CI 1.49 to 1.99; surgery subsequent to consultation: OR 1.46, 95% CI 1.20 to 1.78). Those with localized disease were most likely (OR 2.20, 95% CI 1.87 to 2.58), and those with distant or unstaged disease least likely (OR 0.40, CI 0.32 to 0.73) to undergo surgery after surgical consultation. Regarding nonsurgery consultation, patients in the Northeast also were more likely to receive TACE/TAE after consultation with IR (Northeast 41.7% vs West 26.3% vs Midwest 36.5% vs South 24.7%; $p < 0.001$). The higher likelihood of undergoing TACE/TAE after being seen by the corresponding specialist was also noted in the multivariate regression model (OR for Northeast vs West: 2.12, 95% CI 1.67 to 2.69).

Overall survival was 6.0 months (95% CI 5.7 to 6.3 months); survival among patients with early-stage disease was 15.3 months (95% CI 13.7 to 16.4 months). Tumor stage was the strongest predictor of survival (reference: local disease: regional disease, HR 0.74, 95% CI 0.69 to 0.79 vs distant/unstaged disease, HR 1.24, 95% CI 1.15 to 1.32) (Table 5). Although advanced age at diagnosis predicted worse survival in multivariate adjusted Cox regression analysis, after adjusting for treatment received, this relationship was not noted (Fig. 2). Consultation with a cancer specialist was also associated with a significant survival benefit (HR 0.82, 95% CI 0.70 to 0.94; $p = 0.02$).

DISCUSSION

Hepatocellular carcinoma is a common malignancy, and its incidence is increasing in the United States and worldwide. Unlike other patients with cancer, patients with HCC very often have 2 underlying problems: cirrhosis and cancer. In addition, there are a multitude of

therapeutic options for HCC including resection, ablation, transplantation, intra-arterial therapy, and systemic chemotherapy. Due to the complexity of the patient population as well as the myriad of treatment options, patients with HCC frequently need to see multiple physician specialists. Our group previously reported that surgeon specialty can influence treatment selection for early HCC.¹⁴ Furthermore, we previously showed that nonclinical institution-level factors can affect the choice of therapy.¹⁶ In this study, we sought to investigate further the variation in treatment and outcomes of patients with HCC. Specifically, we examined the differences in rates of referral to cancer specialists. Previous studies have suggested significant variation in referral patterns and treatment choices for patients with esophageal, as well as other cancers.^{4,5,17,18} This study is important because it is the first to examine and determine the impact of demographic and clinical factors on referral patterns and treatment choices for patients with HCC. Using population-based national Medicare data, we identified significant disparities in both specialist consultation and treatment among patients with HCC. Of note, the factors associated with these differences were multifactorial and related to clinical (age, comorbidity, disease stage) as well as nonclinical factors (SES, geographic region).

In general, surgical therapy represents the only potentially curative therapeutic option for patients with HCC. In this study, we found that HCC disease stage was one of the factors that most strongly influenced both referral patterns and receipt of therapy. Not surprisingly, patients with early-stage disease were much more likely to be seen by a surgeon and to receive surgical therapy. In contrast, patients with advanced HCC frequently were seen by an interventional radiologist or medical oncologist (Table 3). Importantly, even among patients with early-stage disease, only 76.7% were referred to a surgeon and 56.6% eventually underwent surgical resection. Our group had previously noted that there may be a significant missed opportunity to improve survival among some patients with HCC due to the lower than expected use of surgical services.¹⁵ In this study, we expanded on this previous work and identified several factors associated with differences in referral to a surgeon. Specifically, among patients with early-stage disease, 83.5% of patients aged 66 to 69 years were referred to a surgeon compared with 71.4% for patients 75 years of age or older. Subsequently, while 68.0% of younger patients had surgery, only 47.5% of patients 75 years of age or older did. Previous data have suggested that surgeons may be more willing to treat younger patients with HCC using more invasive treatments such as liver transplantation or resection.¹⁶ Consequently, use of surgical therapy including resection, transplantation, and ablation has been shown to be lower in older patients with HCC.^{12,24,25} This association of age and lower surgeon consultation and subsequent therapy has been noted for other gastrointestinal cancers.^{5,17} Moreover, it has also been shown that patient age may also adversely affect adherence to proper oncologic principles.²⁶ In this study, although advanced age predicted worse survival, in the multivariate analysis this relationship was not noted (Fig. 2). These data suggest that although age seemed to determine surgical consultation, it should not necessarily be used as an absolute criterion for surgical treatment because surgery can be associated with a survival benefit even in the very elderly. These data are particularly relevant given that other studies have demonstrated that hepatic resection can be performed safely in appropriately selected elderly patients.²⁷

Age also seemed to affect referral patterns and treatment choices with regard to nonsurgical therapies. We did not find an age-related disparity for consultation with a medical oncologist, but receipt of chemotherapy after consultation was more than twice as likely for younger patients compared with the older cohort (OR 2.19, 95% 1.79 to 2.68). Age-related trends were also noted with regard to intra-arterial therapy. Younger patients were more often referred and treated by interventional radiologists compared with older patients. Intra-arterial therapy is generally well tolerated with few complications and age is typically not considered a contraindication to TACE/TAE, but poor patient performance status has been associated with worse outcomes after intra-arterial therapy.²⁸⁻³⁰ In fact, performance status is explicitly included in the Barcelona Clinic Liver Cancer (BCLC) staging system as a key criterion in directing treatment recommendations.³¹ As such, performance status, rather than age, should be used to guide the selection of patients referred to IR. This point is particularly important given that our data suggest that IR techniques may be underused nationally for patients who do not have resection or transplantation.

Significant differences in referral patterns and treatment choices were also found in relation to geographic region, race, and SES. Disparities by geographic region have been noted in treatment of other cancers such as esophageal⁵ and prostate cancer.³² In this study, we found dramatic regional differences in referral and receipt of treatment, but these differences in treatment did not translate into survival differences. The Northeast region had highest receipt of consult and treatment for HCC. Therapy after consultation was lowest in the West region with respect to interventional procedures and in the Midwest and South with respect to medical oncology. Reasons for regional disparities in treatment patterns are likely multifactorial and related to regional differences in access to care, medical practice, and patient preferences. Consistent racial disparities have also been reported in the treatment of multiple cancers including HCC.^{4,5,12,13,18,25} We found that although race had less impact on treatment patterns than age or region, important racial disparities were noted. Specifically, blacks were significantly less likely to receive all potential therapies (eg, surgery, IR procedure, chemotherapy). Blacks similarly had lower receipt of consultation with an interventional radiologist and receipt of chemotherapy after consult with a medical oncologist. Although not accounting for all racial disparities, Yu and colleagues¹² found that blacks more often presented outside Milan criteria and with more advanced tumors, later stage, higher Child-Pugh score, increased alpha-fetoprotein, and lower household income. Even though significant disparities were noted in medical treatment, there was no difference in survival between blacks and whites (HR 1.00, 95% CI 0.90 to 1.10). The impact of SES was relatively small on receipt of consultation and therapy, except that patients in the top 3 SES quintiles more likely to have surgery once seen by a surgeon.

This study had several limitations. Because we used SEER Medicare-linked data, the analyses were limited to patients 65 years or older. Although this population represents the group of patients at highest risk of HCC, whether our findings are generalizable to younger patient populations needs to be further evaluated. The SEER-linked Medicare data also do not capture certain details relevant to decision making, including performance status, alpha-fetoprotein levels, severity of cirrhosis, and location of tumor near key structures. This dataset is also limited by extent of surgical resection, type of ablation performed, type of TACE agents used, and inability to ascertain patient treatment preferences. Finally, although

we examined variation based on geographic regions (eg, Northeast, Midwest, etc), future studies should further examine variation in referral patterns and management by United Network for Organ Sharing (UNOS) region.

CONCLUSIONS

Using a large population-based study that combines SEER registry with Medicare-linked data, we characterized the pattern of referral use and subsequent treatment for patients with HCC. Importantly, we noted that referral to a specialist and subsequent therapy varied considerably. We found significant disparities related to age and to a lesser extent, geographic location and race. We also found apparent barriers to treatment, as only 76.7% of patients with early-stage disease were referred to a surgeon and only 56.6% underwent surgical treatment. The number of patients referred to and treated by surgeons was even lower among older patients. In conclusion, disparities in referral to a specialist and subsequent therapy need to be better understood in order to ensure all patients receive appropriate expert consultation and optimal oncologic care.

Abbreviations and Acronyms

HCC	hepatocellular carcinoma
HR	hazard ratio
IR	interventional radiology
OR	odds ratio
SES	socioeconomic status
TACE	transarterial chemoembolization
TAE	bland embolization

REFERENCES

1. El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. *Gastroenterology*. 2012; 42:1264–1273. e1. [PubMed: 22537432]
2. Altekruse SF, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. *J Clin Oncol*. 2009; 27:1485–1491. [PubMed: 19224838]
3. El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. *Gastroenterology*. 2007; 132:2557–2576. [PubMed: 17570226]
4. Earle CC, Neumann PJ, Gelber RD, et al. Impact of referral patterns on the use of chemotherapy for lung cancer. *J Clin Oncol*. 2002; 20:1786–1792. [PubMed: 11919235]
5. Steyerberg EW, Neville B, Weeks JC, et al. Referral patterns, treatment choices, and outcomes in locoregional esophageal cancer: a population-based analysis of elderly patients. *J Clin Oncol*. 2007; 25:2389–2396. [PubMed: 17557952]
6. Shavers VL, Brown ML. Racial and ethnic disparities in the receipt of cancer treatment. *J Natl Cancer Inst*. 2002; 94:334–357. [PubMed: 11880473]
7. Hodgson DC, Fuchs CS, Ayanian JZ. Impact of patient and provider characteristics on the treatment and outcomes of colorectal cancer. *J Natl Cancer Inst*. 2001; 93:501–515. [PubMed: 11287444]

8. Janssen-Heijnen MLG, Houterman S, Lemmens VE, et al. Prognostic impact of increasing age and co-morbidity in cancer patients: A population-based approach. *Crit Rev Oncol Hematol*. 2005; 55:231–240. [PubMed: 15979890]
9. Howell EA, Chen YT, Concato J. Differences in cervical cancer mortality among black and white women. *Obstet Gynecol*. 1999; 94:509–515. [PubMed: 10511350]
10. Li CI, Malone KE, Daling JR. Differences in breast cancer stage, treatment, and survival by race and ethnicity. *Arch Intern Med*. 2003; 163:49–56. [PubMed: 12523916]
11. Wong LL, Hernandez B, Kwee S, et al. Healthcare disparities in Asians and Pacific Islanders with hepatocellular cancer. *Am J Surg*. 2012; 203:726–732. [PubMed: 22227170]
12. Yu JC, Neugut AI, Wang S, et al. Racial and insurance disparities in the receipt of transplant among patients with hepatocellular carcinoma. *Cancer*. 2010; 116:1801–1809. [PubMed: 20143441]
13. Zak Y, Rhoads KF, Visser BC. Predictors of surgical intervention for hepatocellular carcinoma: race, socioeconomic status, and hospital type. *Arch Surg*. 2011; 146:778–784. [PubMed: 21422327]
14. Nathan H, Bridges JF, Schulick RD, et al. Understanding surgical decision making in early hepatocellular carcinoma. *J Clin Oncol*. 2011; 29:619–625. [PubMed: 21205759]
15. Nathan H, Hyder O, Schulick RD, et al. Surgical therapy for early hepatocellular carcinoma in the modern era: A 10-Year SEER-Medicare Analysis. *Ann Surg*. Jan 7.2013 [Epub ahead of print].
16. Nathan H, Segev DL, Bridges JF, et al. Influence of nonclinical factors on choice of therapy for early hepatocellular carcinoma. *Ann Surg Oncol*. 2013; 20:448–456. [PubMed: 22941170]
17. Steyerberg EW, Earle CC, Neville BA, et al. Racial differences in surgical evaluation, treatment, and outcome of locoregional esophageal cancer: a population-based analysis of elderly patients. *J Clin Oncol*. 2005; 23:510–517. [PubMed: 15659496]
18. Murphy MM, Simons JP, Ng SC, et al. Racial differences in cancer specialist consultation, treatment, and outcomes for locoregional pancreatic adenocarcinoma. *Ann Surg Oncol*. 2009; 16:2968–2977. [PubMed: 19669839]
19. Mayo SC, Gilson MM, Herman JM, et al. Management of patients with pancreatic adenocarcinoma: national trends in patient selection, operative management, and use of adjuvant therapy. *J Am Coll Surg*. 2012; 214:33–45. [PubMed: 22055585]
20. Bach PB, Guadagnoli E, Schrag D, et al. Patient demographic and socioeconomic characteristics in the SEER-Medicare database applications and limitations. *Medical Care*. 2002; 40:IV–19–IV–25.
21. Schneider EB, Hyder O, Brooke BS, et al. Patient readmission and mortality after colorectal surgery for colon cancer: impact of length of stay relative to other clinical factors. *J Am Coll Surg*. 2012; 214:390–398. discussion 398–399. [PubMed: 22289517]
22. Sheffield KM, Crowell KT, Lin YL, et al. Surveillance of pancreatic cancer patients after surgical resection. *Ann Surg Oncol*. 2012; 19:1670–1677. [PubMed: 22143577]
23. Elixhauser A, Steiner C, Harris DR, et al. Comorbidity measures for use with administrative data. *Medical Care*. 1998; 36:8–27. [PubMed: 9431328]
24. van Walraven C, Austin PC, Jennings A, et al. A modification of the Elixhauser comorbidity measures into a point system for hospital death using administrative data. *Medical Care*. 2009; 47:8.
25. Sonnenday CJ, Dimick JB, Schulick RD, et al. Racial and geographic disparities in the utilization of surgical therapy for hepatocellular carcinoma. *J Gastrointest Surg*. 2007; 11:1636–1646. discussion 1646. [PubMed: 17912593]
26. Steele SR, Chen SL, Stojadinovic A, et al. The impact of age on quality measure adherence in colon cancer. *J Am Coll Surg*. 2011; 213:95–103. discussion 104–105. [PubMed: 21601492]
27. Huang J, Li BK, Chen GH, et al. Long-term outcomes and prognostic factors of elderly patients with hepatocellular carcinoma undergoing hepatectomy. *J Gastrointest Surg*. 2009; 13:1627–1635. [PubMed: 19506976]
28. Cabibbo G, Genco C, Di Marco V, et al. Predicting survival in patients with hepatocellular carcinoma treated by transarterial chemoembolisation. *Aliment Pharmacol Ther*. 2011; 34:196–204. [PubMed: 21564144]

29. Dhanasekaran R, Kooby DA, Staley CA, et al. Prognostic factors for survival in patients with unresectable hepatocellular carcinoma undergoing chemoembolization with doxorubicin drug-eluting beads: a preliminary study. *HPB (Oxford)*. 2010; 12:174–180. [PubMed: 20590884]
30. Hsu CY, Huang YH, Chiou YY, et al. Comparison of radiofrequency ablation and transarterial chemoembolization for hepatocellular carcinoma within the Milan criteria: a propensity score analysis. *Liver Transpl*. 2011; 17:556–566. [PubMed: 21506244]
31. Bruix J, Sherman M. Management of hepatocellular carcinoma. *Hepatology*. 2005; 42:1208–1236. [PubMed: 16250051]
32. Mettlin CJ, Murphy GP, Cunningham MP, et al. The National Cancer Data Base report on race, age, and region variations in prostate cancer treatment. *Cancer*. 1997; 80:1261–1266. [PubMed: 9317177]

Figure 1.

Impact of patient characteristics on referral and treatment patterns. Partial R^2 values for each factor in multivariable logistic regressions models: (A) surgery, (B) interventional radiology, and (C) medical oncology. SES, socioeconomic status; TACE, transarterial chemoembolization; TAE, bland embolization.

Figure 2.

Impact of patient characteristics on survival. Partial R^2 values for the unadjusted, full multivariate adjusted, and full multivariate adjusted model with treatment are shown. SES, socioeconomic status.

Table 1

Characteristics of Patients with Hepatocellular Carcinoma from the SEER Registry from 1998 to 2007 (n = 6,752)

Characteristic	n	%
Demographic characteristics		
Age, y		
66–69	1,445	21.4
70–74	1,865	27.6
75–79	1,754	26.0
80	1,688	25.0
Male sex	4,472	66.2
Race		
White	4,022	59.6
Black	468	6.9
Asian	1,454	21.5
Hispanic	745	11.0
Other/unknown	63	0.9
US geographic region		
Northeast	1,313	19.5
West	3,753	55.6
Midwest	832	12.3
South	854	12.7
Year of diagnosis		
1998–99	684	10.1
2000–01	1,359	20.1
2002–03	1,646	24.4
2004–05	1,812	26.8
2006–07	1,251	18.5
Clinical characteristics		
Any comorbidity	3,811	56.4
Liver-related comorbidities		
Hepatitis C virus infection	1,890	28.0
Hepatitis B virus infection	609	9.0
Nonalcoholic cirrhosis	3,573	52.9
Cancer characteristics		
Localized	3,135	46.4
Regional	1,686	25.0
Distant	1,038	15.4
Unstaged	893	13.2

Characteristic	n	%
Multiple tumor foci [*]	1,977	42.6
Bilobar disease [†]	1,232	31.0
Size ≥ 5 cm [‡]	2,740	60.7
Early-stage/potentially curable disease	1,379	20.4

^{*} Data were missing for 2,115 patients.

[†] Data were missing for 2,780 patients.

[‡] Data were missing for 2,238 patients.

Table 2

Physician Consultation and Treatment Characteristics of Patients with Hepatocellular Carcinoma, from the SEER Registry from 1998 to 2007, Who Had One or More Physician Visits in the 6 Months after Diagnosis of Hepatocellular Carcinoma

Characteristic	Full cohort (n = 6,752)		Early-stage disease (n = 1,379)	
	n	%	n	%
Types of physicians ever consulted				
Primary care physicians	5,864	86.7	1,188	86.2
Specialists				
Seen by surgeon	3,790	56.1	1,058	76.7
Seen by interventional radiologist	2,214	32.8	588	42.6
Seen by medical oncologist	4,213	62.4	695	50.4
Seen by radiation oncologist	617	9.1	119	8.6
Seen by gastroenterologist	4,028	59.7	932	67.6
First course of treatment				
Surgery (resection/ablation/transplant)	1,195	17.7	541	39.2
Interventional oncology (TACE/TAE)	383	5.7	118	8.6
Systemic chemotherapy	1,416	21.0	311	22.6
Concurrent surgery and IAT	296	4.4	116	8.4
Supportive care only	3,758	55.7	409	29.7

IAT, intra-arterial therapy; TACE, transarterial chemoembolization; TAE, bland embolization.

Table 3
Odds Ratios (95% Confidence Intervals) from Multivariate Logistic Regression Analysis in the Full Cohort (n = 6,752)

Variable	Surgery	Seen by surgeon	Surgery and seen by surgeon	Interventional oncology	Seen by IR	Interventional oncology and seen by IR	Systemic chemotherapy	Seen by medical oncologist	Chemotherapy and seen by medical oncologist
Age, y									
66–69	3.11 (2.60–3.72)	2.05 (1.77–2.39)	2.48 (1.04–3.07)	1.85 (1.45–2.37)	1.47 (1.26–1.72)	1.43 (1.08–1.87)	1.98 (1.65–2.39)	0.91 (0.78–1.05)	2.19 (1.79–2.68)
70–74	2.26 (1.91–2.67)	1.75 (1.52–2.01)	1.82 (1.49–2.22)	1.77 (1.40–2.23)	1.60 (1.38–1.86)	1.25 (0.96–1.63)	1.89 (1.59–2.25)	1.04 (0.90–1.19)	1.96 (1.62–2.36)
75–79	1.85 (1.56–2.21)	1.53 (1.33–1.76)	1.54 (1.26–1.89)	1.25 (0.98–1.60)	1.43 (1.23–1.66)	0.92 (0.70–1.22)	1.56 (1.31–1.87)	1.19 (1.04–1.37)	1.50 (1.26–1.81)
80	1	1	1	1	1	1	1	1	1
Male sex	0.92 (0.81–1.04)	0.96 (0.87–1.07)	0.88 (0.76–1.02)	1.12 (0.94–1.33)	0.96 (0.86–1.07)	1.21 (1.00–1.47)	1.20 (1.05–1.36)	1.07 (0.96–1.18)	1.20 (1.04–1.38)
Race									
White	1	1	1	1	1	1	1	1	1
Black	0.75 (0.58–0.96)	0.89 (0.73–1.10)	0.76 (0.57–1.01)	0.66 (0.45–0.95)	0.78 (0.62–0.98)	0.81 (0.53–1.24)	0.73 (0.56–0.95)	0.99 (0.80–1.21)	0.72 (0.54–0.96)
Asian	1.14 (0.97–1.34)	1.16 (1.01–1.34)	1.07 (0.89–1.30)	1.06 (0.85–1.33)	1.12 (0.97–1.29)	1.00 (0.77–1.28)	1.03 (0.88–1.22)	0.77 (0.67–0.88)	1.19 (0.99–1.43)
Hispanic	0.78 (0.64–0.97)	0.93 (0.78–1.11)	0.72 (0.62–1.01)	1.08 (0.82–1.42)	1.02 (0.86–1.23)	1.07 (0.79–1.46)	1.07 (0.87–1.31)	0.87 (0.73v1.01)	1.12 (0.90–1.40)
Other/unknown	0.46 (0.22–0.94)	0.74 (0.44–1.25)	0.46 (0.20–1.05)	1.26 (0.59–2.71)	0.91 (0.53–1.57)	1.64 (0.65–4.10)	0.63 (0.32–1.26)	0.80 (0.48–1.34)	0.72 (0.34–1.53)
SES top 3 quintiles	1.20 (1.05–1.35)	1.07 (0.96–1.19)	1.21 (1.05–1.41)	0.99 (0.83–1.18)	1.09 (0.97–1.22)	0.93 (0.77–1.13)	0.98 (0.86–1.11)	0.98 (0.88–1.10)	0.99 (0.86–1.14)
US geographic region									
Northeast	1.82 (1.54–2.14)	1.72 (1.49–1.99)	1.46 (1.20–1.78)	2.10 (1.71–2.59)	1.20 (1.04–1.39)	2.12 (1.67–2.69)	1.19 (1.01–1.40)	1.19 (1.03–1.38)	1.11 (0.93–1.33)
West	1	1	1	1	1	1	1	1	1
Midwest	1.09 (0.90–1.33)	1.34 (1.13–1.58)	0.89 (0.71–1.12)	0.94 (0.70–1.25)	0.58 (0.48–0.70)	1.68 (1.20–2.36)	0.63 (0.51–0.79)	1.07 (0.91–1.27)	0.59 (0.47–0.75)
South	1.11 (0.91–1.36)	1.46 (1.23–1.74)	0.92 (0.73–1.16)	0.93 (0.69–1.24)	1.03 (0.86–1.22)	0.97 (0.70–1.34)	0.67 (0.54–0.83)	1.02 (0.86–1.20)	0.63 (0.50–0.79)
Elixhauser co-morbidity score									
<7	1	1	1	1	1	1	1	1	1
7	1.11 (0.98–1.25)	0.96 (0.86–1.07)	1.20 (1.03–1.40)	1.32 (1.11–1.56)	1.16 (1.04–1.30)	1.18 (0.98–1.43)	1.01 (0.89–1.16)	0.75 (0.67–0.83)	1.16 (1.00–1.34)
SEER stage									
Localized	2.43 (2.11–2.78)	1.70 (1.50–1.93)	2.20 (1.87–2.58)	0.95 (0.79–1.15)	1.06 (0.94–1.20)	0.87 (0.70–1.08)	0.93 (0.81–1.07)	0.70 (0.62–0.80)	1.11 (0.95–1.30)
Regional	1	1	1	1	1	1	1	1	1
Distant/unstaged	0.32 (0.27–0.39)	0.53 (0.46–0.61)	0.40 (0.32–0.50)	0.58 (0.46–0.73)	0.61 (0.53–0.71)	0.84 (0.65–1.10)	0.67 (0.57–0.79)	1.04 (0.91–1.20)	0.66 (0.55–0.78)

IR, interventional radiology; SES, socioeconomic status.

Table 4

Characteristics of Patients with Hepatocellular Carcinoma from the Surveillance, Epidemiology and End Results Registry from 1998 to 2007 (n = 6,752)

Demographic characteristics	Surgery, n (%)	Seen by surgeon, n (%)	TACE/TAE, n (%)	Seen by IR, n (%)	Systemic chemotherapy, n (%)	Seen by medical oncologist, n (%)
Age, y						
66–69	528 (36.5)	909 (62.9)	188 (13.0)	501 (34.7)	362 (25.1)	845 (58.5)
70–74	568 (30.5)	1112 (59.6)	233 (12.5)	681 (36.5)	451 (24.2)	1,159 (62.1)
75–79	458 (26.1)	980 (55.9)	159 (9.1)	589 (33.6)	363 (20.7)	1,159 (66.1)
80	295 (17.5)	789 (46.7)	125 (7.4)	443 (26.2)	240 (14.2)	1,050 (62.2)
Sex						
Male	1,215 (27.2)	2,514 (56.2)	492 (11.0)	1,462 (32.7)	994 (22.2)	2,827 (63.2)
Female	634 (27.8)	1,276 (56.0)	213 (9.3)	752 (33.0)	422 (18.5)	1,386 (60.8)
Race						
White	1,103 (27.4)	2,268 (56.4)	429 (10.7)	1,284 (31.9)	815 (20.3)	2,607 (64.8)
Black	109 (23.3)	259 (55.3)	35 (7.5)	123 (26.3)	74 (15.8)	299 (63.9)
Asian/Pacific Islander	451 (31.0)	844 (58.1)	150 (10.3)	534 (36.7)	339 (23.3)	825 (56.7)
Hispanic	176 (23.6)	390 (52.4)	83 (11.1)	253 (34.0)	178 (23.9)	446 (59.9)
Other/unknown	<11	29 (46.0)	<11	20 (31.8)	<11	36 (57.1)
Locale						
Urban	1,681 (27.8)	3,358 (55.5)	638 (10.6)	2,015 (33.3)	1,308 (21.6)	3,918 (63.1)
Rural	168 (23.9)	432 (61.5)	67 (9.5)	199 (28.4)	108 (15.4)	394 (56.1)
Socioeconomic status						
Lower 2 quintiles	676 (24.4)	1,514 (54.7)	270 (9.8)	861 (31.1)	560 (20.2)	1,723 (62.2)
Upper 3 quintiles	1,173 (29.5)	2,278 (57.1)	435 (10.9)	1,353 (34.0)	856 (15.4)	2,490 (62.5)
US geographic region						
Northeast	426 (32.4)	803 (61.2)	210 (16.0)	467 (35.6)	315 (24.0)	884 (67.3)
West	986 (26.3)	1,996 (53.2)	356 (9.5)	1,286 (34.3)	844 (22.5)	2,255 (60.1)
Midwest	211 (25.4)	477 (57.3)	69 (8.3)	182 (21.9)	123 (14.8)	536 (64.4)
South	226 (26.5)	514 (60.2)	70 (8.2)	279 (32.7)	134 (15.7)	538 (63.0)
Clinical characteristics						
Elixhauser's comorbidity score						
<7	1,255 (26.3)	2,670 (55.9)	459 (9.6)	1,515 (31.7)	994 (20.8)	3,083 (64.6)
7	594 (30.2)	1,120 (56.6)	246 (12.4)	699 (35.3)	422 (21.3)	1,130 (57.1)
Cancer characteristics						
Localized	1,287 (41.1)	2,099 (67.0)	359 (11.5)	1,146 (36.6)	690 (22.0)	1,795 (57.3)
Regional	385 (22.8)	922 (54.7)	198 (11.7)	587 (34.8)	396 (23.5)	1,113 (66.0)
Distant	84 (8.1)	402 (38.7)	68 (6.6)	254 (24.5)	156 (15.0)	753 (72.5)
Unstaged	93 (10.4)	367 (41.1)	80 (9.0)	227 (25.4)	174 (19.5)	552 (61.2)

Table 5

Hazard Ratios (95% Confidence Intervals) from Survival Analysis for Full Cohort (n = 6,752)

Variable	HR univariate	HR adjusted	HR adjusted for treatment
Specialist consultation	0.62 (0.56–0.70)	0.71 (0.63–0.79)	0.82 (0.70–0.94)
Age, y			
66–69	0.80 (0.73–0.88)	0.79 (0.73–0.85)	0.95 (0.88–1.02)
70–74	0.88 (0.81–0.95)	0.86 (0.80–0.92)	0.99 (0.93–1.07)
75–79	0.91 (0.83–0.99)	0.89 (0.83–0.95)	0.98 (0.91–1.05)
80	1	1	1
Male sex	0.96 (0.90–1.02)	1.01 (0.96–1.06)	1.00 (0.94–1.05)
Race			
White	1	1	1
Black	1.05 (0.93–1.18)	1.03 (0.93–1.14)	1.00 (0.90–1.10)
Asian	0.87 (0.81–0.94)	0.89 (0.83–0.95)	0.90 (0.83–0.96)
Hispanic	1.05 (0.95–1.15)	0.99 (0.91–1.08)	0.97 (0.89–1.06)
Other/unknown	1.07 (0.77–1.48)	1.10 (0.85–1.44)	0.94 (0.73–1.23)
SES top 3 quintiles	0.91 (0.85–0.96)	0.94 (0.89–0.99)	0.96 (0.91–1.01)
US geographic region			
Northeast	1.00 (0.93–1.08)	0.90 (0.84–0.97)	1.00 (0.93–1.08)
West	1	1	1
Midwest	1.07 (0.97–1.17)	1.05 (0.97–1.14)	1.07 (0.98–1.16)
South	1.08 (0.98–1.18)	1.08 (0.99–1.18)	1.10 (1.01–1.19)
Elixhauser comorbidity score 7	0.94 (0.88–1.00)	0.97 (0.92–1.02)	1.00 (0.95–1.06)
SEER stage			
Localized	0.73 (0.68–0.78)	0.67 (0.63–0.72)	0.74 (0.69–0.79)
Regional	1	1	1
Distant/unstaged	1.34 (1.23–1.45)	1.37 (1.28–1.46)	1.24 (1.15–1.32)

HR, hazard ratio; SES, socioeconomic status.