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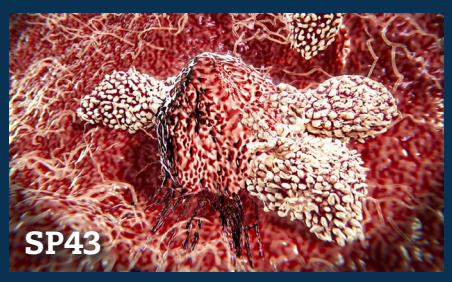

REVIEW

Humanistic and Economic Burden of Hepatocellular Carcinoma: Systematic Literature Review

Christine G. Kohn, PharmD; Prianka Singh, PharmD, MPH; Beata Korytowsky, MA; Jonathan T. Caranfa, PharmD; Jeffrey D. Miller, MS; Bruce E. Sill, PharmD, MS; Alexander C. Marshall, PharmD, MPH; and Neehar D. Parikh, MD, MS

INTRODUCTION

Hepatocellular carcinoma (HCC) is a primary malignancy of the liver occurring predominantly in patients with underlying chronic liver disease. Worldwide, more than half a million new cases of HCC are diagnosed annually,[1-3] with approximately 31,000 new cases expected in the United States in 2018.[1] Unlike most other cancers, the incidence of and deaths from HCC in the United States are rising.[4,5]

HCC and its treatment impose a large humanistic burden on patients and caregivers, as well as an economic burden on patients and payers. Understanding the scale of these burdens (and changes over time) is important for making reimbursement decisions. To gain a current perspective, we performed a systematic review of the direct and indirect costs of HCC and its treatment and the humanistic aspects of HCC and impacts on patient quality of life (QOL).

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ABSTRACT

OBJECTIVE: Worldwide, more than half a million new cases of hepatocellular carcinoma (HCC) are diagnosed annually. The incidence of HCC in the United States is rising with an estimated 31,000 new cases in 2018. Disease prognosis remains poor, with a 5-year survival rate across all disease stages estimated between 10%-20%, and 3% for those diagnosed with distant disease. Although morbidity is significant, especially among patients with advanced-stage disease, limited information exists on the humanistic and economic burden of HCC.

STUDY DESIGN: Systematic literature review.

METHODS: A systematic literature search was conducted using MEDLINE and Embase computerized databases January 1, 2007, to November 1, 2017) to identify studies that evaluated adult HCC populations and quantified humanistic (utility or patient-reported) or economic (costs or resource-utilization) outcomes.

RESULTS: Fifty-seven studies met the inclusion criteria. Overall quality of life (QOL) reported by patients with HCC is poor; those with advanced disease have lower health status/QOL scores compared with those diagnosed at earlier stages of disease. HCC imposes a substantial healthcare resource utilization and cost impact on both patients and payers in the United States. Direct costs of HCC reported in the reviewed literature varied considerably.

CONCLUSIONS: The economic and humanistic burden of HCC in the United States is substantial. Patients need effective new therapies that prolong survival and positively affect QOL. Healthcare payers need to consider clinical outcomes while balancing economic and QOL implications. With the advent of new therapies, particularly immuno-oncology (I-O) therapies, additional research is needed to gain understanding of the economic and humanistic aspects of HCC and its treatment.

METHODS

A systematic literature search was conducted using the MEDLINE and Embase computerized databases from January 1, 2007, to November 1, 2017. This time frame allowed identification of studies performed in the past decade, while excluding older studies using outdated or nonguideline recommended treatments. The search strategy is available in **eAppendix 1**.

Two investigators independently reviewed all citations and screened all potentially relevant, full-text articles for inclusion using a priori defined criteria, with disagreement resolved through discussion. To be eligible for inclusion, studies had to: employ an observational or experimental study design; evaluate a treated adult HCC population; provide data quantifying economic (costs or resource utilization) or QOL outcome data; and be an English-language, full-text publication. Studies investigating treatments for HCC were required to use an evidence-based or standard-of-care approach. Additional inclusion/exclusion criteria are available in **eAppendix 2**. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram is depicted in **eAppendix 3**.[6]

RESULTS

The initial search yielded 2147 nonduplicate citations (eAppendix 3), of which 57 studies representing 59 analyses met the inclusion criteria. Of these, 5 were included in health utility analyses (**Table 1**[7-11]), 24 in patient-reported outcome (PRO) and QOL analyses (**Tables 2**[7,9,12-33] and **3**[7,9,12-33]), 14 in costs and resource utilization analyses (**Tables 4**[34-47] and **5**[34-47]), and 16 in cost-effectiveness analyses (**eAppendices 4-8**[48-53]).

Humanistic Burden

Health Utility Analyses/Measures. Utility measures are expressed as a numeric value from 0 to 1, with 0 representing death and 1 representing perfect health.[54] Five studies reported health utility values among patients with HCC, with lower scores among patients with advanced HCC (aHCC), even while on systemic treatment.[7-11] Although clinical trial data evaluating utilities in HCC exist,[7-9] there is a lack of comparable real-world utility data for these patients (Table 1).

Levy et al interviewed patients with hepatitis B virus (HBV) infection and uninfected respondents using health-state descriptions related to HBV infection (HBV combined with compensated and decompensated cirrhosis, HCC, and liver transplantation) to elicit health utility scores.[11] HCC was among the health states with the lowest mean health utility score in these patients.[11] Similarly, a study in Canadian patients with HCC and HBV found that lower QOL scores in this population were associated with cirrhosis and HCC, rather than with the infection itself.[10] This study reported values of 0.77 to 0.85 for patients with HCC and HBV, depending on the utility assessment instrument used.[10]

Three multicenter, randomized controlled trials (RCTs) reported utility values in patients with aHCC categorized as Child-Pugh class A with Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1.[7-9] Although no statistical analysis was provided, utility values declined as treatment continued.

QOL. Twenty-four studies reported results related to PRO measures evaluating QoL and symptoms in patients with HCC[7,9,12-33]; US-only populations were included in 10 studies (Tables 2 and 3). A detailed summary of the data can be found in **eAppendix 9**.

QOL in aHCC Populations. Patients with aHCC have lower global health scores compared with patients who are diagnosed at earlier stages of disease; the median European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30) score in Barcelona Clinic Liver Cancer (BCLC) stage A disease is 54, declining to 47 and 39 for stages B/C and D, respectively.[23] Kaiser et al reported that 90% of patients with aHCC identified pain as an important concern, which often caused significant functional limitations. In most cases, pain was ongoing and began within 6 months of diagnosis. Other concerns included common symptoms of HCC: diarrhea, fatigue, and loss of appetite; skin toxicity also appeared to be a key issue. It is important to note that most patients in this study received treatment with sorafenib.[22] A small study (n = 18) found that outpatients with aHCC nearing end-of-life reported pain and lack of energy as their most frequent and distressing symptoms; other symptoms included drowsiness and problems with sexual interest or activity.[12]

QOL in HCC Therapies. QOL can reflect benefits or harms associated with therapeutic interventions from a patient perspective. Using the Medical Outcomes Study Short Form 36 (SF-36), previously untreated patients with HCC

reported improved mental health during the first 4 months of treatment with transarterial chemoembolization (TACE) and showed improvement in bodily pain, but worsening vitality scores, after the first TACE procedure.[31] Hinrichs et al prospectively evaluated QOL in 79 patients before and 2 weeks after TACE. Patients reported a 12.1% decrease in global health, as well as major decreases in role, physical, and social functioning; life-impairing symptoms including pain, loss of appetite, and fatigue increased, compared with baseline.[13] Doxorubicin drug-eluting bead TACE (DEB-TACE) demonstrated long-term preservation of QOL among previously untreated patients with HCC with no significant change in any SF-36 domain at 3, 6, and 12 months post–DEB-TACE compared with baseline.[17] A prospective observational study suggested that, despite having more advanced disease (higher tumor burden and BCLC stage), patients with HCC who received yttrium-90 (Y90) radioembolization showed significant increases in several QOL domains, driven in part by social and functional well-being, compared with TACE-treated patients.[28] Chie et al reported that QOL outcomes were similar in HCC patients receiving surgery or embolization, while ablation was less effective at maintaining QOL.[17]

In an RCT comparing sorafenib to selective internal radiotherapy (SIRT) with Y90 in patients with locally advanced or intermediate-stage HCC previously treated with TACE, the global health status subscore was significantly better in the SIRT group versus the sorafenib group.[15] In a multicenter, multinational phase 2 trial, HCC patients receiving combination therapy with sorafenib and everolimus reported a greater decrease in physical well-being and mood, compared with those receiving sorafenib alone, despite worse baseline mood scores in the latter group.[16] Finally, a small, real-world study of sorafenib in patients with aHCC reported significantly decreased overall and domain QOL scores and severe drug-related adverse events (eg, fatigue, hand-foot-skin reaction, thrombocytopenia), leading to a cumulative therapy discontinuation rate of 33%.[25]

Economic Burden

Costs and Healthcare Resource Utilization. Fourteen studies reported results related to costs or resource utilization associated with HCC in the United States (Table 4, eAppendix 10).[34-47]

Direct Costs. Direct cost outcomes varied markedly across the studies (Table 5). For studies reporting overall direct costs for patients with HCC regardless of stage or treatment, per patient per year (PPPY) costs ranged from $29,354[47] to $58,529,[45] with median overall costs of up to $176,456 per patient.[39]

Reported costs varied by stage of disease at diagnosis and by age. In the Surveillance, Epidemiology, and End Results (SEER) registries and linked Medicare (SEER-Medicare) database, 15-year direct costs for HCC were estimated at $54,829, with the highest costs incurred by those with localized disease ($78,553), followed by regional ($49,492) and distant disease ($34,352).[44] In contrast, patients with distant HCC had the highest mean total per patient per month (PPPM) costs ($9585) followed by regional ($8072) and localized disease ($7265); inpatient stays and physician visits were the primary cost drivers.[44] Another SEER-Medicare study found that localized disease accounted for the highest proportion (44.5%) of the total cost of illness, followed by regional (31%) and distant disease (14%).[47] The authors reported that, across age strata, younger patients generally incur higher healthcare costs than older patients.[47]

Two studies in the SEER-Medicare database examined costs stratified by treatment. Shaya et al reported that patients who received no treatment incurred cumulative expenditures of $23,600 to $38,300 in medical costs; this figure nearly doubled for systemic chemotherapy and radiation, while patients treated with liver-directed therapies (ablation and/or TACE) incurred costs of $69,000 to $97,500.[41] There was a general trend towards decreasing costs as disease staging increased; the highest costs were associated with stage I disease, and the lowest with stage IV.[41] These increased costs are likely due to longer survival or increased healthcare utilization associated with specific treatment options, such as surgical resection and associated inpatient stays, compared to the lack of intervention and treatments beyond first-line therapy for patients with more advanced disease. Breunig et al found that for patients receiving TACE, cumulative per-patient Medicare expenditures were $74,788 for 1 course of TACE, increasing with each additional course of therapy.[42] For patients undergoing 4 courses of TACE, cumulative Medicare-paid expenditures were $148,878; those receiving ≥4 TACE courses lived at least 1 additional year versus patients receiving 1 course of TACE.[42] Electronic health data from a transplant center showed that patients with liver transplants incurred higher overall monthly costs ($7492) than nontransplant patients ($4802).[39]

A more recent study using the SEER-Medicare database found that patients with HCC had increased levels of resource utilization compared with noncancer controls, with both inpatient and outpatient charges between 1.15 and 1.55 times higher than charges incurred by non-HCC patients.[34] A study using National (Nationwide) Inpatient Sample (NIS) data from 2005 to 2009 found an increase in the number of inpatient cases of HCC; although inpatient mortality decreased and length of stay remained stable, HCC-associated inpatient charges continued to increase, with total national HCC charges rising from $1.0 billion in 2005 to $2.0 billion in 2009. These findings are consistent with reports confirming an increasing prevalence of HCC in the United States.[43] Another NIS analysis using data from 2002 to 2011 found a decreasing inpatient mortality rate, from 13.5% to 9.9%, during this period; this trend was more prominent for patients admitted with a primary diagnosis of HCC (17% vs 9.8%, respectively) and length of stay (6.5 days vs 5.6 days, respectively).[36] Nevertheless, HCC-related resource utilization continued to increase, with 24,024 hospital admissions in 2002 (10,762 related to HCC as the primary diagnosis) and 50,609 in 2011 (16,350 related to HCC as the primary diagnosis).[36] This may be due not only to increased use of hospital-based healthcare resources, but also to expanding treatment options across the HCC treatment continuum.

Indirect Costs. Two studies included data on indirect costs, specifically reporting costs of lost productivity (eg, lost workdays due to cancer). When calculated using published estimates and salary data, annual estimates of lost productivity were $3553 per patient[47]; when calculated using employee claims and employer payroll data, indirect costs were estimated to be $3594 per patient per 6-month period.[40] In the SEER-Medicare database, the overall (direct and indirect) annual cost of HCC in the United States was estimated to be $454.9 million, with lost productivity accounting for 10.8% ($49.1 million) of the total.[47] Lost productivity was reported to be highest among patients with localized HCC.[47]

Additional Resource Utilization. Despite evidence-based guidelines, patients receiving no treatment are common in studies examining the overall HCC population. A US MarketScan study reported that about 39% of cases did not receive any proven HCC treatment,[46] while a SEER-Medicare database study found that approximately 60% of those diagnosed received no treatment.[41] Shaya et al estimated that more than 33% of untreated patients were diagnosed with early disease (stage I or II), and untreated patients were prevalent at all ages and levels of comorbidity and liver dysfunction; this figure may be falsely elevated since sorafenib use could not be captured in the data set. Of note, the study found a clear survival advantage among patients who had undergone any treatment versus no treatment.[41]

Hospice care is an underutilized measure in patients with HCC, which affords significant savings in healthcare expenditure and resource utilization. In a US MarketScan study, approximately 15% of patients treated from 2002 to 2008 received hospice care.[46] In a SEER-Medicare study involving 7992 patients who died after HCC diagnosis from 2004 to 2011, 63% received hospice care.[37] Although the median time from the first claim for hospice care to death was only 18 days, these patients reported lower rates of emergency department visits not resulting in hospitalization (6.1% vs 16.2%), hospitalization (7.9% vs 47.8%), intensive care unit stays (2.8% vs 25.3%), and inpatient mortality (3.5% vs 58.4%).[37] A study performed using the National Cancer Database, which retrospectively captures approximately 70% of all patients treated for cancer in the United States, included 3267

patients with unresectable HCC receiving palliative therapy from 1998 to 2011.[35] Of these, 8.8% received surgical palliation, 25.3% received palliative radiotherapy, 26.8% received palliative chemotherapy, and 32.6% received pain management therapy; 6.4% received a combination of therapies.[35]

Economic Models. We identified and reviewed 6 articles that focused on economic models in patients with HCC from a US perspective (eAppendices 4-5)[48-53] and identified 10 additional articles that evaluated economic models in other countries (eAppendices 6-7). Details of the included economic model studies are reported in eAppendix 8.

DISCUSSION

The recent introduction of the tyrosine kinase inhibitors lenvatinib and regorafenib, and nivolumab, a novel immuno-oncology (I-O) therapy, has ended a decade-long hiatus in new aHCC treatment options. As the HCC treatment landscape expands, healthcare providers and payers will need firm data about the clinical, economic and humanistic value of new therapies. This systematic review underlines the substantial humanistic and economic burdens associated with aHCC—a condition with a rising prevalence and limited treatment options.

Humanistic Burden

Evidence from this review illustrates the negative impact of HCC on QOL, most notably due to symptoms and effects of the disease itself, disease progression, and adverse effects of treatment. The impact on QOL appears to be greatest in aHCC, where therapy goals include relief of symptoms and improvements in well-being.[15] The literature suggests that continual evaluation of QOL throughout treatment can preserve or improve QOL in patients with aHCC, as knowledge of timing, frequency, and duration of symptoms can improve communication and expectations between patients and their healthcare providers.[13,22,41]

Although utility and QOL end points are increasingly being included in cancer studies, this review found reporting on these metrics for HCC to be limited. Such information is a critical component of value-based oncology care and, in addition to clinical and health economic data, stakeholders are increasingly interested in humanistic aspects of therapies to guide clinical, regulatory, and reimbursement decisions.[55] Consequently, QOL and other PROs will play an important role in health technology assessments, ultimately impacting value-based care in patients with HCC.[55,56] This review revealed important limitations of existing cancer-specific PRO measures for evaluating I-O therapies. Many PRO measures were not designed to evaluate I-O therapies with their unique attributes (eg, delayed response, longer treatment duration, prolonged survival), and may not conform to traditional benchmarks and other measures that would accurately account for the benefits and tolerability of I-O therapies. Accurate measurement of QOL using validated disease- and treatment-specific instruments will be critical in evaluating therapies, creating a potential need to develop unique QOL instruments as novel HCC therapies (eg, I-O therapy) emerge.

Economic Burden

This review has confirmed that aHCC imposes a substantial healthcare resource utilization and cost impact on both patients and payers in the United States. Direct costs of HCC varied considerably between studies, likely due to differences in expenditures across practices and healthcare systems, treatment (including the increased use of sorafenib as standard of care), study design, and cost identification, measurement, and collection. Costs also varied by stage of disease at diagnosis.

This review has also revealed important knowledge gaps. Most of the HCC cost analysis studies are outdated, especially in light of recent developments in the HCC treatment landscape. Moreover, while most of the reviewed studies reported direct overall costs of HCC, there are few data on indirect costs, such as time required to obtain care, caregiver costs, out-of-pocket expenses, and reduced work productivity. Fewer than 20% of the reviewed studies evaluated indirect costs, with limited data showing an increase in lost productivity costs associated with HCC diagnosis. This highlights a clear need for additional studies to fully understand the economic burden associated with disease stage, advanced disease, and therapeutic options offered to patients with HCC. Future studies should aim to integrate both cost and QOL end points to more fully recognize the complexities and value of I-O treatment.

Limitations

This review has several potential limitations. The evaluation of humanistic and economic outcomes was not the primary objective of many of the reviewed studies and thus these outcomes may have been selectively and inconsistently reported. Due to inconsistent or incomplete reporting of PRO and economic end points, many studies failed to meet the inclusion criteria. While this review included over 50 studies, there are potential issues with external validity. Heterogeneity of study populations, study design, methods for data collection (across all outcomes), and differing methods in end point measurement preclude a more rigorous description of the humanistic and economic burden of HCC. Finally, as with any review, there is the possibility of publication bias, although we decreased this risk through our systematic methodology and broad inclusion criteria that did not exclude any observational or experimental study design.

CONCLUSIONS

The economic and humanistic burden of HCC in the United States is substantial; patients need effective new therapies that not only prolong survival, but also positively affect QOL. Likewise, healthcare payers need to consider patient clinical outcomes, including QOL, when determining value. However, the literature on the economic and humanistic burden of HCC is limited and outdated, and it does not accurately reflect current guidelines or the rapidly changing therapeutic landscape. The advent of novel therapies for aHCC, and promising emerging HCC therapies, may bring meaningful improvements in survival and QOL to patients. Additional research, including comparative effectiveness studies, will be needed to develop a better understanding of the economic and humanistic aspects of HCC and these emerging therapies. ◆

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DISCLOSURES

CDK and JDM are employed by IBM Watson Health, which received contracted funding from Bristol-Myers Squibb to conduct the study and prepare the manuscript. PS, BK, BES, ACM are employed by Bristol Myers-Squibb, which funded this study. NDP reports consultancies with Bristol-Myers Squibb. JTC reports no conflicts of interest.

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TABLE 1. Health State Utility Values in Patients With HCC

Reference	Country	Study Design	Utility Instrument	Population	Population Characteristics	Utility Estimates	Key Findings
Kang 2015[7] (N = 202)	Multicenter (Belgium, China, France, Germany, Hong Kong, Hungary, Italy, Japan, Korea, Republic of Slovakia, Taiwan, UK, US)	RCT Questionnaires at baseline, every 4 weeks, EOT	EQ-5D EQ-VAS	Locally advanced or metastatic HCC, previously treated	Child-Pugh A: 100% BCLC-B: 16% BCLC-C: 80% ECOG PS 0-1: 100% Axitinib vs placebo	**EQ-5D (axitinib/placebo)** Overall between-treatment comparison 0.67/0.79 **EQ-VAS (axitinib/placebo)** Overall between-treatment comparison 68.67/75.70	The overall between-treatment comparisons of the utility measures favored the placebo group
Zhu 2015[8] (N = 720)	Multicenter (Europe, North and South America, the Asia-Pacific region)	RCT Questionnaires every 6 weeks, EOT	EQ-5D EQ-VAS	Advanced HCC, previously untreated	Child-Pugh class A: 100% ECOG PS 0 or 1:100% BCLC-C: 87% SOR+E vs SOR	**EQ-5D (SOR+E/SOR only); EQ-VAS (SOR+E/SOR only)** Cycle 1: 0.777/0.774; 74.4/74.7 Cycle 2: 0.753/0.749; 72.6/72.9 Cycle 3: 0.728/0.724; 70.9/71.2 Cycle 4: 0.704/0.700; 69.2/69.4 Cycle 5: 0.679/0.675; 67.4/67.7 Cycle 6: 0.654/0.651; 65.7/65.9	Utility values declined as treatment continued/ disease progressed
Zhu 2015[9] (N = 565)	Multicenter (North and South America, Europe, East Asia)	RCT Questionnaires at baseline, cycle 4, 10, 16, EOT	EQ-5D	Advanced HCC, previously treated with SOR	Child-Pugh A: 98% BCLC-B: 12% BCLC-C: 88% ECOG PS 0-1: 100% Ramucirumab vs placebo	**Change from baseline** Ramucirumab/placebo: Cycle 4: –0.038/–0.046 Cycle 10: –0.054/0.003 Cycle 16: –0.062/–0.012 EOT: –0.129/–0.144	Utility values declined as treatment continued/ disease progressed
Woo 2012[10] (N = 23)	Canada	Survey	Standard gamble EQ-5D EQ-VAS HUI3	HCC+HBV	Mean age: 54 years Asian ethnicity: 69%	Standard gamble: 0.84 EQ-5D: 0.81 EQ-VAS: 0.77 HUI3: 0.85	Lower QOL scores did not appear to be associated with HBV infection itself, but with cirrhosis and HCC
Levy 2008[11] (N = 39)	US, Canada, UK, Spain, China, Hong Kong	Structured questionnaire by trained interviewers	Standard gamble	HCC+HBV HCC without HBV	NR	HCC without HBV = 0.41; HCC+HBV = 0.38 Age- and sex-adjusted values: HCC without HBV/HCC+HBV US: 0.43/0.43 UK: 0.42/0.42 Spain: 0.48/0.48 Canada: 0.47/0.46 China: 0.31/0.31 Hong Kong: 0.38/0.38	HCC had a strong impact on decrements in utility values The observed intercountry differences suggest that economic evaluations may benefit from country-specific utility estimates

BCLC indicates Barcelona Clinic Liver Cancer; E, everolimus; ECOG PS, Eastern Cooperative Oncology Group performance status; EOT, end of treatment; EQ-5D, EuroQol-5 Dimension; EQ-VAS, EuroQol Visual Analog Scale; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HU13, Health Utilities Index Mark 3; NR, not reported; RCT, randomized controlled trial; SF-6D, Short Form 6D; SOR, sorafenib; UK, United Kingdom; US, United States; VAS, visual analog scale.

TABLE 2. Characteristics of Included QOL and PRO Studies

Reference	Study Design	Country	Patient Population	Age, Mean, Years	HCV, %	HBV, %	ALD, %
Hansen 2017[12] (n = 18)	P, longitudinal descriptive	US	Advanced HCC	63	22	6	NR
Hinrichs 2017[13] (n = 79)	P, single-center study	Germany	HCC	66	NR	NR	NR
Sternby 2018[14] (n = 185)	P, open cohort	Norway, Sweden	HCC, any stage	67	50	8	41
Vilgrain 2017[15] (n = 459)	RCT	France	Locally advanced HCC	Median: 66 (SIRT)/65 (SOR)	23	7	59
Koeberle 2016[16] (N = 106)	RCT	Europe	Advanced HCC	Median: 65 (SOR)/66 (SOR+E)	29	17	50
Chie 2015[17] (N = 171)	P, non-randomized, longitudinal	Europe, Asia	HCC	62	NR	NR	NR
Diouf 2015[18] (N = 271[a])	RCT	France	Advanced HCC	<65:33% ≥65: 67%	–	–	–
Kang 2015[7] (N = 202)	RCT	Belgium, China, France, Germany, Hong Kong, Hungary, Italy, Japan, Korea, Republic of Slovakia, Taiwan, UK, US	HCC, previously treated	Median: 61 (axitinib)/63 (placebo)	25	51	–
Klein 2015[19] (N = 222)	P, single-arm, longitudinal	Canada	HCC, intrahepatic cholangiocarcinoma, or liver metastases	Median: 67	22	20	16
Xing 2015[20] (N = 118)	P, Obs, single-arm, longitudinal	US	Unresectable HCC, previously untreated	60	69	10	4
Zhu 2015[9] (N = 565)	RCT	Multicenter, 27 countries	Advanced HCC, previously treated with SOR	63	27	36	NR
Butt 2014[21] (N = 304)	Obs, longitudinal	US	HCC	63.5	NR	NR	NR
Kaiser 2014[22] (N = 10)	Semi-structured interview	US	Advanced HCC	58	HBV/HCV: 50	NR	NR
Meier 2015[23] (N = 130)	P, Obs	US	Previously untreated HCC	Median: 57	73	6	9
Steel 2014[24] (N = 321)	P, Obs	US	HCC or cholangiocarcinoma	65	NR	NR	NR
Brunocilla 2013[25] (N = 36)	P	Italy	HCC	Median: 67	–	–	–
Johnson 2013[26] (N = 1155)	RCT	Multi-country; including US	Advanced HCC, no prior systemic therapy	Median: 60 (SOR)/61 (brivanib)	20	44	16
Montella 2013[27] (N = 60)	R, longitudinal	Italy	Elderly patients with aHCC	Median: 76	68	5	2
Salem 2013[28] (N = 56)	P, Obs, longitudinal	US	HCC	67	NR	NR	NR
Soliman 2013[29] (N = 41)	P	Canada	HCC or liver metastases	Median: 61	12	24	12
Toro 2012[30] (N = 51)	Single-center	Italy	HCC	70	–	–	–
Wible 2010[31] (N = 73)	P, single-center, longitudinal	US	Previously untreated HCC	62	NR	NR	NR
Sun 2008[32] (N = 22)	P, Obs, longitudinal	US	HCC	59	HBV/HCV: 56	NR	NR
Steel 2007[33] (N = 83)	P, cross-sectional	US	Previously untreated HCC	58	30	9	28

aHCC indicates advanced HCC; ALD, alcoholic liver disease; BPI, Brief Pain Inventory; BSC, best supportive care; CLD, chronic liver disease; DEB-TACE, drug-eluting bead TACE; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; EORTC QLQ-HCC18, EORTC QLQ-HCC specific; FACIT-Sp-12, Functional Assessment of Chronic Illness Therapy–Spirituality Subscale; FACT-Hep, Functional Assessment of Cancer Therapy–Hepatobiliary; FHSI-8, FACT Hepatobiliary Symptom Index 8; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; KPS, Karnofsky performance status; Obs, observational; NR, not reported; P, prospective; PRO, patient reported outcome; PS, performance status; QOL, quality of life; R, retrospective; RCT, randomized controlled trial; RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy; SF-36, Short Form 36; SIRT, selective internal radiotherapy; SOR, sorafenib; TACE, transarterial chemoembolization; UK, United Kingdom; US, United States; WHO, World Health Organization; Y90, yttrium 90.
[a]214 for patients with baseline QOL scores.

PRO	Measurement Timing	Therapies Evaluated	Disease Stage	Child-Pugh, %	Baseline PS
Memorial Symptom Assessment Scale	Once a month × 6 months	SOR; TACE; TACE + SOR; Clinical Trial; Radiation; TACE + radiation; No therapy	All patients were beyond Milan criteria for transplantation	NR	NR
EORTC QLQ-C30 EORTC QLQ-HCC18	Pre and 2 weeks post TACE	TACE	NR	A: 76% B: 24%	ECOG: 0: 61% 1: 32% 2: 8%
EORTC QLQ-C30 EORTC QLQ-HCC18	NR	Transplantation; Ablation or resection; TACE; SOR; BSC	BCLC: 0: 3% A: 22% B: 22% C: 47% D: 6%	A: 70% B: 27% C: 3%	ECOG: 0: 53% 1: 31% 2: 14% 3: 2%
EORTC QLQ-C30 EORTC QLQ-HCC18	At baseline, 1 month then every 3 months thereafter	SOR vs SIRT	BCLC: A: 5% B: 28% C: 68%	A (5/6): 83% B (7): 16%	ECOG: 0: 62% 1: 38%
FACT-Hep Linear analog self-assessment	Baseline, every 2 weeks until 12 weeks	SOR vs SOR+E	BCLC: B: 28% C: 72%	A (5/6): 83% B (7): 17%	ECOG: 0: 65% 1: 35%
EORTC QLQ-C30 EORTC QLQ-HCC18	Pre- and post treatment	Surgery; Ablation; Embolization	BCLC: A: ~61%	A: 80.4%	NR
EORTC QLQ-C30	Baseline	NR	BCLC: A: 10% B: 14% C: 69% D: 6%	A: 70% B: 24%	WHO: 0: 36% 1: 46% 2: 16% N/A: 2%
FHSI-8 FACT-Hep	Questionnaires baseline, every 4 weeks, EOT	Axitinib vs placebo	BCLC: A: 4% B: 16% C: 80%	A: 100%	ECOG (N): 0: 58% 1: 42%
EORTC QLQ-C30 FACT-Hep	Baseline, 1, 3, 6, and 12 months after registration	SBRT	NR	B: 5%	ECOG (N): 0-1: 51% ≥2: 49%
SF-36	Pre-therapy, post-therapy, and at 6- and 12-month follow-up	DEB-TACE	BCLC: A: 6% B: 27% C: 60% D: 7%	A: 56% B: 39% C: 5%	ECOG: 0: 43% 1: 46% 2: 11%
FHSI-8	Questionnaires baseline, cycle 4, 10, 16, EOT	Ramucirumab vs placebo	BCLC: B: 12% C: 88%	A: 98% B: 2%	ECOG (N): 0: 55% 1: 45%
FACT-Hep BPI	NR	NR	[cancer stage] 1: 2% 2: 3% 3: 14% 4: 81%	NR	NR
EORTC QLQ-HCC18 FACT-Hep	Interviews completed at average of 11.7 months following diagnosis	Previous/current systemic therapy (80% SOR)	NR	NR	ECOG: ≤2: 100%
EORTC QLQ-C30 EORTC QLQ-HCC18	Baseline	Previously untreated	BCLC: A: 40% B: 17% C: 20% D: 23%	A: 43% B: 35% C: 22%	ECOG: 0-1: 78.5%
FACT-Hep	Baseline	Prior treatment (TACE; Y90; RFA; surgical resection; 5% = NT)	NR	NR	NR
FACT-Hep	Baseline, week 1, months 1 and 2 of therapy	SOR	BCLC: B: 8% C: 92%	A:100%	ECOG: 0: 86% 1: 14%
EORTC QLQ-C30	Baseline, every 6 weeks, EOT	Brivanib vs SOR	BCLC: A: 6% B: 17% C: 77%	A: 92% B: 8%	ECOG: 0: 62% 1: 38%
FHSI-8	Baseline, 2 months, 4 months	SOR	BCLC: B: 78% C: 22%	A: 73% B: 22%	NR
FACT-Hep	Baseline, 2 weeks, 4 weeks	TACE Y90 radioembolization	BCLC: A: 38% B: 36% C: 27%	A: 86% B: 14%	NR
EORTC QLQ-C30 FACT-Hep BPI	Baseline, 1 week, 1, 3, and 6 months after treatment	Palliative liver radiotherapy	NR	A: 83% B: 17%	KPS: 60: 22% 70: 24% 80: 20% 90: 22%
FACT-Hep	Baseline, 3, 6, 12, and 24 months after treatment	Hepatic resection; TACE; RFA; no treatment	NR	A: 55% B: 45%	NR
SF-36	Baseline and during 4, 8, and 12 months of treatment	TACE	Okuda: 1: 55% 2: 42% 3: 3%	A: 46% B: 51% C: 3%	NR
FACT-Hep FACIT-Sp-12	Baseline, 1, 2, 3 months	Receiving treatment (surgery: 46%; chemotherapy: 27%; TACE: 27%)	[cancer stage] 1–3: 33% 4: 67%	NR	NR
FACT-Hep	Baseline	Previously untreated	[cancer stage] 1-2: 20% 3-4: 80%	A: 51% B: 26% C: 1%	NR

TABLE 3. QOL and PROs in HCC

Reference	Patient Population	PRO	Quantitative/Qualitative Results
Hansen 2017[12] (n = 18)	Advanced HCC (beyond Milan transplantation criteria)	Memorial Symptom Assessment Scale	NR
Hinrichs 2017[13] (n = 79)	HCC	EORTC QLQ-C30 EORTC QLQ-HCC18	There was a 12.1% decrease in global health score Major decreases for physical (–21.4%), role (–23.4%), and social (–21.5%) functioning Increases in symptom severity were seen in fatigue (+30.1%), loss of appetite (+25.3%), and pain (+19.4%) after TACE
Sternby 2018[14] (n = 185)	HCC, any stage	EORTC QLQ-C30 EORTC QLQ-HCC18	NR
Vilgrain 2017[15] (n = 459)	Locally advanced HCC	EORTC QLQ-C30 EORTC QLQ-HCC18	Global health status subscore was significantly better in the SIRT group than SOR group (P = .0048)
Koeberle 2016[16] (N = 105)	Advanced HCC	FACT-Hep Linear analog self-assessment	FACT-HS score was preserved over time in the SOR and SOR+E group. The odds of having a clinically relevant improvement in the FACT-HS was higher in the SOR arm vs SOR+E arm (OR, 3.2; 95% CI, 1.0-10.9; P = .03)
Chie 2015[17] (N = 171)	HCC [a]81% Asian; 2.4 years since diagnosis; 57% prior tx	EORTC QLQ-C30 EORTC QLQ-HCC18	Emotional functioning had highest deterioration mean difference pre/post-treatment = 5.6; scale = 0-100 Patients in the surgery group had 3x lower odds of deterioration in role functioning vs ablation group (OR, 0.29; 95% CI, 0.08-1.00; P = .05). Similar trends in embolization vs ablation on worsening of dyspnea (OR, 0.19; 95% CI, 0.05-0.76; P = .019), and appetite loss (OR, 0.23; 95% CI, 0.07-0.77; P = .018)
Diouf 2015[18] (N = 271[a])	Advanced HCC	EORTC QLQ-C30	**EORTC QLQ-C30 scores:** Global health: HR, 1.61; 95% CI, 1.39-1.87; <50 vs ≥50 Physical functioning: HR, 1.51; 95% CI, 1.42-1.59; <58.33 vs ≥58.33 Role functioning: HR, 1.76; 95% CI, 1.31-2.36; <66.67 vs ≥66.67 Fatigue: HR, 2.09; 95% CI, 1.83-2.39; >66.67 vs. ≤66.67 Diarrhea: HR, 1.62; 95% CI, 1.38-1.90; >33.33 vs ≤33.33 Dyspnea: HR, 1.48; 95% CI, 1.27-1.73; >0 vs 0
Kang 2015[7] (N = 202)	HCC, previously treated	FHSI-8 FACT-Hep	**Mean FHSI-8 scores at baseline:** Axitinib/BSC: 26.22 Placebo/BSC: 26.00 **Mean FHSI-8 scores after treatment initiation:** Axitinib/BSC: decreased by ≥3 points Placebo/BSC: unchanged **Median time to deterioration:** Axitinib/BSC: 1.9 months (95% CI, 1.8-1.9) Placebo/BSC: 1.9 months (95% CI, 1.8-2.7)
Klein 2015[19] (N = 222)	HCC, intrahepatic cholangiocarcinoma, or liver metastases	EORTC QLQ-C30 FACT-Hep	**Mean FACT-Hep for HCC:** 122.8 (1 month) 127.9 (6 months) **Mean FACT-Hep for liver metastasis:** 136.5 (1 month) 141.0 (6 months) While scores were lower for patients with HCC, they did not achieve a clinically significant difference
Xing 2015[20] (N = 118)	Unresectable HCC, previously untreated	SF-36	Post-treatment, no significant differences in any of the 8 QOL domains were observed between patients who received ≥4 DEB-TACE vs ≤3 DEB-TACE (P > .05 for all domains at 3-, 6-, and 12-month follow-up) A comparison of 6-month to 12-month follow-up scores revealed a significant decrease in bodily pain (62.5 vs 52.21, P = .02)
Zhu 2015[9] (N = 565)	Advanced HCC, previously treated with sorafenib	FHSI-8	**Change in score from baseline to EOT:** Ramucirumab: –2.44 (FHSI-8) Placebo: –2.86 (FHSI-8) No statistical analysis
Butt 2014[21] (N = 304)	HCC	FACT-Hep BPI	**FACT-G (100); FACT-Hep (180):** Baseline: 77.2; 131.6 2 months: 68.6; 116.8 4 months: 70.6; 119.5 6 months: 78.6; 134.2
Kaiser 2014[22] (N = 10)	Advanced HCC	EORTC QLQ-HCC18 FACT-Hep	–
Meier 2015[23] (N = 130)	Previously untreated HCC	EORTC QLQ-C30 EORTC QLQ-HCC18	Median global QOL = 50%, with only 12% of patients having scores >75% Global QOL declined according to BCLC stage, with median QOL scores of 54%, 47%, and 39% for stage A, B/C, and D tumors, respectively
Steel 2014[24] (N = 321)	HCC or CCC	FACT-Hep	Compared with patients in the lowest QOL tertile, patients scoring in the middle and highest tertiles had higher likelihoods of survival (HR, 2.5 and 2.1, respectively; P < .05)
Brunocilla 2013[25] (N = 36)	HCC (with SOR)	FACT-Hep FHSI-8	**From baseline to week 1, median QOL score deterioration:** FACT-Hep total: –2.22 FACT-G total: –4.63 FACT-G physical well-being: –8.33 FACT-G functional well-being: –3.57 Hepatobiliary subscale: –4.17 FHSI-8: –6.25 No change: social/family well-being and emotional well-being **From baseline to months 1 and 2, median QOL score deterioration (P < .05):** FACT-G physical well-being: –3.93 (month 1); –3.57 (month 2) Hepatobiliary subscale: –5.56 (month 2) Significant improvement in emotional well-being from baseline: 8.33 (months 1 and 2)

Qualitative Results	Additional Key Points
Patients reported pain and lack of energy as the most frequent and distressing symptoms Problems with sexual interest or activity were the fourth most common after drowsiness	Global Distress Index mean scores had notable variability between and within patients over time
ECOG PS >1: associated with increased nausea/vomiting and decreased global health score MELD score >10: associated with increased fatigue and abdominal swelling Increased symptom severity in patients with no symptoms before TACE for pain and abdominal swelling	TACE for treatment of HCC did not result in major loss of QOL QOL questionnaires help to identify patients in need for closer surveillance in the outpatient setting Palliative therapy for TACE can play a significant role
QOL data are prognostic for overall survival Global health status, physical functioning, role functioning, social functioning, fatigue, nausea/vomiting, dyspnea, and appetite loss were significant predictors of mortality by the EORTC QLQ-C30 Fatigue, body image, nutrition, fever and abdominal swelling were significant predictors by the EORTC QLQ-HCC18	The best prognostic power was achieved by combining EORTC QLQ-HCC18 nutrition scale with selected background parameters EORTC QLQ-C30 and -HCC18 combined increased prognostic accuracy slightly
NR	–
Patients treated with SOR+E reported worse scores for global QOL indicators over time vs SOR	During the 12 weeks of study, QOL did not significantly differ between SOR+E and SOR PWB and mood scores worsened in patients treated with SOR+E vs those treated with SOR
At baseline, participants had good QOL scores for all 3 treatments; post-treatment, most patients did not report deterioration in QOL More patients in the ablation group had worsening of role functioning, dyspnea, appetite loss, and body image	This study compared QOL changes in patients with HCC after surgery, ablation, or embolization Although more patients had increased overall or abdominal pain post-surgery, QOL outcomes were similar in patients receiving surgery or embolization, while ablation was not as effective at maintaining QOL Overall, no significant differences in QOL deterioration were observed with any treatment
–	Cutoff values for QOL scales can be useful to identify patients with HCC with very poor prognosis, and thus improve design of clinical trials and treatment adjustment for these patients
–	NR
Mean scores on EORTC QLQ-C30 domains for fatigue and appetite loss worsened at 1 month vs baseline; preserved afterwards Versus baseline, QOL: Stable: 3 months [FACT-Hep/ EORTC QLQ-C30 Global Health/QOL]: 51%/50%; 12 months: 54%/38% Clinically significant worsening: 36%/34% at 3 months and 27%/39% at 12 months Clinically significant improvement: 13%/16% at 3 months and 19%/23% at 12 months	Overall QOL did not decline
Average SF-36 QOL scores in each of the 8 domains at baseline were significantly lower vs an age-adjusted healthy US population ($P < .001$)	DEB-TACE demonstrated long-term preservation of QOL among previously untreated patients with HCC
–	–
Pain: 74 patients reported "no" pain on the 3-item pain scale derived from the FACT-Hep. Two patients reported maximum pain	FACT-Hep pain items for patients with HCC demonstrate validity and sensitivity to change
Pain: 90%, pain was an important concern; 40% experienced no pain in the past 7 days QOL concerns: diarrhea (n = 5), fatigue (n = 5), skin toxicities (n = 5), loss of appetite (n = 4)	Pain was ranked as very important for QOL upon questioning, but was typically not spontaneously reported The FACT-Hep pain items demonstrate content validity
Role functioning was significantly associated with survival after adjusting for Caucasian race, BCLC stage treatment Global QOL and performance functioning were associated with survival on univariate analysis but became nonsignificant after adjusting for important clinical variables	Overall global QOL in HCC was poor QOL (specifically, role function) has prognostic significance and is important to assess in patients with HCC
FACT-Hep subscales were significantly associated with survival, including the physical well-being and symptoms and side effects subscales	QOL was found to be significantly associated with survival after adjusting for demographics, disease-specific factors, and treatment
The cumulative incidence of therapy discontinuation for drug-related AEs was 33% The most common AE was fatigue (66.7 %) The worst score decrease was detected from baseline to week 1 in physical well-being	Treatment withdrawal from AEs was higher than previously reported, significant QOL decrease occurred

continued on SP70

continued from SP69

Johnson 2013[26] (N = 1155)	Advanced HCC, no prior systemic therapy	EORTC QLQ-C30	**Mean score at baseline (SOR/brivanib):** Physical function: 83/83 Role function: 84/85 Change from baseline to 12 weeks (SOR/brivanib): Physical function: –18/–24 Role function: –20/–28
Montella 2013[27] (N = 60)	Elderly patients with aHCC	FHSI-8	–
Salem 2013[28] (N = 56)	HCC	FACT-Hep	**FACT-Hep domains at baseline (TACE vs Y90 radioembolization):** PWB: 20.7/21.8 SWB: 22.9/22.8 EWB: 16.2/18.5 FWB: 15.7/17.3 Overall QoL: 76.0/80.4 Hepatobiliary cancer subscale: 55.1/55.4 FACT-Hep: 131.0/136.0
Soliman 2013[29] (N = 41)	HCC or liver metastases	EORTC QLQ-C30 FACT-Hep BPI	**Mean scores at baseline (all patients):** FACT-G: 61 FACT-Hep: 105 EORTC QLQ-C30 global health status: 36
Toro 2012[30] (N = 51)	HCC	FACT-Hep	Baseline FACT-Hep scores (hepatic resection/TACE/RFA/NT): PWB: 23.9/22.4/23.6/21 SWB: 22.3/21.4/22.6/24.2 EWB: 22.7/22.3/25.8/21.2 FWB: 21.9/19.9/22.1/19.7
Wible 2010[31] (N = 73)	Previously untreated HCC	SF-36	**Rate of change of all SF-36 scale scores in patients at 4 months (preprocedure; rate of change):** Physical functioning: 46.5; 0.6 (–3.7 to 5.0); *P* = .77 Role-physical: 27.9; 8.3 (–3.4 to 20.0); *P* = .15 Bodily pain: 55.3; 1.5 (–4.6 to 7.6); *P* = .58 General health: 48.8; –2.5 (–7.4 to 2.4); *P* = .21 Vitality: 41.2; 2.5 (–1.1 to 6.1); *P* = .15 Social functioning: 56.7; 4.4 (–0.8 to 9.6); *P* = .09 Role-emotional: 48.2; 4.6 (–2.8 to 12.1); *P* = .20 Mental health: 61.1; 5.6 (0.1-11.2); *P* = .05 Rate of change, SF-36 mental health (4/8/12 months): 5.64/5.46/0.69 *P* value = .05/0.1/.67
Sun 2008[32] (N = 22)	HCC	FACT-Hep FACIT-Sp-12	**FACT-Hep (180):** Baseline: 110.6 1 month: 101.4 2 months: 98.2 3 months: 100.3
Steel 2007[33] (N = 83)	Previously untreated HCC	FACT-Hep	**Overall FACT-G:** 74 Lower than other HCC populations studies, likely due to advanced disease

AE indicates adverse event; aHCC, advanced HCC; ALD, alcoholic liver disease; BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; CCC, cholangiocarcinoma; CI, confidence interval; DEB-TACE, drug-eluting bead TACE; E, everolimus; ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; EOT, end of treatment; EWB, emotional well-being; FACIT-Sp-12, Functional Assessment of Chronic Illness Therapy–Spirituality Subscale; FACT-G, Functional Assessment of Cancer Therapy-General; FACT-Hep, FACT-Hepatobiliary; FACT-HS, FACT-Hepatobiliary Subscale; FHSI-8, FACT Hepatobiliary Symptom Index 8; FWB, functional well-being; HCC, hepatocellular carcinoma; HR, hazard ratio; MELD, Model of End-Stage Liver Disease; NR, not reported; NT, no treatment; OR, odds ratio; PRO, patient reported outcome; PWB, psychological well-being; QOL, quality of life; RFA, radiofrequency ablation; SF-36, Short Form-36; SIRT, selective internal radiotherapy; SOR, sorafenib; SWB, social well-being; TACE, transarterial chemoembolization; tx, therapy; US, United States; Y90, yttrium 90.

[a]214 for patients with baseline QOL scores.

TABLE 4. Characteristics of Included Costs and Resource Utilization Studies

Reference	Study Design	Country/Currency/Year	Age, Mean, Years	HCV, %	HBV, %
Golabi 2017[34] (N = 2711)	Database: SEER-Medicare	US/USD/2009	74 (HBV+HCC)/72 (HCV+HCC)	81	19
Hammad 2017[35] (N = 3267)	Database: The National Cancer Database	US/No costs	Median: 61	NR	NR
Jinjuvadia 2017[36] (N = 372,375)	Database: NIS	US/USD/2002	60	–	–
Sanoff 2017[37] (N = 7992)	Database: SEER-Medicare	US/No costs	Median: 73	24	5
Rein 2016[38] (N = 7668)	Database: SEER-Medicare	US/USD/2014	NR	100	NR
Tapper 2016[39] (N = 100)	EHR	US/USD/2013	59	100	NR
Baran 2015[40] (n = 17)	Database: Employer	US/USD/2013	56	100	NR
Shaya 2014[41] (N = 11,047)	Database: SEER-Medicare	US/USD/2011	73% were between 65-84 years	22	6
Breunig 2013[42] (N = 1228)	Database: SEER-Medicare	US/USD/2011	79% were between 65-84 years	37	22
Mishra 2013[43] (N = 26,540)	Database: NIS	US/USD/2009	~62	–	–
White 2012[44] (n = 5712)	Database: SEER-Medicare	US/USD/2009	75	14	5
McAdam-Marx 2011[45] (n = 959)	Database: Optum Insight	US/USD/2009	56	100	–
Sanyal 2010[46] (N = 4406)	Database: MarketScan	US/no costs	64	22	6
Lang 2009[47] (N = 392)	Database: SEER-Medicare	US/USD/2006	NR	–	–

ALD indicates alcoholic liver disease; DME, durable medical equipment; ED, emergency department services; EHR, electronic health record; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HM, home healthcare; HO, hospice care; IP, inpatient treatment; MD, physician/professional services; NIS, National Inpatient Sample; NR, not reported; OP, outpatient hospital services; Rx, pharmaceutical costs (including administration); SEER, Surveillance, Epidemiology, and End Results; SNF, skilled nursing facility; TACE, transarterial chemoembolization; US, United States; USD, US dollars.

[a]Drug costs (oral anticancer and antiemetic medications) that were covered under Medicare Part B were included; however, oral prescription drugs covered under Part D were not available and were thus not included in this analysis.

After 12 weeks of treatment, physical function and role function declined in both arms Decreased scores from brivanib-treated patients were more pronounced vs SOR-treated patients	Brivanib was less well-tolerated than SOR
No difference in QOL was reported from baseline or after 2 months of treatment	In elderly patients, SOR did not worsen QOL
Although 90Y radioembolization was used to treat patients with more advanced disease, it led to significant increases in several QOL domains TACE patients had decreased QOL scores QOL post-treatment (4 weeks) was higher with Y90 radioembolization vs TACE	Y90 radioembolization provided better QOL than TACE
The primary index symptoms were pain (n = 27), abdominal discomfort (n = 6), fatigue (n = 3), nausea (n = 2)	While liver radiotherapy demonstrates useful palliation to patients with pain or abdominal discomfort from HCC, improvement in QOL was seen in a smaller portion of patients Overall disease status is a potential confounding variable
FACT-Hep: After 3 months, there were no significant differences in FACT-Hep scores between treatment groups After 12 months, there was a significant difference in hepatic resection vs TACE as well as NT	Hepatic resection significantly improved QOL after 24 months RFA provides a worse QOL vs hepatic resection, but a higher QOL vs TACE or NT
Patients had decreased pretreatment baseline scores vs a healthy population	Previously untreated patients with HCC experienced mental health score improvement after 4 months of TACE, but not at 8 or 12 months Patients also exhibited improvement in bodily pain, but worsening vitality scores, after the first TACE procedure
Over time, statistically significant worsening of physical and emotional well-being Decline not statistically significant for social and functional well-being Symptom scores were high for weight loss, appetite, fatigue, ability to perform usual activities, and abdominal pain and worsened over time	Patients with HCC suffer from multiple symptoms due to advanced disease that may have a negative effect on overall QOL Overall QOL remains poor through treatment Pain, fatigue, weight loss, and poor appetite are of greatest concern to patients
Significant differences were found between patients with HCC in PWB and overall QOL vs patients with chronic liver disease People diagnosed with HCC reported better social/family well-being vs the general population	Previously untreated patients with HCC had a poorer overall QOL vs chronic liver disease patients and the general population

ALD, %	Male, %	Perspective	Population/Stratification	Direct Costs	Indirect Costs
NR	73 (HBV+HCC)/57 (HCV+HCC)	NR	HBV+HCC or HCV+HCC diagnosis	Yes; IP, OP	No
NR	81	NR	Unresectable HCC/palliative interventions	–	–
–	70-74	Payer (private insurance Medicaid and Medicare)	HCC-related hospitalizations/year (2002-2011)	Yes; IP	No
11	71	NR	HCC/hospice vs no hospice	–	–
NR	NR	NR	HCV+HCC/overall	Yes; overall; Medicare A, B, and D; OP; DME; HM; HO	No
NR	81	Payer	HCV+HCC/overall cost	Yes; IP, OP, MD, Rx	No
NR	70	Payer	HCV+HCC/overall cost	Yes; overall, medical (unspecified), Rx	Yes
12	66	Payer/Medicare	HCC/stage and treatment	Yes; overall, IP, OP, SNF, HM, Rx,[a] HO, MD	No
15	69	Payer/Medicare	HCC with TACE/# TACE procedures	Yes; overall, IP, OP, SNF, HM, Rx,[a] HO, MD	No
–	~74	Payer	HCC/year (2005-2009)	Yes; IP	No
4	65	Payer/Medicare	HCC/overall and SEER stage	Yes; overall, IP, OP, SNF, HM, HO, MD, DME	No
8	71	Payer	HCC+HCV/overall	Yes; overall, IP, ED, OP, Rx, MD	No
12	66	–	–	–	–
–	72	Societal	HCC/SEER stages (localized-distant)	Yes; overall, IP, OP, SNF, HM, Rx, HO, MD	Yes

TABLE 5. Costs and Resource Utilization Associated With HCC

Reference	Country/Currency/Year	Population	Stratification	Cost Unit	Total Costs	
Golabi 2017[34] (N = 2711)	US/USD/2009	HBV+HCC HCV+HCC	Diagnosis (HBV+HCC or HCV+HCC)	Average total charges	**HBV+HCC:** IP charges: $60,471 OP charges: $3840	**HCV+HCC:** IP charges: $56,033 OP charges: $3251
Hammad 2017[35] (N = 3267)	No costs	Unresectable HCC	Palliative interventions	–	–	
Jinjuvadia 2017[36] (N = 372,375)	US/USD/2002	HCC-related hospitalizations	Year (2002-2011)	–	NR	
Sanoff 2017[37] (N = 7992)	No costs	HCC	Hospice	–	–	
Rein 2016[38] (N = 7668)	US/USD/2014	HCV+HCC	HCV+HCC	PPPY PPPM	**PPPY:** $35,011 ($25,760-$43,865)	
Tapper 2016[39] (N = 100)	US/USD/2013	HCV+HCC	Overall cost	MPP PPPM	MPP: $176,456 (IQR, $84,489-$292,192) PPPM: $6279 (IQR, $4043-$9720)	
Baran 2015[40] (N = 17)	US/USD/2013	HCV+HCC	Overall cost	6-month total cost per employee	$41,744	
Shaya 2014[41] (N = 11,047)	US/USD/2011	HCC	Stage and treatment	Mean cumulative expenditures	**Stage I:** No treatment: $35,390 Chemotherapy: $68,824 Radiation: $65,098 Liver-directed therapy: $95,566 **Stage II:** No treatment: $38,265 Chemotherapy: $61,949 Radiation: $78,333 Liver-directed therapy: $97,422	**Stage III:** No treatment: $27,887 Chemotherapy: $54,101 Radiation: $54,115 Liver-directed therapy: $77,069 **Stage IV:** No treatment: $23,791 Chemotherapy: $48,148 Radiation: $49,638 Liver-directed therapy: $69,084
Breunig 2013[42] (N = 1228)	US/USD/2011	HCC with TACE	# of TACE procedures	Adjusted average cumulative Medicare expenses	TACE[b] ×1: $74,788 TACE[b] ×2: $101,126 TACE[b] ×3: $111,776 TACE[b] ×4: $148,878	
Mishra 2013[43] (N = 26,540)	US/USD/2009	HCC	Year (2005-2009)	Median inflation-adjusted charges	–	
White 2012[44] (N = 5712)	US/USD/2009	Elderly patients with HCC	Overall cost and SEER stage	PPPM	$7863	
McAdam-Marx 2011[45] (N = 959)	US/USD/2009	HCV+HCC	Overall cost	PPPY	$58,529	
Sanyal 2010[46] (N = 4406)	No costs	HCC	–	–	NR	
Lang 2009[47] (N = 392)	US/USD/2006	HCC	Stage (SEER)	PPPY	**Healthcare costs:** All stages: $29,354 Localized (SEER): $31,740 Regional (SEER): $29,874 Distant (SEER): $25,848	

DME indicates durable medical equipment; ED, emergency department; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICU, intensive care unit; IP, inpatient; IQR, interquartile range; IV, intravenous; LOS, length of stay; MPP, median price per patient; NR, not reported; OP, outpatient; PPPM, per patient per month; PPPY, per patient per year; RFA, radiofrequency ablation; SEER, Surveillance, Epidemiology, and End Results; TACE, transarterial chemoembolization; US, United States; USD, US dollars.

[a]In Baran 2015, indirect costs were associated with health-related absence days and actual employee cost data.

[b]Total costs comprised only direct costs.

[c]In Lang 2009, indirect costs were estimated based on workdays missed and average wage rates.

Direct Costs	Indirect Costs	Other Healthcare Utilization	
–	–	**HBV+HCC:** Average IP visits: 1.92 Average OP visits: NR Rate of liver transplant: 7.3%	**HCV+HCC:** Average IP visits: 2.02 Average OP visits: 7.39 Rate of liver transplant: 8.9%
–	–	**Treatment:** Surgical palliation: 287 Radiotherapy: 827 Chemotherapy: 877 Pain management: 1067 Combination of above: 209	
Mean total charges per hospitalization for HCC as primary diagnosis: 2002: $33,188 2011: $64,397		Mean LOS for patients hospitalized with HCC as a primary diagnosis: 2002: 7.1 days 2011: 5.9 days	
–	–	63% of patients used hospice before death with a median duration of 18 days Initial treatment with surgery and ablation or chemoembolization/radio-embolization was associated with decreased odds of subsequent hospice use Hospice patients were significantly less likely to be hospitalized, have an ICU stay, or die in the hospital	
PPPM: Medicare Part A: $434 Medicare Part B: $288 OP: $1802 Home health: $305 Hospice: $218 DME: –$8 Medicare Part D: $91	–	–	
–	–	–	
Total direct costs: $38,151 Direct medical costs: $33,494 Direct drug costs: $4657	$3594[a]	–	
Cumulative Medicare expenditures after HCC diagnosis: Untreated patients incurred: $23,600-$38,300 Systemic chemotherapy and radiation patients: nearly double the cost for untreated patients Patients undergoing liver-directed therapy: $69,000-$97,500 Resection patients: approximately $125,000 Transplant patients: $207,000-$244,500	–	–	
–	–	–	
Median hospital inpatient charges, per case: 2005: $29,466 2006: $28,720 2007: $28,947 2008: $31,208 2009: $31,656 **Cost for LOS, per day:** 2005: $7128 2009: $7861	–	–	
IP: $5439 OP: $470 Physician/provider visits: $905 Skilled nursing facility: $321 Home healthcare: $145 Hospice mean: $554 DME: $29	–	–	
IP: $20,358 OP: $16,340 Professional services: $13,623 ED: $152 Pharmacy: $8046	–	–	
–	–	Transplant: 6.7% Surgery: 8.3% TACE: 17.6% RFA: 6.2% SOR: 6.2%	Bevacizumab: 1.6% Chemotherapy, IV: 27.1% Chemotherapy, oral: 11.1% Radiation: 11.1% Hospice: 14.7%
–	**Indirect costs due to lost productivity:** All stages: $3553[c] Localized (SEER): $4332 Regional (SEER): $3470 Distant (SEER): $2118	**Overall cost of illness:** All stages: $32,907 Localized (SEER): $36,071 Regional (SEER): $33,344 Distant (SEER): $27,967	