Transarterial Chemoembolization Treatment: Association between Multiple Treatments, Cumulative Expenditures, and Survival

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ABSTRACT

Objectives: To examine cumulative survival and Medicaid-paid expenses associated with multiple courses of transarterial chemoembolization (TACE) as primary treatment for hepatocellular carcinoma (HCC). Methods: Medicare enrollees diagnosed with primary HCC from 2000 to 2007, ever treated with TACE, but not transplant/resection, followed through 2009 by using the Surveillance, Epidemiology and End-Results Program and linked Medicare databases. Cumulative all-cause/HCC-related survival was estimated by using multivariate Cox proportional hazards models stratified by the total number of TACE treatments. Multivariate weighted Cox regression method estimated cumulative Medicare expenditures adjusted for censoring and covariates. Results: Of 1228 patients, 34% were stage 1, 16% stage 2, 19% stage 3, 6% stage 4, and 26% unstaged. About 44% were aged 65 to 75 years, 69% were men, and 72% were Caucasian. Over half (57%) of the patients received one course, 24% two, 11% three, and 8% four courses of TACE. One-course patients incurred an average $74,788 (95% confidence interval [CI] $71,890–$77,686), two-course patients $101,126 (95% CI $94,395–$107,856), three-course patients $111,776 (95% CI $101,931–$121,621), and four-plus-course patients $148,878 (95% CI $136,346–$161,409). One-course patients lived (all-cause) an average 1.86 (95% CI 1.82–1.90) years after diagnosis. Average risk of all-cause mortality was not significantly different between one/two courses or three/four-plus courses. Conclusions: Cumulative Medicare expenditures nearly doubled from one-course to four-plus-course patients. On average, four-plus-course patients lived one more year than did one-course patients. Physician/patient decisions should be balanced with consideration of efficient use of limited resources, but payer’s intervention in physician discretion may not be important in this setting. Keywords: cost-effectiveness, hepatocellular carcinoma, SEER-Medicare, survival, transarterial chemoembolization.

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer in the world and was the third most common cause of cancer-related death in 2008 [1]. While the prevalence of HCC is highest in developing countries, incidence in the United States has tripled between 1975 and 2005 from 1.6 to 4.9 incidences per 100,000 inhabitants [2]. HCC is an age-dependent cancer that peaks in incidence between 75 and 79 years of age [3]. The hepatitis B and C viruses are the main risk factor for HCC because they promote cirrhosis, which is found in 80% to 90% of HCC cases [4]. Incidence is expected to continue rising in the next few decades because of current trends related to the etiology of HCC as well as an aging population [4]. Recent advances in oncology have led to greater rates of early detection of HCC and more effective treatment [5], yet most HCC is still diagnosed at intermediate or advanced stages for which no curative therapy has been established [6,7].

In early stages of HCC, transplantation, surgical resection, and percutaneous ablation are considered to be potentially curative therapies [5]. Patients in early to intermediate stages, however, are often precluded from these procedures, for instance, because of tumor size, number of lesions, or complicating liver diseases [8,9]. In this case, transarterial chemoembolization (TACE) is often a first-line therapy that has been shown to positively impact survival, although overall survival benefit is largely dependent on the patients’ baseline clinical characteristics [5]. For patients also eligible for ablation, concomitant TACE treatments have been shown recently to be more effective than ablative therapy alone, providing overall survival rates similar to that of surgical resection [10,11]. With TACE, chemotherapeutic agents—commonly doxorubicin or cisplatin [12]—are concentrated and isolated at the tumor site while blocking the primary artery feeding the tumor [7]. Because TACE can cause liver damage, patients with preserved liver function are carefully selected for the treatment [7,12]. Eligible patients often achieve
maximum tumor response after repeated interventions, usually between three and four courses [12–15].

Changes in demographics and expanding therapeutic frontiers including TACE necessitate increased attentiveness of the long-term costs of cancer for payer organizations. Lang et al. [16] conservatively estimated that total health care cost per patient with HCC was an average $29,354 in 2006 US dollars ($34,947 in 2011 US dollars). The cost implications of HCC are particularly relevant for Medicare because many patients with HCC are eligible for Medicare because of age or other qualifying conditions.

Much of the evidence on the effectiveness of TACE comes from randomized clinical trials that often represent nontypical demographics and risk factors. Randomized clinical trials have yet to produce evidence for the effectiveness of repeated courses of TACE in treating HCC, possibly because it is difficult to establish intent to treat when additional courses of TACE are continued according to tumor response. No observational study has evaluated the survival benefit associated with repeated TACE treatments for HCC. Moreover, health care organizations have an interest in knowing the costs of TACE because there are no such evaluations in the populations for which it is most treated. The objective of this study was to examine cumulative survival across Medicare patients who received multiple courses of TACE to treat HCC and examine its association with long-term direct medical costs to Medicare. Real-world evidence will not only inform further analysis of emerging therapies such as TACE but also help guide coverage and budget decisions by payers and providers for patients with HCC at different stages.

Methods

Data Source

The National Cancer Institute’s Surveillance, Epidemiology and End Results (SEER)-Medicare-linked database collects clinical information on incident-based cancer diagnoses from cancer registries covering nearly 26% of the U.S. population. Data collected include demographic characteristics, date of diagnosis, details about the cancer (e.g., histology, stage, and grade), and cause of death, if applicable. Medicare enrollment and claims files from Parts A (inpatient), B (provider), and D (drugs) are linked to SEER such that information can be collected regarding utilization, particularly types and timing of treatments undertaken, as well as underlying comorbidity. The database has been found representative of the national population and is described in detail elsewhere [17] (http://seer.cancer.gov).

We selected patients with primary HCC initially diagnosed between January 1, 2000, and December 31, 2007. Patients were excluded if they were enrolled in a health maintenance organization (HMO) within 12 months prior to the diagnosis of HCC. This was to eliminate possible censoring of information due to switching between an HMO and Part A/B enrollment. Patients were also excluded if they had an unknown diagnosis month or year, had a history of other cancers within 5 years prior to diagnosis, or for whom cancer was diagnosed upon death. Eligible patients were followed until the week of death or until censored because of the loss of Part A/B coverage, HMO enrollment, or December 31, 2009.

Survival

Survival was calculated as the number of weeks from diagnosis to death. Mortality was defined as all-cause or as HCC-related if the cause of death was indicated as “liver.”

TACE Treatments

The sample consists of all patients with HCC who met the inclusion and exclusion criteria above and had undergone at least one course of TACE in the follow-up period. Patients who received transplant or resection in the follow-up period were excluded (n = 228) because these therapies dominate alternative therapies in the Barcelona Clinic Liver Cancer staging system, the most widely used system for staging and treatment [5,7]. TACE is often used to reduce the dropout rate for patients on the waiting list for liver transplantation (bridge-therapy) or to downstage patients not initially meeting the criteria for transplantation or resection eligibility [18,19]. Patients were not precluded from the receipt of percutaneous ablation, systemic chemotherapy, or radiation therapy before or after their TACE treatment(s). A large fraction of TACE patients had undertaken multiple courses of TACE throughout the follow-up period. We delineate patients who received two, three, or four or more TACE treatments from those who received only one.

Patient Characteristics

Age, sex, and race/ethnicity were recorded for all patients at diagnosis. Patients were categorized into four age brackets: younger than 65 years, 65 to 74 years, 75 to 84 years, and older than 84 years. Race/ethnicity was categorized as Caucasian, African American, Hispanic, or other race. Patients resided in either urban or rural counties.

Patients with HCC were classified as stage 1, 2, 3, 4, or unstaged upon diagnosis. For patients diagnosed after 2003, cancer stage was determined by using the American Joint Committee on Cancer 6th edition staging system. The TNM staging system was used prior to 2003. Patient comorbidities were assessed by using Medicare Part A or B claims for 1 year prior to HCC diagnosis. Indicators for hepatitis B and C, alcohol-related liver disease (ALD), and moderate-severe liver disease (MSLD) were created. A modified Charlson comorbidity index (CCI) was constructed by excluding liver-related risk factors, and patients were categorized into three categories: CCI = 0, 1, or greater than 1.

Costs

Economic costs were assessed from Medicare’s perspective over the follow-up period (i.e., patient costs, including indirect cost, were not considered). All patients were covered under Medicare Part A, which covers inpatient care in short- and long-stay hospitals, skilled nursing facilities, home health, and hospice care. All patients were covered under Part B, which covers physician services, outpatient care, durable medical equipment, and home health in some cases. Medicare-paid expenditures for each patient were ascertained from Parts A and B claims data. Total direct medical costs to Medicare per patient per month were calculated from diagnosis until end of follow-up. Total Medicare expenditures may be somewhat underestimated. While several oral anticancer and antiemetic drugs are/were covered under Medicare Part B, data for oral prescription drugs covered under Part D were not available prior to 2007 and therefore not incorporated into the analysis. All expenditures were inflated to represent 2011 U.S. dollars by using the Bureau of Labor Statistics’ annual average Consumer Price Index for medical care.

Statistical Analysis

The frequencies and proportions of patients who underwent one, two, three, or four or more courses of TACE were calculated. Chi-square tests were conducted to compare patient characteristics between the latter four cohorts because all variables were
categorical. Kaplan-Meier analyses were used to estimate mean all-cause and HCC-related mortality in the presence of censoring. The Kaplan-Meier method was also used to estimate the censoring-adjusted mean time between diagnosis and repeated TACE treatments.

Mean years survived after diagnosis was calculated as the area under the survival curve estimated with multivariate Cox proportional hazards models, stratified by TACE cohort and adjusted for risk factors (i.e., age, sex, race/ethnicity, cancer stage, comorbidity, hepatitis B and C, ALD, and MSLD) and other therapies undergone (i.e., ablation, radiation, and/or chemotherapy). Stratification allowed for baseline hazards to vary between the TACE cohorts. A weighted Schoenfeld residuals score test indicated nonproportional hazards for TACE cohorts and other therapies, an expected result given heterogeneous treatment patterns over follow-up.

A multivariate weighted Cox regression was used to assess the relative risk of all-cause and HCC-related mortality between TACE cohorts, adjusted for the patient risk factors and other therapies undergone. The weighted Cox regression provided a method for estimating the average relative risk of mortality over the follow-up period, regardless of whether that risk varied over time [20]. In general, weighted Cox regression estimates hazard ratios averaged over time using a weight function that reflects the relative importance attached to the hazard ratios in different time periods. An average hazard ratio (AHR) is generally defined as

$$
AHR = \frac{\int_0^T (h_{R}(t)/h_{T}(t)) w_{T}(t) dt}{\int_0^T (h_{R}(t)/h_{T}(t)) w_{T}(t) dt}, 0 \leq w(t) \leq 1
$$

where \( h_{R}(t) \) and \( h_{T}(t) \) denote respective hazards of a reference group and comparison group at time \( t \), \( h(t) \) is the sum of these hazards at time \( t \), and \( w(t) \) is the density function for the events in time. Using censored data, the weight function \( w(t) = S(t)G(t)^{-1} \) reflects the proportion of individuals affected by a hazard ratio at time \( t \), where \( S(t) \) and \( G(t) \) denote the Kaplan-Meier estimators of the survival function and the censoring distribution, respectively.

AHRs estimated under the proportional hazards assumption are obtained when \( w(t) = 1 \). For “proportional” covariates, \( w(t) = S(t)G(t)^{-1} \approx 1 \), and so there will be little difference between the hazard ratio estimated under the proportional hazards assumption and the AHR estimated by using weighted Cox regression. Schemper et al. [20] provide greater detail on weighted Cox regression, including a description of the weighted partial likelihood for Cox’s regression model and confirmation of its empirical performance. We used SAS version 9.2 software (SAS Institute, Cary, NC) for all survival analyses. Weighted Cox regression was implemented by using the SAS macro program WCM provided on the Web by Heinze [21].

SEER-Medicare data are right-censored because the data availability is approximately 2 to 3 years old. Mean cumulative expenditures will be underestimated because expenses after censoring are unknown. The partitioned estimator proposed by Bang and Tsiatis [22] was used to estimate censoring-adjusted mean cumulative expenditures for TACE cohorts. This method consisted of partitioning the study period into 84 monthly intervals. The period was truncated at 84 months because of small numbers after this time point (16 patients across all four cohorts). Observed expenditures in each interval were weighted by the inverse probability of not being censored at the beginning of the interval, estimated by the Kaplan-Meier method. The cohort’s mean cumulative expenditures were then calculated by summing the inverse probability-weighted (IPW) expenditures across all partitions and dividing by the total cohort size in the first period.

Lin’s [23] partitioned IPW least squares regression method was performed to estimate mean cumulative Medicare expenditures for each TACE cohort adjusted for the following covariates: age, sex, race/ethnicity, rural residence, cancer stage, Charlson comorbidity index, liver conditions, and receipt of ablation, chemotherapy, and radiation therapy. Separate IPW ordinary least squares regression analyses were estimated for each of the 84 monthly partitions. In each partition, cumulative monthly Medicare expenditures for each patient were regressed on indicators for the two-, three-, and four-or-more-course cohorts and the remaining covariates. The coefficients on each variable were summed across the 84 partitions to obtain the cumulative, incremental expenditures associated with each variable [23,24]. Mean cumulative expenditure for the baseline group (i.e., one course of TACE) was then calculated by summing the estimated cumulative intercept with the cumulative coefficients on each covariate multiplied by the sample mean of that covariate. Mean cumulative expenditures for the two-, three-, and four-or-more-course cohorts were obtained by summing the mean expenditures for the baseline group and the cumulative coefficient on the indicator for each cohort, respectively. Confidence intervals (CIs) for the cumulative expenditures coefficients were calculated by using a bootstrap approach, in which the process of 84 regression analyses and the summation of the coefficients was repeated 1000 times by using sampling with replacement [24]. We used STATA version 10.1 software (Statacorp, College Station, TX) for all cost analyses.

Results

Descriptive Statistics

The study sample consisted of 1228 nontransplant/resection patients. The largest portion of TACE recipients was diagnosed at stage 1 (36%), the next largest portion being unstaged (26%). A total of 16% of the patients were stage 2, 19% were stage 3, and 6% were stage 4. A majority of the patients were between the ages of 65 and 84 years (79%), men (69%), and Caucasian (72%). Table 1 reports the demographic and clinical profile of the study sample as well as patients stratified by the total number of courses of TACE received in the follow-up period. Fifty-seven percent (n = 696) received only one course of TACE, 24% (n = 297) received two courses, 11% (n = 133) received three, and 8% (n = 102) received four or more (maximum = 10 courses). The median weeks between diagnosis and first TACE treatment was 12 weeks, 12.5 weeks between the first and second, 15 weeks between the second and third, and 17 weeks between the third and fourth treatments.

There were significant differences across the strata according to cancer stage, underlying health status (CCI), the presence of ALD, and race. Patients who received one, two, or four or more courses were most likely to be diagnosed at stage 1, and patients who received three courses were most likely unstaged. There was no substantive difference across TACE cohorts regarding proportions in cancer stages 2, 3, or 4. Three or more-course patients tended to be in better underlying health than two or fewer-course patients and were also less likely to have ALD. Slightly larger proportions of African Americans (49%) and other, non-Caucasian patients (51%) were more likely to receive more than one course of TACE compared with Caucasians (41%).

TACE patients who had undergone multiple courses of TACE were more likely to have also undergone ablation, systemic chemotherapy, or radiation therapy. Patients who received four or more courses were more likely than others to have undergone systemic chemotherapy. The utilization of repeated TACE treatments or concomitant therapies may be associated with aggressive treatment of tumor burden or with palliative care.

Survival Comparisons

Figure 1 presents unadjusted Kaplan-Meier estimates stratified by the total number of courses of TACE undergone. There were
Table 1 – Clinical and demographic description of SEER-Medicare HCC patients (2000–2007) who received one or more courses of TACE.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total (n = 1228)</th>
<th>1 TACE (n = 696)</th>
<th>2 TACE (n = 297)</th>
<th>3 TACE (n = 133)</th>
<th>4+ TACE (n = 102)</th>
<th>P</th>
</tr>
</thead>
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<tr>
<td></td>
<td>n col%</td>
<td>n col%</td>
<td>n col%</td>
<td>n col%</td>
<td>n col%</td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>411 33.5</td>
<td>249 35.8</td>
<td>94 31.6</td>
<td>36 27.1</td>
<td>32 31.4</td>
<td>0.020</td>
</tr>
<tr>
<td>Stage 2</td>
<td>190 15.5</td>
<td>105 15.1</td>
<td>49 16.5</td>
<td>18 13.5</td>
<td>18 17.6</td>
<td></td>
</tr>
<tr>
<td>Stages 3–4†</td>
<td>307 25.0</td>
<td>168 24.1</td>
<td>79 26.6</td>
<td>33 24.8</td>
<td>27 26.5</td>
<td></td>
</tr>
<tr>
<td>Unstaged</td>
<td>320 26.1</td>
<td>174 25.0</td>
<td>75 25.3</td>
<td>46 34.6</td>
<td>25 24.5</td>
<td></td>
</tr>
<tr>
<td>CCI = 0</td>
<td>446 36.3</td>
<td>247 35.5</td>
<td>103 34.7</td>
<td>56 42.1</td>
<td>40 39.2</td>
<td>0.012</td>
</tr>
<tr>
<td>CCI = 1</td>
<td>341 27.8</td>
<td>186 26.7</td>
<td>77 25.9</td>
<td>38 28.6</td>
<td>40 39.2</td>
<td></td>
</tr>
<tr>
<td>CCI &gt; 1</td>
<td>441 35.9</td>
<td>263 37.8</td>
<td>117 39.4</td>
<td>39 29.3</td>
<td>22 21.6</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>130 10.6</td>
<td>69 9.9</td>
<td>31 10.4</td>
<td>14 10.5</td>
<td>16 15.7</td>
<td>0.370</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>448 36.5</td>
<td>259 37.2</td>
<td>113 38.0</td>
<td>43 32.3</td>
<td>33 32.4</td>
<td>0.529</td>
</tr>
<tr>
<td>ALD</td>
<td>184 15.0</td>
<td>117 16.8</td>
<td>45 15.2</td>
<td>x</td>
<td>x</td>
<td>0.220</td>
</tr>
<tr>
<td>MSLD</td>
<td>150 12.2</td>
<td>96 13.8</td>
<td>31 10.4</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Age &lt;65 y</td>
<td>231 18.8</td>
<td>141 20.3</td>
<td>56 18.9</td>
<td>23 17.3</td>
<td>11 10.8</td>
<td>0.130</td>
</tr>
<tr>
<td>Age 65–74 y</td>
<td>543 44.2</td>
<td>282 40.5</td>
<td>146 49.2</td>
<td>66 49.6</td>
<td>49 48.0</td>
<td></td>
</tr>
<tr>
<td>Age 75–84 y/ &gt; 84 y</td>
<td>454 37.0</td>
<td>273 39.2</td>
<td>95 32.0</td>
<td>44 33.1</td>
<td>42 41.2</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>842 68.6</td>
<td>461 66.2</td>
<td>213 71.7</td>
<td>100 75.2</td>
<td>68 66.7</td>
<td>0.112</td>
</tr>
<tr>
<td>Caucasian</td>
<td>686 55.9</td>
<td>408 58.6</td>
<td>151 50.8</td>
<td>77 57.9</td>
<td>50 49.0</td>
<td>0.008</td>
</tr>
<tr>
<td>African American</td>
<td>66 5.4</td>
<td>33 4.7</td>
<td>22 7.4</td>
<td>†</td>
<td>†</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>197 16.0</td>
<td>116 16.7</td>
<td>52 17.5</td>
<td>†</td>
<td>†</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>279 22.7</td>
<td>139 20.0</td>
<td>72 24.2</td>
<td>31 23.3</td>
<td>37 36.3</td>
<td></td>
</tr>
<tr>
<td>Ablation received</td>
<td>275 22.4</td>
<td>146 21.0</td>
<td>65 21.9</td>
<td>36 27.1</td>
<td>28 27.5</td>
<td>0.259</td>
</tr>
<tr>
<td>Systemic chemo received</td>
<td>298 23.4</td>
<td>142 20.4</td>
<td>83 27.9</td>
<td>37 27.8</td>
<td>36 35.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Radiation received</td>
<td>154 12.5</td>
<td>77 11.1</td>
<td>40 24.0</td>
<td>24 18.0</td>
<td>13 12.7</td>
<td>0.151</td>
</tr>
</tbody>
</table>

ALD, alcohol-related liver disease; CCI, Charlson comorbidity index; chemo, chemotherapy; MSLD, moderate to severe liver disease; radiation, includes both external beam and selective internal radiation therapies; TACE, transarterial chemoembolization.

*P value was estimated by using expanded definitions of categories, despite the aggregation of two of the categories for presentation.
† Stages 3 and 4 combined because of too few observations (n < 12) of stage 4 patients among 3 TACE and 4+ TACE patients to report.
‡ Too few 4+ TACE patients (n < 12) with ALD and MSLD to report; too few 3 and 4+ African American patients to report.

There were substantive differences in all-cause and HCC-related survival through approximately 225 weeks as the number of TACE treatments increased. Log rank tests indicate significant differences in cumulative survival between the 1 TACE and 2 TACE strata (P = 0.001) and the 2 TACE and 3 TACE strata (P = 0.001), but not between the 3 TACE and 4+ TACE strata (P = 0.070). Using HCC-related mortality, there are still significant differences between the 1 TACE and 2 TACE strata (P = 0.014) and the 2 TACE and 3 TACE strata (P = 0.012), and not between the 3 TACE and 4+ TACE strata (P = 0.402).

Table 2 presents the average risk of mortality over the follow-up period, adjusting for concomitant therapies and risk factors. There was no significant difference in the average risk of all-cause mortality between one-course and two-course patients (AHR = 0.92, 95% CI 0.79–1.09); however, the average risk of HCC-related mortality was 19% less (AHR = 0.81; 95% CI 0.66–0.99). Three-course patients had a 32% lower risk of all-cause mortality than did one-course patients (AHR = 0.68; 95% CI 0.55–0.84) and a 49% lower risk of HCC-related mortality (AHR = 0.51; 95% CI 0.39–0.67). Four or more course patients had 36% lower all-cause mortality risk (AHR = 0.64; 95% CI 0.52–0.79) and 54% lower HCC-mortality risk (AHR = 0.46; 95% CI 0.39–0.63). Chi-square tests indicate significant differences in all-cause (HCC-related) mortality between two-course and three-course patients (P = 0.005/P = 0.002) but not between three-course and four or more-course patients (P = 0.663/P = 0.606). The models were expanded to delineate between patients who received four courses of TACE and five or more courses, but no further reduction in mortality was associated with the fourth treatment, nor with five or more (results not shown).

Differences in average mortality risk should not be interpreted as incremental treatment effects because patients could not be sufficiently randomized into TACE cohorts. HCC is an aggressive and complex disease that is difficult to evaluate and treat [5,7]. There is no way to discern whether a patient was assigned multiple courses of TACE as part of a patient-specific treatment protocol determined at the outset of treatment. In the real world, a repeated course of TACE may have been prescribed in an ad hoc manner, according to patient-specific tumor response to prior course and eligibility for further treatment. For instance, Figure 2 illustrates censoring-adjusted means for the weeks between HCC diagnosis and discontinuation of TACE, as well as for weeks survived. Expectedly, patients who had received more courses of TACE tended to do so over a longer span of time. On average, however, patients who received one, two, or three total courses of TACE survived similar lengths of time after discontinuing TACE, between 13.6 and 14.7 months (59–64 weeks); 11.5 months (50 weeks) for four or more-course patients.

The all-cause (HCC-related) mortality risk for TACE patients who had also undergone ablation was lower than that for non-ablation patients (AHR = 0.63, 95% CI 0.53–0.74/AHR = 0.56, 95% CI 0.45–0.69) (Table 2). Both systemic chemotherapy (AHR = 0.58; 95% CI 0.47–0.72) and radiation therapy (AHR = 0.67; 95% CI 0.52–0.86) had lower HCC mortality. Patients diagnosed at later stages...
and those with MSLD prior to HCC diagnosis tended to show greater risk of mortality in the follow-up period. “Other races” had lower risk of all-cause mortality than did Caucasians (AHR = 0.83; 95% CI 0.70–0.99). Patients aged 65 to 74 years (AHR = 1.36; 95% CI 1.03–1.80) showed higher HCC mortality, and patients aged 75 to 84 (AHR = 1.32; 95% CI 1.06–1.64) showed higher all-cause mortality. No other patient characteristics were significant factors for survival.

Cumulative Medicare Expenditures

The unadjusted IPW average for cumulative Medicare expenditures per patient was $71,029 if one course of TACE was undergone, $101,402 for two courses, $110,538 for three courses, and $143,961 for four or more courses (Figure 2). Table 3 presents the average cumulative Medicare expenditures for the TACE cohorts, adjusted for censoring, concomitant therapies, and clinical and demographic characteristics. Mean years survived was calculated by using the adjusted survival curves shown in Figure 3. One-course patients survived an average 1.86 (95% CI 1.82–1.90) years following diagnosis and incurred an average $74,788 (95% CI $71,890–$77,686). Two-course patients lived an average 2.09 (95% CI 2.05–2.13) years and incurred $101,126 (95% CI $94,395–$107,856). Three-course patients lived 2.81 (95% CI 2.66–2.97) years and incurred $111,776 (95% CI $101,931–$121,621). Four or more-course patients lived 3.06 years on average and incurred $148,878 (95% CI $136,346–$161,409).

If mortality is restricted to be HCC-related, then a consistent survival advantage associated with additional courses of TACE is no longer evident. One-course patients survived an average 3.24 (95% CI 3.12–3.36) years after diagnosis, while two-course patients survived only 2.86 (95% CI 2.77–2.95) years after diagnosis. Three-course patients survived an average 4.09 years, while four or more-course patients survived 3.82 (95% CI 3.55–4.10) years.

Discussion

Prior research has examined the economic burden of caring for HCC in the United States [16]; however, to our knowledge, this study is the first to examine the long-term costs associated with repeated applications of TACE in treating the disease. In an era of concern over wasteful spending in the health care sector, there is greater focus by payers and providers to balance the effective use of allocated budgets with sufficient intensity of therapy for their patients. Hence, health care organizations have an interest in knowing the costs of TACE as it is applied in the real-world
practice environment, especially in the population for which TACE is most treated.

This analysis was a retrospective study of Medicare beneficiaries who resided within SEER-registry areas and were diagnosed with HCC between 2000 and 2007. Of the 1228 patients who received at least one TACE treatment, never received transplant or resection, and met the inclusion criteria, less than half had undergone multiple courses of TACE; 24% (n = 297) received two courses, 11% (n = 133) received three courses, and 8% (n = 102) received four or more (up to 10 courses). Adjusted average cumulative Medicare-paid expenditure for one-course patients after diagnosis was $74,788 (95% CI $71,890–$77,686). Cumulative expenditures were 35% higher for two-course patients, 50% higher for three-course patients, and nearly double with four or more courses. Balancing expenditures with additional years of life showed that spending driven by greater survival may explain a portion of the increased expenditures. One-course patients lived an average 1.86 (95% CI 1.82–1.9) years after diagnosis. Two-course patients lived about 12% longer than did one-course patients, three-course patients 51% longer, and four or more-course patients 65% longer. Average years survived did not consistently increase with additional courses of TACE when we analyzed only HCC-related mortality.

It is unlikely that a comparison of average rates of Medicare spending would be reflective of the value of repeated courses of TACE. While it is inappropriate to attribute all expenditures to TACE, it is also inappropriate to attribute all life to TACE. First, adjusting for concomitant therapies and patient risk factors, the average risk of all-cause mortality over the follow-up period was not significantly lower with two courses of TACE versus only one course of TACE. The average risk of mortality was lower for three or more courses versus one course, but no significant difference was found between three courses and four or more courses. Using HCC-related mortality, average risk over follow-up for two, three, or four or more courses was

<table>
<thead>
<tr>
<th>Covariates</th>
<th>All-cause mortality</th>
<th>HCC-related mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AHR 95% CI</td>
<td>AHR 95% CI</td>
</tr>
<tr>
<td>1 TACE</td>
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<td>0.81 0.66–0.99</td>
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<td>0.51 0.39–0.67</td>
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<td>3 TACE</td>
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<td>0.46 0.39–0.63</td>
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<td>4+ TACE</td>
<td>0.64 0.52–0.79</td>
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<td>Ablation</td>
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<td>0.70 0.47–0.72</td>
</tr>
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<td>1.04 0.74–0.54</td>
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<tr>
<td>Stage 2</td>
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<td>1.02 0.84–1.22</td>
</tr>
<tr>
<td>Stage 3</td>
<td>1.82 1.49–2.22</td>
<td>1.15 0.88–1.50</td>
</tr>
<tr>
<td>Stage 4</td>
<td>1.72 1.24–2.40</td>
<td>1.38 1.00–1.90</td>
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<td>Stage unknown</td>
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<td>1.38 1.00–1.90</td>
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<td>CCI &gt; 1</td>
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<td>1.38 1.00–1.90</td>
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<td>Age 65–74 y</td>
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<td>2.40 2.38–2.42</td>
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<td>Age 75–84 y</td>
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<td>Age &gt;84 y</td>
<td>1.31 0.75–2.29</td>
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<tr>
<td>Male</td>
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<td>1.36 1.03–1.80</td>
</tr>
<tr>
<td>Caucasian</td>
<td>Reference</td>
<td>1.09 0.94–1.26</td>
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<tr>
<td>African American</td>
<td>1.26 0.97–1.64</td>
<td>1.09 0.94–1.26</td>
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<td>Hispanic</td>
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<td>1.36 1.03–1.80</td>
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<tr>
<td>Other race/ethnicity</td>
<td>0.83 0.70–0.99</td>
<td>1.36 1.03–1.80</td>
</tr>
<tr>
<td>Censored</td>
<td>185 of 1228</td>
<td>652 of 1228</td>
</tr>
</tbody>
</table>

AHR, average hazard ratio estimated by using weighted Cox regression model; ALD, alcohol-related liver disease; CCI, Charlson comorbidity index; chemo, chemotherapy; CI, confidence interval; HCC, hepatocellular carcinoma; MSLD, moderate to severe liver disease; radiation, includes both external-beam and selective-internal radiation therapies; TACE, transarterial chemoembolization.
significantly lower than for one-course patients, yet there was also no significant difference between three and four or more courses of TACE.

Second, HCC is an aggressive disease that is difficult to evaluate and treat. SEER-Medicare is limited in nuanced clinical data used by physicians to determine severity or progression of the disease and may preclude patients from further treatment. Thus, patients who had undergone repeated courses of TACE as a part of a patient-specific treatment protocol could not be delineated from patients prescribed more than one course of TACE according to continued eligibility for further treatment or tumor response to the prior course. For instance, we found striking similarity across all TACE cohorts in the unadjusted average time of survival after TACE is discontinued (between 13.6 and 14.7 months for one to three courses and 11.5 with four or more courses). Much of the survival advantage across cohorts tended to accrue prior to the final course of TACE. If it is assumed that further TACE treatments are undergone through patient/physician choice, then any survival benefit of repeated TACE may tend to be realized until sufficient progression of the disease facilitates discontinuing treatment. Conversely, if greater survival is reflective of only selection of the fittest patients into further TACE treatments, then clinical benefits associated with repeated TACE would be overstated.

An advantage of SEER-Medicare database is that it allowed observation of the long-term survival and medical expenditures of cancer patients. Yet, clinical data are limited to that which can be obtained from Medicare claims or provided by SEER at the time of cancer diagnosis. While observed risk factors were largely balanced across the TACE groups, unobserved differences may have confounded cost and mortality comparisons between the four TACE groups.

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**Fig. 2** – Mean weeks from HCC diagnosis until final course of TACE and until mortality, with unadjusted average cumulative cost per patient (2011 US $). TACE, transarterial chemoembolization. Means were calculated by using Kaplan-Meier analyses to adjust for censoring. Unadjusted average cumulative cost per patient estimated by using Bang and Tsiatis’s [22] method for estimating medical costs with censored data.

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**Table 3** – Adjusted average cumulative Medicare expenses (2011 US $) and adjusted mean years survival associated with multiple TACE treatments for HCC.

<table>
<thead>
<tr>
<th></th>
<th>1 TACE</th>
<th>2 TACE</th>
<th>3 TACE</th>
<th>4+ TACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted average cumulative Medicare expenses (95% CI)*</td>
<td>$74,788 ($71,890–$77,686)</td>
<td>$101,126 ($94,395–$107,856)</td>
<td>$111,776 ($101,931–$121,621)</td>
<td>$148,878 ($136,346–$161,409)</td>
</tr>
<tr>
<td>Using all-cause mortality Adjusted mean years survived after diagnosis (95% CI)*</td>
<td>1.86 (1.82–1.90)</td>
<td>2.09 (2.05–2.13)</td>
<td>2.81 (2.66–2.97)</td>
<td>3.06 (2.95–3.18)</td>
</tr>
<tr>
<td>Using HCC-related mortality Adjusted mean years survived after diagnosis (95% CI)*</td>
<td>3.24 (3.12–3.36)</td>
<td>2.86 (2.77–2.95)</td>
<td>4.09 (3.75–4.44)</td>
<td>3.82 (3.55–4.10)</td>
</tr>
</tbody>
</table>

*CI, confidence interval; HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; 4+, four or more courses of TACE undergone in the follow-up period (maximum 10).

* To adjust for censoring and patient characteristics, expenditure coefficients for TACE cohorts were estimated by using partitioned, inverse probability-weighted, multivariate least squares regression. Estimates represent the additional cumulative Medicare expenditures compared with patients who received only one TACE. The model includes as covariates age, sex, race, Hispanic ethnicity, rural residence, cancer stage, Charlson comorbidity index, liver conditions, and receipt of ablation, chemotherapy, and external-beam or selective-internal radiation therapy. Estimates were calculated by using the bootstrap approach, in which the process of performing 84 (monthly) partitioned regression analyses and summing coefficients across partitions was repeated 1000 times by using sampling with replacement.

† Cumulative years survived calculated as the total area under the respective adjusted survival curve, divided by 52 weeks per year, estimated by using Cox proportional hazards models stratified by TACE cohorts.
Cumulative Medicare expenditures may be somewhat underestimated. While several oral anticancer and antiemetic drugs are/were covered under Medicare Part B, data for oral prescription drugs covered under Part D were not available prior to 2007 and therefore were not incorporated into the analysis. We did not anticipate costs to be underestimated for any particular TACE cohort more than others. IPW least squares regression was used to estimate cumulative costs in the presence of censoring in the sample. Estimators based on IPW can sometimes be biased if censoring is large or dependent on covariates [25]. Only 15% (n = 183) of the observations were censored in this sample, and the correlation coefficient between censored observations and any covariate was relatively low (\( \rho = 0.14 \) for stage 1, and 0.00 < \( \rho < 0.10 \) for all other variables). The bootstrap procedure was used to approximate the variance of the regression coefficients. Despite no formal proof of consistency of the bootstrap estimator in this setting, we followed the suggestions and examples of other authors using bootstrap in similar settings [24–27]. As argued by Griffiths et al. [26], further research is needed regarding the strengths and weaknesses of bootstrap for long-term cost estimators.

Physician and patient choice is an important determinant of quality cancer care, but, from a policy standpoint, the current health care environment necessitates treatment choice to be balanced with considerations of costs. Our findings show that Medicare expenditures doubled between one and four or more TACE treatments, but expenses were distributed over more than an additional year of life. Our results may have implications for patients and Medicare as well as health care organizations concerned with the efficient use of resources for treating the growing population of patients with HCC. Data limitations prevented methods for the randomization of patients necessary for an unbiased cost-effectiveness analysis of repeated TACE treatments. However, cost-effectiveness analysis through randomized controlled trials would be unethical. In the absence of complete comparative and cost-effectiveness evidence of TACE, our results provide data on the association between multiple TACE treatments, cumulative expenditures, and survival.

Fig. 3 – Patient survival (in weeks from diagnosis), per number of TACE courses; adjusted models. * TACE, transarterial chemoembolization. *Adjusted for age, sex, race, Hispanic ethnicity, cancer stage, Charlson comorbidity index, liver conditions, and receipt of ablation, chemotherapy, and radiation therapy.
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REFERENCES