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Journal of Hepatology xx (2005) 1–9

Journal of Hepatology

www.elsevier.com/locate/jhep

Treatment and outcomes of treating of hepatocellular carcinoma among medicare recipients in the United States: A population-based study

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***Background Aims*: There are several treatment alternatives available for patients diagnosed with hepatocellular carcinoma (HCC). Yet, neither the extent to which potentially curative or palliative therapy is used to treat HCC, nor the determinants of using such therapies are known. Further, it is unclear how effective different modalities are for treating HCC.**

***Methods*: We used the linked SEER-Medicare dataset to identify patients diagnosed with HCC between 1992 and 1999.We identified 2963 patients with continuous Medicare enrollment who were not enrolled in a Medicare-HMO. HCC treatments were categorized as potentially curative therapy (resection, transplant, local ablation), or palliative (trans-arterial chemoembolization (TACE), chemotherapy), and no therapy. Demographic (age, sex, race, geographic region), clinical (comorbidity, risk factors and severity of liver disease) and tumor factors (tumor size, extent of disease) were examined as potential determinants of therapy, as well as survival in univariate and multivariable analyses. Survival curves were also generated and compared among the different treatment modalities.**

***Results*: The median age at diagnosis was 74 years (range: 32–105), and most patients (91%) were older than 65 years. Approximately 68% were White, 10% Black, 4% Hispanic, 8% Asian, and 9% were of other race. Thirteen percent of the patients received potentially curative therapy (transplant 0.9%, resection 8.2%, local ablation 4.1%), 4% received TACE, 57% received other palliative therapy, and 26% received no specific therapy. Only 34% of 513 patients with single lesions, and 34% of 143 patients with lesions <3.0 cm received potentially curative therapy. However, 19.2% of patients with unfavorable tumor features (lesion >10.0 cm) received such therapy. Among patients who received potentially curative therapy ($n=392$), resection was the most common procedure ($n=243$, 62%) followed by local ablation ($n=122$, 31%) and finally transplantation ($n=27$, 7%). In regression analyses, geographic variations in the extent and type of curative therapy persisted after adjusting for demographic, clinical, and tumor features. Median overall survival was 104 days following HCC diagnosis with the longest survival in the transplant group (852 days) and the shortest survival in**

Received 17 April 2005; received in revised form 27 September 2005; accepted 11 October 2005

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Abbreviations HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; SEER, surveillance epidemiology and end-results Program.

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doi:10.1016/j.jhep.2005.10.002

the group with no treatment (58 days). In the survival analysis, transplantation led to the longest survival, followed by resection. Neither ablation nor TACE yielded prolonged survival (3 year survival was less than 10%).

***Conclusions*: In this predominantly 65 years and older Medicare population, there are marked geographic variations in the management of HCC that seem to be at least as important as clinical and tumor-related features in determining the extent and type of HCC therapy. There is underutilization of potentially curative therapy, even among those with favorable tumor features.**

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***Keywords*: Outcomes; SEER-Medicare; Resection; Transplant; Treatment; HCC**

1. Background

The incidence of hepatocellular carcinoma (HCC) has doubled over the last 20 years, with a substantial proportion of this increase attributed to hepatitis C [1]. The overall prognosis of patients with HCC in the US is poor, especially for patients who do not receive specific therapy [2]. Potentially curative therapy for HCC includes surgical resection, liver transplantation, and possibly local ablation with alcohol and radiofrequency [3]. These therapies have been shown in uncontrolled series to be associated with longer survival than expected without therapy, particularly among patients with smaller tumor size, fewer lesions, and less severe liver disease [4]. In addition, some forms of palliative therapy such as trans-arterial chemoembolization (TACE) have also been shown in a recent meta-analysis of randomized controlled trials to be associated with longer survival in patients with relatively preserved liver function [5]. However, most of these studies evaluated a small number of patients, and focused on selected patient populations.

The outcomes of HCC in the US population are unclear due to the lack of population-based data on HCC therapy. These outcomes depend on the effectiveness of therapy but also on the extent of using these therapies for HCC. Establishing estimates of the extent of diffusion of therapies is important in determining the effectiveness of treatment and in identifying gaps in the equity of care. The registries of the Surveillance, Epidemiology, and End Results (SEER) Program collect population-based cancer incidence and survival data from different sites across the country [6]. The SEER-Medicare database merges SEER and Medicare, and contains demographic, clinical and medical claims data including treatment on cancer patients mostly over age 65 at diagnosis [7]. It has been extensively used to examine the outcomes of therapy for several cancers but not liver cancer. Using SEER-Medicare, we examined the extent and potential determinants of receiving (and type) of treatment, and the effects of receiving different modalities on survival of patients with HCC.

2. Methods

2.1. Data source

The SEER-Medicare dataset contains Medicare claims data dating back to 1991 for all Medicare-enrolled patients identified by SEER registries between 1992 and 1999.SEER collects population-based cancer incidence and survival data on incident cancer cases from 11 population-based cancer registries that account for approximately 14% of the population in the US. Medicare is the primary health insurer for approximately 97% of individuals age 65 years and older in the US. Persons less than 65 years of age are eligible for Medicare benefits if they are disabled or have end stage renal disease.

2.2. Study population

All Medicare-enrolled patients with a diagnosis of HCC in SEER registries between 1992 and 1999 were eligible for inclusion. Diagnostic confirmation of HCC was defined as having positive histology, cytology, laboratory test/marker study, direct visualization of tumor or a positive radiology test. We excluded patients diagnosed with stomach, colon, rectum, lung, pancreas, or breast cancers within the 5 years prior to the date of HCC diagnosis to avoid metastatic liver cancers.

To study patients with equal exposure to risk factor information, we selected only those with continuous enrollment in Medicare for at least one year prior to HCC diagnosis. We also excluded patients enrolled in a health maintenance organization (HMO) during this time period because Medicare HMO plans have not been required to submit individual claims to CMS for specific services received by patients enrolled in Medicare.

2.3. HCC treatment

Transplantation had the highest precedence, followed by resection, ablation, and TACE. Patients with none of these procedures were grouped into a separate category.

2.4. Risk factors for liver disease

HBV, HCV, diabetes, and alcoholic liver disease were identified from inpatient and outpatient files from 1 year preceding and for 2 years succeeding the date of HCC diagnosis or until death.

2.5. Disease comorbidity

To estimate the severity of liver disease, we identified the following conditions during the 1-year prior to HCC diagnosis: encephalopathy, ascites, esophageal varices, and hepatorenal syndrome.

We also identified patients with Child C cirrhosis based on an algorithm derived from a dataset of 159 patients with newly diagnosed HCC in whom the Child score was calculated based on medical record review. A logistic regression model predicting 'Child C' was performed with ascites, encephalopathy, alcoholism, HCV, HBV, cirrhosis, and CT of the abdomen as predictor variables, and a C-statistic of 0.75 (indicates the predictive ability of the model) was reached. Parameter estimates obtained for the seven predictor variables in the fitted model was attached to each observation of the current SEER-Medicare HCC cohort ($n=2963$) and a logistic regression model was used to calculate the Child Class score variable in this cohort. The score was converted to a categorical variable with probability ≥ 0.28 indicating Child C; this cutoff is associated with a negative predictive value of 82%.

In addition, we constructed a general disease comorbidity index based on outpatient and inpatient diagnoses recorded within one year prior to the

diagnosis of HCC. We followed the methods previously described and validated by Klaubunde using the linked SEER-Medicare dataset [8].

2.6. Statistical analysis

The frequency and proportions of patients receiving each treatment modality were calculated. Potential determinants of therapy were compared among the groups. These included demographic, clinical, and tumor features. Chi-square tests were conducted for categorical variables and t-tests for continuous variables. Multivariable logistic regression analyses were also conducted to examine the simultaneous effect of several determinants on choice of therapy.

We conducted the following two-way comparisons of survival between [1] transplant and surgical resection groups, [2] surgical resection and local ablation, [3] surgical resection and TACE, [4] local ablation and TACE, and finally [5] TACE vs. the rest of patients who belong to none of the other therapeutic categories. Kaplan Meier survival analyses were performed. Multivariable Cox proportional hazard analyses were also conducted to examine the simultaneous effect of several determinants on risk of mortality.

In order to minimize bias related to the non-random allocation of treatment, we adjusted for propensity score to receive a given therapy. A logistic regression model was constructed from variables that influence choice of treatment (tumor stage, tumor size, medical comorbidity, demographics) to estimate the probability of receiving a given therapy (vs. the comparison); this probability is referred to as the propensity score [9]. We subsequently adjusted for propensity score by matching, stratified analyses, and adjusting for the score as a continuous variable in the Cox proportional model. For the stratified analyses, for each comparison, we created three categories based on tertiles of propensity scores, and survival was compared within each stratum.

3. Results

There were 2963 patients with HCC diagnosed between 1992 and 1999 who fulfilled our inclusion and exclusion criteria. The method of diagnosis was histology in 63%, cytology in 20%, abnormal lab test in 2%, direct visualization in 1% or radiology tests in 14%. Approximately, two-thirds of patients (62.5%) had codes indicative of cirrhosis or its complications. The median age of patients was 74 (range: 32–105), and most patients (91%) were older

Table 1
Sociodemographic characteristics of SEER-Medicare patients with HCC ($n=2963$) by therapy received, 1992–1999

	Total ($n=2963$)	Transplant ($n=27$)		Resection ($n=243$)		Ablation ($n=122$)		TACE ($n=131$)		Rest ($n=2440$)		*P*-value*
		n	%	*n*	%	*n*	%	*n*	%	*n*	%	
Year of diagnosis												
1992–1995	1414	9	33.3	115	47.3	36	29.5	52	39.7	1202	49.3	0.0001
1996–1999	1549	18	66.7	128	52.7	86	70.5	79	60.3	1238	50.7	
Age												
<65	270	4	14.8	16	6.6	12	9.8	17	13.0	221	9.1	<0.0001
65–74 years	1351	23	85.2	139	57.2	74	60.7	77	58.8	1038	42.5	
75+ years	1342	0	0.0	88	36.2	36	29.5	37	28.2	1181	48.4	
Gender												
Female	939	12	44.4	92	37.9	36	29.5	40	30.5	759	31.1	0.1340
Male	2024	15	55.6	151	62.1	86	70.5	91	69.5	1681	68.9	
Race												
White	2028	22	81.5	147	60.5	71	58.2	67	51.2	1721	70.5	<0.0001
Non-White	935	5	18.5	96	39.5	51	41.8	64	48.8	719	29.5	
SEER Registry												
Atlanta	142	4	14.8	11	4.5	10	8.2	8	6.1	109	4.5	<0.0001
Connecticut	329	3	11.1	15	6.2	11	9.0	12	9.2	288	11.8	
Detroit	461	1	3.7	40	16.5	11	9.0	10	7.6	399	16.4	
Hawaii	146	0	0.0	14	5.8	16	13.1	18	13.7	98	4.0	
Iowa	263	2	7.4	24	9.9	5	4.1	6	4.6	226	9.3	
Los Angeles	640	11	40.7	56	23.1	38	31.2	30	22.9	505	20.7	
New Mexico	158	1	3.7	10	4.1	12	9.8	3	2.3	132	5.4	
San Francisco	337	2	7.4	28	11.5	7	5.7	16	12.2	284	11.6	
San Jose	143	0	0.0	12	4.9	3	2.5	14	10.7	114	4.7	
Seattle	275	3	11.1	21	8.6	9	7.4	12	9.2	230	9.4	
Utah	69	0	0.0	12	4.9	0	0.0	2	1.5	55	2.3	
No. comorbidities												
0	1461	14	51.9	130	53.5	50	41.0	55	42.0	1212	49.7	0.1310
1	810	8	29.6	70	28.8	36	29.5	44	33.6	652	26.7	
2+	692	5	18.5	43	17.7	36	29.5	32	24.4	576	23.6	
Historic stage												
Localized	984	17	63.0	182	74.9	59	48.4	51	38.9	675	27.7	<0.0001
Regional	700	3	11.1	36	14.8	36	29.5	46	35.1	579	23.7	
Distant	544	1	3.7	15	6.2	10	8.2	8	6.1	510	20.9	
Unstaged	735	6	22.2	10	4.1	17	13.9	26	19.9	676	27.7	
Medicare/Medicaid dual enrolment	746	8	29.6	66	27.2	30	24.6	8	6.1	602	24.7	0.0305

than 65 years. Men comprised 68% of these patients. The racial composition was 68% White, 10% Black, 4% Hispanic, 8% Asian, and 9% other race. Of those, 27 (0.9%) received liver transplantation, 243 (8.2%) surgical resection, 122 (4.1%) local ablation, 131 (4.4%) TACE, 57% other palliative therapy (12% systemic chemotherapy and 45% radiotherapy), and 26% received no specific HCC therapy.

There were significant differences in HCC treatment according to tumor-related and clinical factors (Tables 1 and 2). Approximately, 28% of the patients with more than one lesion received no therapy, compared to 15% of patients with a single lesion. Patients infected with HBV were more likely to receive curative therapy than patients with other risk factors, followed by those with HCV. During the latter half of the study period, there were small increases in the proportions of patients receiving potentially curative therapy (15.0%) or TACE (5.1%). The proportions of patients treated with curative therapy ranged from 8.7% in Connecticut to 20.6% in Hawaii. Approximately, a quarter of Asians with HCC received potentially curative therapy, which was significantly greater than the proportions in other racial groups (range: 11.8–14.8%).

However, in the full multivariable logistic regression model, Asian race was not an independent determinant of receiving potentially curative therapy (Table 3). Similarly, there were no significant temporal changes in the receipt of curative therapy when adjusted for the variables mentioned above. The presence of multiple lesions (65%), metastatic disease (−84%), tumor size >5.0 cm (−30%), and diabetes (−27%) were significant negative determinants of receiving potentially curative therapy, whereas HCV (+20%) and HBV (+218%) were significant independent positive determinants of obtaining such therapy. Lastly, significant geographic variations persisted in the fully adjusted model.

Among 392 patients who received potentially curative therapy, the majority received surgical resection (62%), followed by local ablation (31%), and liver transplant (7%). There were no significant differences in sex, or race. However, there were significant geographic differences related to the type of curative therapy. All three types of curative therapy were performed more frequently in patients from the Los Angeles registry. In the full multivariable logistic regression model, the more recent time period (−48%), multiple HCC lesions (−47%), metastatic disease

Table 2
Risk factors and severity of liver disease in 2963 patients with HCC identified in SEER-Medicare between 1992 and 1999

	Total (n=2963)	Transplant (n=27)		Resection (n=243)		Ablation (n=122)		TACE (n=131)		Rest (n=2440)		P-value*
		n	%	n	%	n	%	n	%	n	%	
Risk factors												
Alcoholic liver disease												
Yes	669	9	33.3	38	15.6	30	24.6	43	32.8	549	22.5	0.0023
No	2294	18	66.7	205	84.4	92	75.4	88	67.2	1891	77.5	
HBV												
Yes	262	7	25.9	34	14.0	29	23.8	30	22.9	162	6.6	<0.0001
No	2701	20	74.1	209	86.0	93	76.2	101	77.1	2278	93.4	
HCV												
Yes	491	21	77.8	45	18.5	39	32.0	45	34.4	341	14.0	<0.0001
No	2472	6	22.2	198	81.5	83	68.0	86	65.6	2099	86.0	
Diabetes												
Yes	1158	11	40.7	78	32.1	51	41.8	67	51.2	951	39.0	0.0095
No	1805	16	59.3	165	67.9	71	58.2	64	48.8	1489	61.0	
Liver disease severity												
Ascites												
Yes	1213	18	66.7	78	32.1	52	42.6	58	44.3	1007	41.3	0.0029
No	1750	9	33.3	165	67.9	70	57.4	73	55.7	1433	58.7	
Encephalopathy												
Yes	481	15	55.6	20	8.2	26	21.3	31	23.7	389	15.9	<0.0001
No	2482	12	44.4	223	91.8	96	78.7	100	76.3	2051	84.1	
Esophageal varices												
Yes	423	10	37.0	16	6.6	21	17.2	26	19.9	350	14.3	<0.0001
No	2540	17	63.0	227	93.4	101	82.8	105	80.1	2090	85.7	
Hepatorenal syndrome												
Yes	100	3	11.1	8	3.3	2	1.6	7	5.3	80	3.3	0.1027
No	2863	24	88.9	235	96.7	120	98.4	124	94.7	2360	96.7	
Child C score												
Yes	395	19	70.4	17	7.0	21	17.2	20	15.3	318	13.0	<0.0001
No	2568	8	29.7	226	93.0	101	82.8	111	84.7	2122	87.0	

Table 3
Results from the multiple logistic regression analysis examining receipt of potentially curative therapy (vs. TACE, other palliative therapy or no therapy) and the effect of several potential determinants including demographic, clinical, and tumor features; the model contained all the variables listed in the table

	Adjusted odds ratio	95% confidence interval	*P*-value
Year of diagnosis			
1992–1995	1.00	–	Reference
1996–1999	1.21	0.94–1.54	0.134
Age (Years)			
<65	1.00	–	Reference
65–74	1.83	1.18–2.86	0.007
>75	0.85	0.53–1.36	0.496
Gender			
Women	1.00	–	Reference
Men	1.25	0.96–1.62	0.092
Race			
White	1.00	–	Reference
Black	1.06	0.69–1.63	0.800
Hispanic	0.89	0.48–1.64	0.711
Asian	1.47	0.93–2.32	0.100
Other	1.01	0.64–1.60	0.971
SEER registry			
San Jose	1.00	–	Reference
Connecticut	2.41	1.12–5.18	0.024
Detroit	1.77	0.86–3.61	0.119
Hawaii	2.02	0.94–4.36	0.072
Iowa	2.15	1.01–4.55	0.047
Los Angeles	2.47	1.28–4.74	0.007
New Mexico	2.85	1.29–6.29	0.010
San Francisco	1.47	0.73–3.00	0.287
Atlanta	3.24	1.46–7.19	0.004
Seattle	1.24	0.60–2.59	0.565
Utah	3.65	1.41–9.42	0.008
Medicare/Medicaid dual enrolment	0.81	0.59–1.60	0.180
Extent of disease			
Single lesion	1.00	–	Reference
Multiple lesions	0.35	0.27–0.46	<0.0001
Metastatic disease	0.16	0.10–0.26	<0.0001
Not recorded	0.17	0.11–0.27	<0.0001
Co-morbidity index			
0	1.00	–	Reference
1–2	1.21	0.90–1.61	0.204
>2	0.83	0.51–1.35	0.459
Tumor size (cm)			
<5.0	1.00	–	Reference
>5.0	0.70	0.53–0.93	0.014
Not recorded	0.22	0.16–0.31	<0.0001
Risk factors			
HCV	1.20	0.88–1.63	0.246
HBV	2.18	1.48–3.22	<0.0001
Alcoholic liver disease	0.68	0.49–0.95	0.022
Diabetes	0.73	0.54–0.99	0.041
Liver disease severity			
Encephalopathy	0.94	0.67–1.34	0.7448
Esophageal varices	0.77	0.53–1.13	0.1865

A total of 2963 patients, of whom 392 received potentially curative therapy.

(−69%), and severe underlying liver disease (−83%) were significant independent negative determinants, whereas HCC size >5.0 cm (+214%) was a positive determinant of surgical resection (Table 4).

We identified 96 patients who hypothetically were ideal candidates for transplantation: patients younger than 70 with one mass <5 cm HCC or <3 tumors. Of these, 11 (11.5%) had transplant, 15 (15.6%) had surgical resection, and 13 (13.5%) had local ablation. We also identified 124 patients who might have been good candidates for surgical resection (size <10 cm and absence of codes for cirrhosis or hepatic decompensation), and of those 12.9% received surgical resection. Lastly, of 56 patients with tumor size <3 cm and single or multiple lesions (but not metastatic or unknown) who might have been good candidates for local ablation, only 14.3% received such therapy. Interestingly, a relatively large proportion (19.3%) of patients with unfavorable tumor features for potentially curative therapy (HCC lesion(s) > 10.0 cm) received such therapy; most of these patients (81.6%) received surgical resection. In addition, 4.9% of those recorded as having metastatic disease received a form of potentially curative therapy.

There were significant differences in survival among the treatment groups (Table 5 and Fig. 1). The median overall survival was 104 days following HCC diagnosis with the longest survival in the transplant group (852 days) and the shortest survival in the group with no treatment (58 days). The risk of mortality was reduced by 32% in patients who received transplant as compared to resection. In a Cox proportional hazard model that adjusted for propensity score, the mortality risk was reduced even further (by approximately 65%) with transplant compared to surgical resection.

In the Kaplan Meier analysis, the cumulative survival of patients who received surgical resection was significantly higher than ablation ($P=0.005$). The unadjusted Cox model showed a 35% mortality reduction with resection compared to ablation. However, in a Kaplan Meier analysis of 69 patients in each group matched on propensity score to receive surgical resection, these differences in survival fell short of statistical significance (P: 0.08). Similarly, in the adjusted full model, surgical resection was no longer a significant predictor of lowered mortality (Table 6). Most of the adjustment resulted from including the propensity score variable. Further, in a conditional logistic regression model that examined only 64 patients in each group matched on propensity score, the unadjusted hazard ratio with surgical resection was also not significant (0.90 (0.53, 1.52)) (data not shown).

The cumulative survival in patients who received either surgical resection or TACE in the entire group, as well as 68 patients from each group matched on propensity score were then compared. In the unadjusted Cox proportional model, there was a 32% lower mortality risk with surgical resection compared with TACE. The survival benefit with resection

Table 4
Results from the multiple logistic regression analysis examining receipt of surgical resection (vs. transplant or ablation); (total 392 patients of whom 243 received resection)

	Adjusted odds ratio	95% confidence interval	*P*-value
Year of diagnosis			
1992–1995	1.00	–	Reference
1996–1999	0.47	0.28–0.81	0.007
Age (Years)			
<65	1.00	–	Reference
65–74	1.51	0.55–4.13	0.422
>75	2.40	0.79–7.27	0.121
Gender			
Men	1.00	–	Reference
Women	1.28	0.74–2.21	0.383
Race			
White	1.00	–	Reference
Black	1.53	0.61–3.87	0.366
Hispanic	0.82	0.22–3.03	0.766
Asian	1.32	0.52–3.35	0.561
Other	1.20	0.47–3.11	0.705
SEER registry			
Atlanta	1.00	–	Reference
Connecticut	2.02	0.55–7.48	0.292
Detroit	6.25	1.86–20.94	0.003
Hawaii	1.10	0.27–4.60	0.893
Iowa	4.70	1.22–18.15	0.025
Los Angeles	1.27	0.44–3.64	0.658
New Mexico	1.44	0.36–5.79	0.607
San Francisco	5.21	1.39–19.50	0.014
San Jose	4.52	0.82–24.92	0.084
Seattle	2.48	0.70–8.74	0.158
Utah	7.10	1.24–20.8	0.014
Medicare/Medicaid dual enrolment	1.66	0.84–3.28	0.144
Extent of disease			
Single lesion	1.00	–	Reference
Multiple lesions	0.44	0.25–0.77	0.004
Metastatic disease	0.31	0.11–0.87	0.026
Not recorded	0.29	0.10–0.68	0.024
Co-morbidity index			
0	1.00	–	Reference
1–2	0.75	0.40–1.38	0.350
>2	0.47	0.17–1.29	0.144
Tumor size (cm)			
<5.0	1.00	–	Reference
>5.0	2.72	1.52–4.86	0.001
Not recorded	0.88	0.42–1.86	0.744
Risk factors			
HCV	0.60	0.32–1.11	0.103
HBV	0.57	0.27–1.22	0.147
Alcoholic liver disease	1.10	0.58–2.09	0.777
Diabetes	0.86	0.45–1.62	0.633
Liver disease severity			
Encephalopathy	0.38	0.18–0.79	0.0101
Esophageal varices	0.67	0.29–1.56	0.3541
Ascites	0.78	0.44–1.36	0.3723
Hepatorenal syndrome	1.70	0.40–7.26	0.4733

The model contained all the variables listed in the table.

persisted but was attenuated in a model that adjusted for the propensity score, as well as in the full model (data not shown).

Fig. 1 shows a higher cumulative survival in patients who received ablation compared to those who received TACE ($P=0.008$). These differences persisted ($P=0.012$) in analyses of 65 patients in each group matched on propensity score. Ablation was associated with approximately 30% reduction in mortality risk in the unadjusted as well as in the fully adjusted Cox proportional model (Table 7). In a conditional Cox proportional hazard analysis limited to 65 patients in each group matched on propensity score, the hazard ratio was 0.55 (95% CI: 0.32, 0.94).

Apart from the type of therapy, other significant predictors of increased mortality risk were the presence of distant disease and more comorbidities. On the other hand, gender, race, age, and year of HCC diagnosis were not significant predictors of mortality.

4. Discussion

This is the first population-based study of the extent and determinants of HCC therapy in the United States and the outcomes of these therapies. Three main findings indicate potentially significant inappropriate management of HCC during the years 1992–1999. First, the great majority of patients with HCC did not receive potentially curative therapy. More importantly, only a third of patients with favorable tumor features who were most likely to benefit received such therapy. Second, potentially inappropriate use of curative therapy, mostly resection, was observed in approximately a fifth of patients with unfavorable features such as lesions >10 cm [3]. Lastly, there were remarkable geographic variations indicative of wide practice variations in the extent and type of curative, as well as palliative, therapies.

Given the lack of population-based studies, the acceptable proportion of HCC patients in whom potentially curative or palliative therapy should be applied is not known. Estimates from non population-based large referral centers such as the Barcelona Clinic Liver Center, indicate that 28% of 2114 consecutive patients HCC presenting between 1987 and 2002 were treated with potentially curative therapy (resection 6%, transplantation 9%, ablation 13%) [10]. Data from the Cancer of the Liver Italian Program (CLIP) on 650 patients diagnosed between 1990 and 1997 indicate that 41% received liver resection or local ablation, and 16% received TACE/TAE [11]. In the CLIP data, about 31% of patients 70 years and older received potentially curative therapy. Neither study was a true population-based study. Nevertheless, our results, with only 13% receiving potentially curative therapy suggest marked underutilization of such therapy.

There are several possible explanations for this apparent underutilization of HCC therapy. The severity of liver

Table 5
Observed survival in patients with HCC categorized by the type of treatment received

	Median survival in days (25th–75th)	30-day mortality		Survival 1-year		Survival 2-year		Survival 3-year	
		No.	%	No.	%	No.	%	No.	%
Transplant ($n=27$)	852 (297–1614)	0	0.0	20	74.1	14	51.9	11	40.7
Surgical resection ($n=243$)	568 (200–1279)	17	7.0	150	61.7	105	43.2	75	30.9
Ablation ($n=122$)	458 (213–772)	1	0.8	73	59.8	35	28.7	12	9.8
TACE ($n=131$)	324 (151–633)	7	5.3	58	44.3	24	18.3	8	6.1
None of the above ($n=2440$)	82 (41–202)	384	15.7	318	13.0	135	5.5	63	2.6

disease, comorbid illness, and functional status are important determinants of treatment and prognosis of patients with HCC. In this study, we relied on diagnostic codes of ascites, encephalopathy, and bleeding esophageal varices to define decompensated liver disease because laboratory testing and imaging studies were not available. We also estimated disease comorbidity. However, it is possible that there was residual unmeasured comorbidity that would explain some of the observed underutilization of therapy.

Our findings indicate remarkable geographic variations in the extent and type of curative and palliative therapies independent of demographic, clinical, and tumor features. The lack of a uniformly accepted standardized staging system for HCC could have contributed to these findings. Moreover, except for the Barcelona Clinic Liver Cancer staging system, the other staging systems are not directly coupled to treatment modalities. Lastly, healthcare providers' experience with diagnosis and treatment of HCC was unlikely to be great, especially in the earlier years of the study period due to the relative infrequency of this cancer at that time.

Our data also show that the most effective treatment option for HCC is liver transplantation. Transplantation offered the best chance for long-term survival, and when efforts to adjust for propensity score were included, the mortality risk was two-thirds less as compared with surgical resection. Compared with the Mazzaferro data, which yielded a 4-year survival of 75%, our 3-year survival with transplantation was only about 40% [12]. A much higher percentage of our patients had Child's C cirrhosis, and our patients were also significantly older than those in Mazzaferro's study (median age was 52). It is also unclear how many patients of ours received transplants outside of established criteria. Previous studies support our finding that ablation seems to be more effective than TACE [13,14]. However, our data suggest in a population-based sample that neither is an effective long-term curative strategy. Survival with ablation was not different from resection in the first year but dropped off quickly after this.

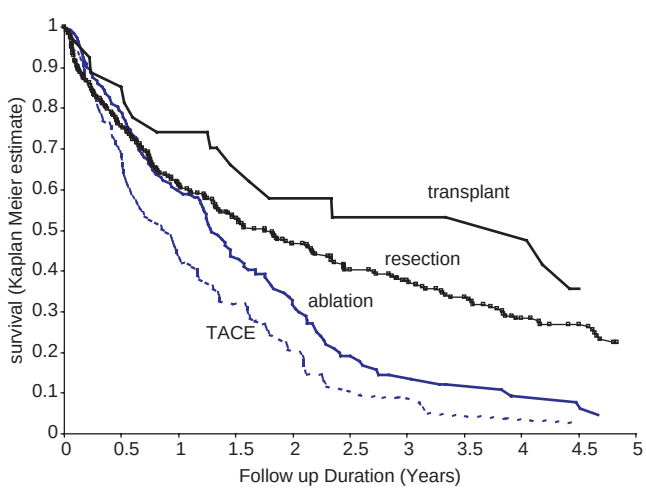

Fig. 1. The cumulative 5-year survival in 2963 patients with HCC diagnosed between 1992 and 1999 and identified in SEER-Medicare datasets. Patients were grouped into four groups depending on the type of therapy received. [This figure appears in colour on the web.]

These findings have to be interpreted within the potential limitations of our study. This study included only Medicare-enrolled patients, so most patients were 65 years and older. Thus, generalization to younger patients is limited. However, data from SEER registries indicate that 55.4% of HCC patients are 65 years and older. The use of diagnostic and procedure codes to identify therapy may also carry some variability depending on the facility and providers. Further, the study period preceded the introduction of the MELD scores in 2000, and the likely wider use of RFA. Estimation of average treatment effects in observational studies requires adjustment in pre-treatment variables. Rosenbaum and Rubin proposed an alternative method for adjusting for pre-treatment variables based on the propensity score, which is the conditional probability of receiving treatment given pre-treatment variables [9]. Therefore, we used propensity scores to mimic randomization; however in the absence of true randomization, baseline differences between the groups could still account for the observed differences in survival.

In summary, the findings of this population-based study of predominantly 65 years and older patients with HCC indicate wide practice variations in management. Of particular concern is the apparent underutilization of potentially curative therapy in patients with favorable tumor features. The barriers to implementing appropriate treatment should be identified and strategies for increasing the utilization of these therapies should be developed. We found that transplantation offers the best chance for

Table 6
Risk of mortality in patients treated with surgical resection or local ablation: results of a Cox PH model

	Hazard ratio	95% CI
Resection vs ablation unadjusted	0.65	0.51, 0.83
Resection vs ablation adjusted for propensity score	0.80	0.60, 1.07
Resection vs ablation adjusted for variable list below	0.78	0.58, 1.04
Year of diagnosis		
1996–1999	0.90	0.66
1992–1995	Reference	1.23
Age		
65–74	0.71	0.45, 1.13
75+	0.81	0.50, 1.31
<65	Reference	
Race		
Non-white:White	0.91	0.68, 1.21
Gender		
Male:female	1.04	0.79, 1.37
Geographic location		
Atlanta	0.45	0.21, 0.96
Connecticut	0.64	0.33, 1.24
Detroit	0.77	0.45, 1.30
Hawaii	0.50	0.26, 0.96
Iowa	0.61	0.33, 1.11
Los Angeles	0.58	0.35, 0.98
New México	0.71	0.36, 1.40
San Jose	0.57	0.28, 1.20
Seattle	1.12	0.62, 2.02
Utah	1.34	0.63, 2.84
San Francisco	Reference	
Comorbidities		
1	1.44	1.08, 1.92
2+	1.09	0.77, 1.54
0	Reference	
Stage		
Regional	1.14	0.78, 1.68
Distant	2.24	1.37, 3.66
Unstaged	0.96	0.56, 1.66
Localized	Reference	
Propensity score (continuous)[a]	0.34	0.12, 0.96
Child score		
Child C	0.98	0.65, 1.49
Child A or B	Reference	

[a] Propensity score includes the variables age, race, sex, comorbidities, registry, year of diagnosis, stage, 4 risk factors, and indicators of liver disease are included in the model as a continuous variable.

Table 7
Risk of mortality in patients treated with local ablation or TACE: Results of a Cox PH model

	Hazard ratio	95% CI
Ablation vs TACE unadjusted	0.70	0.54, 0.91
Ablation vs TACE adjusted for propensity score	0.71	0.54, 0.95
Ablation vs TACE adjusted for variable list below	0.68	0.50, 0.91
Year of diagnosis		
1996–1999	0.92	0.63, 1.33
1992–1995	Reference	
Age		
65–74	0.89	0.57, 1.39
75+	1.36	0.84, 2.19
<65	Reference	
Race		
Non-white:White	1.06	0.74, 1.52
Gender		
Male:female	1.11	0.81, 1.52
Geographic location		
Atlanta	0.43	0.19, 0.98
Connecticut	0.64	0.29, 1.42
Detroit	0.43	0.20, 0.91
Hawaii	0.53	0.28, 1.02
Iowa	0.68	0.30, 1.53
Los Angeles	0.63	0.31, 1.28
New México	0.55	0.20, 1.51
San Jose	0.58	0.28, 1.22
Seattle	1.18	0.61, 2.29
Utah	2.45	0.51, 11.81
San Francisco	Reference	
Comorbidities		
1	1.44	1.02, 2.03
2+	2.13	1.47, 3.08
0	Reference	
Stage		
Regional	1.20	0.87, 1.66
Distant	3.52	2.00, 6.22
Unstaged	1.02	0.60, 1.72
Localized	Reference	
Propensity score (continuous)[a]	1.16	0.24, 5.51
Child score		
Child C	1.09	0.73, 1.62
Child A or B	Reference	

[a] Propensity score includes the variables age, race, sex, comorbidities, registry, year of diagnosis, stage, four risk factors, and indicators of liver disease are included in the model as a continuous variable.

long-term survival. Resection offers the next best survival, followed by ablation, and finally TACE. Unlike previous studies, which have suggested that ablation is a potentially curative treatment, here it yielded a 3-year survival of only about 10%.

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