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Earlier presentation and application of curative treatments in hepatocellular carcinoma

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Abstract

Purpose—To assess the use of curative therapies for hepatocellular carcinomas (HCC) in the population.

Methods—HCC treatment patterns were examined in SEER 18 registries (28% of U.S.). Joinpoint regression analyses were performed to assess 2000–2010 incidence trends by tumor size, count and receipt of potentially curative treatments (transplantation, resection and ablation). SEER-Medicare data enabled evaluation of treatment patterns including receipt of sorafenib or TACE by HCC-associated co-morbidities.

Results—Diagnoses of tumors ≥ 5.0 cm in diameter significantly increased during 2000–2010, surpassing diagnosis of larger tumors. Overall, 23% of cases received potentially curative treatment. Joinpoint models indicated incidence rates of treatment with curative intent increased 17.6% per year during 2000–2005, then declined by -2.9% per year during 2005–2010 ($P < 0.001$). Among HCC cases with a single tumor ≤ 5.0 cm and no extension beyond the liver, use of ablative therapy significantly increased during 2000–2010. Use of invasive surgery for single tumors, regardless of size, significantly increased during the initial years of the decade then plateaued. The group most likely to receive curative treatment in the SEER-Medicare cases was patients with one, small tumor confined to the liver (657 of 1597 cases, 41%), with no difference in treatment by hepatic co-morbidity status ($P=0.24$). A higher proportion of cases with reported liver-associated co-morbidities were, however diagnosed with tumors ≥ 5.0 cm in diameter (1745 of 2464, 71%) compared to patients with no reported co-morbidities (996 of 2596, 38%, $P < 0.001$).

Conclusion—Although more HCC patients were diagnosed with early disease over time, the use of curative treatments in this patient group has recently plateaued. Efforts to identify and treat more eligible candidates for curative therapy could be beneficial.

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Keywords

liver resection; liver transplantation; RFA; TACE; SEER

Introduction

Hepatocellular carcinoma (HCC) is the sixth most commonly occurring cancer worldwide and has been increasing in incidence over recent decades (1, 2). Although advances in treatment have contributed to improved survival, overall five-year survival is still less than 25%(3). Screening has been shown in a large randomized trial of HBV-infected patients to increase detection rates of early-stage HCC resulting in reduced mortality.(4) Similarly, retrospective studies indicate that surveillance among patients with cirrhosis improves survival and facilitates receipt of curative treatment (5, 6). Based on such findings, surveillance is recommended every six months for at-risk patients in the US according to the AASLD guidelines published in 2005(7).

Over the past 10 years, the treatment paradigm for HCC has evolved to include not only surgical options such as transplantation and resection, but also non-surgical options with curative intent, particularly radiofrequency ablation. In addition, non-curative treatment options for patients with intermediate-stage disease have become more prevalent with improvement in survival documented for TACE (transarterial chemoembolization) and for more advanced stage disease, sorafenib (8, 9). However, treating patients with HCC is complicated, having to take into account not only the cancer itself but also the underlying liver disease (7).

HCC incidence trends during 2000–2010 were examined in SEER 18 cancer registries, by tumor size, count and treatment. Sub-analyses examined treatment by liver associated co-morbidities. We hypothesized that as more patients are diagnosed with early stage HCC a shift would be seen in treatment, with greater use of therapies with curative intent (i.e. resection, transplantation and ablation).

Methods

Population

Incident cases were identified in Surveillance, Epidemiology, and End Results (SEER 18) cancer registries(10) covering approximately 28% of the United States population. The SEER 18 registries are Metropolitan Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Utah, Los Angeles, San Jose and Monterrey, Rural Georgia, the Alaska Native Tumor Registry, Greater California, Kentucky, Louisiana, New Jersey, and Greater Georgia. All cases were diagnosed between January 1, 2000 and December 31, 2010 and 76% were histologically confirmed. Cases were identified using the International Classification of Diseases for Oncology, Third Edition(11). Topography codes used were those for primary liver (C22)(11). Morphology codes used were those for HCC (8170–8175)(11). All cases were restricted to first primary HCCs.

Case Attributes

Demographic characteristics including gender, age at diagnosis, race and ethnicity of HCC cases were evaluated. In addition, attributes related to clinical care were examined including year of diagnosis and size of the largest primary tumor. The SEER variable, “First Course Surgery of the Primary Site,” captured data on both liver-directed invasive surgery and ablative therapy. Cases with no surgery or ablation or missing data were classified as having no reported surgery or ablation. Cases receiving any surgery or ablation were classified into four categories: resection, transplantation, radiofrequency ablation and other and unspecified surgery or ablation. Other and unspecified surgery or ablation included cases with unspecified ablation (2%) and other methods of local tumor destruction (1.5%): ethanol injection, ultrasound, acetic acid, cryosurgery, electrocautery, laser or photodynamic therapy as well as cases with unspecified surgery (0.2%). The SEER variable “Extent of Disease, Extension” enabled classification of cases into the following categories, single nodule confined to liver, multiple nodules confined to liver, extension beyond liver, number of nodules not otherwise specified. Patterns of surgery and ablation were examined by tumor size. Trends in treatment were also examined by the size and number of HCC tumor nodules among cases with tumors confined to the liver.

Additional analyses of HCC cases were performed using data from the SEER-Medicare data linkage for the years 2000–2009. The analysis included 5,058 cases, examined during three diagnostic time periods 2000–2003, 2004–2006, and 2007–2009. We examined treatment by tumor size and the presence of one or multiple tumor nodules. Cases were restricted to those most likely to be eligible for curative therapy (liver confined tumors). This database enabled analysis of treatment by HCC-associated co-morbidities (ascites, cirrhosis, esophageal varices, hepatoencephalopathy, and portal vein thrombosis) in the 12 months prior to HCC diagnosis. Of 2,462 cases with liver-associated co-morbidities, 2,348 (95%) had cirrhosis. Portal vein thrombosis was diagnosed in 64 cases (2.6%), generally in combination with cirrhosis.

Treatment categories were: no reported treatment, sorafenib or trans-arterial chemoembolization (TACE) or both without curative therapy, and any surgery or ablation within 6 months after HCC diagnosis. Co-morbidities were abstracted from health claims based on ICD-9 (12) Clinical Modification codes. Sorafenib was identified on the Medicare Part D record (2007–2009 diagnoses only) within 6 months after diagnosis based on the brand name, Nexavar, or generic name, Sorafenib Tosylate.

Statistical Analysis

Annual incidence rates per 100,000 were age-adjusted by the direct method to the 2000 US standard population (19 age groups)(13). Joinpoint regression analyses(14) were performed to fit age-adjusted incidence trends during 2000–2010, allowing up to two time trends (Joinpoint v3.5.0, IMS Incorporated, Calverton, MD). Trends were estimated for annual incidence rates of all HCC cases, by size of largest primary tumor at diagnosis (≤ 5 centimeters, >5 centimeters, unknown size) and by treatment. The annual percent change (APC) was deemed statistically significant if the Joinpoint segment slope differed from zero

($P<0.05$). The Chi square statistic was used to test the significance of contingency table distributions (SAS 9.3, Cary, NC).

Results

Demographics

There were 47,040 cases of HCC diagnosed between 2000 and 2010 in the SEER18 database (Table 1). The majority of persons with HCC (76%) were male. Age at diagnosis was equally distributed between the 50–64 and 65+ year age groups (44% each). Fifty percent of all cases were white while Asian/Pacific Islanders and Hispanics each accounted for 18% and blacks accounted for 13% of cases. More than one third of cases (36%) had tumors ≤ 5 cm in size. Forty-five percent of cases were diagnosed during the years 2007–2010. Seventy-seven percent of cases had no reported surgery or ablation. Resection was the most frequent curative modality employed (9%), followed by transplantation (6%) and radiofrequency ablation (6%).

HCC incidence trends

Tumors were divided into three groups: small tumors (≤ 5 cm), large tumors (> 5 cm) and tumors of unknown size. There was a crossover around 2005, when the rate of diagnosis of smaller tumors began to exceed that of larger tumors (Figure 1). Rates of unknown size tumors dropped throughout the decade.

Treatment Trends

Figure 2A shows age-adjusted HCC incidence trends between 2000 and 2010, based on joinpoint regression modeling. Incidence increased significantly from 2000 to 2007, with a statistically significant annual percent change (APC) of 5.4% ($P<0.001$). Between 2007 and 2010, incidence rates plateaued and the rate of increase was no longer significant (APC=2.3%, $P=0.16$). The percentage of HCC cases that did not receive surgery or ablation significantly increased from 2000–2010 (APC=4.3%, $P<0.001$). The percentage of cases treated with resection, ablation or transplantation (potentially curative therapy) significantly increased from 2000–2005 (APC=17.6%, $P<0.001$), then significantly decreased during 2005–2010 (APC=−2.9%, $P<0.001$). The rate of receipt of potentially curative therapy varied with tumor size (Figure 2B). In the initial years of the decade, rates of receipt of curative therapy significantly increased for cases with tumors ≤ 5 cm in size and cases with tumors >5 cm but did not change for cases with unknown tumor size. In the final years of the decade, rates of receipt of curative therapy significantly decreased in cases with tumors >5 cm (APC=−5.7%, $P=0.03$) and cases with unknown tumor size (−14.1%, $P=0.006$). The rate of decrease in receipt of curative therapy among cases with tumors ≤ 5 cm in size during 2006–2010 was not statistically significant (APC=−2.9%, $P=0.07$).

The subset of patients most likely to receive curative therapy were those with a single tumor confined to the liver. Among these cases, those with tumors less than or equal to 5 cm in diameter, the use of resection or transplantation significantly increased during 2000–2006 (APC=15.9%, $P<0.001$), and was stable during 2006–2010 (APC=−1.4, $P=0.65$) (Figure 3). Among cases with a single tumor less than or equal to 5 cm in diameter, the use of ablative

therapy significantly increased during 2000–2004 (APC=39.0%, $P=0.001$), and 2004–2010 (APC=4.7, $P=0.03$). Similar trends were seen among cases with a single tumor less than or equal to 3 cm in diameter, who accounted for the majority of ablative therapy cases with a single tumor (data not shown). Among cases with a single tumor larger than 5 cm in diameter, use of resection or transplantation significantly increased during 2000–2007 (APC=9.9%, $P=0.005$), and non-significantly decreased from 2007–2010 (APC=-5.8, $P=0.42$).

Changes in specific surgery and ablation treatment patterns were seen in the interval from 2000 through 2010 (Figure 4). Resection was consistently the most common treatment with curative intent and the number of cases receiving resection rose throughout the interval. Radiofrequency ablation was uncommon in 2000 however; by the end of the decade it had become the second most common treatment modality. The number of cases receiving transplantation increased from 2000 to 2006, but declined thereafter. The frequency of other ablative and unspecified surgeries also declined after 2006.

Size, Multiplicity and Treatment

Surgery and ablation therapy data for 24,285 liver confined HCC cases with complete data for tumor size and count are presented in Table 2. The number of cases meeting these criteria increased from 4961 to 12,357 (2.5 fold) from 2000–2003 to 2007–2010. Cases with small (< 5 cm in diameter), single tumors comprised 7941 (33%) of all cases in Table 2. The number of cases with small, single tumors increased from 1545 to 4232 (2.7 fold) in 2000–2003 and 2007–2010, respectively.

The proportion of cases that received curative treatment remained relatively constant throughout the decade, with small peaks in use of curative treatment during 2004–2006, particularly for cases with small tumors. The proportion of cases who received curative therapy was highest for cases with small single tumors (52%), followed by those with small multiple tumors (35%), and large (> 5 cm in diameter) single tumors (33%). Cases with multiple large tumors confined to liver had the lowest receipt of curative therapy (15%).

Liver related co-morbidities and TACE/Sorafenib

Table 3 presents treatment of HCC cases by tumor size, count and the presence or absence of liver-associated co-morbidities from the SEER-Medicare dataset with diagnoses during the years 2000 through 2009. Regardless of tumor characteristic and co-morbidity status, the proportion of cases receiving curative treatment was higher during the years 2000–2003 than in subsequent years. Patients that received curative therapy most often were those with single tumors < 5 cm in diameter. This was true among both cases with co-morbidities (430 of 1,018, 42%) and those without co-morbidities (227 of 579, 39%), $P=0.47$. Other patient groups among whom at least 20% received curative therapy were those with multiple small tumors, regardless of co-morbidity status, and patients without any reported liver-associated co-morbidities with a single tumor >5 cm in diameter.

The proportion of cases that received TACE only, without curative therapy, was approximately double among cases with co-morbidities compared to those without. During 2007–2009, more than 20 percent of cases with reported co-morbidities received TACE

only, compared to approximately 12% of cases without reported co-morbidities. Data were available on the use of sorafenib in the absence of curative therapy for 178 cases diagnosed during 2007–2009. Among these cases, sorafenib was administered most often to those with large tumors or multiple tumors. Of the 178 cases 25(14%) had a single tumor ≤ 5 cm in diameter while 70 (39%) had multiple tumors >5 cm in diameter (data not shown). Of 240 cases with small single tumors confined to the liver and no reported co-morbidities, 35 (15%) received sorafenib (N=11) or TACE (n=29) without curative treatment.

A higher proportion of cases with reported co-morbidities were diagnosed with tumors ≤ 5 cm in diameter (1745 Of 2464, 71%) compared to patients with no reported co-morbidities (996 of 2596, 38%), $P<0.001$). Among cases with multiple tumors ≤ 5 cm in diameter, 221 of the 727 cases with co-morbidities (30%) received curative treatment compared to 85 of 417 cases without co-morbidities (20%, $P<0.001$). No differences in the application of curative therapy were observed by liver associated co-morbidity for cases with single tumors ≤ 5 cm, single tumors >5 cm, or multiple tumors >5 cm in diameter ($p=0.24$, $p=0.27$ and $p=0.39$ respectively).

Discussion

This study found that mixed progress has been made in the early diagnosis and treatment of HCC in the United States. An encouraging finding was the increasing diagnosis of smaller HCC tumors between 2000 and 2010. Despite this, only 23% of cases received any surgery or ablation. Furthermore, after a period of increase, the receipt of resection, ablation or transplantation (potentially curative therapies) decreased between 2005 and 2010. Of note, use of ablation to treat small single tumors continued to increase as use of surgical therapies for these tumors plateaued. This suggests that patterns of application of potentially curative therapies may be explained by careful selection of patients. Other plausible explanations include failure to refer eligible cases for specialized HCC care in addition to the unavailability of liver transplant organs. Among cases with single small HCC tumors confined to the liver, 52% received curative therapy. According to treatment guidelines, patients with these tumor characteristics could be candidates for treatment with curative intent if permissible based on their performance status (7). In the present study, only 39% of SEER-Medicare cases with single small tumors and no reported liver related co-morbidities received curative therapy. No difference in receipt of curative treatment was seen by hepatic co-morbidity status in patients with single small tumors. Our findings are consistent with another SEER-Medicare study that found many eligible patients with early HCC do not receive surgical treatment or ablation. (15).

Improved screening and imaging modalities may have contributed to the increase in detection of small tumors in the present study (4, 16). The use of screening among patients with cirrhosis could help to explain our findings from the SEER-Medicare data linkage that cases with liver related co-morbidities were more likely to be diagnosed with small tumors than patients without these co-morbidities (71% versus 38%, $P<0.001$). This finding supports that screening is effective for detecting small tumors in at-risk patients in the general population. A large randomized trial among HBV-infected patients showed that those who received ultrasonography with AFP testing every six months were more likely to

be diagnosed with earlier stage disease, receive curative treatment and have reduced mortality(4). Another factor which may have affected physician behavior during the 10 years of this study is the publication of the AASLD HCC screening and treatment guidelines in 2005 (7). Recent studies document challenges in the implementation of HCC screening programs. In a study of HCV-infected persons in the Veterans Affairs-population, only 5.7% of persons underwent HCC screening every six months during the two years prior to HCC diagnosis (17). Evaluating persons with cirrhosis, a study in the SEER-Medicare population found that 17% of persons underwent regular surveillance and 38% received inconsistent screening (18). In another study, only 20% of HCC patients had undergone surveillance (19). The main reasons for underutilization of screening were failure of clinicians to instigate surveillance (47%) and under-diagnosis of liver disease (40%). Patient compliance contributed only 3% to the failure rate (19). Specialized hepatology care has been associated with increased adherence to surveillance guidelines (18, 19).

The results of this study indicate that treatment modalities for liver-confined HCC are changing. Between 2005 and 2010 use of overall curative therapy declined. The overall decline in use of these procedures may be attributable to the more careful selection of patients for treatment with curative intent. For example, use of ablation for small single liver confined tumors continued to increase through 2010. Furthermore, other non-curative modalities such as TACE or chemotherapy with sorafenib are now available (8, 9, 20, 21). The present analysis in the SEER-Medicare data linkage confirmed that use of sorafenib and TACE increased with tumor size, count and liver related co-morbidity. However these non-curative therapies alone were also used in 15% of patients with small single tumors and no reported HCC-associated co-morbidities in 2007–2009. Assuming acceptable performance status, these patients would presumably be eligible for curative treatment. Decreasing use of transplantation was observed (22). This is likely to be a consequence of limited donor organ availability, but could also reflect the proportion of HCC patients who are suitable candidates for this procedure (23). The use of radiofrequency ablation and resection both increased between 2000 and 2010. While radiofrequency ablation was a rare treatment in 2000, it emerged as the second most common modality in the second half of the decade. Radiofrequency ablation is recommended for selected patients with tumors ≤ 3 cm in diameter (24–28). Our findings indicate adherence to these recommendations in clinical settings. Among cases with single tumors, the majority of cases receiving ablation had tumors ≤ 3 cm in diameter.

Strengths of the present analysis include its population-based design, covering 28% of the US population and its sizeable number of cases (n=47,040). Relationships between curative treatments could be examined by tumor size, count and liver related co-morbidities. Limitations included the absence of etiologic data and the complete set of variables required for Barcelona-Clinic Liver Cancer (BCLC) staging. Furthermore Medicare patient co-morbidity and treatment patterns may not be generalizable to the population.

In summary, this population-based study found improvements in the early diagnosis of HCC. Despite this encouraging finding, the application of curative therapy did not completely follow the same increasing trend. HCC cases with liver related co-morbidities tended to be diagnosed with smaller tumors than those without these conditions. Based on

current treatment guidelines, a higher proportion of patients may be candidates for curative therapy. Screening and early diagnosis are essential but not sufficient to reverse the increasing HCC mortality rate in the United States². Patients should be evaluated and treated by multidisciplinary teams in HCC specialized centers, where potentially curative options such as transplantation, resection and ablation are available. Although HCC treatment has evolved over the decade, a need remains for new and more effective HCC treatment strategies to improve HCC prognosis and survival.

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List of Abbreviations

HCC	Hepatocellular Carcinoma
RFA	Radiofrequency ablation
TACE	Trans Arterial Chemoembolization
SEER	Surveillance, Epidemiology, and End Results cancer registries

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Figure 1.
HCC Incidence trends by tumor size, SEER 18 2000–2010

Figure 2.

A) Overall HCC incidence trends and potentially curative treatment trends. B) Trends by receipt of potentially curative therapy and tumor size, SEER 18, 2000–2010* * Potentially curative therapies: resection, ablation and transplant

Figure 3.
Trends in the treatment of single HCC tumors confined to the liver by tumor size

Figure 4. Number of HCC cases with reported resection, radiofrequency ablation, transplantation, and other ablation or unspecified surgery/ablation by year, 2000–2010, SEER 18.

Table 1

Demographic and case attributes of 47,040 HCC cases, SEER 18, 2000–2010

	No.	%
Gender		
male	35,728	76%
female	11,312	24%
Age at diagnosis (years)		
0–49	5,429	12%
50–64	20,691	44%
65+	20,920	44%
Race and ethnicity		
non-Hispanic white	23,480	50%
non-Hispanic black	5,898	13%
non-Hispanic AI/AN *	508	1%
non-Hispanic API **	8,510	18%
Hispanic	8,489	18%
Year of diagnosis		
2000–2003	13,047	28%
2004–2006	12,652	27%
2007–2010	21,341	45%
Surgery or Ablation		
no surgery or ablation	36,009	77%
resection	4,085	9%
transplantation	2,618	6%
radiofrequency ablation	2,589	6%
other ablation, unspecified surgery	1,739	4%
Extent of disease (Size)		
5 cm	17,149	36%
>5 cm	15,976	34%
unknown size	13,915	30%
Extent of Disease (location and count)		
Single nodule confined to liver	14,050	30%
Multiple nodules confined to liver	14,765	31%
Extension beyond liver	4,790	10%
NOS ***	13,435	29%

* AI/AN=American Indian/Alaska Native

** API=Asian/Pacific Islander

*** No information on number of nodules

Reported surgery, ablation or transplplantation among cases with one or multiple tumors confined to liver, SEER 18 diagnosis years 2000–2010

Table 2

Tumor characteristics	Group	2000–2003		2004–2006		2007–2010		2000–2010	
		N	%	N	%	N	%	N	%
5 cm, single tumor	All Cases	1545		2164		4232		7941	
	Received Curative Tx	809	52%	1241	57%	2090	49%	4140	52%
5 cm, multiple tumors	All Cases	1155		1677		3199		6031	
	Received Curative Tx	438	38%	713	43%	971	30%	2122	35%
> 5 cm, single tumor	All Cases	1087		1453		2226		4766	
	Received Curative Tx	371	34%	518	36%	660	30%	1566	33%
> 5 cm, multiple tumors	All Cases	1174		1673		2700		5547	
	Received Curative Tx	227	19%	273	16%	344	13%	844	15%
Cases with reported count, size	All Cases	4961		6967		12357		24285	
	Received Curative Tx	1845	37%	2745	39%	4065	33%	8672	36%

Table 3

Reported treatments of HCC cases by tumor size, count and liver-associated co-morbidity status, SEER-Medicare diagnosis years 2000–2009*

Tumor Characteristic				Year of Diagnosis								Total	
				2000-2003		2004-2006		2007-2009					
				Size	Count	Treatment**	N	%	N	%	N	%	N
Yes	5.0 cm	Single	All cases	238	100	321	100	459	100	1,018	100		
			Curative tx	110	46.2	145	45.2	175	38.1	430	42.2		
			TACE only	36	15.1	52	16.2	101	22.0	189	18.6		
		Multiple	All cases	150	100	247	100	330	100	727	100		
			Curative tx	55	36.7	84	34.0	82	24.8	221	30.4		
			TACE only	27	18.0	45	18.2	94	28.5	166	22.8		
	5.1 cm	Single	All cases	95	100	118	100	117	100	330	100		
			Curative tx	20	21.1	30	25.4	15	12.8	65	19.7		
			TACE only	13	13.7	19	16.1	31	26.5	63	19.1		
		Multiple	All cases	101	100	123	100	163	100	387	100		
Curative tx			16	15.8	15	12.2	11	6.7	42	10.9			
TACE only			14	13.9	18	14.6	33	20.2	65	16.8			
No	All	All	Curative tx	201	34.4	274	33.9	283	26.5	758	30.8		
			Total	584		809		1,069		2,462			
			All cases	140	100	199	100	240	100	579	100		
		Single	Curative tx	63	45.0	81	40.7	83	34.6	227	39.2		
			TACE only	6	4.3	22	11.1	24	10.0	52	9.0		
			All cases	97	100	147	100	173	100	417	100		
		Multiple	Curative tx	28	28.9	30	20.4	27	15.6	85	20.4		
			TACE only	10	10.3	22	15.0	21	12.1	53	12.7		
			All cases	218	100	275	100	329	100	822	100		
	5.1 cm	Single	Curative tx	58	26.6	58	21.1	70	21.3	186	22.6		
TACE only			18	8.3	26	9.5	46	14.0	90	10.9			
All cases			195	100	274	100	309	100	778	100			

Tumor Characteristic				Year of Diagnosis						Total	
				2000–2003		2004–2006		2007–2009			
Hepatic co-morbidity*	Size	Count	Treatment**	N	%	N	%	N	%	N	%
			Curative tx	26	13.3	17	6.2	29	9.4	72	9.3
			TACE only	27	13.8	36	13.1	34	11.0	97	12.5
	All	All	Curative tx	175	26.9	186	20.8	209	19.9	570	22.0
			Total	650		895		1,051		2,596	
	Curative tx			376	30.5	460	27.0	1051	23.2	1328	26.6
	Grand Total			1,234		1,704		2,120		5,058	

* Ascites, varices, hepatic encephalopathy, cirrhosis, or portal vein thrombosis 0–12 months before HCC dx. Among these cases, 2,348 (95%) had cirrhosis. Portal vein thrombosis was diagnosed in 64 cases (2.6%).

** Ablation, surgery, and/or transplant 0–5 months after HCC dx

Abbreviation: Treatment=tx