Journal of Surgical Oncology 2015;112:872–876

Natural History and Treatment Trends in Hepatocellular Carcinoma Subtypes: Insights From a National Cancer Registry

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Background: Histopathologic advancements have identified several rare subtypes of hepatocellular carcinoma (HCC), but the clinical significance of these distinctions is incompletely understood. Our aim was to investigate pathologic and treatment differences between HCC variants.
Methods: The American College of Surgeons National Cancer Data Base (1998–2011) was queried to identify 784 patients with surgical management of six rare HCC subtypes: fibrolamellar (FL, n = 206), scirrhous (SC, n = 29), spindle cell (SP, n = 20), clear cell (CC, n = 169), mixed type (M, n = 291), and trabecular (T, n = 69). We examined associations between demographic, tumor and treatment-specific variables, and overall survival (OS).
Results: Patients with FL-HCC were younger than other variants (median age 27 vs. 54–61, $P < 0.001$), more commonly female (56.3%, $P < 0.001$), and less likely to receive a transplant (3.66%, $P < 0.001$). Patients with FL- and Sp-HCC presented more frequently with larger tumors (>5 cm, $P < 0.001$) and node-positive disease ($P < 0.001$). Better OS was associated with lower pathologic stage, node-negative disease, FL-HCC, and liver transplant. Adjuvant therapy (11% of patients) was not associated with better OS.
Conclusions: This largest series of recognized HCC variants demonstrates distinct differences in presentation, treatment, and prognosis. These findings can provide a valuable reference for clinicians and patients who encounter these rare clinical entities.
J. Surg. Oncol. 2015;112:872–876.

KEY WORDS: histopathology; fibrolamellar variant of hepatocellular carcinoma; scirrhous carcinoma; spindle cell carcinoma; clear cell carcinoma

INTRODUCTION

Hepatocellular carcinoma (HCC) is the 5th most common solid organ tumor and the third leading cause of cancer-related death worldwide [1]. The incidence of HCC in the United States has been steadily increasing over the past two decades and is currently the 7th most common and the fastest growing cause of cancer-related death in the United States [2]. HCC typically occurs in the setting of chronic liver inflammation and fibrosis, and in Western populations, white male patients in the 5th to 6th decade of life are most commonly affected [3]. The best opportunity for long-term survival is surgical resection, transplantation, or ablation of early stage tumors [4]. However, in spite of improvements in screening and detection of early stage disease, patients tend to present with advanced disease, and recurrence and tumor-related mortality remain high [1,5].

In 1978, the World Health Organization (WHO) published guidelines on histologic typing of hepatic, biliary, and pancreatic tumors, including HCC [6]. Since then, multiple different histologic subtypes have been identified, some with unique clinical characteristics and prognostic profiles. The WHO International Classification of Diseases for Oncology, version 3 (ICD-O.3) currently recognizes seven subtypes of HCC: fibrolamellar, scirrhous, spindle cell, clear cell, pleomorphic, mixed type, and trabecular adenocarcinoma [7]. However, there are very few published series of these subtypes in Western populations, and most that do exist are small and/or from single institutions. In the current study, we characterize demographic, pathologic, treatment, and prognostic differences between recognized histologic subtypes of HCC from a comprehensive national cancer registry.

METHODS

Data Source

Data for this study were drawn from the American College of Surgeons National Cancer Data Base (NCDB) Liver Participant User File (PUF). This is a nationwide, facility-based, clinical data set that captures 70% of all diagnosed malignancies in the US [8]. The NCDB collects de-identified patient level data from nationally accredited cancer registries using standardized data items and coding definitions. These data include patient demographics as well as detailed information regarding cancer staging, tumor histology, treatment types and courses, short-term surgical outcomes, and long-term survival.

Patient Cohort

The liver PUF was queried for all patients treated for HCC between 1998 and 2011 (n = 43,859). From these, we identified 2,837 patients with histopathologic diagnosis of one of six different WHO-recognized histologic variants of HCC: fibrolamellar (n = 206), scirrhous (n = 29), spindle cell (n = 20), clear cell (n = 169), mixed type (n = 291), and trabecular (n = 69). There were no patients with pleomorphic subtype identified in this series. We studied 784 of these patients who underwent surgical management of their disease (resection, transplant, or local ablation). Demographic information was collected and included age

Grant sponsor: University of Cincinnati Department of Surgery.

Conflicts of interest: None.

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Received 13 October 2015; Accepted 17 October 2015

DOI 10.1002/jso.24083

Published online 24 November 2015 in Wiley Online Library (wileyonlinelibrary.com).

(years), gender, and race (Asian, black, white, or other). Disease-specific information included tumor size (<2 cm, 2–5 cm, >5 cm), tumor grade (well differentiated, moderately differentiated, poorly differentiated, or other), American Joint Committee on Cancer (AJCC) clinical stage (I, II, III, or IV), and presence or absence of positive lymph nodes. Treatment and pathologic-specific variables included type of surgical therapy (transplant, resection, or local ablation), resection margin status (R0, R1, or R2), whether lymph nodes were examined (yes or no), and adjuvant therapy (surgery only, surgery with adjuvant chemotherapy, or surgery with adjuvant chemotherapy and radiation).

Statistical Analysis

The six subtypes of interest were compared according to each of the previous variables using χ^2 tests for categorical variables and rank-sum tests for continuous variables. Kaplan–Meier survival analysis was used to determine median overall survival and compare survival between four of the groups (scirrhous and spindle cell subtypes were omitted from this analysis due to $n < 30$). Per NCDB guidelines, survival data for patients after 2006 were not included. Cox regression analysis was used to determine factors associated with overall mortality. Included in this model were histology, tumor grade, surgical procedure, nodal status, AJCC stage, and adjuvant treatment group. The data were analyzed using SAS® 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics and Tumor-Specific Characteristics

Mixed type HCC was the most common subtype seen in our data set (37%, 291/784) followed by fibrolamellar (26%, 206/784) and clear cell (22%, 169/784). Scirrhous, spindle cell, and trabecular were much less common (Fig. 1). Univariate analyses demonstrated multiple differences between histologic subtypes in patient- and tumor-specific characteristics, shown in Table I. The median age of patients with fibrolamellar disease was significantly lower than for any other subtypes (27 vs. 54–62 years, $P < 0.001$). The majority of patients included in the overall cohort were white (79.6%, 624/784), followed by Asian (9.1%, 71/784), black (8.5%, 67/784), and other/unreported (2.8%, 22/784). However, this varied significantly between subtypes. Relative to the total group, white patients comprised a higher proportion of fibrolamellar, scirrhous, and spindle cell disease and a lower proportion of trabecular disease. Asian patients, on the other hand, made up a smaller proportion of fibrolamellar, scirrhous, and spindle cell disease and a larger proportion of trabecular disease while black patients comprised small proportions of fibrolamellar and scirrhous disease. There was a male preponderance overall (57.8% of total patients, 453/784) while female patients made up the majority of the fibrolamellar subtype.

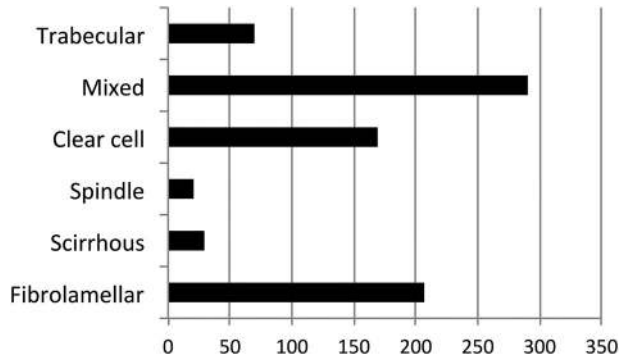

Fig. 1. Total numbers of each of the HCC subtypes.

Of all the tumors in the total cohort with a recorded size, the majority of tumors were >5 cm on pathologic examination (55.3%, 415/750), followed by 2–5 cm (35.9%, 269/750) and <2 cm (8.8%, 66/750). As shown in Table I, this varied widely across subtypes, with fibrolamellar and spindle cell disease much more frequently presenting as tumors >5 cm. In the overall cohort, 43.6% (335/769) of patients had nodes resected and examined with the pathologic specimen, though again there was significant variability between subtypes. Nodal examination was more common in patients with fibrolamellar or spindle cell disease and less common in scirrhous, clear cell, and trabecular subtypes. Of those who had nodes examined, nodal metastases were most common in fibrolamellar and scirrhous subtypes, followed by mixed type. The remaining subtypes had no noted positive lymph nodes. This is reflected in the AJCC pathologic staging, with fibrolamellar and scirrhous subtypes more likely to be stage III or IV compared to other subtypes. The majority of all tumors were moderately differentiated, while scirrhous subtypes were much more commonly poorly differentiated compared to other subtypes.

Treatment Variability

Surgical treatment trends for all subtypes are shown in Table II. Resection was the most common surgical treatment modality in the overall cohort, with 77.6% (544/701) of patients undergoing resection, 20% (140/701) receiving orthotopic liver transplant, and 2.4% (17/701) undergoing local ablative procedures. Higher rates of resection were seen in fibrolamellar, spindle cell, and clear cell subtypes while there were higher rates of transplant in scirrhous, mixed, and trabecular subtypes. For those patients undergoing resection, R0 margin status was achieved in 95% (643/677) of cases. Only spindle cell subtypes had a significantly lower rate of R0 resection. Only 11% (86/784) of patients received any form of adjuvant therapy, most frequently in the form of chemotherapy. The highest rates of adjuvant therapy were seen in fibrolamellar, spindle cell, and mixed subtypes.

Survival Differences Between Subtypes and Predictors of Overall Mortality

The median follow-up for the patients in this study was 7.0 years with a 95% confidence interval (CI) of 6.38–7.44. Kaplan–Meier overall survival curves are shown in Figure 2 (scirrhous and spindle cell subtypes were omitted from survival analyses due to insufficient sample sizes). Fibrolamellar subtype had the highest median survival of 6.2 years (95%CI 4.49–7.50), followed by clear cell (2.99 years, 95%CI 2.08–4.55), trabecular type (2.91, 95%CI 1.88–8.86), and mixed type (2.22, 95%CI 1.61–2.70). Fibrolamellar subtype was associated with lower mortality relative to other subtypes in Cox regression analysis with a hazard ratio for mortality of 0.36. Other significant contributors to mortality are shown in Table III. Transplantation was associated with significantly lower mortality than resection or local ablation. Node positive disease and increasing pathological stage were associated with worse mortality. Adjuvant therapy led to no significant change in mortality.

DISCUSSION

In this study, we characterized differences between surgically managed HCC histopathologic subtypes on the basis of presentation, surgical therapy, and overall survival. We demonstrated unique profiles with respect to demographic factors, disease-specific presentation, treatment trends, and overall survival for these different subtypes. This represents the largest collective series currently available for all of the

TABLE I. Demographic and Tumor Specific Variables for Each of the Six HCC Subtypes

	HCC subtypes						
Variables	Fibrolamellar	Scirrhous	Spindle cell	Clear cell	Mixed	Trabecular	*P*-value
Total number of patients	206	29	20	169	291	69	
Age—median yrs (IQR)	27 (18)	61 (13)	54 (20)	62 (14)	60 (17)	60 (15)	<0.0001
Race							<0.0001
White	186	27	18	124	228	41	
Black	9	1	2	20	27	8	
Asian	2	1	0	21	28	19	
Other	4	0	0	1	3	0	
Gender							<0.0001
Female	116	6	6	81	103	19	
Male	90	23	14	88	188	50	
Tumor size							<0.0001
Size <2 cm	5	6	0	14	36	5	
Size 2–5 cm	31	14	5	61	120	38	
Size >5 cm	158	7	12	90	125	23	
Nodes examined							<0.0001
No	70	17	6	123	162	56	
Yes	133	11	13	43	122	13	
Nodes positives							<0.0001
Nodes negative	72	11	8	43	98	13	
Nodes positive	61	0	5	0	24	0	
AJCC stage							<0.0001
Stage I	52	9	1	81	79	18	
Stage II	33	10	4	45	95	28	
Stage III	80	8	8	36	80	17	
Stage IV	41	2	7	7	37	6	
Tumor grade							<0.0001
Well differentiated	27	5	0	28	20	17	
Moderately differentiated	60	13	1	79	115	35	
Poorly differentiated	10	4	12	26	78	8	
Other	0	0	4	2	6	1	

IQR, interquartile range.

combined variants in a Western population, and should serve as a reference for providers and patients who are faced with counseling and treatment decisions for these rare entities.

Fibrolamellar type is probably the best-studied subtype in the United States with several previous series reported based on national samples [9,10]. Our study found similar demographic characteristics to previous reports with younger age of onset and female predominance.

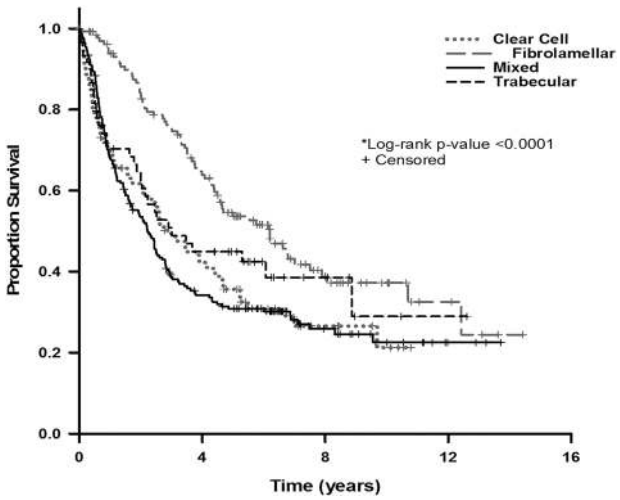

Fig. 2. Kaplan–Meier survival analysis for overall survival in four of the HCC subtypes. There was a significant difference in overall survival by subtype (log-rank *P*-value <0.0001). Scirrhous and spindle cell subtypes were omitted from survival analyses due to low sample size.

Likewise, we again observed the trend of patients with fibrolamellar disease presenting with later-stage disease (larger tumors and more nodal metastasis) yet still having better overall survival after surgery. Unfortunately, this dataset is limited in the availability of data regarding comorbidities, so it remains unclear whether this truly represents disease-specific survival or if it is related to other comorbid conditions.

In contrast to fibrolamellar disease, the scirrhous subtype of HCC is very poorly characterized in the United States. There are several studies from Asian populations that demonstrate lower rates of viral hepatitis in scirrhous disease, but reports are conflicting regarding overall survival [11,12]. Our study demonstrates presentation with earlier stage, node-negative disease, and tumors that are predominantly well or moderately differentiated. Patients in this subtype were also more likely to undergo transplant versus resection or local ablation. Due to the small numbers of patients in the study, a formal statistical analysis of overall survival was not possible in this subtype, but the preliminary trend was toward improved overall survival.

Spindle cell HCC has been described in a few small Asian studies as a sarcomatous transformation that presents with a highly aggressive biology pattern [13]. Our findings in this study support the conclusion that spindle cell subtypes presented more frequently as advanced disease with larger tumors, more nodal metastasis, and more poorly differentiated tumors. Resection was the most common treatment and patients from this group were most likely to receive adjuvant therapy. However, as with scirrhous HCC, the numbers of patients were too small to permit a formal statistical analysis of overall survival.

Clear cell HCC is poorly characterized in Western literature, but small case series and Asian studies have demonstrated a prevalence of female patients and a strong association with viral hepatitis and cirrhosis [14,15]. There is no current consensus in the literature regarding the effect of clear cell features on prognosis. The majority of clear cell HCC patients in our study were male, although there were a large number of female patients

TABLE II. Treatment-Specific Variables for Each of the HCC Subtypes

	HCC subtypes						
Variables	Fibrolamellar	Scirrhous	Spindle cell	Clear cell	Mixed	Trabecular	*P*-value
Surgical therapy							<0.0001
Transplant	7	10	2	23	80	18	
Resection	182	10	16	118	173	45	
Local ablation	2	5	0	3	5	2	
Margin status							0.0068
R0 Resection	176	25	9	140	237	56	
R1 Resection	7	0	2	5	8	0	
R2 Resection	3	0	2	3	3	1	
Adjuvant therapy							0.0017
Surgery only	173	28	15	164	252	66	
Adjuvant chemo	29	1	4	4	35	3	
Adjuvant chemo/rad	4	0	1	1	4	0	

relative to most other subtypes (47.9% female). The majority of tumors were larger than 5 cm but there were no nodal metastases observed and relatively low rate of poorly differentiated tumors. We found no significant difference in overall mortality with clear cell subtype relative to other subtypes. Mixed type represents an HCC subtype with combined features of HCC and cholangiocarcinoma that is typically associated with high recurrence rates and poor prognosis [16,17]. In our analysis, mixed subtypes tended to present as moderately advanced tumors with size greater than 2 cm and moderately or poorly differentiated histology. There was a relatively high rate of transplantation for management of mixed type HCC in our study. Overall survival for mixed type was the lowest of the four subtypes we compared but was not significantly different from the other subtypes.

Trabecular subtype is perhaps the least understood variant of HCC presented in this study. In our study, trabecular HCC was associated with a relatively high proportion of Asian patients and presented with moderate sized tumors and low rates of nodal metastasis. Tumors were primarily well or moderately differentiated and the majority of patients had pathological stage I or II disease. Median survival was better than that for mixed type but was not significantly different.

In addition to the previously described limitations of this study, there are several other key factors to consider. First, survival data are only available through 2006 in the NCDB. This limits the numbers available for survival analysis and as a result we omitted two subtypes from the survival analysis due to small sample size. Also, several of the subtypes studied have only been recognized and included in the NCDB in more recent years. As this database matures, it will become an even more powerful tool to study these rare tumors.

TABLE III. Predictors of Mortality in Patients With HCC Subtypes

Variable	Hazard ratio for mortality	95%CI	*P*-value
Histology			
Trabecular (n = 69)	1.00	Reference	
Fibrolamellar (n = 206)	0.36	(0.21–0.62)	<0.001
Clear cell (n = 169)	1.1	(0.64–1.89)	0.729
Mixed (n = 291)	1.35	(0.85–2.14)	0.206
Surgical treatment			
Transplant (n = 140)	1.00	Reference	
Resection (n = 544)	1.72	(1.15–2.55)	0.008
Local ablation (n = 17)	3.07	(1.34–7.01)	0.008
Nodal status			
Negative (n = 245)	1.00	Reference	
Positive (n = 90)	1.87	(1.19–2.92)	0.006
Pathologic stage			
Stage I (n = 240)	1.00	Reference	
Stage II (n = 215)	1.88	(1.19–2.96)	0.007
Stage III (n = 229)	3.05	(1.98–4.70)	<0.001
Stage IV (n = 100)	3.83	(2.32–6.32)	<0.001

CI, confidence interval.
Scirrhous and spindle cell subtypes were omitted from the survival analyses due to low sample size.

Another important consideration is the often rapidly-evolving nature of cancer diagnosis and therapy. This data set was collected over 13 years and contains data from three different AJCC staging editions. As such, staging data must be interpreted with caution. Likewise, the use of adjuvant therapy has changed over the period included in this database. Our analysis demonstrated no survival benefit associated with adjuvant therapy. However, since 2007, the use of sorafenib in HCC patients has increased. This is not captured by our data set as the survival data only extends through 2006. This will be an important point to revisit as data with new adjuvant therapies become available.

CONCLUSIONS

These rare subtypes of HCC represent unique clinicopathologic entities with distinct tumor biology. However, there is little data to guide hepatobiliary surgeons who encounter rare HCC subtypes, either in preoperative biopsy specimens or in postoperative pathology specimens. This relatively large national sample adds to the current understanding of the tumor biology in these rare variants and can serve as an initial guide for discussions between clinicians in multidisciplinary care teams trying to plan therapy. It may also serve as a resource for clinicians as they have conversations with patients on the prognosis and imminent direction to be taken in poorly defined disease processes. However, it will be crucial to augment these findings with future data from the NCDB as well as with more granular data on the other patient, disease- and treatment-specific factors that may improve outcomes.

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