Predictors and survival of primary clear cell carcinoma of liver: a population-based study of an uncommon primary liver tumor

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Background: The clinicopathological features and prognostic factors of primary clear cell carcinoma of the liver (PCCCL) remain unknown for the rarity. We aimed to determine the clinical and therapeutic characteristics of PCCCL and the effects of these factors on the prognosis.

Methods: Patients were selected from the Surveillance, Epidemiology, and End Results (SEER) database. Data were analyzed with the Kaplan-Meier, Cox proportional hazards regression analyses and the multivariable competing risk model.

Results: We included 223 PCCCL patients and the majority of them had an age under 75 years (82.5%). Most patients were white people (63.2%). The patients diagnosed at localized stage (63.7%), T1 (49.8%), N0 (96.0%), M0 (87.4%) and American Joint Committee on Cancer (AJCC) I (44.4%) made up the majority of the population. More PCCCL tumors had a size beneath 4 cm (74.9%) and no vascular invasion (63.2%). The 3-, 5-, and 10-year overall survival (OS) probabilities and disease-specific survival (DSS) rates were 35.8%, 24.3%, 14.4%, and 41.6%, 29.4%, 22.2%, respectively. The patients with tumor ≥1 cm [OS, hazard ratio (HR) =1.822; DSS, HR =1.959] had a higher risk of death than those patients with tumor <1 cm. Among surgical means, hepatectomy (OS, HR =0.070; DSS, HR =0.050) and total hepatectomy plus transplant (OS, HR =0.074; DSS, HR =0.065) were more beneficial to PCCCL.

Conclusions: PCCCL patients were inclined to be young, white people-prevalent, localized and early. PCCCL tend to had a slow growth and be weakly aggressive. However, comparing with previous reports, we found that PCCCL had a relatively poor outcome. Tumor size and surgery were the independent prognostic factors for OS and DSS.

Keywords: Primary clear cell carcinoma of the liver (PCCCL); Surveillance, Epidemiology, and End Results (SEER); pathology; demographic; prognosis

Introduction

Liver cancer is the third most common cause of cancer-related mortality, and >90% of the cases are hepatocellular carcinoma (HCC) (1). HCC could be subdivided into clear cell, spindle cell, fibrolamellar, scirrhous, and pleomorphic types, and combined HCC with cholangiocarcinoma (2). The primary clear cell carcinoma of the liver (PCCCL) is a specific and rare histological subtype of HCC accounting for 7.5–12.5% of all liver cancers (3). PCCCL cells do not stain with hematoxylin and eosin due to the prominent cytoplasmic

accumulation of lipid droplets and glycogens (4). Decreased number and size of organelles, and metabolic impairment can be observed in these cells (5). HCC with >50% clear cells is generally diagnosed as PCCCL (6).

The clinical and pathological characteristics of PCCCL have been controversial for long. It is generally accepted that PCCCL has a favorable clinical outcome (4,7,8), except for several reports (9,10). In fact, PCCCL prognosis and prognostic factors largely remain unknown due to the limited number of cases. Additionally, studies have suggested that PCCCL mainly occurs in patients >50 years old (11) and was more conducive to capsule formation (12) and cirrhosis development (13). It tends to have less vascular infiltration (14) and low-grade malignancy (15). However, due to the lack of effective large case studies, the clinical and pathological features remain unclear.

As a rare HCC variant, PCCCL has largely been described in case reports or by small, single-institution studies, rendering the conclusions questionable. Hence, in this study, we expanded the number of the study cases by utilizing the Surveillance, Epidemiology, and End Results (SEER) database to clarify the tumor features, epidemiology, therapies, and prognostic factors.

We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/tcr-21-9).

Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Study population

The SEER database was supported by the National Cancer Institute and contained the information of 18 population based registered cancer institutes. The US population accounts for 28.0% of the SEER database. SEER program was established to collect cancer patient's information including cancer incidence, prevalence, treatments, clinicopathological features and survival data from U.S. cancer registries, which is broadly represents the population of the US population. It serves to minimize the potential biases, reduce the cancer burden and provide first-hand evidence for clinicians to perform studies focusing on oncologic disease (16). As the patients data in the SEER dataset are publicly available, therefore, no approval was required from any institutional review board (17).

The study we designed was a population based longitudinal cohort study. And we utilized the SEER database to identify patients diagnosed with PCCCL (SEER codes 8174/3) from 2004 to 2016 according to the 3rd edition of International Classification of Disease for Oncology (ICD-0-3) and the 6th edition of American Joint Committee on Cancer (AJCC). The exclusion criteria were as follows: (I) diagnostic confirmation that is not "positive histology"; (II) sequence number that is not "one primary only"; (III) AJCC T that is "TX, T0, NA, or blank"; (IV) AJCC N that is "NX, NA, or blank"; (V) AJCC M that is "MX, NA, or blank"; (VI) reason no cancer-directed surgery that is "recommended, unknown if performed" and "unknown; death certificate; or autopsy only"; (VII) race recode that is "unknown"; (VIII) size recode that is "unknown".

The patient information including diagnostic confirmation, histology/behavior (ICD-O-3), SEER combined summary stage, AJCC stage (6th), AJCC T stage (6th), AJCC M stage (6th), AJCC N stage (6th), surgery primary site (1998+), radiation therapy, tumor size, CS extension, CS lymph nodes [2004–2015], CS metastasis at distance [2004–2015], SEER cause-specific death classification, survival months, sequence number, age at diagnosis, gender, race, and pathological grade were extracted from the database. The details of chemotherapy was not included in the SEER database. No private identity information were acquired from the SEER database.

Definition of variables and grouping criteria

Age was defined as the age at diagnosis as PCCCL and was classified into 2 groups: "<75" and "≥75" years old. Race was recoded as follows: white, black, or others. Sex was described as male and female. Tumor size was assigned into three groups: "<1 cm" and "≥1 cm". AJCC T stage was classified as four subgroups: "T1", "T2", "T3" and "T4". AJCC N stage was categorized into two subgroups: "N0" and "N1". AJCC M stage was divided into two subgroups: "M0" and "M1". AJCC stage was assigned into four groups: "I", "II", "III (IIIA, IIIB, IIIC)", and "IV". SEER stage was classified as three subgroups: "localized", "regional" and "distant". The radiotherapy was divided into two groups: "Yes" which means the patients underwent radiotherapy and "No" means not. The methods of surgery was assigned into the following six types: "none", "local tumor destruction", "lobectomy", "extended lobectomy", "wedge or/and segmental resection", "hepatectomy" and "total hepatectomy plus transplant"

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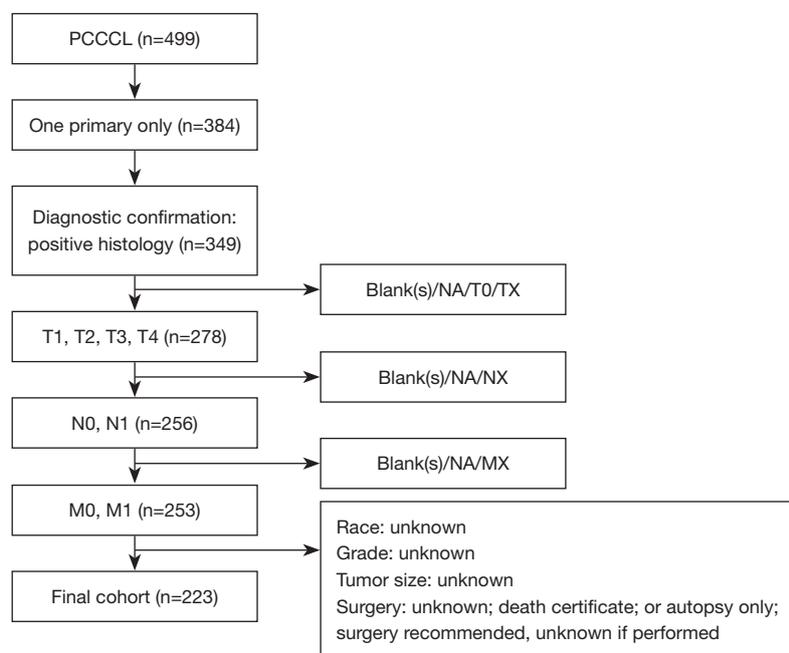
Figure 1 Flow diagram of study cohort selection. A flow diagram describing the inclusion and exclusion criteria for the patient selection. According to the 6th edition of AJCC, we excluded those patients with T0, TX, NX, MX and unspecific information, including unknown surgery methods, unknown race and unknown tumor size. Those PCCCL patients with blank information and NA were also excluded from the cohort. AJCC, American Joint Committee on Cancer; PCCCL, primary clear cell carcinoma of liver; NA, not applicable.

and "partial hepatectomy plus bile duct excision". Tumor extension was categorized as follows: "no vascular invasion", "intrahepatic vascular invasion", "gallbladder extension", "intrahepatic vascular invasion plus gallbladder extension", "surface of parenchyma extension", "major vascular invasion: major branch(es) of portal or hepatic vein(s)", and "hepatic artery or vena cava invasion", "coronary, falciform, hepatoduodenal, hepatogastric, round (of liver), triangular, perforation of visceral peritoneum, parietal peritoneum, pancreas, pleura, stomach extension".

Statistical analysis

The demographic, clinical, and pathological characteristics of PCCCL patients were analyzed with basic statistics. The primary endpoints were overall survival (OS) and disease-specific survival (DSS). OS and DSS were defined as the time intervals from diagnosis to death by any cause and PCCCL-related reasons, respectively. The Kaplan-Meier method and log-rank test were used to validate the prognostic factors and statistical significance for the OS and DSS. The univariate and multivariable Cox proportional hazards regression were performed to identify

the independent prognostic variables. The hazard ratio (HR) and 95% confidence interval (CI) were measured for assessing the correlation strength between each variable and survival. The multivariable competing risk model (Fine & Gray model) was used to validate the independent factors affecting the risk for DSS. The GraphPad Prism 6 software was applied to draw the figures and charts. SPSS 19.0 (SPSS, Inc., Chicago, IL, USA) was for data analysis. SEER*STAT version 8.3.5 (Surveillance Research Program, NCI, Bethesda, MD, USA) was utilized to extract patient information from the SEER database (18). And the StataMP 14 was utilized to make competing risk model analysis. P<0.05 was considered statistically significant.

Results

Patient population

PCCCL cases during 2004–2016 (n=499) were extracted from the SEER database. Subsequently, 223 cases were recruited to our study cohort according to the inclusion and exclusion criteria as shown in *Figure 1*. Patient-related general information was listed in *Table 1*. The average age

Table 1 Characteristics of patients with PCCCL diagnosed from 2004 to 2016 obtained from the SEER database

Parameter	Subgroup	Number (%)
Age at diagnosis	Mean ± SD	63.8±12.4
Age	<75	184 (82.5)
	≥75	39 (17.5)
Race	White	141 (63.2)
	Black	27 (12.1)
	Others	55 (24.7)
Sex	Male	128 (57.4)
	Female	95 (42.6)
Summary stage	Localized	142 (63.7)
	Regional	51 (22.8)
	Distant	30 (13.5)
T stage	T1	111 (49.8)
	T2	46 (20.6)
	T3	55 (24.7)
	T4	11 (4.9)
N stage	N0	214 (96.0)
	N1	9 (4.0)
M stage	M0	195 (87.4)
	M1	28 (12.6)
Radiation	Yes	6 (2.7)
	No	217 (97.3)
Tumor size (cm)	<1 cm	167 (74.9)
	≥1 cm	56 (25.1)
AJCC stage	I	99 (44.4)
	II	42 (18.8)
	III	54 (24.2)
	IV	28 (12.6)
Surgery	None	107 (48.0)
	Local tumor destruction	21 (9.4)
	Lobectomy	28 (12.6)
	Extended lobectomy	4 (1.8)
	Wedge or/and segmental resection	47 (21.1)
	Hepatectomy	4 (1.8)
	Total hepatectomy + transplant	11 (4.9)
	Partial hepatectomy + bile duct excision	1 (0.4)

Table 1 (*continued*)

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Table 1 (*continued*)

Parameter	Subgroup	Number (%)
Extension	No vascular invasion	141 (63.2)
	Intrahepatic vascular invasion and/or gallbladder extension	26 (11.7)
	Surface of parenchyma extension	29 (13.0)
	Major vascular invasion: major branch(es) of portal or hepatic vein(s)	16 (7.2)
	Hepatic artery or vena cava invasion	2 (0.9)
	Coronary, falciform, hepatoduodenal, hepatogastric, round (of liver), triangular, perforation of visceral peritoneum, parietal peritoneum, pancreas, pleura, stomach extension	9 (4.0)

Table 1: characteristics of patients with PCCCL. PCCCL, primary clear cell carcinoma of liver; SEER, Surveillance, Epidemiology, and End Results.

at diagnosis was 63.8±12.4 years with 57.4% male; 63.2%, 12.1%, and 24.7% were white, black, and of other ethnicity, respectively. Tumor was present in 74.9% (<1 cm) and 25.1% (≥1 cm) of the patients. Nearly half the patients (49.8%) were diagnosed at T1, 20.6% at T2, 24.7% at T3, and 4.9% at T4 stages. The overwhelming majority of the patients (N0, 96.0%) had no regional lymph node or tumor distant metastasis (M0, 87.4%). The patients diagnosed as early AJCC stage I, or stages II, III, and IV accounted for 44.4%, 18.8%, 24.2%, and 12.6% of the sample size, respectively. Regarding SEER staging, 63.7%, 22.8%, and 13.5% of the patients had localized, regional, and distant extent of PCCCL, respectively. The patients with no vascular invasion corresponded to 63.2%. Only a few people (2.7%) underwent radiotherapy. Approximately half the patients (48.0%) had no surgical treatment; 9.4% and 12.6% received local tumor destruction and lobectomy, respectively; 1.8% underwent extended lobectomy; 21.1%, 1.8%, 4.9% and 0.4% underwent wedge or/and segmental resection, hepatectomy, total hepatectomy plus transplant and partial hepatectomy plus bile duct excision, respectively.

Clinical prognosis and survival analysis

To understand whether these variables would affect the survival of patients, we first analyzed the association strength between each variable and survival. The Kaplan-Meier survival analysis showed that the 5-year OS and DSS rates were 24.3% and 29.4%, respectively, and thus indicated a relatively poor clinical (*Figure 2A,B*). The median OS and DSS were 21 and 26 months, respectively (*Table 2*). The Kaplan-Meier analysis results showed that the patients ≥75 years old exhibited a poorer outcome than that of the

younger patients, with a median OS of 15 *vs.* 25 months (log-rank P=0.048). However, age had no statistically significant effect on the DSS (log-rank P=0.230) (*Figure 3A,B*, *Table 2*). Additionally, higher T stage correlated with decreased OS and DSS (log-ranks P<0.001 for both) with patients at T4 or T3 stage having a dismal prognosis (T4 median OS and DSS, both 9 months; T3 median OS and DSS, both 12 months) (*Figure 3C,D*, *Table 2*). Poor prognosis could be observed in the patients with N1 stage (OS log-rank P=0.017, DSS log-rank P=0.004, median OS and DSS, both 8 months) and M1 stage (OS log-rank P<0.001, median OS: 7 months; DSS log-rank P<0.001, median DSS: 8 months) (*Figure 3E,F,G,H*, *Table 2*). Regarding AJCC stage, shorter survival was observed in the stage IV patients (median OS and DSS: 7 and 8 months, respectively) and stage III patients (median OS and DSS: both 13 months), while, the opposite trend could be observed in those with stage II (median OS: 26 months; median DSS: 30 months) and stage I (median OS: 41 months; median DSS: 50 months) (OS and DSS log-ranks, both P<0.001) (*Figure 4A,B*, *Table 2*). Additionally, later summary stage (distant) correlated with decreased survival (median OS: 6 months; median OS: 7 months) compared with localized stage (median OS and DSS: 34 and 42 months, respectively) and regional stage (median OS and DSS, both 13 months) (OS and DSS log-ranks, both P<0.001) (*Figure 4C,D*, *Table 2*). The median OS and DSS of the patients with tumor <1 cm were 30 and 36 months, respectively, which were longer than those of the patients with tumors ≥1 cm (median OS and DSS, both 12 months) (OS and DSS log-ranks, both P<0.001) (*Figure 4E,F*, *Table 2*). Shorter survival could be observed in patients with parenchyma surface extension (median OS and DSS, both 11 months), major vascular invasion (median OS
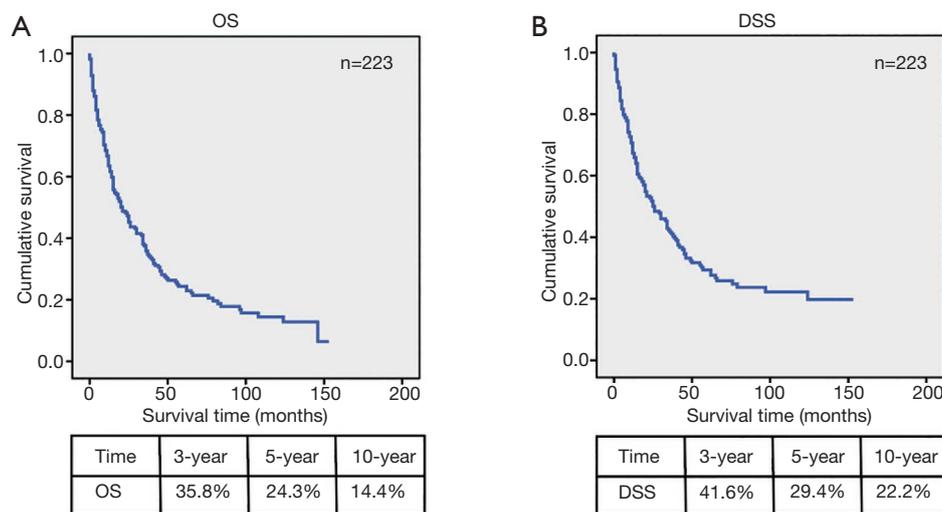
Figure 2 Kaplan-Meier analysis: OS curves (A) and DSS curves (B) of PCCCL for the entire cohort. Three-, 5-, and 10-year OS rates were 35.8%, 24.3%, and 14.4%, respectively. Three-, 5-, and 10-year DSS rates were 41.6%, 29.4%, and 22.2%, respectively. Median OS and DSS were 21 and 26 months, respectively. OS, overall survival; DSS, disease-specific survival; PCCCL, primary clear cell carcinoma of liver.

and DSS: both 12 months), hepatic artery or vena cava invasion (median OS and DSS, both 4 months), or coronary, falciform, hepatoduodenal, hepatogastric, round (of liver), triangular, perforation of visceral peritoneum, parietal peritoneum, pancreas, pleura, stomach extension (median OS and DSS: 13 and 3 months, respectively) compared with those without vascular invasion (median OS and DSS: 34 and 42 months, respectively) (OS and DSS log-ranks, both P<0.001) (*Figure 5A,B*, *Table 2*). With reference to different surgery methods, a median OS and DSS of 37 and 42 months, respectively, were observed for patients receiving local tumor destruction, 56 (OS) and 62 months (DSS) for patients undergoing wedge or/and segmental resection, 34 months (for both OS and DSS) for patients accepting lobectomy, 41 months (for both OS and DSS) for those having extended lobectomy, 62 months (for both OS and DSS) for those with hepatectomy, and 124 months (OS) for those after total hepatectomy plus transplant. Conversely, the clinical outcome of the patients without any surgery was poor (median OS and DSS: 9 and 10 months, respectively; OS and DSS log-ranks, both P<0.001) (*Figure 5C,D*, *Table 2*). However, no statistically significant differences in OS and DSS could be observed in patients of both genders (OS log-rank P=0.756, DSS log-rank P=0.811) and different races. (OS log-rank P=0.394, DSS log-rank P=0.869) (*Figure 6A,B,C,D*). It should be noted that there was no significant difference in OS (log-rank, P=0.960) or DSS (log-rank, P=0.785) in patients with

or without radiation (*Figure 6E,F*, *Table 2*).

Uni- and multivariate analyses

To further dissect the independent predictors for OS and DSS of the PCCCL patients, we performed uni- and multivariate analyses. Summary stages, surgery, tumor size, TNM stage, AJCC, and extension were markedly correlated with both the OS and DSS (*Table 2*). The univariate analysis showed that the summary stage was a significant predictor of OS and DSS (P<0.001 for both). Relative to patients with localized stage, increased HR could be observed in the patients with distant stage (OS: HR =3.545, 95% CI: 2.288–5.492; DSS: HR =3.718, 95% CI: 2.313–5.977) or regional stage (OS: HR =1.931, 95% CI: 1.347–2.769; DSS: HR =2.176, 95% CI: 1.482–3.194). Lower survival occurred in M1 stage (OS: HR =2.771, 95% CI: 1.800–4.266; DSS: HR =2.738, 95% CI: 1.715–4.372), N1 stage (OS: HR =2.305, 95% CI: 1.121–4.738; DSS: HR =2.719, 95% CI: 1.317–5.616), and T3 (OS: HR =2.676, 95% CI: 1.854–3.863; DSS: HR =3.511, 95% CI: 2.370–5.203) and T4 stages (OS: HR =2.562, 95% CI: 1.317–4.981; DSS: HR =3.452, 95% CI: 1.751–6.802) than in M0, N0, and T1 stages, respectively. The patients with tumors <1 cm had poorer prognosis (OS: HR =1.806, 95% CI: 1.284–2.538; DSS: HR =1.992, 95% CI: 1.388–2.859) than those with tumors ≥1 cm. PCCCL extended in parenchyma surface (OS: HR =2.145, 95% CI: 1.383–3.327; DSS: HR =2.595, 95% CI:

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Table 2 Results of univariate analysis of potential patient characteristics influencing DSS and OS using the Cox proportional HRs

Parameter	Subgroup	OS			DSS		
		MST (m)	HR (95% CI)	P value	MST (m)	HR (95% CI)	P value
Whole group		21			26		
Age				0.054			0.238
	<75	25	1		29	1	
	≥75	15	1.466 (0.994, 2.161)	0.054	18	1.299 (0.841, 2.004)	0.238
Summary stage				0.000			0.000
	Localized	34	1		42	1	
	Regional	13	1.931 (1.347, 2.769)	0.000	13	2.176 (1.482, 3.194)	0.000
	Distant	6	3.545 (2.288, 5.492)	0.000	7	3.718 (2.313, 5.977)	0.000
M stage				0.000			0.000
	M0	25	1		33	1	
	M1	7	2.771 (1.800, 4.266)	0.000	8	2.738 (1.715, 4.372)	0.000
N stage				0.023			0.007
	N0	21	1		29	1	
	N1	8	2.305 (1.121, 4.738)	0.023	8	2.719 (1.317, 5.616)	0.007
T stage				0.000			0.000
	T1	36	1		46	1	
	T2	26	1.082 (0.709 ,1.653)	0.714	26	1.249 (0.780, 2.000)	0.356
	T3	12	2.676 (1.854, 3.863)	0.000	12	3.511 (2.370, 5.203)	0.000
	T4	9	2.562 (1.317, 4.981)	0.006	9	3.452 (1.751, 6.802)	0.000
Race				0.408			0.872
	White	20	1		25	1	
	Black	15	1.350 (0.852, 2.138)	0.201	26	1.024 (0.593, 1.766)	0.932
	Others	24	0.980 (0.681, 1.410)	0.912	25	0.905 (0.609, 1.346)	0.623
Tumor size (cm)				0.001			0.000
	<1 cm	30	1		36	1	
	≥1 cm	12	1.806 (1.284, 2.538)	0.001	12	1.992 (1.388, 2.859)	0.000
Sex				0.760			0.814
	Male	18	1		25	1	
	Female	25	0.954 (0.703, 1.294)	0.760	26	1.040 (0.748, 1.446)	0.814

Table 2 (*continued*)

Table 2 (*continued*)

Parameter	Subgroup	OS			DSS		
		MST (m)	HR (95% CI)	P value	MST (m)	HR (95% CI)	P value
Extension				0.000			0.000
	No vascular invasion	34	1		42	1	
	Intrahepatic vascular invasion and/or gallbladder extension	26	1.000 (0.605, 1.655)	0.999	30	1.139 (0.665, 1.952)	0.636
	Surface of parenchyma extension	11	2.145 (1.383, 3.327)	0.001	11	2.595 (1.633, 4.123)	0.000
	Major vascular invasion: majorbranch of portal or hepatic vein(s)	12	3.069 (1.781, 5.289)	0.000	12	3.650 (2.063, 6.457)	0.000
	Hepatic artery or vena cava invasion	4	6.940 (1.660, 29.020)	0.008	4	9.248 (2.188, 39.094)	0.002
	Coronary, falciform, hepatoduodenal, hepatogastric, round (of liver), triangular, perforation of visceral peritoneum, parietal peritoneum, pancreas, pleura, stomach extension	13	2.008 (0.974, 4.141)	0.059	3	2.536 (1.221, 5.269)	0.013
Radiation				0.961			0.788
	No	17	1		17	1	
	Yes	21	1.023 (0.419, 2.493)	0.961	26	0.885 (0.362, 2.162)	0.788
Surgery				0.000			0.000
	None	9	1		10	1	
	Local tumor destruction	37	0.374 (0.219, 0.639)	0.000	42	0.321 (0.174, 0.591)	0.000
	Wedge or/and segmental resection	56	0.204 (0.129, 0.324)	0.000	62	0.201 (0.122, 0.331)	0.000
	Lobectomy	34	0.237 (0.139, 0.404)	0.000	34	0.270 (0.156, 0.466)	0.000
	Extended lobectomy	41	0.238 (0.075, 0.758)	0.015	41	0.185 (0.045, 0.757)	0.019
	Hepatectomy	62	0.090 (0.020, 0.413)	0.002	62	0.073 (0.010, 0.529)	0.010
	Total hepatectomy + transplant	124	0.085 (0.032, 0.225)	0.000	NA	NA	NA
	Partial hepatectomy + bile duct excision	5	2.409 (0.332, 17.493)	0.385	NA	NA	NA
AJCC stage				0.000			0.000
	I	41	1		50	1	
	II	26	1.109 (0.703, 1.749)	0.658	30	1.215 (0.729, 2.025)	0.454
	III	13	2.798 (1.913, 4.093)	0.000	13	3.549 (2.363, 5.330)	0.000
	IV	7	3.945 (2.456, 6.338)	0.000	8	4.409 (2.616, 7.429)	0.000

Table 2: SEER summary stage, M stage, N stage, T stage, tumor size (cm), extension status, surgery and AJCC stage were significantly related to the OS and DSS of PCCCL patients. 0.000 means P<0.001. DSS, disease-specific survival; OS, overall survival; HR, hazard ratio; MST, median survival time; CI, confidence interval; NA, not applicable; AJCC, American Joint Committee on Cancer; SEER, Surveillance, Epidemiology, and End Results; PCCCL, primary clear cell carcinoma of liver.

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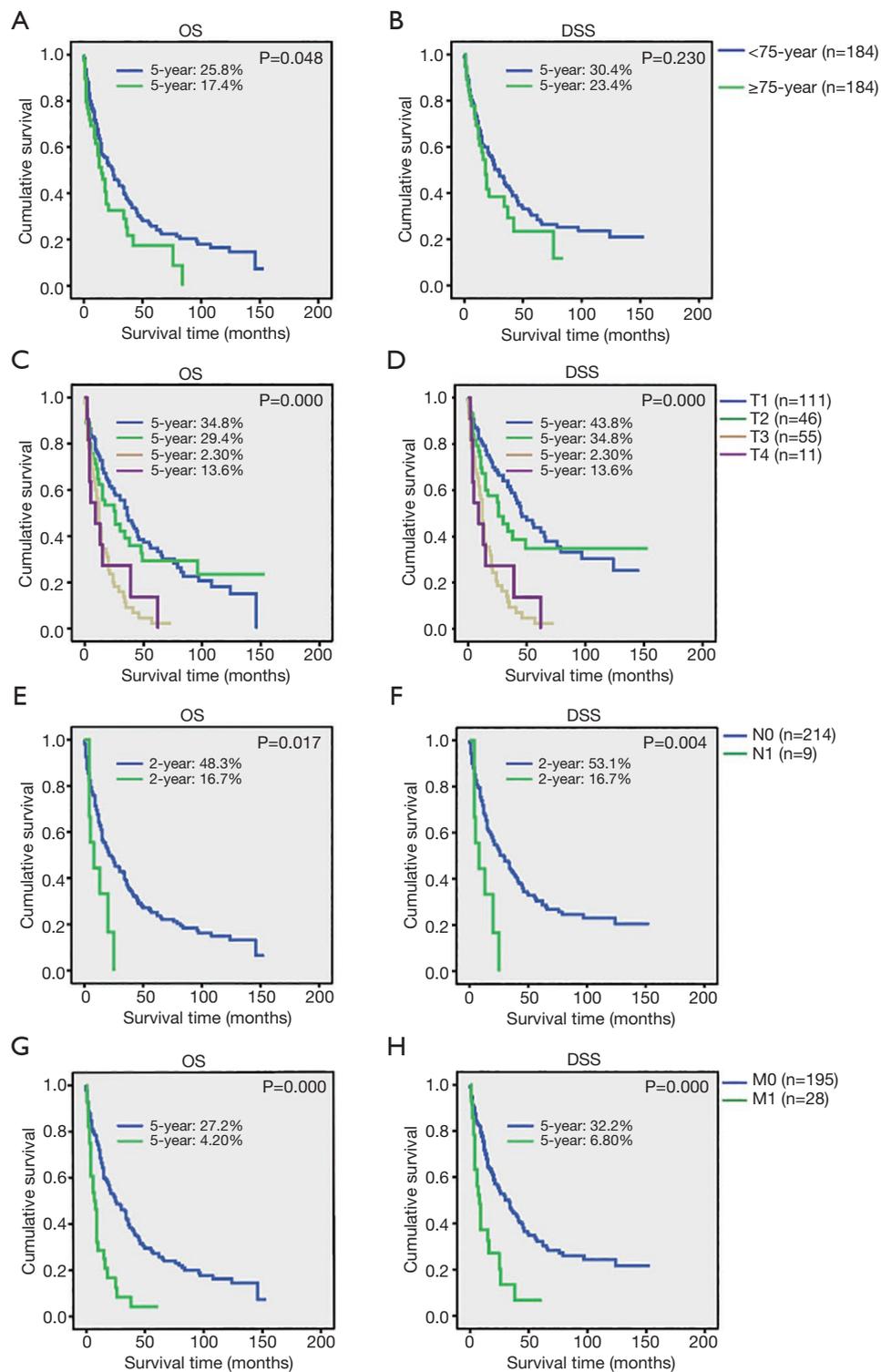
Figure 3 Kaplan-Meier analysis of the variables. Kaplan-Meier estimates of the OS and DSS stratified by (A,B) age, (C,D) AJCC T stage, (E,F) AJCC N stage, (G,H) AJCC M stage. And the 2- or 5-year survival rate of PCCCL patients in each group were listed in the corresponding pictures. 0.000 means P<0.001. OS, overall survival; DSS, disease-specific survival; AJCC, American Joint Committee on Cancer; PCCCL, primary clear cell carcinoma of liver.
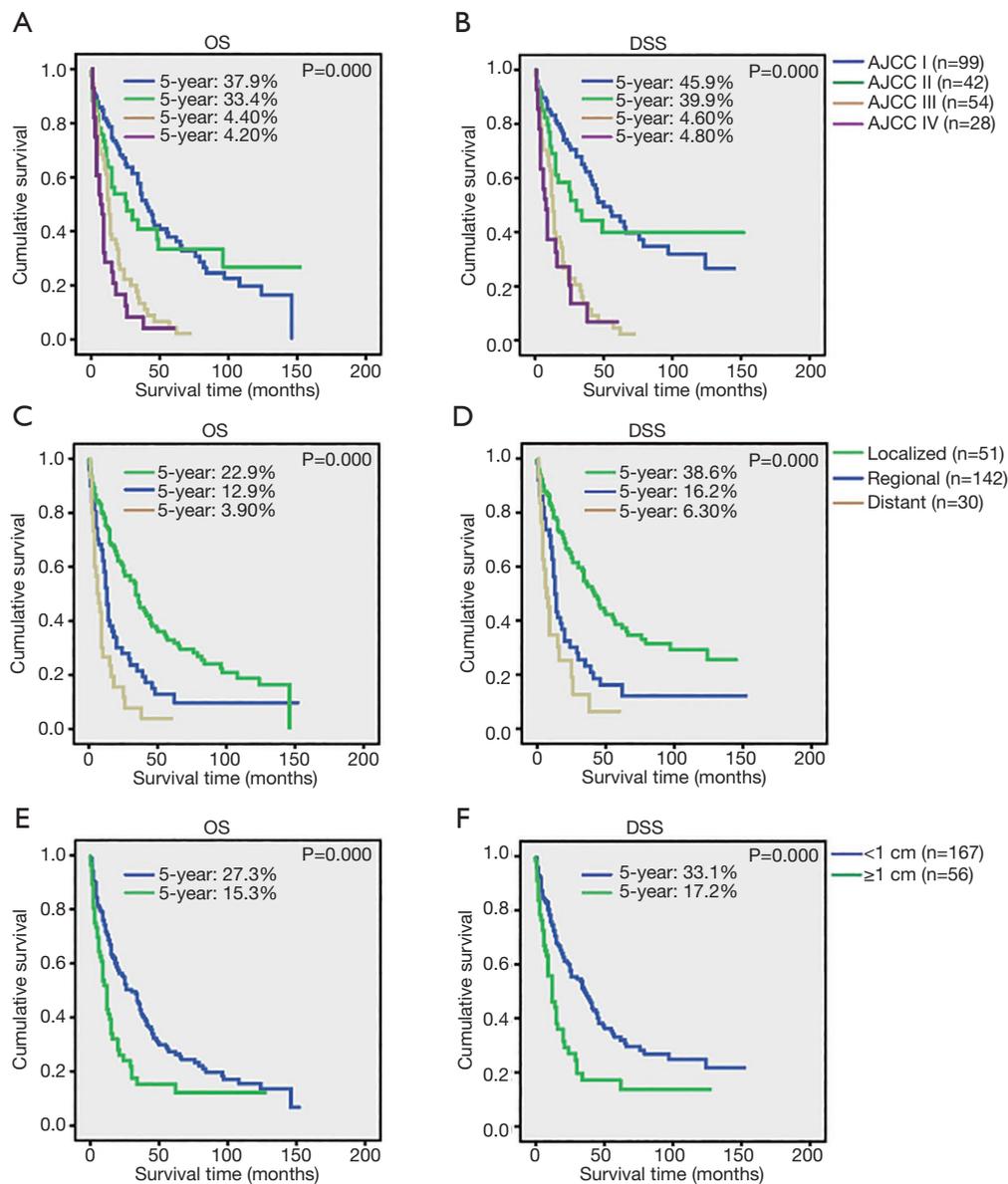
Figure 4 Kaplan-Meier analysis of the variables (continued from *Figure 3*). Kaplan-Meier estimates of the OS and DSS stratified by (A,B) AJCC stage, (C,D) summary stage, (E,F) tumor size. And the 5-year survival rate of PCCCL patients in each group were listed in the corresponding pictures. 0.000 means P<0.001. OS, overall survival; DSS, disease-specific survival; AJCC, American Joint Committee on Cancer; PCCCL, primary clear cell carcinoma of liver.

1.633–4.123), major branches of portal or hepatic vein(s) (OS: HR =3.069, 95% CI: 1.781–5.289; DSS: HR =3.650, 95% CI: 2.063–6.457), hepatic artery or vena cava (OS: HR =6.940, 95% CI: 1.660–29.020; DSS: HR =9.248, 95% CI: 2.188–39.094), or with coronary, falciform, hepatoduodenal, hepatogastric, round (of liver), triangular, perforation of visceral peritoneum, parietal peritoneum, pancreas, pleura,

or stomach extension (OS: HR =2.008, 95% CI: 0.974–4.141; DSS: HR =2.536, 95% CI: 1.221–5.269) had higher risks than those without vascular invasion. Compared with patients without surgery, those who underwent local tumor destruction (OS: HR =0.374, 95% CI: 0.219–0.639; DSS: HR =0.321, 95% CI: 0.174–0.591), wedge or/and segmental resection (OS: HR =0.204, 95% CI: 0.129–0.324; DSS:
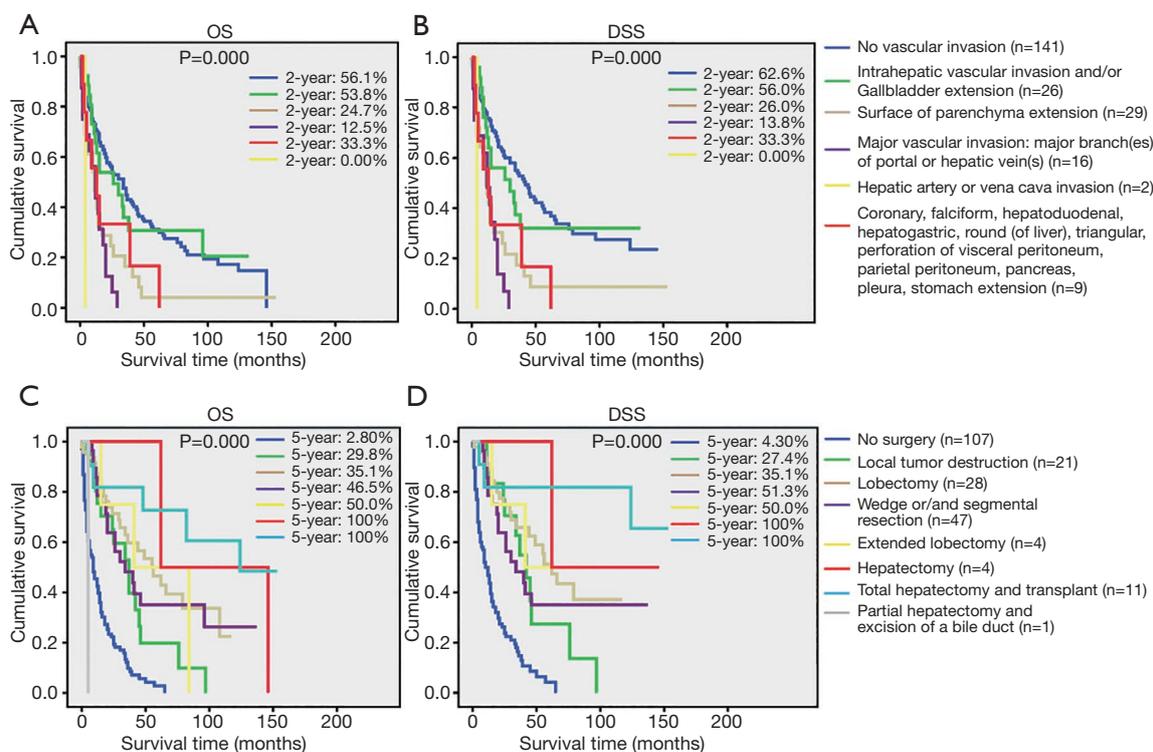
Figure 5 Kaplan-Meier analysis of the variables (continued from *Figure 4*). Kaplan-Meier estimates of the OS and DSS stratified by (A,B) extension, (C,D) surgery. And the 2- or 5-year survival rate of PCCCL patients in each group were listed in the corresponding pictures. 0.000 means P<0.001. OS, overall survival; DSS, disease-specific survival; PCCCL, primary clear cell carcinoma of liver.

HR =0.201, 95% CI: 0.122–0.331), lobectomy (OS: HR =0.237, 95% CI: 0.139–0.404; DSS: HR =0.270, 95% CI: 0.156–0.466), extended lobectomy (OS: HR 0.238, 95% CI: 0.075–0.758; DSS: HR =0.185, 95% CI: 0.045–0.757), hepatectomy (OS: HR =0.090, 95% CI: 0.020–0.413; DSS: HR =0.073, 95% CI: 0.010–0.529) or total hepatectomy plus transplant (OS: HR =0.085, 95% CI: 0.032–0.225) had reduced risks of death. Patients diagnosed as AJCC III (OS: HR =2.798, 95% CI: 1.913–4.093; DSS: HR =3.549, 95% CI: 2.363–5.330) or AJCC IV (OS: HR =3.945, 95% CI: 2.456–6.338; DSS: HR =4.409, 95% CI: 2.616–7.429) showed significantly high risks of death than those with AJCC I or II. However, age, race, sex and radiotherapy had no impacts on the hazard rate.

Next step, to determine the independent prognostic factors, we performed multivariate cox proportional analysis model of OS and DSS (*Table 3*) for those variables whose P value <0.05 according to the univariate analyses results in *Table 2*. As shown in *Table 3*, for the whole cohort, tumor size and surgery were independent determinants of OS and DSS. Relative to the patients with tumor <1 cm, those with

lesion ≥1 cm possessed shorter survival (OS: HR =1.822, 95% CI: 1.222–2.717; DSS: HR =1.959, 95% CI: 1.283–2.990). Receiving surgery had improved OS and DSS. Using no surgery as a reference, patients accepting local tumor destruction (OS: HR =0.505, 95% CI: 0.285–0.895; DSS: HR =0.464, 95% CI: 0.242–0.890), wedge or/and segmental resection (OS: HR =0.237, 95% CI: 0.146–0.386; DSS: HR =0.240, 95% CI: 0.142–0.405), lobectomy (OS: HR =0.216, 95% CI: 0.118–0.394; DSS: HR =0.244, 95% CI: 0.131–0.454), extended lobectomy (OS: HR =0.349, 95% CI: 0.107–1.138; DSS: HR =0.296, 95% CI: 0.070–1.243), hepatectomy (OS: HR =0.070, 95% CI: 0.016–0.312; DSS: HR =0.050, 95% CI: 0.006–0.386), and total hepatectomy plus transplant (OS: HR =0.074, 95% CI: 0.025–0.219; DSS: HR =0.065, 95% CI: 0.018–0.237) had a good clinical outcome. In the final model as shown in *Table 4*, tumor size and surgery had impacts on the OS and DSS. The patients having small tumor (<1 cm) and undergoing surgery possessed a better clinical outcome.

Consistent with the above results, the regression results of multivariate competitive risk model for PCCCL
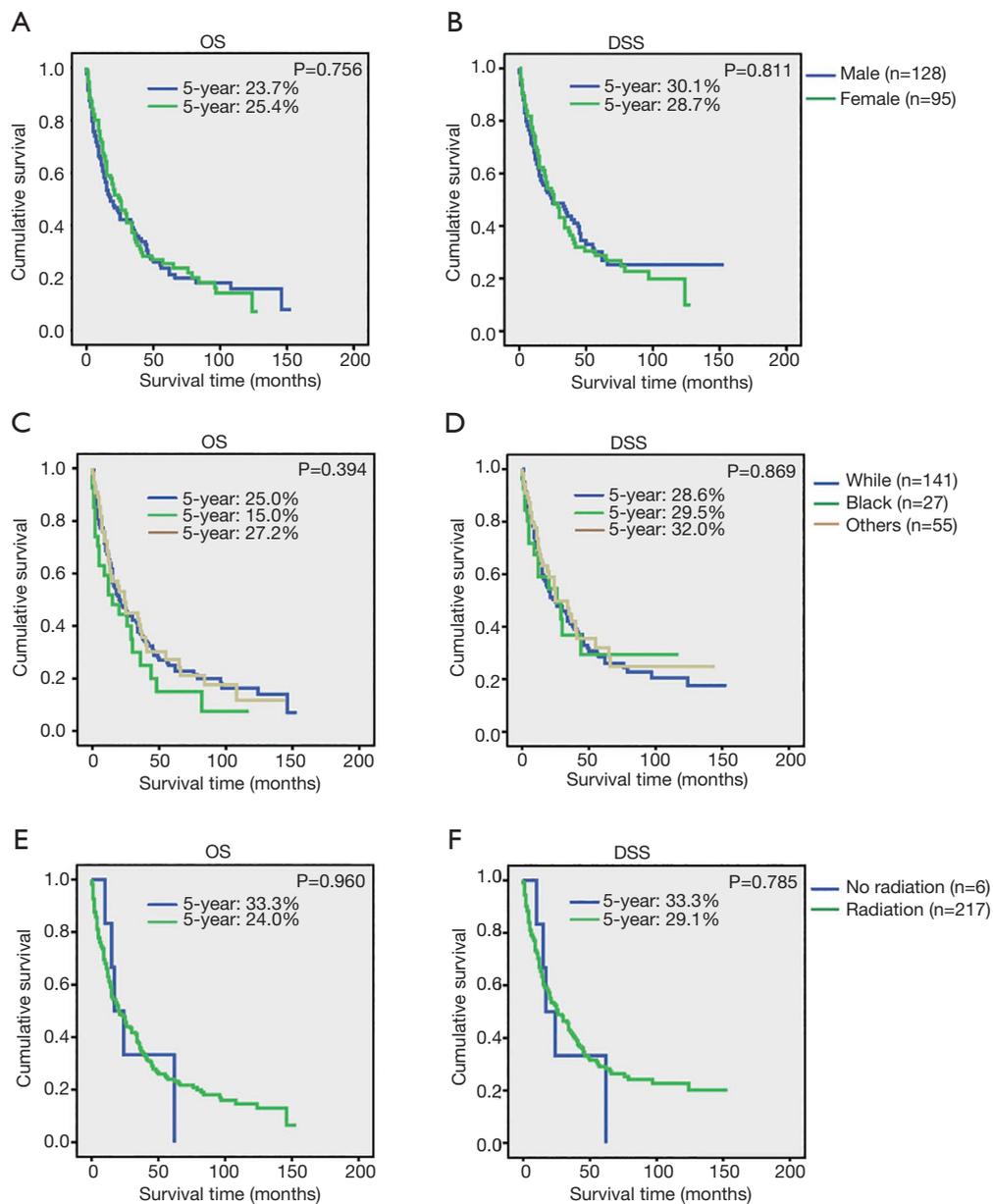
Figure 6 Kaplan-Meier analysis of the variables (continued from *Figure 5*). Kaplan-Meier estimates of the OS and DSS stratified by (A,B) sex, (C,D) race, (E,F) radiation. And the 5-year survival rate of PCCCL patients in each group were listed in the corresponding pictures. OS, overall survival; DSS, disease-specific survival; PCCCL, primary clear cell carcinoma of liver.

showed that tumor size and surgery were significantly correlated with DSS (*Table 5*), and tumor ≥1 cm had higher risk for death due to PCCCL comparing to those patients with tumor <1 cm. As for surgery, we found that partial hepatectomy along with bile duct excision, total hepatectomy and transplant combination, hepatectomy and extended lobectomty were more inversely associated

with risk for DSS, followed by lobectomy, wedge or/and segmental resection and local destruction (*Figure 7A,B*).

Discussion

Due to the glycogen accumulation and fat storage in the cytoplasm, cytoplasmic clearing to the hematoxylin-eosin

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Table 3 Results of multivariate analysis of potential patient characteristics influencing DSS and OS using the Cox proportional HRs

Parameter	Subgroup	OS			DSS		
		HR	(95% CI)	P value	HR	(95% CI)	P value
Summary stage				0.323			0.331
	Localized	1			1		
	Regional	0.799	(0.332, 1.921)	0.616	0.835	(0.326, 2.138)	0.706
	Distant	2.674	(0.415, 17.225)	0.301	2.868	(0.428, 19.219)	0.278
M stage				0.999			0.806
	M0	1			1		
	M1	0.999	(0.141, 7.063)	0.999	0.774	(0.100, 5.972)	0.806
N stage				0.712			0.999
	N0	1			1		
	N1	0.856	(0.375, 1.953)	0.712	0.999	(0.427, 2.340)	0.999
T stage				0.692			0.866
	T1	1			1		
	T2	0.797	(0.207, 3.071)	0.742	1.311	(0.311, 5.530)	0.712
	T3	0.595	(0.181, 1.953)	0.392	0.901	(0.243, 3.344)	0.876
	T4	0.856	(0.375, 1.953)	0.712	0.999	(0.427, 2.340)	0.999
Tumor size (cm)				0.003			0.002
	<1 cm	1			1		
	≥1 cm	1.822	(1.222, 2.717)	0.003	1.959	(1.283, 2.990)	0.002
Extension				0.230			0.214
	No vascular invasion	1			1		
	Intrahepatic vascular invasion and/or gallbladder extension	0.757	(0.353, 1.623)	0.474	0.697	(0.308, 1.576)	0.386
	Surface of parenchyma extension	1.750	(0.591, 5.185)	0.281	1.713	(0.587, 4.998)	0.324
	Major vascular invasion: majorbranch of portal or hepatic vein(s)	1.751	(0.591, 5.185)	0.312	1.573	(0.503, 4.921)	0.436
	Hepatic artery or vena cava invasion	2.794	(0.569, 13.726)	0.206	4.238	(0.804, 22.337)	0.089
	Coronary, falciform, hepatoduodenal, hepatogastric, round (of liver), triangular, perforation of visceral peritoneum, parietal peritoneum, pancreas, pleura, stomach extension	0.561	(0.192, 1.641)	0.291	0.835	(0.260, 2.678)	0.761

Table 3 (*continued*)

Table 3 (*continued*)

Parameter	Subgroup	OS			DSS		
		HR	(95% CI)	P value	HR	(95% CI)	P value
Surgery				0.000			0.000
	None	1			1		
	Local tumor destruction	0.505	(0.285, 0.895)	0.019	0.464	(0.242, 0.890)	0.021
	Wedge or/and segmental resection	0.237	(0.146, 0.386)	0.000	0.240	(0.142, 0.405)	0.000
	Lobectomy	0.216	(0.118, 0.394)	0.000	0.244	(0.131, 0.454)	0.000
	Extended lobectomy	0.349	(0.107, 1.138)	0.081	0.296	(0.070, 1.243)	0.096
	Hepatectomy	0.070	(0.016, 0.312)	0.000	0.050	(0.006, 0.386)	0.004
	Total hepatectomy + transplant	0.074	(0.025, 0.219)	0.000	0.065	(0.018, 0.237)	0.000
	Partial hepatectomy + bile duct excision	2.124	(0.263, 17.153)	0.480	0.000	(0.000, 9.64E+224)	0.970
AJCC stage				0.153			0.296
	I	1			1		
	II	2.305	(0.595, 8.923)	0.227	1.639	(0.382, 7.038)	0.506
	III	3.143	(0.978, 10.101)	0.055	2.598	(0.709, 9.520)	0.150
	IV	0.999	(0.141, 7.063)	0.999	0.774	(0.100, 5.972)	0.806

Table 3: tumor size (cm) and surgery were the independent prognostic factors of the OS and DSS of PCCCL patients. 0.000 means P<0.001. DSS, disease-specific survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; AJCC, American Joint Committee on Cancer; PCCCL, primary clear cell carcinoma of liver.

Table 4 Final model

Parameter	Subgroup	OS			DSS		
		HR	(95% CI)	P value	HR	(95% CI)	P value
Tumor size (cm)				0.000			0.000
	<1 cm	1			1		
	≥1 cm	2.103	(1.463, 3.022)	0.000	2.250	(1.532, 3.306)	0.000
Surgery				0.000			0.000
	None	1			1		
	Local tumor destruction	0.419	(0.244, 0.721)	0.002	0.364	(0.196, 0.675)	0.001
	Wedge or/and segmental resection	0.199	(0.125, 0.317)	0.000	0.195	(0.118, 0.323)	0.000
	Lobectomy	0.196	(0.114, 0.339)	0.000	0.219	(0.125, 0.383)	0.000
	Extended lobectomy	0.245	(0.077, 0.780)	0.017	0.190	(0.046, 0.780)	0.021
	Hepatectomy	0.070	(0.016, 0.314)	0.001	0.051	(0.007, 0.373)	0.003
	Total hepatectomy + transplant	0.093	(0.035, 0.247)	0.000	0.080	(0.024, 0.265)	0.000
	Partial hepatectomy + bile duct excision	3.070	(0.421, 22.414)	0.269	0.000	(0.000, 3.103E+213)	0.969

Table 4: tumor size (cm) and surgery were the independent prognostic factors of the OS and DSS of PCCCL patients. 0.000 means P<0.001. OS, overall survival; DSS, disease-specific survival; HR, hazard ratio; CI, confidence interval; PCCCL, primary clear cell carcinoma of liver.

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Table 5 Multivariate analysis of clinical and pathological prognostic factors in PCCCL by using competing risk model

Parameter	DSS		
	SHR	(95% CI)	P value
Age	1.087678	(0.8582179, 1.378489)	0.487
Summary stage	1.283481	(0.6530953, 2.522332)	0.469
M stage	0.6030417	(0.2264641, 1.605814)	0.311
N stage	1.265471	(0.5495094, 2.914266)	0.580
T stage	1.497253	(0.8926923, 2.511243)	0.126
Race	0.9776276	(0.810782, 1.178807)	0.813
Tumor size (cm)	1.637863	(1.076864, 2.491118)	0.021
Sex	1.105136	(0.7762916, 1.573283)	0.579
Extension	0.9866813	(0.8808094, 1.105279)	0.817
Radiation	0.9831528	(0.6981763, 1.384449)	0.922
Surgery	0.6968248	(0.6052874, 0.802205)	0.000
AJCC stage	1.102177	(0.6625611, 1.833481)	0.708

Table 5: regression results of competitive risk model for PCCCL patients. 0.000 means P<0.001. PCCCL, primary clear cell carcinoma of liver; DSS, disease-specific survival; SHR, subdistribution HR; HR, hazard ratio; CI, confidence interval; AJCC, American Joint Committee on Cancer.
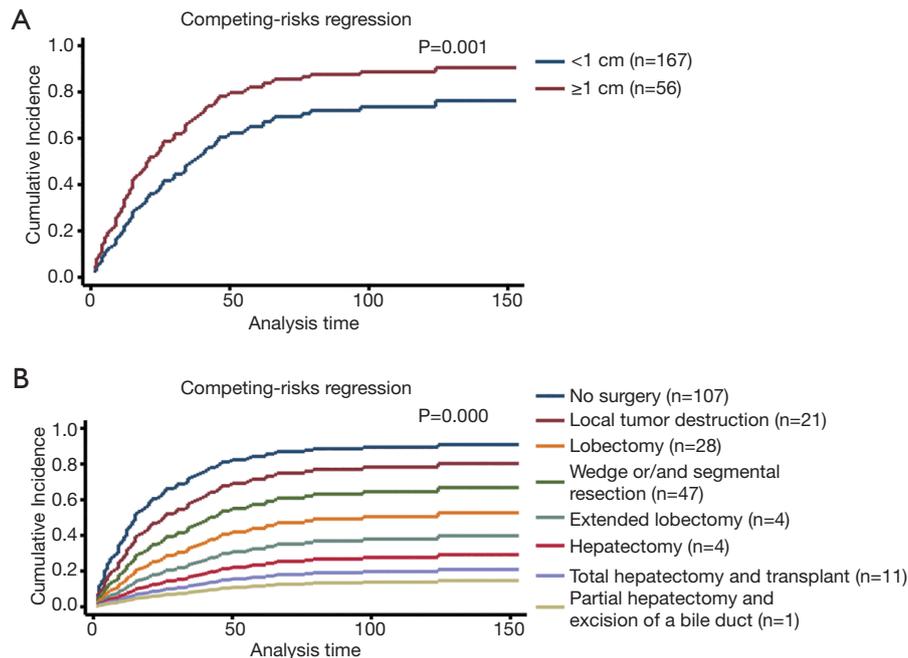
Figure 7 CIF of interesting events in PCCCL according to different clinical and pathological factors in presence of competing risks was analyzed by Gray test. (A) Different tumor size at diagnosis; (B) different surgery method. 0.000 means P<0.001. CIF, cumulative incidence function; PCCCL, primary clear cell carcinoma of liver.

staining is a distinguishing feature of PCCCL (19). Owing to the relative rareness, most studies regarding PCCCL have been case reports or small, single-institution studies, rendering the epidemiology, etiology, and pathogenesis poorly understood (20). To the best of our knowledge, the present study included the largest published cohort of PCCCL patients and was the first to characterize the clinicopathologic properties, demographic features, treatment outcomes, and prognostic factors.

PCCCL has previously been reported to have low mortality and incidence (<10% of HCC cases) (12,13,21-23). A morbidity of 8.7% has been observed in America (22). Additionally, PCCCL has been detected in 9.3% (9), and 6.7–13.3% (4,24) of the HCC patients in Japan and China, respectively. As expected, our results confirmed the rarity of PCCCL; we found that, between 2004 and 2016, 33,345 cases (data not shown) were diagnosed as single primary HCC with positive histology confirmation, and 349 of them (1.05%) were PCCCL.

In this study, the average age of PCCCL patients was 63.8 (range: 18–94) years, which was older than those reported by Liu (14) (52 years) and Lee (25) (58.8 years). Regarding sex, our study indicated a male-to-female ratio of 1.34, indicating that males were more prone than females. This observation is in agreement with previous reports (4,6). Additionally, most patients (63.2%) were of white ethnicity, reflecting the race distribution of western population. We also observed that the tumors were mostly (74.9%) <1 cm. It is extremely rare for HCC to be found in less than 1 cm in size. And it may be attributable to that PCCCL tend to have tumor capsule formation. Our observation differed from the previous observations of the high prevalence of big tumors of PCCCL [>2.1 cm (9) or 7.28 cm (14) on average]. This difference was likely due to the relatively small numbers of cases in these two previous studies (20 cases per study). Furthermore, the observations of Kida *et al.* are in agreement with ours (12,26).

In this study, more PCCCL patients were diagnosed as T1 (49.8%), N0 (96.0%), or M0 (87.4%) stage, in addition to more AJCC stage I (44.4%) or localized stage (63.7%) patients, in accordance with several studies that have shown that PCCCL tends to have less vascular invasion (4,12), lymph node metastases (14), and extra- or intrahepatic metastasis (3). This may be attributable to the high incidence of tumor capsule formation (11,27), presumably caused by the stable expression of type I and III procollagen (4,28). In line with this, our study showed that the patients without vascular invasion accounted for 63.2% of the

sample size.

The clinical prognosis of PCCCL patients remains disputed. Most studies have indicated that patients with PCCCL had better outcome than those with other subtypes of HCC (10,22,29,30). Liu *et al.* (4) have reported that PCCCL patients had a 5-year OS rate of 39% and a median OS of 40 months. Xu *et al.* (5) have suggested a good prognosis, with a 5-year OS and DSS of 58.5% of 48.6%, respectively, whereas another study (11) has estimated 35.9% and 28.1%. Even the spontaneous regression of primary and metastatic PCCCL lesions occasionally occur (19). Meanwhile, several studies have claimed that the prognosis of PCCCL is poor (9). However, the limited numbers of cases render these conclusions unreliable. Here, we observed a 5-year OS and DSS of 24.3% and 29.4%, respectively, and a median OS and DSS of 21 and 26 months. Accordingly, our findings support the former view that PCCCL patients have a relatively bad clinical outcome. Although our results are inconsistent with the mainstream, we have included 223 cases of PCCCL patients in the cohort study, reinforcing the reliability of our conclusions.

Kaplan-Meier, Cox regression analyses and the regression results of multivariate competitive risk model revealed that the increased tumor size was independently correlated with low OS and DSS rates in PCCCL patients. This association agreed with the conclusion of Chen *et al.* (11) that tumor size was a prognostic indicator for OS, disagreeing with Xu *et al.* (5), who have claimed that the Edmondson grade is the only independent risk. This difference may be attributable to the involvement of a small patient cohort (38 cases in the study of Xu *et al.*), hindering an accurate estimation.

Surgery may be the most important factor affecting the survival. Since PCCCL is more prone to forming capsules, surgical resection is an effective way to eliminate lesions containing intact capsules, thereby improving the survival (31). Surgery has been suggested to provide a long-term survival for PCCCL patients (27). Here, we found that the PCCCL patients who received no surgery had a shorter survival (median OS: 9 months; median DSS: 10 months) than those who underwent surgeries. We observed that total hepatectomy and transplant combination offered the longest survival (median OS: 124 months) for the PCCCL patients, followed by hepatectomy (median OS and DSS: both 62 months), wedge or/and segmental resection (median OS: 56 months and median DSS: 62 months) and extended lobectomy (median OS and DSS: both 41 months). And the regression results of multivariate competitive risk model also showed the similar trend. However, we found that

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partial hepatectomy along with bile duct excision offered a poor survival (median OS: 5 months) but a least risk for DSS. It may be explained that there was only one patient in this group, which would lead to deviation and cannot represent the overall level. Therefore, surgical interventions should be used as the first-line treatment.

Although surgical resection is effective in treating PCCCL, adjuvant treatments, such as radiation therapy, has increasingly been receiving attention. Radiation therapy has been reported as an important clinical application in various tumors (32). However, our results showed that radiotherapy had no significant effect on the prognosis of PCCCL patients. This observation may be due to the special pathological type of PCCCL. Similarly, traditional chemo- and radio-therapy are largely ineffective in treating any renal cell carcinoma subtype, and the underlying mechanistic reasons need to be further explored (33).

Similar with other retrospective studies using data from the SEER database, there are some limitations in our research. Firstly, the detailed chemotherapy information was not available in the database. Lack of these data is not conducive to our understanding of the treatments for PCCCL. Secondly, the patient data mainly illustrated the clinical characteristics of PCCCL in America and might not be globally applicable. Thirdly, we failed to collect the data about the proportion of clear cells and capsule formation. However, most studies indicated that capsule formation or high proportion of clear cells is beneficial to prolong the survival time (5). Fourthly, there are no data about any PCCCL-related genetic abnormalities in the SEER database. As known, oncogenic mutations or DNA abnormalities play an important role in the progression and chemo- and radio-sensitivities of various tumors (34). Aggressive morphologic features and aneuploidy have been reported to be associated with the prognosis of PCCCL (35). Clear cell HCC shows a higher frequency of IDH1 mutation, which is associated with shorter survival times (25). Lack of such information limits our full understanding of PCCCL. We should notice the limitation of patient size which should be overcome by collecting more cases for a longer time.

In conclusion, in our exploratory research on PCCCL patients, we used the SEER dataset to characterize the demographic, clinical, survival, and therapeutic features of PCCCL patients. We found that PCCCL was more common in white people and prone to be localized, early with small size and weak aggressiveness. Our study showed a relatively poorer outcome of PCCCL than previous studies. Moreover, tumor size and surgery were independent prognostic factors for the OS and DSS of the PCCCL patients. Surgery intervention could improve the outcome; however, radiotherapy failed to lengthen the survival time.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://dx.doi.org/10.21037/tcr-21-9

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/tcr-21-9). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). As the patients data in the SEER dataset are publicly available, therefore, no approval was required from any institutional review board. Informed consent was waived.

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