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Liver

Sex difference in recurrence and survival after liver resection for hepatocellular carcinoma: A multicenter study ☆,☆☆

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ABSTRACT

Background: There is a striking sex difference in the incidence of hepatocellular carcinoma, with a strong predominance for men; however, the impact of sex on the incidence of recurrence after curative resection of hepatocellular carcinoma remains controversial. This study aimed to assess sex differences in the risks of recurrence and mortality for patients treated with curative resection of hepatocellular carcinoma.

Methods: We retrospectively reviewed data from 1,435 hepatocellular carcinoma patients treated with curative resection (1,228 men and 207 women) between 2004 and 2014 at 5 institutions in China. Patients' baseline characteristics, operative variables, and rates of early recurrence (≤2 years after resection), late recurrence (>2 years after resection), and cancer-specific mortality were evaluated and compared. To clarify the true oncologic impact of sex, multivariable competing-risks regression analyses were performed to identify predictors associated with early and late recurrence, as well as cancer-specific mortality.

Results: The early recurrence rates between men and women were similar (43.3% vs 42.0%, $P = .728$), but the late recurrence and rates of cancer-specific mortality in men were greater compared with women (17.2% vs 11.2%, $P = .044$; and 42.8% vs 34.3%, $P = .022$, respectively). Multivariable competing-risks regression analyses revealed no sex difference in early recurrence; however, men had greater late recurrence rate (hazard ratio, 1.752; 95% confidence interval, 1.145–2.682; $P = .010$) and rate of cancer-specific mortality (hazard ratio, 1.307; 95% confidence interval, 1.015–1.683; $P = .038$).

Conclusion: There was no difference in early recurrence rate (≤2 years after resection between men and women, but men had significantly greater late recurrence (>2 years) and rates of cancer-specific mortality after hepatocellular carcinoma resection than women.

Introduction

Hepatocellular carcinoma (HCC) is one of the most prevalent cancers in the world, with approximately 750,000 new cases occurring annually.[1] Etiologically, infections with hepatitis B virus (HBV) and hepatitis C virus account for about 78% of worldwide cases of HCC.[2] In China, HCC is the third and fourth leading causes of cancer-related death among men and women, respectively.[3] Re-

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gardless of geographic area, etiologic factors, ethnicities, and predisposing factors, a striking sex disparity in the incidence of HCC has been consistently identified, with men found to be 3 to 8 times more likely to develop the disease than women.[4,5] Apart from sex differences in health-related behaviors, such as cigarette smoking and alcohol consumption, sex hormones are considered to be partially responsible for this sex gap in the incidence of HCC, although the exact underlying mechanisms are not fully understood.[6-12] Recently a large case-control study revealed that the use of estrogen menopause hormone therapy could decrease the risk of HCC incidence and increase overall survival in female patients with HCC.[13]

Liver resection is the mainstay of curative treatment for HCC with appropriate candidate selection,[14] but the high incidence of postoperative recurrence remains a major issue even after curative resection of HCC.[15-38] Approximately 70% of patients with HCC develop recurrence, generally in the hepatic remnant, within 5 years after curative resection.[15,16,36] HCC has 2 clear patterns of recurrence: (1) early recurrence ($\leq$2 years after resection) as a result of occult metastasis or microscopic dissemination of the original tumor, and (2) late recurrence or de novo tumors ($>$2 years after resection) possibly as a result of new malignant clones.[15,36,39,40] Many previous studies have reported consistently that early recurrence is likely to be associated with aggressive pathologic factors of the neoplasm, such as large tumor size, multiple tumors, poor differentiation, macro- and microvascular invasion, and satellite lesions, whereas late recurrence is more likely related to underlying liver conditions, such as presence of cirrhosis and active hepatitis.[16-24] Differentiation of the 2 has potential implications on the strategies of surveillance, prevention, and management of HCC recurrence.[36]

The impact of sex on HCC recurrence after curative resection remains controversial. A few studies indicated that women have a lower rate of tumor recurrence and better disease-free survival than men, but the authors explained that these differences might be attributed to the baseline disparities of the enrolled patients and distinct oncologic characteristics by sex.[41–43] The majority of previous studies on recurrence after resection of HCC, however, failed to reveal a close correlation between sex and recurrence using univariable and multivariable analyses.[17–22,25–33] What is noteworthy in these studies is that, first, most of the studies had a small sample size ($<$200 enrolled patients) or came from a single center; second, most of the studies did not account for the different mechanisms of early and late recurrences after resection of HCC; and third, almost all the studies did not take into account the competing risk events (ie, patient mortality preceding recurrence), which was predominantly caused by hepatic deterioration or upper gastrointestinal hemorrhage as a result of severe liver cirrhosis.

To address these issues, using a multivariable competing-risks regression method we conducted a large, multicenter study to clarify the true impact of sex on the rates of early and late recurrences and cancer-specific mortality (CSM) in patients treated with curative resection of HCC.

Methods

Patient selection

With approval of the Institutional Review Boards at each of the institutions, we retrospectively analyzed 2,059 patients who underwent resection of HCC with curative intent from January 2004 to December 2014 in the following 5 medical centers in China: Eastern Hepatobiliary Surgery Hospital, Ziyang First People's Hospital, Pu'er People's Hospital, Liuyang People's Hospital, and Fourth Hospital of Harbin. Patients were considered for resection if they had resectable tumors, an adequate size of the liver remnant taking into account their liver metabolic function, and absence of any distant metastasis. All patients in this study underwent a primary R0 liver resection, which was defined as curative resection. Patients with recurrent HCC ($n=287$), ruptured HCC ($n=81$), fibrolamellar HCC ($n=5$), or combined HCC-cholangiocarcinoma ($n=59$) were excluded. From consecutive patients who underwent HCC resection, we excluded patients who had microscopically positive margins (R1 liver resection, $n=75$), grossly positive margins (R2 liver resection, $n=32$), or unknown margins ($n=28$). Because this study focused on the long-term outcomes, we also excluded patients with perioperative death ($n=18$) or who were lost to follow-up within 90 days after resection ($n=39$). Finally, the data of the remaining 1,435 patients were analyzed. The database was closed in December 2016. Informed consent for clinical analyses was obtained from each patient at each institution involved, and all the analyses were performed in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical Studies of the Eastern Hepatobiliary Surgery Hospital of Shanghai.

Clinicopathologic variables

The medical records were reviewed for clinicopathologic variables including sex, age at resection, body mass index, cigarette smoking, alcohol consumption, hypertension, diabetes mellitus, cause of liver diseases, Child-Pugh grading, preoperative α-fetoprotein (AFP) level, and presence of cirrhosis or portal hypertension. Cirrhosis was confirmed by histopathologic examination. Portal hypertension was defined by the presence of either esophageal varices or splenomegaly with a decreased platelet count ($\leq 100\times10^9$/L). *Smoking* refers to patient-reported use of any cigarette products of $\geq$1 pack daily and *alcohol consumption* refers to the intake of 1 drink (as of 0.6 fl oz or 14 g of pure alcohol) daily of any form of alcohol. Tumor pathologic data included maximum tumor size, presence of multiple tumors or satellite lesions, macroscopic or microscopic vascular invasion, and tumor differentiation. Operative variables included intraoperative blood loss, need for intraoperative blood transfusion, extent of hepatectomy, and type of liver resection. Major hepatectomy was defined as resection of 3 or more Couinaud liver segments, and minor hepatectomy as resection of fewer than 3 segments. Anatomic resections were defined by the Brisbane 2000 nomenclature of liver anatomy and resections,[44] whereas nonanatomic resections included wedge resection or limited resection.

Patient follow-up

Patients were prospectively followed at each of the participating institutions. The postoperative surveillance strategy for recurrence consisted of a physical examination, serum AFP level, ultrasonography, contrast-enhanced computed tomography (CT), or magnetic resonance imaging (MRI) of the chest and abdomen at 2-month intervals for the first half year, at 3-month intervals thereafter for the next 1.5 years, and once every 6 months at 2 years or later after resection at each institution. CT, MRI, angiography, bone scan, or positron emission tomography were performed when recurrence or distant metastasis was suspected. Tumor recurrence was defined as new appearance of intra- or extrahepatic tumor nodule(s), with or without an increase in serum AFP level, and we divided recurrences into early and late recurrences, setting 2 years as the cutoff between early and late phases. Treatment of recurrence was based on the pattern of recurrent tumor, residual hepatic functional reserve, and general condition of the patient, and included re-resection, liver transplantation, local ablation therapy, transcatheter arterial chemoembolization, oral sorafenib, radiotherapy, or supportive therapy. The dates of initial recurrence, last follow-up, and mortality, as well as initial sites of recurrence

Table 1
Comparisons of patient baseline characteristics and operative variables between men and women.

N *(%)*	*Total* (N = *1435*)	*Men* (N = *1228*)	*Women* (N = *207*)	P
Age, y*	51.7 ± 11.3	51.6 ± 11.2	52.1 ± 12.3	.539
Cigarette smoking	430 (30.0)	425 (34.6)	5 (2.4)	<.001
Alcohol consumption	258 (18.0)	253 (20.6)	5 (2.4)	<.001
Hypertension	170 (11.8)	145 (11.8)	25 (12.1)	.908
Diabetes mellitus	86 (6.0)	72 (5.9)	14 (6.8)	.634
BMI, kg/m^2*	24.0 ± 3.4	23.9 ± 3.4	24.1 ± 3.5	.475
ASA score				
≤2	1,278 (89.1)	1,096 (89.3)	182 (87.9)	.549
>2	157 (10.9)	132 (10.7)	25 (12.1)	
HBsAg (+)	1,292 (90.0)	1,107 (90.1)	185 (89.4)	.708
Anti-HCV (+)	46 (3.2)	36 (2.9)	10 (4.8)	.196
Cirrhosis	977 (68.1)	842 (68.6)	135 (65.2)	.335
Portal hypertension	381 (26.6)	333 (27.1)	48 (23.2)	.269
Child-Pugh grade				
A	1,306 (91.0)	1,116 (90.9)	190 (91.8)	.793
B	129 (9.0)	112 (9.1)	17 (8.2)	
Preoperative serum AFP level				
≤400 ug/L	882 (61.5)	760 (61.9)	122 (58.9)	.440
>400 ug/L	553 (38.5)	468 (38.1)	85 (41.1)	
Maximum tumor size, cm*	6.5 ± 4.1	6.5 ± 4.1	6.4 ± 4.4	.919
≤5 cm	693 (48.3)	591 (48.1)	102 (49.3)	.764
>5 cm	742 (51.7)	637 (51.9)	105 (50.7)	
Tumor number				
Solitary	1,046 (72.9)	894 (72.8)	152 (73.4)	.933
Multiple	389 (27.1)	334 (27.2)	55 (26.6)	
Macroscopic vascular invasion	195 (13.6)	174 (14.2)	21 (10.1)	.128
Microscopic vascular invasion	892 (62.2)	764 (62.2)	128 (61.8)	.938
Satellite lesions	422 (29.4)	363 (29.6)	59 (28.5)	.805
Poor differentiation	1,092 (76.1)	938 (76.4)	154 (74.3)	.822
Intraoperative blood loss, mL*	350 (30–8,000)	350 (30–8,000)	350 (50–3,500)	.415
Intraoperative blood transfusion	357 (24.9)	310 (25.2)	47 (22.7)	.487
Extent of hepatectomy				
Major hepatectomy	461 (32.1)	399 (32.5)	62 (30.0)	.520
Minor hepatectomy	974 (67.9)	829 (67.5)	145 (70.0)	
Type of resection				
Anatomic	589 (41.0)	500 (40.7)	89 (43.0)	.542
Nonanatomic	846 (59.0)	728 (59.3)	118 (57.0)	

* Values are mean ± standard deviation or median (range) unless otherwise indicated.
ASA, American Society of Anesthesiologists; *BMI,* body mass index; *HBsAg,* hepatitis B surface antigen; *HCV,* hepatitis C virus.

(intrahepatic or extrahepatic) and causes of mortality (CSM or non-CSM) were also recorded. The main causes of non-CSM included hepatic deterioration or upper gastrointestinal hemorrhage as a result of severe liver cirrhosis and cardiovascular or cerebrovascular accidents.

Statistical analysis

Patient baseline characteristics and operative variables between male and female patients were summarized using frequency and percentage for categorical covariates and mean ± standard deviation or median (range) for continuous covariates. Categorical and continuous covariates were compared using the Fisher exact test and Wilcoxon rank sum test, respectively. The primary outcome of this study were the incidences of early and late recurrences, and the secondary outcome was the incidence of CSM. To clarify the true oncologic impact of sex, we used the Fine and Gray subdistribution hazard regression model,[45,46] one of the most recognized multivariable competing-risks regression methods, to identify predictors of early and late recurrences, taking into account the competing risk of patient mortality before detection of recurrence. Likewise, we repeated this competing-risks analysis to identify predictors of CSM, accounting for the competing risk of non-CSM. Those variables found significant at $P < .1$ in univariable analyses were entered into multivariable competing-risks regression models. Because sex was a major concern in this study, it was forced into the model all along. When considering the issue of late recurrence, those patients who had developed early recurrence or died at 2 years after resection were excluded from the corresponding analysis population. In other words, the predictors of late recurrence were identified among those patients who were recurrence free and alive at 2 years after resection of HCC. Statistical analyses were performed using SPSS Software Version 22.0 (IBM Corp, Armonk, NY) or R Version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria). *P* values were 2-sided.

Results

Clinical and pathologic characteristics

A total of 1,435 patients who underwent curative liver resection for HCC were included in this cohort study, including 1,228 men (85.6%) and 207 women (14.4%). The median age at resection for these patients was 51 years (range, 15–86 years). The majority of patients (90.0%) had chronic HBV infection, and only 46 patients (3.2%) had chronic hepatitis C virus infection. Nearly 70% of patients had cirrhosis, and 26.6% were accompanied with portal hypertension. The comparisons of patients' baseline characteristics and operative variables between the men and the women are illustrated in Table 1. Except for a greater likelihood of cigarette smoking and alcohol consumption in men, there were no differences in any of these variables between men and women, suggesting a balance of patient clinicopathologic features between sexes (all $P > .1$).

Table 2
Comparisons of long-term outcomes between men and women.

N *(%)*	*Total* (N = *1435)*	*Men* (N = *1228)*	*Women* (N = *207)*	P
Duration of follow-up, months*	46.0 ± 32.0	45.4 ± 31.3	49.3 ± 36.0	.108
Recurrence during the follow-up	854 (59.5)	740 (60.3)	114 (55.1)	.160
Early recurrence (within 2 y)	619 (43.1)	529 (43.1)	90 (43.5)	.914
Later recurrence (beyond 2 y)	235 (16.4)	211 (17.2)	24 (11.2)	.044
Initial recurrence site				
Intrahepatic	732 (51.0)	639 (52.0)	93 (44.9)	.822
Extrahepatic	21 (1.5)	18 (1.5)	3 (1.4)	
Intrahepatic and extrahepatic	101 (7.0)	86 (7.0)	15 (7.2)	
Mortality during the follow-up	746 (52.0)	648 (52.8)	98 (47.3)	.148
CSM	596 (41.5)	525 (42.8)	71 (34.3)	.022
Non-CSM	150 (10.5)	123 (10.0)	27 (13.0)	.218

* Values are mean ± standard deviation.

Table 3
Univariable and multivariable competing-risks regression models predicting early recurrence in 1,435 patients treated with curative resection of hepatocellular carcinoma.

Variables	*HR comparison*	*UV HR (95% CI)*	*UV* P	*MV HR (95% CI)*	*MV* P*
Sex	Male versus female	1.050 (0.837–1.317)	.673	NS	.677
Age	≤60 y vs >60 y	0.963 (0.796–1.165)	.700		
Cigarette smoking	Yes versus no	1.309 (0.713–2.422)	.384		
Alcohol consumption	Yes versus no	1.128 (0.833–1.567)	.473		
Hypertension	Yes versus no	1.197 (0.863–1.660)	.280		
Diabetes mellitus	Yes versus no	1.269 (1.068–1.507)	.024	NS	.349
BMI	≤30.0 vs >30.0 kg/m^2	1.211 (0.910–1.478)	.108		
ASA score	≤2 vs >2	0.975 (0.645–1.494)	.878		
HBsAg (+)	Yes versus no	1.048 (0.805–1.365)	.726		
Anti-HCV (+)	Yes versus no	1.282 (0.929–1.737)	.123		
Cirrhosis	Yes versus no	1.114 (0.939–1.323)	.215		
Child-Pugh grade	A versus B	1.224 (0.940–1.595)	.133		
Preoperative AFP level	≤400 ug/L vs >400 ug/L	1.887 (1.611–2.210)	<.001	1.354 (1.149–1.596)	<.001
Maximum tumor size	≤5 cm vs >5 cm	2.819 (2.379–3.341)	<.001	1.885 (1.570–2.264)	<.001
Tumor number	Solitary versus multiple	2.112 (1.794–2.488)	<.001	1.396 (1.161–1.678)	<.001
Macroscopic vascular invasion	Yes versus no	2.333 (1.982–2.746)	<.001	1.442 (1.206–1.725)	<.001
Microscopic vascular invasion	Yes versus no	2.532 (2.106–3.045)	<.001	1.574 (1.286–1.928)	<.001
Satellite lesions	Yes versus no	2.449 (2.085–2.876)	<.001	1.808 (1.530–2.137)	<.001
Tumor differentiation	Well versus poor	1.688 (2.375–2.073)	<.001	NS	.269
Intraoperative blood loss	≤400 mL vs >400 mL	1.918 (1.637–2.247)	<.001	NS	.104
Intraoperative blood transfusion	Yes versus no	2.039 (1.724–2.412)	<.001	1.384 (1.161–1.648)	<.001
Extent of hepatectomy	Major versus minor	2.226 (1.896–2.612)	<.001	NS	.493
Type of resection	Anatomic versus nonanatomic	1.128 (0.962–1.323)	.137		

* Those variables found significant at $P < .1$ in univariable analyses and sex were entered into multivariable competing-risks regression models.
ASA, American Society of Anesthesiologists; *BMI,* body mass index; *HBsAg,* hepatitis B surface antigen; *HCV,* hepatitis C virus; *MV,* multivariable; *NS,* not significant; *UV,* univariable.

Recurrence and survival

During a median follow-up of 46.0 months, recurrence was identified in 854 patients (59.5%), among whom 619 patients (43.1%) had early and 235 (16.4%) late recurrences. First recurrence was intrahepatic ($n = 833$, 97.5%), without or with extrahepatic metastases ($n = 732$, 85.7%, and $n = 101$, 11.8%, respectively). Extrahepatic metastases without intrahepatic recurrence was only found in 21 patients (1.5%). Overall, 746 patients (52.0%) died during the follow-up period, 596 (41.5%) as a result of cancer and 150 (10.5%) of other causes (hepatic failure = 84, upper gastrointestinal hemorrhage = 36, miscellaneous = 30). In the entire cohort, the 1-, 3-, and 5-year overall survival (OS) and recurrence-free survival (RFS) rates were 83.8%, 60.2%, and 51.0%, and 64.0%, 42.7%, and 34.2%, respectively.

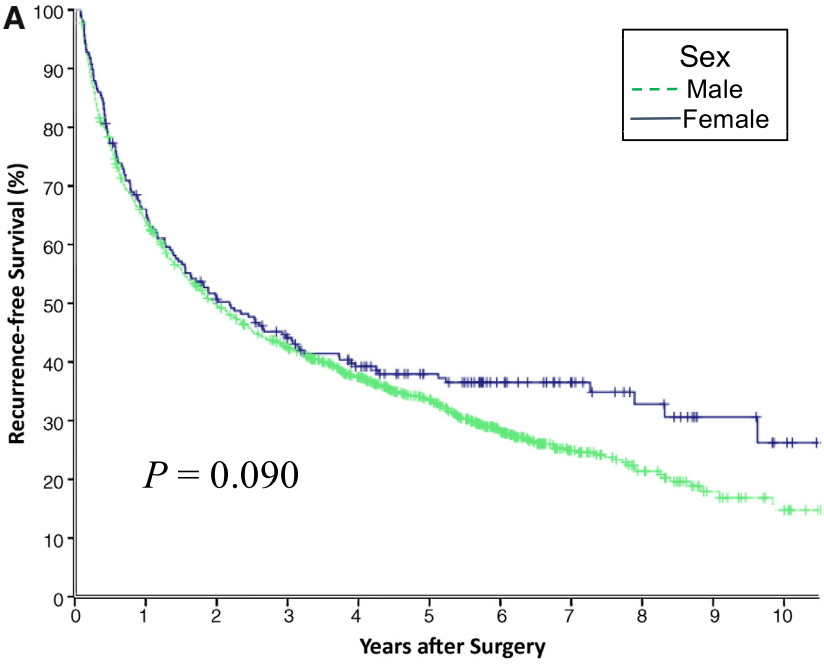
As shown in Table 2, there were no significant differences in overall and early recurrence rates between men and women (60.3% vs 55.1%, $P = .160$, and 43.1% vs 43.5%, $P = .914$, respectively), but the late recurrence rate in men was greater than that in women (17.2% vs 11.2%, $P = .044$). There were no significant differences in overall mortality and non-CSM between men and women (52.8% vs 47.3%, $P = .148$, and 10.0% vs 13.0%, $P = .218$, respectively), but men had a greater CSM than women (42.8% vs 34.3%, $P = .022$).

Comparisons of overall and recurrence-free survival curves by sex are shown in Fig 1. The 1-, 3-, and 5-year OS in men and women were 83.5%, 60.0%, and 50.4% vs 85.3%, 61.4%, and 55.0%, respectively, and there was no significant difference between them (hazard ratio [HR], 1.147; 95% confidence interval [CI], 0.946–1.448, $P = .146$). The 1-, 3-, and 5-year RFS in men and women were 63.7%, 42.5%, and 33.6% vs 66.0%, 44.1%, and 38.0%, respectively, but there was a trend toward a better RFS in women (HR, 1.172; 95% CI, 0.975–1.409, $P = .090$).

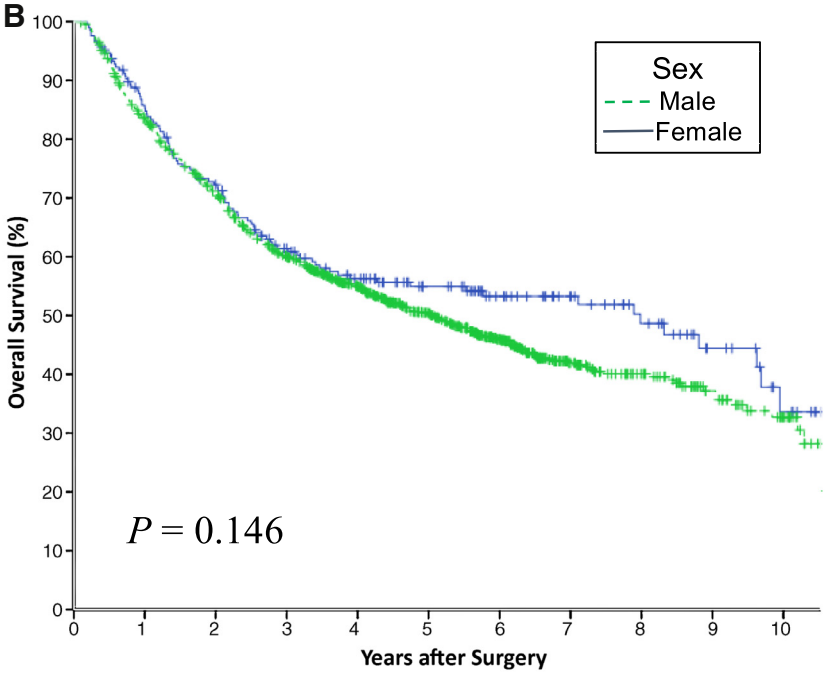
Multivariable analyses in predicting early and late recurrences

Table 3 depicts the univariable and multivariable competing-risks regression models to identify predictors of early recurrence in all the 1,435 patients who had been treated with curative resection of HCC. No significant differences were found in the cumulative incidences of early recurrence between men and women on multivariable analysis (HR, 1.032; 95% CI, 0.821–1.296, $P = .677$). Figure 2, *A,* presents the sex-stratified cumulative incidences of early recurrence obtained by competing-risks regression model.

Table 4 depicts the univariable and multivariable competing-risks regression models in identifying predictors of late recurrence in 697 patients who were alive and recurrence free at 2 years



Patients at risk	Total	1yr	2yrs	3yrs	4yrs	5yrs	6yrs	7yrs	8yrs	9yrs	10yrs
The male group	1228	775	592	492	383	287	164	74	41	17	6
The female group	207	134	102	83	68	52	36	25	16	8	4



Patients at risk	Total	1yr	2yrs	3yrs	4yrs	5yrs	6yrs	7yrs	8yrs	9yrs	10yrs
The male group	1228	1009	838	684	550	419	271	129	85	49	24
The female group	207	171	142	112	94	74	55	41	30	17	8

Fig 1. Recurrence-free (A) and overall survival (B) curves comparisons between the male and female groups.

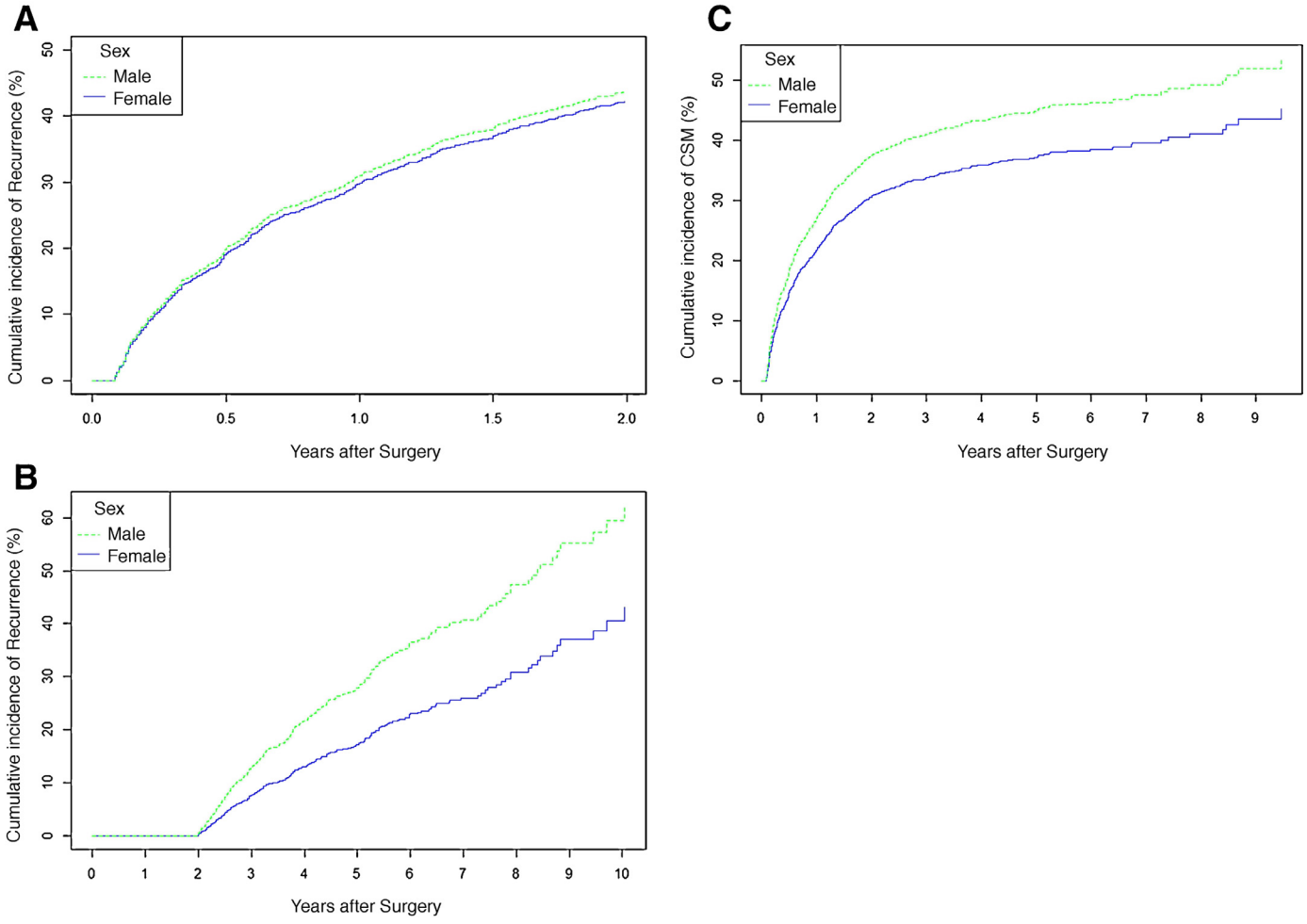


Fig 2. Cumulative incidence of (A) early recurrence (≤2 years after resection), (B) late recurrence (>2 years after resection), and (C) cancer-specific mortality (CSM) from competing-risk model stratified by sex.

Table 4
Univariable and multivariable competing-risks regression models predicting late recurrence in 697 patients who were recurrence-free and alive at 2 years after curative resection of hepatocellular carcinoma.

Variables	*HR comparison*	*UV HR (95% CI)*	*UV* P	*MV HR (95% CI)*	*MV* P*
Sex	Male versus female	1.759 (1.150–2.688)	.009	1.752 (1.145–2.682)	.010
Age	≤60 y vs >60 y	1.108 (0.744–1.391)	.913		
Cigarette smoking	Yes versus no	1.121 (0.965–1.304)	.136		
Alcohol consumption	Yes versus no	1.128 (0.833–1.567)	.473		
Hypertension	Yes versus no	1.214 (0.847–1.691)	.247		
Diabetes mellitus	Yes versus no	1.288 (0.977–1.790)	.108		
BMI	≤30.0 vs >30.0 kg/m^2	1.542 (0.928–2.560)	.090	NS	.712
ASA score	≤2 vs >2	1.079 (0.740–1.581)	.706		
HBsAg (+)	Yes versus no	0.960 (0.634–1.454)	.847		
Anti–HCV (+)	Yes versus no	2.138 (1.245–3.672)	.013	NS	.542
Cirrhosis	Yes versus no	1.452 (1.086–1.941)	.012	1.366 (1.017–1.834)	.038
Child-Pugh grade	A versus B	1.500 (0.926–2.428)	.099	NS	.516
Preoperative AFP level	≤400 ug/L vs >400 ug/L	1.095 (0.939–1.462)	.214		
Maximum tumor size	≤5 cm vs >5 cm	1.411 (1.087–1.831)	.010	1.305 (1.008–1.706)	.048
Tumor number	Solitary versus multiple	1.592 (1.164–2.177)	.004	1.462 (1.066–2.006)	.019
Macroscopic vascular invasion	Yes versus no	1.559 (1.138–2.136)	.006	NS	.139
Microscopic vascular invasion	Yes versus no	1.523 (1.175–1.974)	.001	1.381 (1.057–1.804)	.018
Satellite lesions	Yes versus no	1.516 (1.101–2.087)	.011	NS	.208
Tumor differentiation	Well versus poor	1.507 (1.116–2.036)	.007	NS	.129
Intraoperative blood loss	≤400 mL vs >400 mL	1.119 (0.851–1.471)	.421		
Intraoperative blood transfusion	Yes versus no	1.533 (1.107–2.122)	.010	NS	.149
Extent of hepatectomy	Major versus minor	1.396 (1.037–1.878)	.028	NS	.578
Type of resection	Anatomic versus nonanatomic	1.162 (0.890–1.518)	.271		

* Those variables found significant at $P < .1$ in univariable analyses and sex were entered into multivariable competing-risks regression models.

ASA, American Society of Anesthesiologists; *BMI*, body mass index; *HBsAg*, hepatitis B surface antigen; *HCV*, hepatitis C virus; *MV*, multivariable; *NS*, not significant; *UV*, univariable.

Table 5
Univariable and multivariable competing-risks regression models predicting cancer-specific mortality (CSM) in 1,435 patients treated with curative resection of hepatocellular carcinoma.

Variables	*HR comparison*	*UV HR (95% CI)*	*UV* P	*MV HR (95% CI)*	*MV* P*
Sex	Male versus female	1.287 (1.006–1.647)	.045	1.307 (1.015–1.683)	.038
Age	≤60 y vs >60 y	0.796 (0.648–0.976)	.029	NS	.442
Cigarette smoking	Yes versus no	1.193 (0.964–1.649)	.183		
Alcohol consumption	Yes versus no	1.128 (0.933–1.667)	.193		
Hypertension	Yes versus no	1.214 (0.847–1.691)	.247		
Diabetes mellitus	Yes versus no	1.170 (0.967–0.424)	.121		
BMI	≤30.0 vs >30.0 kg/m^2	0.825 (0.679–1.003)	.054	NS	.138
ASA score	≤2 vs >2	1.063 (0.860–1.315)	.830		
HBsAg (+)	Yes versus no	0.889 (0.678–1.175)	.370		
Anti-HCV (+)	Yes versus no	1.021 (0.627–1.660)	.935		
Cirrhosis	Yes versus no	1.111 (0.932–1.324)	.242		
Child-Pugh grade	A versus B	1.411 (1.086–1.833)	.010	NS	.508
Preoperative AFP level	≤400 ug/L vs >400 ug/L	2.022 (1.722–2.375)	<.001	1.422 (1.204–1.681)	<.001
Maximum tumor size	≤5 cm vs >5 cm	3.143 (2.641–3.741)	<.001	1.917 (1.587–2.314)	<.001
Tumor number	Solitary versus multiple	2.475 (2.098–2.921)	<.001	1.374 (1.058–1.783)	<.001
Macroscopic vascular invasion	Yes versus no	2.581 (2.188–3.044)	<.001	1.479 (1.233–1.773)	<.001
Microscopic vascular invasion	Yes versus no	2.765 (2.284–3.346)	<.001	1.582 (1.282–1.952)	<.001
Satellite lesions	Yes versus no	2.816 (2.392–3.316)	<.001	1.570 (1.209–2.040)	<.001
Tumor differentiation	Well versus poor	2.281 (1.814–2.867)	<.001	1.356 (1.066–1.725)	<.001
Intraoperative blood loss	≤400 mL vs >400 mL	2.082 (1.772–2.446)	<.001	NS	.657
Intraoperative blood transfusion	Yes versus no	2.576 (2.179–3.044)	<.001	1.660 (1.394–1.977)	<.001
Extent of hepatectomy	Major versus minor	2.568 (2.185–3.019)	<.001	NS	.252
Type of resection	Anatomic versus nonanatomic	1.007 (0.855–1.186)	.934		

* Those variables found significant at $P < .1$ in univariable analyses and sex were entered into multivariable competing-risks regression models.
ASA, American Society of Anesthesiologists; *BMI,* body mass index; *HBsAg,* hepatitis B surface antigen; *HCV,* hepatitis C virus; *MV,* multivariable; *NS,* not significant; *UV,* univariable.

after resection. Multivariable analysis indicated that men had a greater cumulative incidence of late recurrence than women (HR, 1.759; 95% CI, 1.145–2.682; $P = .010$). Figure 2, *B,* presents the sex-stratified cumulative incidence of late recurrence obtained by the competing-risks regression model.

Multivariable analyses in predicting CSM

The univariable and multivariable competing-risks regression models in identifying predictors of CSM after curative resection of HCC are shown in Table 5. Multivariable analysis indicated a greater cumulative incidence of CSM in men than in women (HR, 1.307; 95% CI, 1.015–1.683; $P = .038$). Figure 2, *C,* presents the sex-stratified cumulative incidence of CSM obtained by the competing-risks regression model.

Discussion

Differences in patient characteristics, candidate selection, and surgical practice of liver resection for HCC have been widely acknowledged between Eastern and Western centers.[47–49] In this Chinese multicenter cohort of patients undergoing liver resection for HCC, HBV-related HCC was the predominant type of HCC, which is distinctly different from the disease pattern in the United States and Europe. Moreover, a considerable proportion of surgical patients in our cohort had intermediate or advanced HCCs (eg, large tumors, multiple tumors, and gross or macroscopic vascular invasion) or had Child-Pugh grade B liver function or concurrent portal hypertension, which also differs markedly from their Western counterparts. In this multicenter study we analyzed the sex difference in postoperative recurrence and mortality in patients treated with curative resection of HCC. Considering the different mechanisms and risks of recurrence at different stages, we divided tumor recurrence into 2 patterns: early (≤2 years after resection) and late recurrences (>2 years after resection). Competing-risks analyses among our patients from a large multicenter cohort revealed that compared with women, men had a significantly greater late recurrence rate, which was often attributed to multicentric origins of HCC. The sex difference in late recurrence echoes the fact that the incidence of HCC is greater in men than in women. Furthermore, our study also identified that the CSM, other than the overall mortality or non-CSM, was significantly greater in men than in women. To our knowledge, no previous studies have compared the patterns of postoperative mortality after HCC resection between the different sexes.

In contrast to previous studies,[35,41–43] a significant difference in RFS between men and women was not found in our study, despite there a trend toward poorer RFS in men on univariable analysis (HR, 1.172; 95% CI, 0.975–1.409, $P = .090$). As shown in Fig 1, *A,* the RFS curves of men and women were very close to each other in the early follow-up period, but they gradually separated with time in the late follow-up period. The RFS at 8 years after resection was 36.5% in women compared with 25.0% in men. Taking into account the different mechanisms between early and late recurrences of HCC, different rates for late recurrence in men and women are expected. We therefore performed further analyses for early and late recurrences, and the results verified our initial hypothesis. In addition, the use of multivariable competing-risks models further supports the hypothesis of this study.

In the present study, aside from the difference in certain health-related lifestyles (cigarette smoking and alcohol consumption), no significant difference was found in baseline characteristics and operative variables between men and women. After adjustment, patient sex remained an independent risk factor for late recurrence, which might support the previous findings that difference in the probability of late recurrence with multiclonal carcinogenesis is derived from other factors such as sex hormone.[6–12]

Our findings provided further evidence for formulation of an optimum follow-up strategy after HCC resection. Currently, most centers are adopting imaging tests, such as regular ultrasonography or contrast CT or MRI with or without AFP testing, as their follow-up tests, but with distinctly varying time intervals. Cautious centers would ask their patients to undergo follow-up once a month or once every 2 months within the first 6 months after operation because almost half of tumor recurrences occur within the first year after resection of the primary HCC. Meanwhile, because some

of the initial HCCs are detected early and the risk of recurrence after resection is low, there is no need for these patients with early HCC to undergo such stringent follow-up programs. Previous studies have reported considerable differences in independent risk factors for early and late recurrences.[16–24] Thus we suggest that an individualized postoperative follow-up program be established considering the following issues: (1) whether the patient is at high risk of early or late recurrences; (2) the number of risk factors and the relevant hazard ratio of the patient, and (3) the duration between the follow-up and the patient's initial operation ($\leq$ or $>$2 years after resection). To date, no adjuvant therapies have been accepted universally to prevent tumor recurrence after curative resection of HCC. The present study could offer useful guidance to clinicians and patients to tailor an individualized follow-up program and plan adjuvant therapy trials for high-risk patients.

All the involved centers of this study practice a relatively stringent follow-up program for patients in the first 2 years after resection (once every 1–2 months). After this time, because the risk of subsequent tumor recurrence is significantly less, a less stringent follow-up scheme is then used (once every 3–6 months). The most notable finding of this multicenter study is that men have a greater rate of late but not early recurrence than women. This finding calls for close monitoring for men in the late period of postresection follow-up, which has also been proposed by Cucchetti et al.[23] Consistent with our study, cirrhosis has also been identified as an independent risk factor for late HCC recurrence after resection in many other studies.[18–21,37,38] Interestingly, unlike other studies,[18-20,36,37] we found that large tumor size, multiple tumors, and microscopic vascular invasion were also independent predictors of late, as well as early, recurrences on multivariable competing-risks analyses. This observation raises questions about whether using 2 years after resection of the initial HCC as a cutoff point of early and late recurrences is justifiable based on the assumptions that early recurrence is more likely due to metastasis or residual tumor and late recurrence is more likely due to formation of new malignant clones.[23,36,40] For patients with poor tumor features, even if they are free of early recurrence, they are still at high risk of late recurrence. Thus a more stringent postoperative follow-up strategy is needed for these patients. We will work in our future studies to develop a predictive model for late HCC recurrence, based on the risk factors and their corresponding hazard ratios as identified in this study, in an attempt to identify HCC patients who require a stringent long-term postoperative follow-up program.

Notably, only 21 of the 1,435 patients in this study (1.5%) had their tumor recurrence first detected as isolated extrahepatic metastatic lesions, and all these recurrences occurred in the early follow-up period. In other words, all the late recurrences were intrahepatic recurrences with or without extrahepatic metastases. Consequently, modalities to detect extrahepatic metastasis, such as pulmonary CT and skeletal emission CT, are unnecessary in patients who are already free of early recurrence.

Animal models of liver carcinogenesis and epidemiologic studies in humans have suggested close associations between sex hormones and HCC, and previous studies have reported that sex disparities on the incidences of HCC can be attributed to the protective role of estrogen and the upregulation of androgen receptors.[4–12] No information regarding the possible impacts of menopause and the use of estrogen replacement in women on recurrence, however, was available, because these data were not included in the database sheet used for this multicenter study. We will consider the inclusion of such information in our future studies.

In conclusion, this large multicenter study found that men have a significantly greater late recurrence rate ($>$2 years) after curative resection of HCC than women, although the difference in early recurrence rates ($\leq$2 years after resection) was not significant between men and women. In addition, men had significantly poorer cancer-specific survival after curative resection of HCC than women. Our findings suggest that it is necessary to define an individually planning surveillance strategy with various follow-up intervals based on patient sex and other risk factors for patients treated with HCC resection. Meanwhile, it also suggests that further research and trials are warranted to evaluate potential value of sex hormone treatment as an adjuvant therapy for the prevention of HCC recurrence in the future.

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