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ORIGINAL RESEARCH

Incidence, risk factors, and prognosis in patients with primary hepatocellular carcinoma and lung metastasis: a population-based study

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Aims: The study aims to explore the incidence, risk factors, and prognosis in patients with primary hepatocellular carcinoma (HCC) and synchronous lung metastasis using a large-scale population-based cancer registry database.

Patients and methods: Data of 33,177 HCC patients were retrieved from the Surveillance, Epidemiology, and End Results (SEER) database from 2010 to 2015. Multivariate logistic and Cox regression model analysis were applied for the recognition of risk factors and prognostic factors associated with lung metastasis among HCC patients. The overall survival and cancer-specific survival of HCC patients with initial pulmonary metastasis were estimated by Kaplan–Meier analysis, and the survival curves were compared by log-rank tests.

Results: Total 2,084 (6.28%) HCC patients diagnosed with initial pulmonary metastasis were enrolled for analysis. Male gender, younger age, non-white race, unmarried status, uninsured status, elevated alpha-fetoprotein, larger primary liver tumor size, positive lymph node status, synchronal bone or brain metastasis, and tumor poor pathological differentiation were relevant to higher risk of lung metastasis in HCC cohort. The 1-, 3-, 5-year overall survival and cancer-specific survival rates for HCC lung metastasis patients were 12.8% vs 15.3%, 4.0% vs 5.7%, and 1.6% versus 2.4%, respectively. The median overall and cancer-specific survival time in HCC lung metastasis group were both 3 months, while the corresponding time in HCC lung metastasis-free group were 19 and 25 months (P<0.05). Older age, unmarried status, poor tumor differential grade, and absence of surgery were identified as unfavorable prognosis factors.

Conclusion: The survival of patients with HCC lung metastasis was dismal. Several clinicopathological factors were found to be significantly relevant to the development and prognosis of HCC lung metastasis. These new findings could be useful for a precise and individualized therapeutic schedule.

Keywords: liver cancer, lung metastasis, risk factor, prognosis factor, SEER

Introduction

Hepatocellular carcinoma (HCC) is the most frequent subtype of primary liver cancer with high lethality.[1] Recent statistical data demonstrated that the 5-year survival rate of HCC is still below 20%.[2,3] One of reasons responsible for high mortality is the extrahepatic spread of primary tumor loci with partly elucidated mechanism.[4,5] Till now, lung is considered as the most favored organ for HCC metastatic colonization, counting for 51% of all extrahepatic metastasis.[6] Result from a large-scale population study showed that the 1-year overall survival (OS) and cancer-specific survival (CSS) was 10% and 12.6% in patients diagnosed with HCC lung metastasis (HCCLM).[7]

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Previously, HCC initiated with lung metastasis was regarded as the late stage of disease with poor survival.[1] With the conceptual update in treatment modalities, new attempts, such as simultaneous hepatectomy and pulmonary metastasectomy, have been made by surgeons in selected individuals to achieve a better survival.[8–10] In addition, Yang et al elucidated that patients receiving combined treatment had a better survival by analyzing 76 consecutive HCC patients initially presenting with lung metastasis.[11] However, primary and secondary prevention strategies also played a pivotal role in cancer remedy. Early recognition of patients with high risk for development of HCCLM and subsequent surveillance should be proposed. A previous article illustrated that HCC <7 cm in diameter had higher risk of forming lung metastasis after primary liver cancer resection.[12] Due to a low prevalence of HCCLM, a large-scale population-based study is needed for systematic identification of the morbidity, potential risk factors, and clinical prognosis of initial HCCLM patients.

In the present research, we retrospectively reviewed data from the Surveillance, Epidemiology, and End Results (SEER) database to explore the actual incidence and identify factors contributing to initially diagnosed HCCLM. Furthermore, stratified survival estimates and variables affecting either OS or CSS recognition were also conducted.

Patients and methods

Data source and patient enrollment

Original data were retrieved from the SEER database maintained by the National Cancer Institute. The SEER program consists of 18 population-based cancer registries, covering ~28% of all population in the USA. The distant metastasis status were collected until 2010 due to the intrinsic reason of the database and the latest revision was released on April 16, 2018. The inclusion criteria were as follows: 1) primary site labeled as "C22.0 Liver" and ICD-O-3 histology/behavior marked with "8,170/3: hepatocellular carcinoma, not otherwise specified," "8,171/3: hepatocellular carcinoma, fibrolamellar," "8,172/3: hepatocellular carcinoma, scirrhous," "8,173/3: hepatocellular carcinoma, spindle cell variant," "8,174/3: hepatocellular carcinoma, clear cell type," or "8,175/3: hepatocellular carcinoma, pleomorphic type"; 2) the year at diagnosis from 2010 to 2015; and 3) the age at diagnosis older than 18 years. Individuals who had unclear TNM stage record, unknown survival time, missing cause of death, or unknown diagnostic confirmation were subsequently excluded. For further analysis, cases were grouped by the existence of lung metastasis (Figure 1).

We obtained the SEER data access permission before the project initiation. The study complied with the Declaration

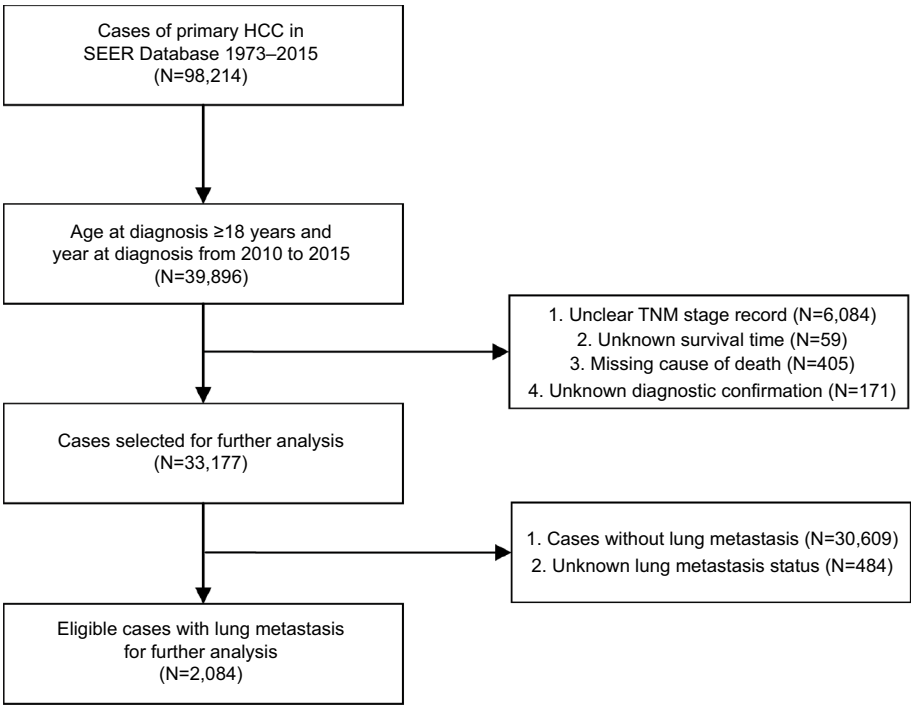

Figure 1 Flowchart of the enrolled patients in the study according to inclusion and exclusion criterion.
Abbreviations: HCC, hepatocellular carcinoma; SEER, Surveillance, Epidemiology, and End Results.

of Helsinki and followed the ethical principles of Huashan Hospital, Fudan University.

Variables definition and stratification

The definition of incidence was the proportion of patients with lung metastasis in the entire HCC patients. We stratified total cohort by age at diagnosis, gender, race, marital status at diagnosis, insurance status, alpha-fetoprotein (AFP) interpretation, maximum of tumor size, 7th AJCC TNM staging, lymph node status, surgery, pathological grade, and other distant site metastasis (brain and bone). Liver metastasis and pathological subtypes were not included for analysis because the records were unable to be distinguished clearly. The variable race comprised of white, black, and others (American Indian/Alaska Native, Asian/Pacific Islander). AFP level was interpreted as elevated, normal, borderline, as well as unknown. Surgery for primary site was classified as no surgery, local tumor destruction, surgery, and unknown. OS was defined as the duration between the surgery and death or the last follow-up, while the CSS was the period between the surgery and the death due to cancer.

Statistical analyses

Data were downloaded by SEER*Stat Software version 8.3.5 (National Cancer Institute, Bethesda, MD, USA). SPSS version 13.0 (IBM Inc., Chicago, IL, USA) was used for statistical analysis, and survival curves were generated using GraphPad Prism version 6.0 (GraphPad-Prism Software Inc., San Diego, CA, USA). Continuous variables were presented as mean±SD or median (minimum, maximum), and the categorical variables were shown as number (percent). Association between categorical data was analyzed using the chi-squared test or Fisher's exact test, while continuous values using Student's *t*-test or Mann–Whitney test, when appropriate. The Kaplan–Meier method and Cox regression analysis were applied to determine prognostic factors associated with OS or CSS. Two tailed $P<0.05$ was regarded as statistically significant.

Results

Incidence of HCCLM

Among finally enrolled 33,177 patients with HCC from 2010 to 2015, 2,084 patients were initially diagnosed with HCCLM with an incidence rate 6.28% (Figure 1). No statistical significance could be found between different years. Only 44 (2.1%) individuals with HCCLM received surgery (including local tumor destruction), while remaining 97.8% patients treated conservatively (Table 1).

Risk factors for HCCLM

As depicted in Table 1, male gender (OR: 1.131, 95% CI: 1.014–1.260, $P=0.026$), non-white race, unmarried status (OR: 1.313, 95% CI: 1.186–1.454, $P<0.001$), uninsured status (OR: 1.988, 95% CI: 1.661–2.380, $P<0.001$), maximum primary liver tumor size over 50 mL (mm), positive lymph node status (OR: 4.326, 95% CI: 3.838–4.875, $P<0.001$), synchronal bone (OR: 5.495, 95% CI: 4.827–6.255, $P<0.001$) or brain metastasis (OR: 11.492, 95% CI: 7.892–16.734, $P<0.001$), and tumor poor pathological differentiation were relevant to higher risk of initial HCCLM. Additionally, patients with HCC older than 40 years or normal AFP level had lower risk of developing lung metastasis (Table 1).

Survival and prognostic factors of HCCLM patients

Median OS in HCC lung metastasis-free (HCCLMF) group and HCCLM group were 19 months and 3 months, while the median CSS in the group of HCCLMF and HCCLM were 25 months and 3 months. The 1-, 3-, and 5-year OS rates for HCC patients without or with lung metastasis were 59.8% vs 12.8%, 33.4% vs 4.0%, and 24.1% versus 1.6%, respectively (Figure 2A). In addition, the homologous proportions of CSS were 65.2% vs 15.3%, 41.1% vs 5.7%, and 32.4% versus 2.4% (Figure 2B). Further, log-rank analysis revealed that age at diagnosis, gender, lymph node status, maximum primary tumor size, tumor differentiation, AFP level interpretation, and surgical intervention had impact on HCCLM cohort patients' OS with statistical significance ($P<0.05$, Figure 3). Besides factors above, bone metastasis was also associated with CSS in HCCLM cohort ($P<0.05$, Figure 4).

Using the univariate and multivariate Cox regression model, age at diagnosis older than 40 years, unmarried status (HR: 1.134, 95% CI: 1.019–1.261, $P=0.021$), poor differentiation (HR: 1.732, 95% CI: 1.355–2.213, $P<0.001$) or undifferentiation (HR: 1.732, 95% CI: 1.355–2.213, $P<0.001$), and surgical intervention (including local tumor destruction and surgery) were identified as worse prognosis factors for OS (Table 2). Similarly, these factors were also associated with a higher risk of mortality caused by cancer (Table 3).

Discussion

HCCLM is a Gordian knot for clinicians because of its poor survival and limited effective treatment modalities. Previous articles mainly focused on the lung metastasis followed by primary liver tumor resection, while little is known about the simultaneous HCC and lung metastatic tumor. In the current

Table 1 Baseline clinical demographics and multivariable logistic regression for analyzing risk factor for initial lung metastasis of primary hepatocellular carcinoma patients in SEER database (2010–2015)

Variables	Lung metastasis free		Lung metastasis		OR (95% CI)	*P*-value
	No. of patients	%	No. of patients	%		
Gender						0.026
Female	7,111	23.2	440	21.1	1 (Reference)	1
Male	23,498	76.8	1,644	78.9	1.131 (1.014–1.260)	0.026
Age at diagnosis (years)						<0.001
18–39	298	1.0	61	2.9	1 (Reference)	1
40–59	10,484	34.2	758	36.4	0.353 (0.266–0.470)	<0.001
60–79	16,992	55.5	1,051	50.4	0.302 (0.228–0.401)	<0.001
≥80	2,835	9.3	214	10.3	0.369 (0.271–0.502)	<0.001
Race						<0.001
White	21,304	69.6	1,322	63.4	1 (Reference)	1
Black	4,192	13.7	361	17.3	1.388 (1.230–1.566)	<0.001
Others	4,960	16.2	392	18.8	1.274 (1.133–1.432)	<0.001
Unknown	153	0.5	9	0.5	NA	NA
Marital status at diagnosis						<0.001
Married	22,396	73.2	1,429	68.6	1 (Reference)	1
Unmarried	6,602	21.5	553	26.5	1.313 (1.186–1.454)	<0.001
Unknown	1,611	5.3	102	4.9	NA	NA
Insurance status						<0.001
Insured	29,010	94.8	1,893	90.8	1 (Reference)	1
Uninsured	1,110	3.6	144	6.9	1.988 (1.661–2.380)	<0.001
Unknown	489	1.6	47	2.3	NA	NA
Year at diagnosis						0.968
2010	4,374	14.3	295	14.2	1 (Reference)	1
2011	4,655	15.2	324	15.6	1.032 (0.877–1.215)	0.705
2012	5,034	16.5	355	17.0	1.046 (0.891–1.227)	0.584
2013	5,296	17.3	361	17.3	1.011 (0.862–1.185)	0.896
2014	5,576	18.2	371	17.8	0.987 (0.842–1.155)	0.866
2015	5,674	18.5	378	18.1	0.988 (0.844–1.156)	0.878
Alpha-fetoprotein interpretation						<0.001
Positive/elevated	17,845	58.3	1,414	67.9	1 (Reference)	1
Negative/normal	7,062	23.1	211	10.1	0.377 (0.325–0.437)	<0.001
Borderline	65	0.2	6	0.3	1.165 (0.504–2.693)	0.721
Unknown	5,637	18.4	453	21.7	NA	NA
Maximum primary tumor size (mm)						<0.001
0–20	3,364	11.0	69	3.3	1 (Reference)	1
20–50	13,101	42.8	234	11.2	0.871 (0.664–1.142)	0.317
50–100	7,737	25.3	541	26.0	3.409 (2.645–4.394)	<0.001
≥100	3,970	13.0	605	29.0	7.430 (5.768–9.571)	<0.001
Unknown	2,437	7.9	635	30.5	NA	NA
7th AJCC TNM staging						<0.001
I	13,735	44.9	0	0.0	1 (Reference)	1
II	6,615	21.6	0	0.0	NA	NA
III	6,078	19.9	0	0.0	NA	NA
IV	4,181	13.6	2084	100	1.498 (1.472–1.525)	<0.001
Lymph node status						<0.001
Negative	28,144	91.9	1,290	61.9	1 (Reference)	1
Positive	2,073	6.8	411	19.7	4.326 (3.838–4.875)	<0.001
Unknown	392	1.3	383	18.4	NA	NA
Bone metastasis						<0.001
No	29,436	96.2	1,667	80.0	1 (Reference)	1
Yes	1,128	3.7	351	16.8	5.495 (4.827–6.255)	<0.001
Unknown	45	0.1	66	3.2	NA	NA

(*Continued*)

Table 1 (*Continued*)

Variables	Lung metastasis free		Lung metastasis		OR (95% CI)	*P*-value
	No. of patients	%	No. of patients	%		
Brain metastasis						<0.001
No	30,501	99.7	1960	94.1	1 (Reference)	1
Yes	65	0.2	48	2.3	11.492 (7.892–16.734)	<0.001
Unknown	43	0.1	76	3.6	NA	NA
Surgery for primary site						<0.001
No surgery	22,213	72.6	2038	97.8	1 (Reference)	1
Local tumor destruction[a]	3,613	11.8	19	0.9	0.057 (0.036–0.090)	<0.001
Surgery	4,712	15.4	25	1.2	0.058 (0.039–0.086)	<0.001
Unknown	71	0.2	2	0.1	NA	NA
Grade						<0.001
Well differentiated	3,424	11.2	103	4.9	1 (Reference)	1
Moderately differentiated	5,225	17.1	236	11.3	1.501 (1.187–1.900)	0.001
Poorly differentiated	2,140	7.0	276	13.3	4.287 (3.397–5.410)	<0.001
Undifferentiated	167	0.5	21	1.0	4.180 (2.550–6.853)	<0.001
Unknown	19,653	64.2	1,448	69.5	NA	NA

Note: [a]Local tumor destruction includes percutaneous ethanol injection, heat-radiofrequency ablation, cryosurgery, photodynamic therapy, electrocautery, fulguration (includes use of hot forceps for tumor destruction), laser, and others (ultrasound, acetic acid).
Abbreviation: SEER, Surveillance, Epidemiology, and End Results.

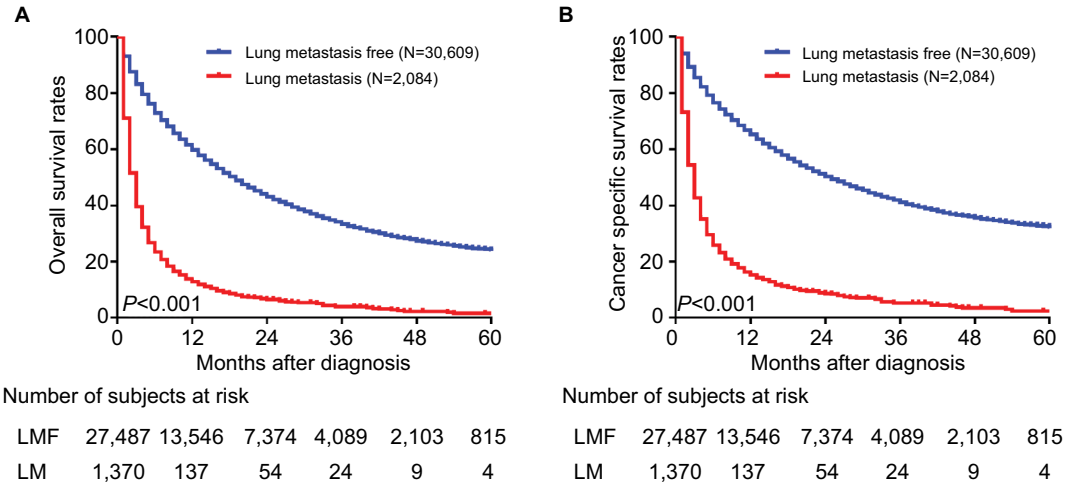

Figure 2 Kaplan–Meier analysis of **(A)** overall survival and **(B)** cancer-specific survival in hepatocellular carcinoma patients with or without initial lung metastasis.
Abbreviations: LM, lung metastasis; LMF, lung metastasis free.

study, the epidemiological result indicated that 6.28% patients with HCC presented with synchronous lung metastasis. Similarly, result from a Chinese cohort revealed that 39 of 862 (4.5%) HCC patients presented with initial lung metastasis.[13] However, a national follow-up survey of primary liver cancer in Japan showed that more than two-fifths of HCC patients developed pulmonary metastatic tumor.[14] The difference between our result and results from Japan study may be due to the discrepancy of enrolled patients. Our study only focused on the initial HCCLM cases, while Japan group analyzed all pulmonary metastatic cases during HCC progression. But, our result could be underestimated on account of the fact that asymptomatic HCCLM patients are unable to be detected. Strikingly, application of newly effective treatment modalities by clinicians may contribute to a slight increase in OS and CSS compared with data 3 years ago.[7]

Follow-up analysis identified several risk factors of HCCLM, including younger patient (<40 years), non-white race, unmarried or uninsured status, elevated AFP level, larger primary tumor size, positive lymph node status, syn-

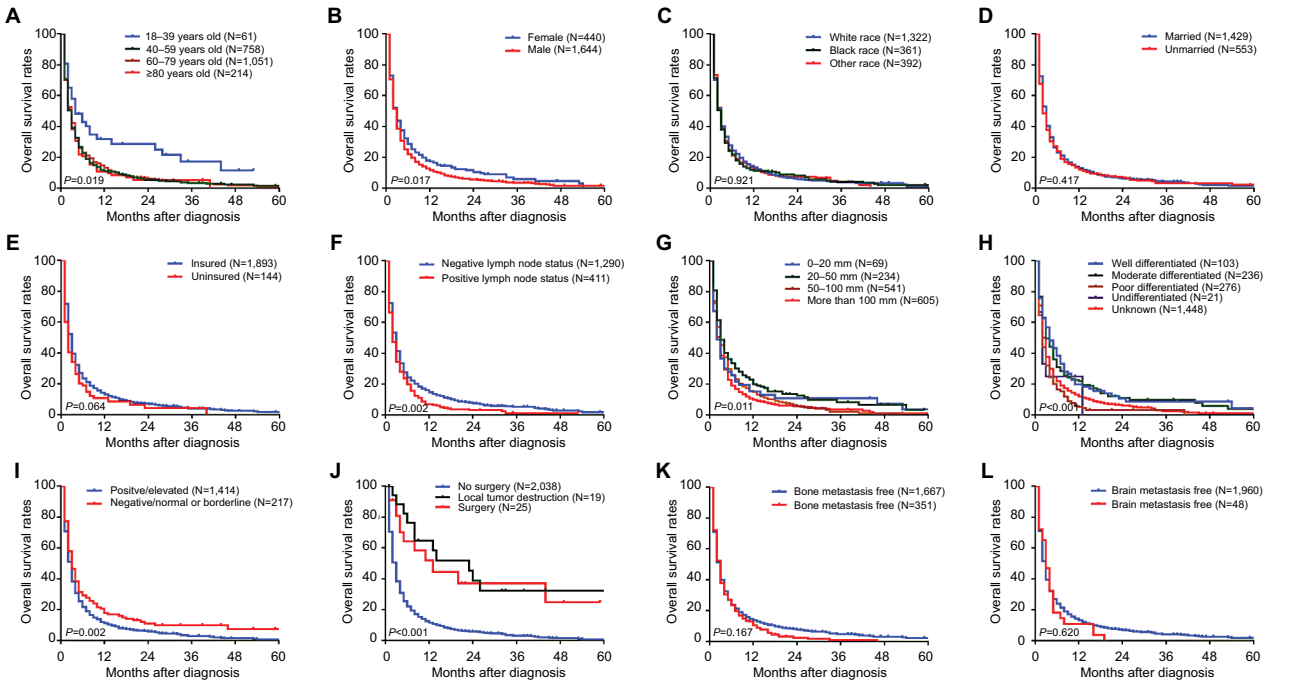

Figure 3 Kaplan–Meier analysis of overall survival in hepatocellular carcinoma patients with initial lung metastasis stratified by **(A)** age at diagnosis, **(B)** gender, **(C)** race, **(D)** marital status at diagnosis, **(E)** insurance status at diagnosis, **(F)** lymph node status, **(G)** maximum primary tumor size, **(H)** primary tumor differential grade, **(I)** alpha-fetoprotein level, **(J)** surgery for primary tumor, **(K)** bone metastasis, and **(L)** brain metastasis.

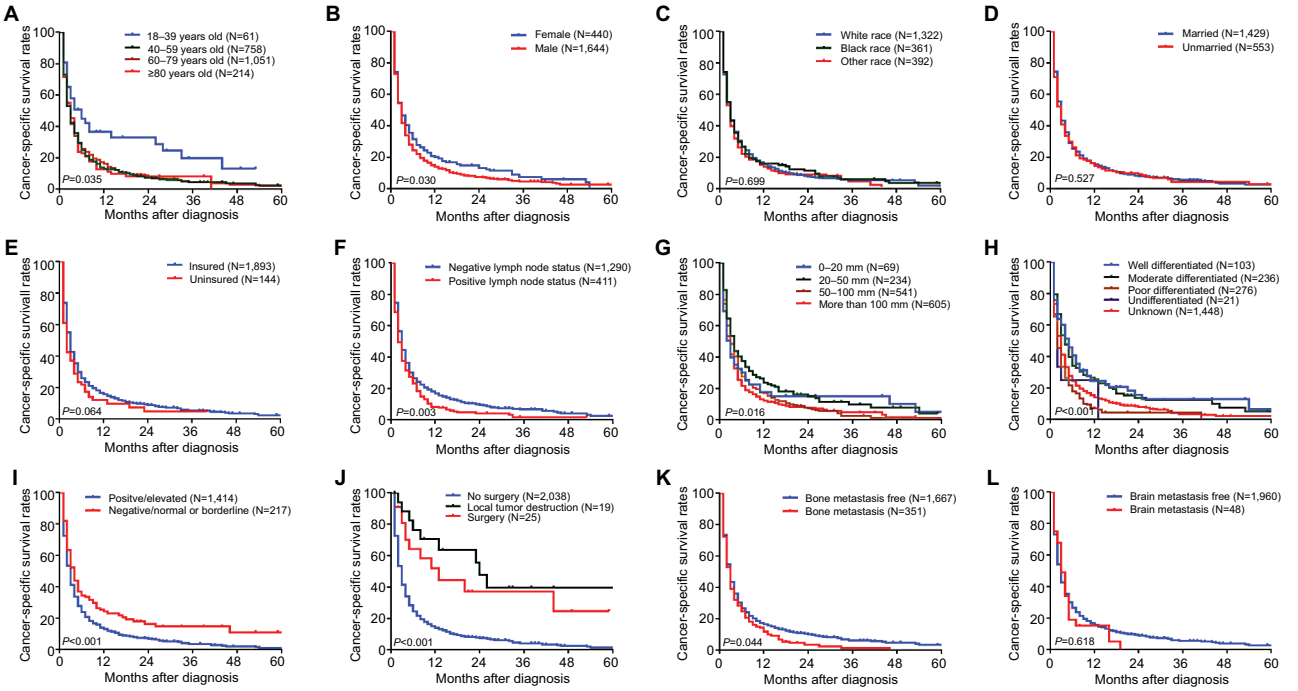

Figure 4 Kaplan–Meier analysis of cancer-specific survival in hepatocellular carcinoma patients with initial lung metastasis stratified by **(A)** age at diagnosis, **(B)** gender, **(C)** race, **(D)** marital status at diagnosis, **(E)** insurance status at diagnosis, **(F)** lymph node status, **(G)** maximum primary tumor size, **(H)** primary tumor differential grade, **(I)** alpha-fetoprotein level, **(J)** surgery for primary tumor, **(K)** bone metastasis, and **(L)** brain metastasis.

Table 2 Univariate and multivariate analysis of overall survival in patients with primary hepatocellular carcinoma lung metastasis in SEER database (2010–2015)

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Gender				
Female	Reference			
Male	1.089 (0.974–1.219)	0.134		
Age at diagnosis (years)				
18–39	Reference		Reference	
40–59	1.793 (1.321–2.434)	<0.001	1.860 (1.365–2.533)	<0.001
60–79	1.774 (1.310–2.402)	<0.001	1.883 (1.384–2.563)	<0.001
≥80	1.868 (1.345–2.595)	<0.001	2.068 (1.478–2.896)	<0.001
Race				
White	Reference			
Black	0.975 (0.864–1.100)	0.680		
Others	0.942 (0.836–1.061)	0.322		
Unknown	NA	NA		
Marital status at diagnosis				
Married	Reference		Reference	
Unmarried	1.198 (1.003–1.431)	0.046	1.134 (1.019–1.261)	0.021
Unknown	NA	NA	NA	NA
Insurance status				
Insured	Reference			
Uninsured	1.088 (0.982–1.206)	0.107		
Unknown	NA	NA		
Alpha-fetoprotein interpretation				
Positive/elevated	Reference		Reference	
Negative/normal	0.811 (0.695–0.946)	0.008	0.882 (0.754–1.030)	0.113
Borderline	0.140 (0.137–1.324)	0.140	0.473 (0.152–1.470)	0.196
Unknown	NA	NA	NA	NA
Surgery for primary site				
No surgery	Reference		Reference	
Local tumor destruction	0.268 (0.151–0.473)	<0.001	0.282 (0.159–0.500)	<0.001
Surgery	0.335 (0.201–0.557)	<0.001	0.390 (0.232–0.654)	<0.001
Unknown	NA	NA	NA	NA
Maximum primary tumor size (mm)				
0–20	Reference			
20–50	0.923 (0.696–1.225)	0.581		
50–100	1.059 (0.814–1.379)	0.669		
≥100	1.182 (0.909–1.536)	0.212		
Unknown	NA	NA		
Lymph node status				
Negative	Reference		Reference	
Positive	1.152 (1.026–1.294)	0.017	1.099 (0.977–1.236)	0.117
Unknown	NA	NA	NA	NA
Bone metastasis				
No	Reference			
Yes	1.010 (0.896–1.138)	0.876		
Unknown	1.201 (0.928–1.555)	0.165		
Brain metastasis				
No	Reference			
Yes	1.073 (0.798–1.443)	0.639		
Unknown	NA	NA		
Grade				
Well differentiated	Reference		Reference	
Moderately differentiated	1.159 (0.902–1.489)	0.247	1.206 (0.938–1.551)	0.145
Poorly differentiated	1.705 (1.337–2.176)	<0.001	1.732 (1.355–2.213)	<0.001
Undifferentiated	1.912 (1.163–3.142)	0.011	2.217 (1.342–3.661)	0.002
Unknown	NA	NA	NA	NA

Abbreviation: SEER, Surveillance, Epidemiology, and End Results.

Table 3 Univariate and multivariate analysis of cancer-specific survival in patients with primary hepatocellular carcinoma lung metastasis in SEER database (2010–2015)

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Gender				
Female	Reference			
Male	1.105 (0.982–1.244)	0.098		
Age at diagnosis (years)				
18–39	Reference		Reference	
40–59	1.716 (1.255–2.347)	0.001	1.738 (1.268–2.382)	0.001
60–79	1.685 (1.235–2.299)	0.001	1.747 (1.277–2.391)	<0.001
≥80	1.704 (1.214–2.392)	0.002	1.832 (1.300–2.583)	0.001
Race				
White	Reference			
Black	0.936 (0.823–1.065)	0.317		
Others	0.971 (0.858–1.099)	0.643		
Unknown	NA	NA		
Marital status at diagnosis				
Married	Reference			
Unmarried	1.070 (0.961–1.193)	0.218		
Unknown	NA	NA		
Insurance status				
Insured	Reference		Reference	
Uninsured	1.214 (1.008–1.462)	0.041	1.163 (0.963–1.405)	0.117
Unknown	NA	NA	NA	NA
Alpha-fetoprotein interpretation				
Positive/elevated	Reference		Reference	
Negative/normal	0.734 (0.621–0.868)	<0.001	0.792 (0.669–0.937)	0.007
Borderline	0.152 (0.021–1.079)	0.060	0.174 (0.024–1.235)	0.080
Unknown	NA	NA	NA	NA
Surgery for primary site				
No surgery	Reference		Reference	
Local tumor destruction	0.246 (0.132–0.459)	<0.001	0.276 (0.148–0.516)	<0.001
Surgery	0.370 (0.222–0.617)	<0.001	0.430 (0.256–0.722)	0.001
Unknown	NA	NA	NA	NA
Maximum primary tumor size (mm)				
0–20	Reference			
20–50	0.906 (0.675–1.218)	0.514		
50–100	1.049 (0.797–1.381)	0.733		
≥100	1.165 (0.886–1.531)	0.274		
Unknown	NA	NA		
Lymph node status				
Negative	Reference		Reference	
Positive	1.177 (1.043–1.328)	0.008	1.112 (0.983–1.257)	0.091
Unknown	NA	NA	NA	NA
Bone metastasis				
No	Reference			
Yes	1.043 (0.922–1.181)	0.501		
Unknown	NA	NA		
Brain metastasis				
No	Reference			
Yes	1.105 (0.813–1.501)	0.524		
Unknown	NA	NA		
Grade				
Well differentiated	Reference		Reference	
Moderately differentiated	1.159 (0.902–1.489)	0.274	1.182 (0.907–1.542)	0.216
Poorly differentiated	1.765 (1.366–2.280)	<0.001	1.762 (1.362–2.281)	<0.001
Undifferentiated	1.920 (1.136–3.246)	0.015	2.139 (1.259–3.633)	0.005
Unknown	NA	NA	NA	NA

Abbreviation: SEER, Surveillance, Epidemiology, and End Results.

chronal bone or brain metastasis, tumor poor pathological differentiation, and absence of surgery. This result suggested that clinicians should consider the possibility of lung metastasis when visiting HCC patients with above characteristics. Therefore, routine chest radiograph or low-dose computed tomography of lung was considered for these patients. Regrettably, other reported risk factors, such as microvascular invasion and tumor encapsulation, could not be assessed owing to no record in SEER.

Survival estimates elucidated that age below 40 years, female, negative lymph node status, smaller tumor size, better tumor differentiation, normal AFP level, and surgery received may contribute to an optimistic survival. Prognostic factors for HCCLM were further investigated. The HCC patients with characteristics of age at diagnosis older than 40 years, unmarried status, tumor poor differentiation, and existence of surgery had a significantly higher risk of mortality. According to these recognized factors, clinicians could approximately assess the survival and prognosis of HCCLM patients.

Collectively, age at diagnosis, surgery for primary tumor, and tumor differential grade were crucial factors for both risk and prognosis prediction. Although HCC patients younger than 40 years had higher risk for lung metastasis, their OS and CSS appeared the best performance. The underlying causes perhaps were younger patients usually held more positive attitude toward treatment and had better physical status to tolerant various treatment modalities. In addition, the majority of patients did not receive surgery in this study, which most likely led to a lower survival rate compared with the reported data.[11] Consistent with previous reports, larger tumor size and positive AFP level predicted high risk for lung tumor colony formation.[4,12] Notably, concomitant brain or bone metastasis had no impact on OS among HCCLM patients.

Limitations

First, only patients diagnosed after 2010 are enrolled for analysis because metastatic sites had been recorded until 2010. Second, inevitable bias exists because of absent details of tumor pathology and patient performance status. Third, SEER database represents merely US population, and other countries with high incidence of HCC were unable to be enrolled for global analysis. Last, the research is retrospective and the result still needs prospective trials to confirm a precise conclusion.

Conclusion

Generally, the incidence of initial pulmonary metastasis in HCC patients is 6.28% and the 5-year OS is still poor. Some clinicopathological features, such as age at diagnosis, tumor differential grade, and surgery for primary tumor, are highly predictive of HCCLM and significantly affect patients' survival. To our knowledge, the study is the first attempt to explore the epidemiological characteristics and identify the associated risk or prognostic factors of HCCLM using a population-based cancer registry database. The conclusion could be useful for a precise and individualized therapeutic schedule.

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Disclosure

The authors report no conflicts of interests in this work.

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