Original Article

Treatments and prognostic outcomes of combined hepatocellular-cholangiocarcinoma with distant metastasis: an analysis based on SEER data

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Background: Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) is a rare liver cancer with a poor prognosis, often diagnosed at an advanced stage. The management of cHCC-CCA with distant metastasis remains challenging, and prognostic factors are not well-defined. This study aimed to investigate prognostic factors and treatment outcomes for cHCC-CCA patients with distant metastasis.

Methods: Retrospective analysis was conducted using data from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database. Patients with distant metastasis [stage M1, according to the American Joint Committee on Cancer (AJCC) 7th edition] between January 2010 and December 2020 were included. Their characteristics, clinical profiles, and prognostic information were evaluated. Cox multifactorial survival analysis and Kaplan-Meier survival curves were used for statistical analysis.

Results: A total of 130 patients were included, with 78 (60%) receiving chemotherapy. Cox multivariate survival analysis revealed worse prognosis for Black individuals compared to White individuals (P<0.05). The median overall survival was 2 months for Black patients and 5 months for White patients. Chemotherapy significantly improved patient prognosis (P<0.05), while lung metastasis emerged as an independent risk factor (P<0.05). Kaplan-Meier survival curves confirmed the impact of lung metastasis and chemotherapy on overall survival. Patients with lung metastasis had lower survival rates (P<0.05), and those receiving chemotherapy had higher survival rates (P<0.05). Subgroup analysis based on age showed lower survival rates in patients aged 75 years or older compared to those below 75 years. Chemotherapy showed significant beneficial effects on the prognosis of patients below 75 years old, but no significant difference was observed in patients aged 75 years or above.

Conclusions: Chemotherapy improves the prognosis of cHCC-CCA patients with distant metastasis, especially for those under 75 years old. Black race and lung metastasis are poor prognostic factors.

Keywords: Combined hepatocellular-cholangiocarcinoma (cHCC-CCA); lung metastasis; prognosis; chemotherapy; overall survival

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Introduction

Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) is a rare yet challenging tumor type characterized by the simultaneous presence of hepatocellular carcinoma and cholangiocarcinoma, displaying mixed histopathological features (1,2). The incidence of cHCC-CCA accounts for less than 5% of all liver cancer cases (3-5). Due to the complex and diverse pathological characteristics of cHCC-CCA (6), it tends to have a poorer prognosis compared to a single type of liver cancer (4,5,7,8). Currently, various treatment modalities, such as surgical resection, liver transplantation, radiation therapy, chemotherapy, and targeted therapy, are employed for the management of cHCC-CCA (9-11). However, there is a lack of clear guidelines to guide treatment decisions for patients with cHCC-CCA (12).

Compared with other types of liver cancer, clinical symptoms of cHCC-CCA are usually associated with advanced disease, including fatigue, obstructive jaundice, weight loss, or abdominal discomfort (13). Due to non-specific symptoms, cHCC-CCA is often diagnosed at an advanced stage with intrahepatic or distant metastasis, posing a great challenge for treatment (14). Furthermore, distant metastasis of cHCC-CCA may contain both hepatocellular carcinoma and cholangiocarcinoma components, or solely hepatocellular carcinoma or cholangiocarcinoma components, which increases the complexity of disease management (6,15).

Although studies have reported on the clinical characteristics and treatment outcomes of cHCC-CCA, there is still limited cognition regarding the prognosis and influencing factors of cHCC-CCA with distant metastasis. Therefore, the primary objective of this study is to extensively investigate the prognostic and therapeutic outcomes of distant metastasis in cHCC-CCA, aiming to provide some help for clinical treatment. We present this article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-447/rc).

Highlight box

Key findings

- Chemotherapy improves the prognosis of combined hepatocellular-cholangiocarcinoma (cHCC-CCA) patients with distant metastasis, especially those under 75 years old.

What is known and what is new?

- Chemotherapy is an effective treatment for patients with cHCC-CCA with metastases.
- Elderly patients should be carefully evaluated and selected when choosing chemotherapy.

What is the implication, and what should change now?

- The prognosis of advanced mixed hepatocellular carcinoma is extremely poor, and chemotherapy plays a crucial role in improving outcomes. However, it is advisable to thoroughly assess elderly patients before considering chemotherapy.

Methods

Data sources

This study utilized data from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database as the primary data source. The database collected comprehensive patient characteristics and clinical data from 2010 to 2020. The cut-off date for data collection was November 2022. We adhered strictly to relevant guidelines and regulations for methodology and data processing. All the data for this study are from public databases and do not involve any personally identifiable information, so no institutional ethical review board approval is required. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Data collection

We included patients diagnosed with cHCC-CCA [International Classification of Diseases of Oncology (ICD-O) histological code 8180/3] and presenting with distant metastasis [M1 stage, according to the American Joint Committee on Cancer (AJCC) 7th edition] between January 2010 and December 2020 from the SEER database. Exclusion criteria were as follows: (I) patients younger than 18 years; (II) patients with incomplete data related to chemotherapy; (III) patients with unknown status of bone, brain, liver, or lung metastasis; (IV) patients with insufficient clinical follow-up data; and (V) patients who died within a short period of time (survival time less than 1 month).

We collected demographic, clinicopathological, treatment, and survival data, including gender, age (≤59, 60–74, ≥75 years), race (White, Black, Hispanic, Asian), marital status (unmarried, married, separated/divorced/widowed), T stage (T1, T2, T3, T4) (based on AJCC 7th), lymph node metastasis (N stage: N0, N1) (based on

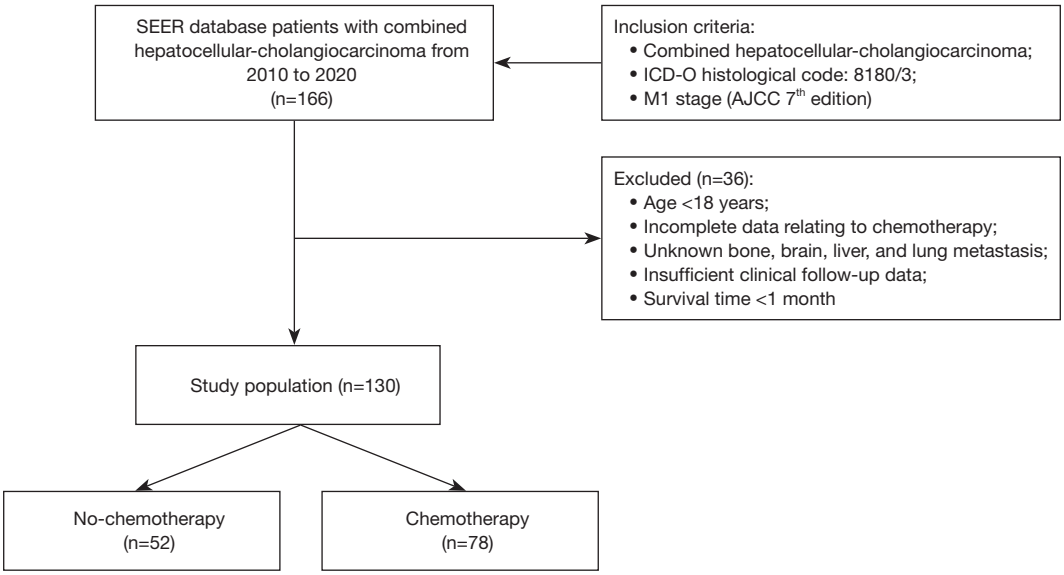

Figure 1 Patient screening flow chart. SEER, National Cancer Institute Surveillance, Epidemiology, and End Results; ICD-O, International Classification of Diseases of Oncology; AJCC, American Joint Committee on Cancer.

AJCC 7th), tumor metastasis (intrahepatic, lung, bone, brain), household income (<$55,000, $55,000–$75,000, >$75,000), and treatment modalities such as chemotherapy, radiotherapy, and surgical interventions.

We categorized patients into two groups based on their chemotherapy treatment. Patients who underwent chemotherapy during their treatment were grouped as the chemotherapy group, while those who did not receive chemotherapy were grouped as the non-chemotherapy group. The primary endpoint of our study was overall survival, which was defined as the duration from the time of diagnosis to the occurrence of death from any cause.

Statistical analyses

Student's *t*-test and χ^2 test were used in this study to compare the general characteristics of the different groups of patients. Overall survival and cancer-specific survival were analyzed using Kaplan-Meyer curves, and differences were assessed using the log-rank test. Univariate and multivariate Cox proportional risk models were used to analyze factors affecting survival prognosis. Results were expressed as hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). P value less than 0.05 was considered statistically significant. Data were analyzed using SPSS IBM version 27.0 or GraphPad Prism 10.1 software.

Results

Baseline characteristics

A total of 166 patients with stage M1 cHCC-CCA met the inclusion criteria, and after the screening process, we excluded 36 patients. The final sample included 130 patients (*Figure 1*). Among them, 78 patients (60.0%) received chemotherapy. The mean age was 65.1±11.5 years, with 40 patients (30.8%) aged 59 years or younger, 64 patients (49.2%) aged between 60 and 74 years, and 26 patients (20.0%) aged 75 years or older. Most patients were male (73.8%), White (57.7%), and married (56.2%). Based on the T stage, 16 patients (12.3%) were in T1 stage, 19 patients (14.6%) were in T2 stage, 21 patients (16.2%) were in T3 stage, and 12 patients (9.2%) were in T4 stage. There were 57 patients (43.8%) in N0 stage and 65 patients (50.0%) in N1 stage. Regarding tumor metastasis, 20 patients (15.4%) had intrahepatic metastasis, 43 patients (33.1%) had lung metastasis, 30 patients (23.1%) had bone metastasis, and 1 patient (0.8%) had brain metastasis. In addition, 19 patients (14.6%) received radiotherapy. Among them, 8 patients (6.2%) underwent surgical intervention, including 2 patients of liver transplantation, 4 patients of liver resection, and 2 patients of ultrasound-guided intervention (*Table 1*).

Chemotherapy is the primary treatment method for advanced cHCC-CCA. We compared the general data and

Table 1 Characteristics of patients with metastatic cHCC-CCA grouped according to chemotherapy

Variables	Total (n=130)	No chemotherapy (n=52)	Chemotherapy (n=78)	P
Gender, n (%)				0.33
Female	34 (26.2)	16 (30.8)	18 (23.1)	
Male	96 (73.8)	36 (69.2)	60 (76.9)	
Age (years), n (%)				0.47
≤59	40 (30.8)	14 (26.9)	26 (33.3)	
60–74	64 (49.2)	25 (48.1)	39 (50.0)	
≥75	26 (20.0)	13 (25.0)	13 (16.7)	
Race, n (%)				0.74
White	75 (57.7)	29 (55.8)	46 (59.0)	
Black	16 (12.3)	7 (13.5)	9 (11.5)	
Hispanic	23 (17.7)	11 (21.2)	12 (15.4)	
Asian	16 (12.3)	5 (9.6)	11 (14.1)	
Marriage, n (%)				0.21
Unmarried	28 (21.5)	8 (15.4)	20 (25.6)	
Married	73 (56.2)	27 (51.9)	46 (59.0)	
Divorced/separated/widowed	25 (19.2)	13 (25.0)	12 (15.4)	
T stage, n (%)				0.51
T1	16 (12.3)	6 (11.5)	10 (12.8)	
T2	19 (14.6)	4 (7.7)	15 (19.2)	
T3	21 (16.2)	5 (9.6)	16 (20.5)	
T4	12 (9.2)	5 (9.6)	7 (9.0)	
N stage, n (%)				0.18
N0	57 (43.8)	26 (50.0)	31 (39.7)	
N1	65 (50.0)	22 (42.3)	43 (55.1)	
Intrahepatic metastasis, n (%)	20 (15.4)	8 (15.4)	12 (15.4)	>0.99
Lung metastasis, n (%)	43 (33.1)	16 (30.8)	27 (34.6)	0.76
Bone metastasis, n (%)	30 (23.1)	15 (28.8)	15 (19.2)	0.18
Brain metastasis, n (%)	1 (0.8)	1 (1.9)	0 (0.0)	0.22
Household income, n (%)				0.08
<$55,000	17 (13.1)	10 (19.2)	7 (9.0)	
$55,000–$75,000	49 (37.7)	22 (42.3)	27 (34.6)	
>$75,000	64 (49.2)	20 (38.5)	44 (56.4)	
Radiotherapy, n (%)	19 (14.6)	7 (13.5)	12 (15.4)	0.76
Surgical interventions, n (%)	8 (6.2)	2 (3.8)	6 (7.7)	0.37

cHCC-CCA, combined hepatocellular-cholangiocarcinoma.

clinical characteristics between the chemotherapy group and the non-chemotherapy group. The results showed no significant differences between the two groups regarding general data, staging, metastasis status, and other treatments (*Table 1*).

Analysis of factors associated with patient survival

Firstly, a univariate Cox survival analysis was performed, and the results indicated that race, age, lung metastasis, chemotherapy, and surgical interventions were identified as potential prognostic factors (P<0.05). Subsequently, multivariable Cox analysis revealed that compared to the white race, the prognosis of the Black race was worse (HR =1.844; 95% CI: 1.038–3.274; P=0.04). The presence of lung metastasis (HR =1.770; 95% CI: 1.164–2.691; P=0.008) was identified as an adverse prognostic factor, while chemotherapy (HR =0.505; 95% CI: 0.339–0.751; P=0.001) demonstrated the potential to improve prognosis (*Table 2*).

Analysis of patient's overall survival

The overall survival rate of patients was calculated using the Kaplan-Meier method. In terms of overall survival, patients who received chemotherapy showed significantly better survival (log-rank P=0.002, *Figure 2A*). The median survival time of the chemotherapy group was 6 months, while the median survival time of the no-chemotherapy group was 2 months.

The survival rate of the lung metastasis group was significantly lower than that of the no-lung metastasis group (log-rank P=0.008, *Figure 2B*). The median survival time of the lung metastasis group was 2 months, while the median survival time of the no-lung metastasis group was 6 months.

On subgroup analysis by race, the median overall survival time was: 5 months for White patients, 2 months for Black patients, 2 months for Hispanic patients, and 2 months for Asian patients. The 6-month survival rates were: 38.7%, 12.5%, 26.1%, and 31.3%, respectively. The log-rank test results showed that the survival differences among the racial groups were not statistically significant (P=0.10).

Prognostic analysis of patients stratified by age

In Cox univariate survival analysis, patients aged over 75 years or older had a poorer prognosis compared to younger patients (≤59 years) (HR =1.963; 95% CI: 1.170–3.292, P=0.01). Therefore, we divided the patients into two groups based on age: the elderly group, comprising patients aged 75 years or older, and the younger group, comprising patients aged 74 years or younger. We utilized the Kaplan-Meier method to compare the survival outcomes between the two groups of patients. The results revealed that the elderly group had a lower survival rate compared to the younger group (P<0.001) (*Figure 3A*). The median survival time for patients aged 75 years or older was 2 months, while for patients younger than 75 years, it was 4 months.

Comparison of prognosis based on age and lung metastasis

In our study, we stratified the comparison based on age. In the younger group, the survival rate of patients with lung metastasis was significantly lower than those without lung metastasis (P=0.001) (*Figure 3B*). However, in the elderly group, there was no significant difference in survival rates between patients with and without lung metastasis (*Figure 3C*).

Comparison of prognosis based on age and chemotherapy

In the younger group, the survival rate of patients receiving chemotherapy was significantly higher than those who did not receive chemotherapy (P<0.010) (*Figure 3D*). In the elderly group, there was no significant difference in survival rates between patients who received chemotherapy and those who did not (P=0.34) (*Figure 3E*).

Furthermore, we compared the cancer-specific survival rates based on the cause of death, where cancer-specific survival was defined as the time from diagnosis to death specifically attributed to cHCC-CCA. Upon comparison, we found that in the younger group, the cancer-specific survival rate was higher for patients receiving chemotherapy compared to those who did not, although the difference was not statistically significant (P=0.08) (*Figure 3F*). In the older group, the cancer-specific survival rate for patients receiving chemotherapy was not higher than those who did not receive chemotherapy (P=0.48) (*Figure 3G*). This finding suggests that chemotherapy may improve the survival of young patients with mixed liver cancer, while the decision to undergo chemotherapy in elderly patients should be made after a comprehensive evaluation.

Discussion

cHCC-CCA was often diagnosed at an advanced stage, and

Table 2 Results of cox univariate and multivariate survival analysis

Variables	Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P
Gender				
Female	1			
Male	0.774 (0.508–1.178)	0.23		
Age (years)				
≤59	1	0.005	1	0.07
60–74	0.900 (0.590–1.372)	0.63	0.785 (0.507–1.216)	0.28
≥75	1.963 (1.170–3.292)	0.01	1.395 (0.796–2.445)	0.25
Race				
White	1	0.18	1	0.19
Black	1.874 (1.068–3.286)	0.03	1.844 (1.038–3.274)	0.04
Hispanic	1.190 (0.720–1.965)	0.50	1.198 (0.707–2.032)	0.50
Asian	1.070 (0.590–1.942)	0.82	1.372 (0.738–2.550)	0.32
Marriage				
Unmarried	1	0.71		
Married	1.089 (0.682–1.740)	0.72		
Divorced/separated/widowed	1.269 (0.713–2.257)	0.42		
T stage				
T1	1	0.97		
T2	1.026 (0.499–2.111)	0.94		
T3	0.896 (0.445–1.801)	0.76		
T4	0.895 (0.403–1.991)	0.79		
N stage				
N0	1			
N1	0.736 (0.504–1.074)	0.11		
Intrahepatic metastasis	1.314 (0.788–2.192)	0.30		
Lung metastasis	1.828 (1.227–2.722)	0.003	1.770 (1.164–2.691)	0.008
Bone metastasis	1.280 (0.823–1.990)	0.27		
Brain metastasis	3.486 (0.478–25.411)	0.22		
Household income				
<$55,000	1	0.65		
$55,000–$75,000	0.766 (0.431–1.359)	0.36		
>$75,000	0.839 (0.480–1.467)	0.54		
Chemotherapy	0.595 (0.409–0.865)	0.007	0.505 (0.339–0.751)	0.001
Radiotherapy	0.709 (0.417–1.205)	0.20		
Surgical interventions	0.413 (0.193–0.881)	0.02	0.500 (0.229–1.093)	0.08

HR, hazard ratio; CI, confidence interval.

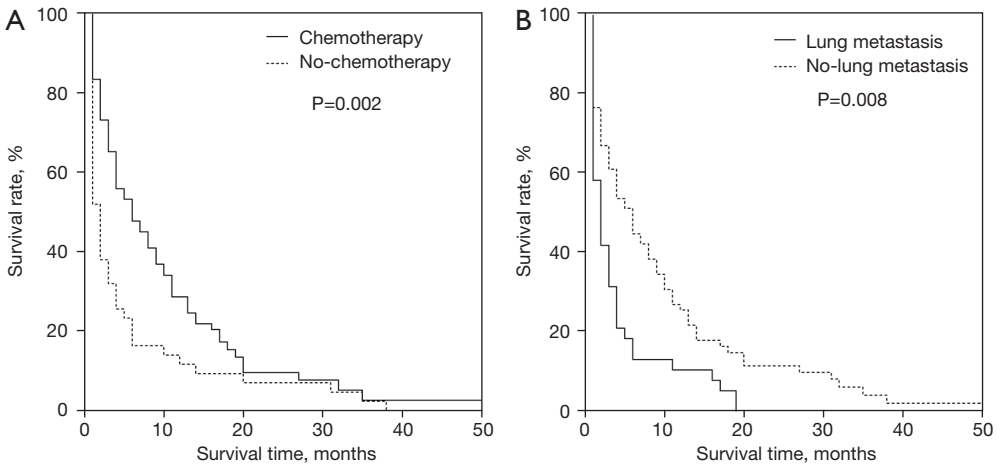

Figure 2 Survival of patients with metastatic cHCC-CCA: (A) grouped according to chemotherapy; (B) grouped according to lung metastasis. cHCC-CCA, combined hepatocellular-cholangiocarcinoma.

this study focused on the treatment and prognosis analysis of patients with distant metastasis (M1 stage). The results demonstrated that chemotherapy significantly improves the prognosis of patients, while Black race and lung metastasis independently posed a poor prognostic factor. Furthermore, by stratifying the patients by age, it was found that chemotherapy did not prolong the survival time of patients aged 75 years or older.

Chemotherapy remains the mainstay of treatment for advanced cHCC-CCA, given that most patients present with unresectable or metastatic disease (14,16). Our findings support the survival benefit of chemotherapy in this setting, consistent with previous retrospective studies (9,14,17-19). However, the optimal chemotherapy regimen for advanced cHCC-CCA remains undefined. Gemcitabine plus cisplatin is a standard first-line regimen for advanced biliary tract cancers (20), while sorafenib and other targeted therapies have shown efficacy in advanced HCC (21). Prospective trials are needed to evaluate the comparative effectiveness of different systemic regimens in cHCC-CCA, taking into account the unique pathobiology of this rare tumor type.

Age is a crucial factor affecting patient prognosis. Individuals aged 75 years and above are classified as the 'old-old' population (22). Therefore, this study used 75 years as the age cut-off point. The study found that patients aged 75 and above did not benefit from chemotherapy in improving their prognosis. It may be related to factors such as the presence of multiple comorbidities and poor physical tolerance in elderly patients.

Although our study observed some differences in survival outcomes among racial groups, with White patients having the longest overall survival and black patients the shortest, these differences did not reach statistical significance based on the log-rank test results. Similar trends have been reported in HCC and intrahepatic cholangiocarcinoma (5-8). The lack of statistically significant differences in our cohort might be attributed to the relatively small sample size and the overall poor prognosis of metastatic cHCC-CCA.

Although we observed disparities in survival outcomes by race, with White patients having the longest median overall survival, these differences did not reach statistical significance. This contrasts with prior studies in HCC and intrahepatic cholangiocarcinoma showing significantly worse outcomes in Black patients (23-26). The lack of a statistically significant difference in our cohort may be due to the small sample size and poor overall prognosis of metastatic cHCC-CCA.

The prognostic significance of lung metastasis in our cohort is noteworthy and warrants further study. It is unclear whether this reflects a unique tropism of cHCC-CCA for lung involvement, or if lung metastases represent a more aggressive disease phenotype. Incorporating data on other distant metastatic sites such as peritoneum and adrenal glands in future analyses would provide a more complete picture of metastatic patterns in cHCC-CCA (3,4).

Surgery is the only potentially curative treatment for cHCC-CCA (7), and it should be the preferred treatment option for patients who are eligible for radical tumor resection. However, there is limited research on the benefits of curative surgery for patients with distant metastasis (M1

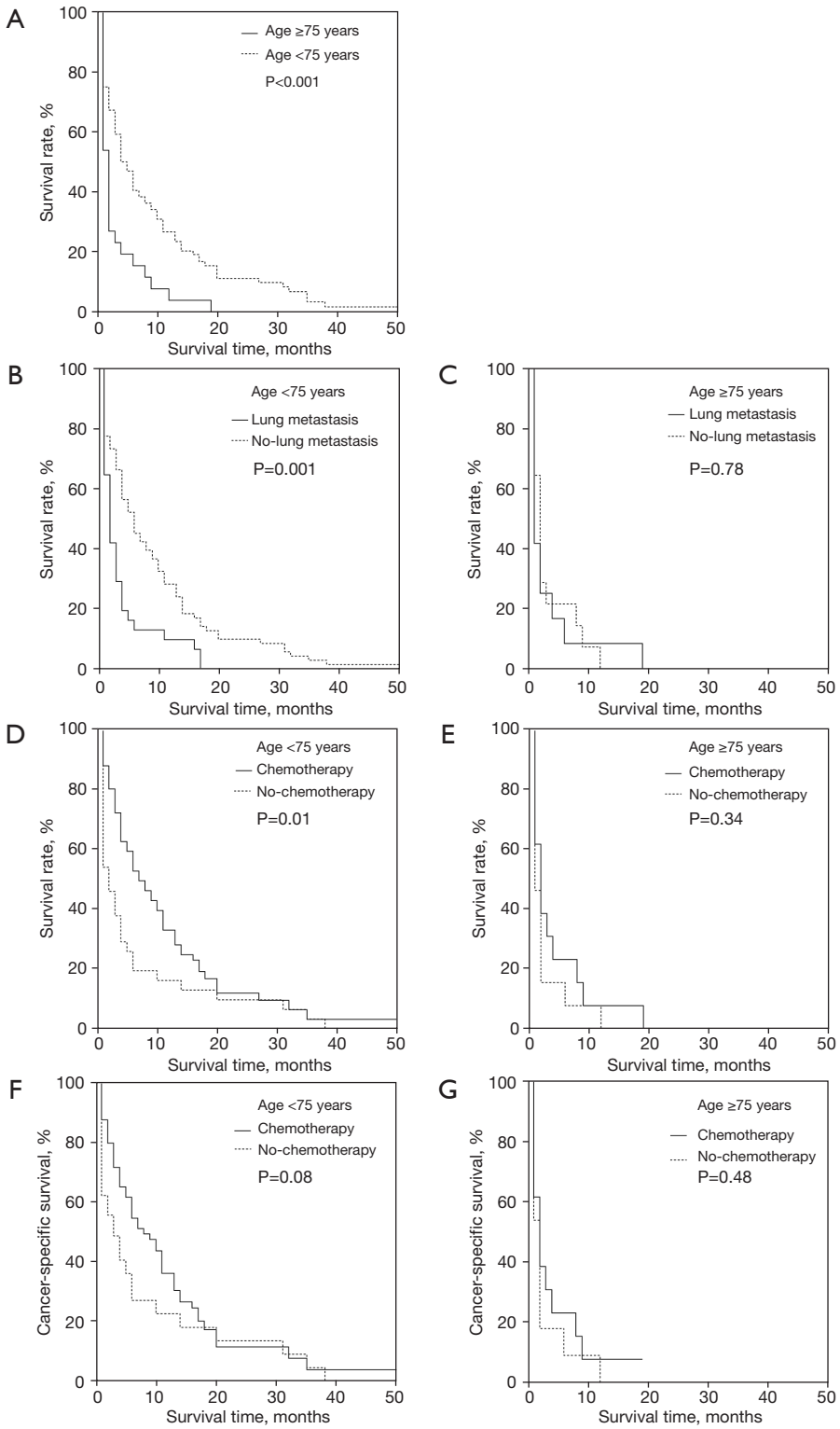

Figure 3 Survival of patients with metastatic cHCC-CCA: based on age: (A) <75 *vs.* ≥75 years; (B) <75 years stratified by lung metastasis; (C) ≥75 years stratified by lung metastasis; (D) <75 years stratified by chemotherapy; (E) ≥75 years stratified by chemotherapy; (F) cancer-specific survival in <75 years patients stratified by chemotherapy; (G) cancer-specific survival in ≥75 years patients stratified by chemotherapy. cHCC-CCA, combined hepatocellular-cholangiocarcinoma.

stage). In the univariate Cox analysis of this study, surgical treatment was found to improve prognosis, but it lost significance in the multivariate analysis. Therefore, further research is needed.

Our study has several limitations. Firstly, the retrospective design introduces the possibility of recall bias and incomplete information. Secondly, the SEER database does not provide granular data on chemotherapy regimens, targeted therapy agents, disease progression, or treatment-related adverse events, precluding a more nuanced analysis of treatment outcomes. Thirdly, we lacked data on important prognostic variables such as performance status, Child-Pugh score, and molecular markers, as these are not captured in SEER.

Conclusions

In conclusion, our study provides new insights into the prognosis and treatment outcomes of cHCC-CCA patients with distant metastasis. We found that chemotherapy improves survival in this population, particularly for patients younger than 75 years, while Black race, advanced age, and lung metastasis are associated with worse outcomes. These findings can inform prognostic discussions and treatment decision-making for patients with metastatic cHCC-CCA. We look forward to future research that can validate and expand upon these findings, aiming to assist in developing personalized treatment approaches for cHCC-CCA patients.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-447/rc

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-447/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-447/coif). 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).

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