Original Article

Clinical characteristics and prognosis of liver metastases with unknown primary site

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Background: Liver metastases from cancer of unknown primary (CUPL) constitute a rare disease, particularly among individuals younger than 50 years old. This paper aims to investigate the clinical characteristics of patients with CUPL and analyze prognostic differences across distinct age groups.

Methods: Data pertaining to patients with CUPL were extracted from the Surveillance, Epidemiology, and End Results (SEER) database. Propensity score matching (PSM) was employed to adjust for clinical variables. Cox regression analysis identified risk factors influencing overall survival (OS), while competing-risk analyses were conducted to determine prognostic factors for cancer-specific survival (CSS). Survival differences were compared using the Kaplan-Meier method and cumulative incidence function (CIF).

Results: The study encompassed 4,691 patients, with 319 (6.8%) in the age <50 years group and 4,372 (93.2%) in the age ≥50 years group. Individuals with unexplained liver metastases exhibited a 1-year OS rate of 14.7% and a 1-year CSS rate of 23%. Following matching, age, histology, brain metastases, and chemotherapy were identified as independent prognostic factors affecting OS. Additionally, race, grade, histology, brain metastases, and chemotherapy were recognized as independent prognostic factors influencing CSS. Notably, the age <50 years group demonstrated superior OS and CSS compared to the age ≥50 years group before and after PSM. Among patients undergoing chemotherapy, the age <50 years group exhibited enhanced OS and CSS compared to their age ≥50 years counterparts. Furthermore, in individuals subjected to radiotherapy, the age <50 years group demonstrated superior OS, although no significant difference in CSS was observed.

Conclusions: The survival prognosis of patients with CUPL was found to be poor. However, both OS and CSS were more favorable in the age <50 years group compared to the age ≥50 years group. Additionally, radiotherapy and chemotherapy were associated with an OS benefit for patients in the age <50 years group.

Keywords: Liver metastasis; cancers of unknown primary site (CUP site); age; prognosis; Surveillance, Epidemiology, and End Results (SEER)

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Introduction

The liver is susceptible to metastasis from various malignant tumors and stands out as one of the primary sites for metastatic cancer (1). Malignant tumors originating in the gastrointestinal tract, pancreas, lung, breast, kidney, ovary, among others, have the propensity to metastasize to the liver, with the digestive system being the most prevalent source (2,3). Identifying the primary site holds significant clinical value, guiding subsequent treatment steps and

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enhancing the survival prognosis for patients with tumors. While most patients with liver metastases can pinpoint the primary site through various examinations, some cannot, leading to the categorization of these cases as cancers of unknown primary (CUP), constituting approximately 3–5% of all malignant tumors (4). Even in autopsy cases, primary foci remain elusive in 20–50% of subjects (5).

Given the low incidence and heterogeneity of CUP, coupled with the scarcity of evidence-based medicine and limitations in clinical practitioners' understanding of the disease, diagnosing and treating CUP pose substantial challenges. CUP carries an exceedingly poor prognosis, with an average survival time of 6–16 months, primarily due to concurrent metastases from other sites upon diagnosis (6,7). Notably, there are no extensive studies analyzing the characteristics and prognosis of patients with liver metastases from cancer of unknown primary (CUPL). To gain comprehensive insights into unexplained liver metastases, we utilized the Surveillance, Epidemiology, and End Results (SEER) database to elucidate the clinicopathologic characteristics and prognostic factors for these patients. On the contrary, given the clinical rarity of patients under 50 years old with liver metastases of unknown primary origin (8), we also conducted a comparative analysis of clinical characteristics and survival disparities among various age groups in this study. This study aims to offer timely interventions for such cases, with the ultimate goal of improving patient survival. We present this article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-136/rc).

Highlight box

Key findings

- Although the occurrence of unexplained liver metastases in patients under 50 years of age was infrequent, this group exhibited significantly improved overall survival (OS) and cancer-specific survival (CSS) compared to those aged 50 and above.

What is known and what is new?

- Limited information exists regarding liver metastases of unknown primary origin, especially in individuals below 50 years of age.
- Among those in the age <50 years group with unexplained liver metastases, a 1-year OS rate of 27.5% and a 1-year CSS rate of 35% were observed.

What is the implication, and what should change now?

- In patients below 50 years of age, enhancing patient survival can be achieved through the implementation of aggressive radiation and chemotherapy by clinicians.

Methods

Study population and variables

Patients with liver metastasis of unknown origin were identified from the SEER database for the period spanning 2010 to 2020 using SEER*Stat version 8.4.2.

Selection criteria involved isolating patients categorized as having an unknown primary site, denoted by the primary site code "C80.9-Unknown primary site", and specifically setting the SEER Combined Mets at DX-liver (2010+) to "YES". This limitation arises from the fact that the SEER database has been collecting data on liver metastases only since 2010. A total of 6,528 patients were retrieved for analysis. Exclusion criteria were applied as follows: (I) cases lacking pathological information (N=1,829); and (II) cases without recorded survival months (N=8). Ethical approval was not deemed necessary as the SEER database is openly accessible to researchers worldwide. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Demographic data encompassed various factors, such as age, gender, race, marital status, year of diagnosis, histologic differentiation, presence of bone, brain, and lung metastases, information on radiotherapy and chemotherapy, as well as follow-up details. We classified patients into two age groups: <50 and ≥50 years, primarily considering the notable increase in diagnosed cases of liver metastases of unknown primary site after the age of 50 years (*Figure 1*) and the division between early-onset and late-onset cancers at the age of 50 years (9). The definition of overall survival (OS) encompassed the time elapsed from the date of diagnosis to the date of death from any cause or the date of the last follow-up. Cancer-specific survival (CSS) was defined as the time from diagnosis to cancer-specific death (CSD) or the date of the last follow-up.

Statistical analysis

Statistical analyses were performed using R 4.3.2 software. Count data were assessed through the χ^2 test or Fisher's exact probability method, while measures were analyzed using Student's *t*-test. To address disparities in variables between the age <50 years group and the age ≥50 years group, we utilized propensity score matching (PSM).

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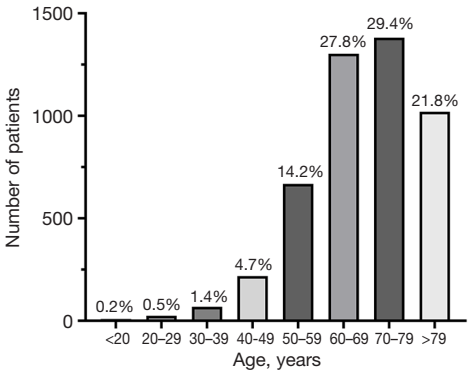

Figure 1 Number of cases diagnosed across various age groups among patients with liver metastases of unknown primary site.

Prognostic factors influencing patients were assessed through both univariate and multivariate Cox regression analyses for OS, and Fine and Gray's competing risk regression analysis for CSS. OS curves were generated using the Kaplan-Meier method, and statistical differences between the survival curves were assessed with the log-rank test. The cumulative incidence function (CIF) was employed to illustrate the probability for each event, with differences in CIFs between groups estimated using Gray's test. A P value of less than 0.05 indicated statistical significance.

Results

Patients characteristics

The study encompassed a total of 4,691 patients, with 319 (6.8%) classified in the age <50 years group and 4,372 (93.2%) in the age ≥50 years group. *Figure 1* demonstrates a notable rise in the diagnosis of patients with liver metastases of unknown primary site beyond the age of 50 years. The median age across all patients was 69 years (range, 1–90+ years), with a median survival time of 1 month (range, 0–121 months) and a mean survival time of 5.61±12.47 months. The majority of patients in both the age <50 and age ≥50 years groups identified as White race (72.1% *vs.* 80.2%, P=0.003), and the predominant histological type was adenocarcinoma not otherwise specified (NOS) (36.4% *vs.* 41.4%, P=0.004). In comparison, the age <50 years group exhibited a higher incidence of lung metastasis than the age ≥50 years group (41.7% *vs.* 29.9%, P<0.001). Regarding treatment modalities, a significant proportion of age <50 years group patients received chemotherapy compared to the age ≥50 years group (56.1% *vs.* 24.8%, P<0.001). Refer to *Table 1* for a detailed breakdown of these findings.

PSM

To effectively mitigate confounding bias between the age <50 and age ≥50 years groups, we employed the PSM method. Consequently, a total of 610 patients were included in the evaluation, with 305 patients in each of the subgroups. Following 1:1 matching with a caliper value of 0.01, no significant differences were observed between the variables in the two groups (refer to *Table 2*). The matching process encompassed key factors such as sex, marital at diagnosis, race, grade, histology, year of diagnosis, bone metastases, brain metastases, lung metastases, as well as details regarding chemotherapy, and radiation.

Cox regression analysis for OS

Table 3 presents the comprehensive results of both univariable and multivariate Cox analyses for patients with liver metastasis of unknown origin before PSM. In the univariable analysis of OS, factors such as age, race, gender, histology, grade, presence of brain and lung metastases, as well as the administration of chemotherapy and radiotherapy, emerged as prognostic indicators for unexplained liver metastasis. In the multivariable analysis of OS, several variables were identified as significantly associated with improved survival, including age <50 years, neuroendocrine tumor, well-differentiated and moderately differentiated histology, absence of lung metastases, and the utilization of radiotherapy and chemotherapy. These findings highlight the multifaceted nature of factors influencing the prognosis of patients with liver metastasis of unknown origin. Even after PSM, the results of multifactorial Cox regression still indicated that age remained an independent prognostic factor influencing OS [hazard ratio (HR) =0.78, 95% confidence interval (CI): 0.65–0.93, P=0.006] (*Table 4*).

Competing-risk analyses for CSS

Table 5 provides a detailed presentation of both univariable and multivariate competing-risk analyses results for patients with liver metastasis of unknown origin before PSM. In the univariable analysis of CSS, prognostic factors encompassed age, race, histology, grade, presence of bone and brain metastases, lung metastases, as well as the administration of chemotherapy and radiotherapy. In the multivariable

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Table 1 Demographic and clinical characteristics of patients with liver metastases from cancer of unknown primary

Characteristics	Total (n=4,691)	Age <50 years (n=319)	Age ≥50 years (n=4,372)	P
Age (years), median [range]	69 [1–90+]	43 [1–49]	71 [50–90+]	<0.001
Race, N (%)				0.003
White	3,738 (79.7)	230 (72.1)	3,508 (80.2)	
Black	586 (12.5)	54 (16.9)	532 (12.2)	
Others	340 (7.2)	34 (10.7)	306 (7.0)	
Unknown	27 (0.6)	1 (0.3)	26 (0.6)	
Gender, N (%)				0.30
Male	2,375 (50.6)	152 (47.6)	2,223 (50.8)	
Female	2,316 (49.4)	167 (52.4)	2,149 (49.2)	
Marital at diagnosis, N (%)				0.02
Married	2,228 (47.5)	129 (40.4)	2,099 (48.0)	
Others	2,249 (47.9)	170 (53.3)	2,079 (47.6)	
Unknown	214 (4.6)	20 (6.3)	194 (4.4)	
Year of diagnosis, N (%)				0.19
2010–2013	1,073 (22.9)	85 (26.6)	988 (22.6)	
2014–2017	1,621 (34.6)	99 (31.0)	1,522 (34.8)	
2018–2020	1,997 (42.6)	135 (42.3)	1,862 (42.6)	
Histology, N (%)				0.004
Carcinoma, NOS	764 (16.3)	41 (12.9)	723 (16.5)	
Adenocarcinoma, NOS	1,925 (41.0)	116 (36.4)	1,809 (41.4)	
Neuroendocrine tumor	1,155 (24.6)	83 (26.0)	1,072 (24.5)	
Others	847 (18.1)	79 (24.8)	768 (17.6)	
Grade, N (%)				0.44
Well	47 (1.0)	4 (1.3)	43 (1.0)	
Moderately	73 (1.6)	6 (1.9)	67 (1.5)	
Poorly	238 (5.1)	19 (6.0)	219 (5.0)	
Undifferentiated	37 (0.8)	5 (1.6)	32 (0.7)	
Unknown	4,296 (91.6)	285 (89.3)	4,011 (91.7)	
Bone metastases, N (%)				0.19
Yes	1,284 (27.4)	98 (30.7)	1,186 (27.1)	
No/unknown	3,407 (72.6)	221 (69.3)	3,186 (72.9)	
Brain metastases, N (%)				0.03
Yes	287 (6.1)	29 (9.1)	258 (5.9)	
No/unknown	4,404 (93.9)	290 (90.9)	4,114 (94.1)	

Table 1 (*continued*)

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Table 1 (*continued*)

Characteristics	Total (n=4,691)	Age <50 years (n=319)	Age ≥50 years (n=4,372)	P
Lung metastases, N (%)				<0.001
Yes	1,442 (30.7)	133 (41.7)	1,309 (29.9)	
No/unknown	3,249 (69.3)	186 (58.3)	3,063 (70.1)	
Chemotherapy, N (%)				<0.001
Yes	1,262 (26.9)	179 (56.1)	1,083 (24.8)	
No/unknown	3,429 (73.1)	140 (43.9)	3,289 (75.2)	
Radiotherapy, N (%)				0.10
Yes	456 (9.7)	40 (12.5)	416 (9.5)	
No/unknown	4,235 (90.3)	279 (87.5)	3,956 (90.5)	
Survival months, median [range]	1 [0–121]	4 [0–121]	1 [0–121]	<0.001

NOS, not otherwise specified.

Table 2 Comparison of baseline differences between the two groups after adjustment

Characteristics	Age <50 years (n=305)	Age ≥50 years (n=305)	P
Race, N (%)			0.39
White	230 (75.4)	233 (76.4)	
Black	51 (16.7)	40 (13.1)	
Others	23 (7.5)	29 (9.5)	
Unknown	1 (0.3)	3 (1.0)	
Gender, N (%)			0.94
Male	150 (49.2)	148 (48.5)	
Female	155 (50.8)	157 (51.5)	
Marital at diagnosis, N (%)			0.34
Married	127 (41.6)	133 (43.6)	
Others	158 (51.8)	160 (52.5)	
Unknown	20 (6.6)	12 (3.9)	
Year of diagnosis, N (%)			0.73
2010–2013	81 (26.6)	74 (24.3)	
2014–2017	94 (30.8)	92 (30.2)	
2018–2020	130 (42.6)	139 (45.6)	
Histology, N (%)			0.65
Carcinoma, NOS	39 (12.8)	46 (15.1)	
Adenocarcinoma, NOS	110 (36.1)	118 (38.7)	
Neuroendocrine tumor	81 (26.6)	72 (23.6)	
Others	75 (24.6)	69 (22.6)	

Table 2 (*continued*)

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Table 2 (*continued*)

Characteristics	Age <50 years (n=305)	Age ≥50 years (n=305)	P
Grade, N (%)			0.67
Well	4 (1.3)	6 (2.0)	
Moderately	5 (1.6)	2 (0.7)	
Poorly	16 (5.2)	14 (4.6)	
Undifferentiated	5 (1.6)	3 (1.0)	
Unknown	275 (90.2)	280 (91.8)	
Bone metastases, N (%)			0.93
Yes	89 (29.2)	87 (28.5)	
No/unknown	216 (70.8)	218 (71.5)	
Brain metastases, N (%)			>0.99
Yes	25 (8.2)	24 (7.9)	
No/unknown	280 (91.8)	281 (92.1)	
Lung metastases, N (%)			0.28
Yes	182 (59.7)	196 (64.3)	
No/unknown	123 (40.3)	109 (35.7)	
Chemotherapy, N (%)			0.81
Yes	165 (54.1)	169 (55.4)	
No/unknown	140 (45.9)	136 (44.6)	
Radiotherapy, N (%)			>0.99
Yes	37 (12.1)	36 (11.8)	
No/unknown	268 (87.9)	269 (88.2)	

NOS, not otherwise specified.

analysis of CSS, several variables were identified as significantly associated with improved survival, including age <50 years, neuroendocrine tumor, well-differentiated histology, and the use of radiotherapy and chemotherapy. These results underscore the diverse set of factors that play a role in determining the CSS outcomes for patients with liver metastasis of unknown origin. Following matching, no significant survival difference was observed between the age <50 and age ≥50 years groups (P=0.056) (*Table 4*).

Survival analysis after PSM

The OS of patients with liver metastasis of unknown origin was 14.7% at 1 year, while CSS stood at 23% at 1 year. Individuals in the age <50 years group exhibited a 1-year OS rate of 27.5% and a 1-year CSS rate of 35%. In contrast, those in the age ≥50 years group demonstrated a 1-year OS rate of 13.8% and a 1-year CSS rate of 22%. Upon conducting a comparative analysis following PSM, it was evident that the age <50 years group demonstrated superior OS and CSS outcomes in comparison to the age ≥50 years group, as illustrated in *Figure 2*. Further subgroup analyses before and after PSM demonstrated that the age <50 years group displayed improved OS and CSS compared to the age ≥50 years group among patients treated with chemotherapy (*Figure 3*). Additionally, within patients subjected to radiotherapy, the age <50 years group demonstrated superior OS compared to the age ≥50 years group, although no significant difference was observed in CSS (*Figure 4*). These findings highlight age-specific variations in both overall and CSS rates, especially within distinct treatment subgroups.

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Table 3 Univariate and multivariate Cox analyses for overall survival in patients before adjustment

Characteristics	Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P
Age				
<50 years	0.59 (0.52–0.67)	<0.001	0.72 (0.63–0.82)	<0.001
≥50 years	Reference		Reference	
Race				
White	1.87 (1.14–3.06)	0.01	2.31 (1.41–3.78)	<0.001
Black	1.77 (1.08–2.91)	0.02	2.24 (1.36–3.69)	0.001
Others	1.68 (1.01–2.78)	0.04	2.05 (1.24–3.40)	0.005
Unknown	Reference		Reference	
Gender				
Male	1.08 (1.02–1.15)	0.01	1.09 (1.02–1.15)	0.008
Female	Reference		Reference	
Marital at diagnosis				
Married	0.87 (0.75–1.01)	0.08		
Others	1.05 (0.90–1.21)	0.56		
Unknown	Reference			
Year of diagnosis				
2010–2013	1.09 (1.01–1.18)	0.03	1.05 (0.97–1.14)	0.23
2014–2017	0.94 (0.88–1.01)	0.11	0.94 (0.88–1.01)	0.10
2018–2020	Reference		Reference	
Histology				
Carcinoma, NOS	1.29 (1.17–1.43)	<0.001	1.20 (1.08–1.33)	<0.001
Adenocarcinoma, NOS	1.11 (1.02–1.20)	0.02	1.08 (0.99–1.18)	0.07
Neuroendocrine tumor	0.52 (0.47–0.57)	<0.001	0.49 (0.44–0.54)	<0.001
Others	Reference		Reference	
Grade				
Well	0.34 (0.24–0.49)	<0.001	0.45 (0.31–0.65)	<0.001
Moderately	0.78 (0.61–0.99)	0.04	0.84 (0.66–1.07)	0.15
Poorly	1.31 (1.15–1.50)	<0.001	1.21 (1.05–1.39)	0.007
Undifferentiated	1.18 (0.86–1.64)	0.31	1.70 (1.23–2.36)	0.001
Unknown	Reference		Reference	
Bone metastases				
Yes	1.10 (1.03–1.18)	0.007	1.15 (1.07–1.24)	<0.001
No/unknown	Reference		Reference	

Table 3 (*continued*)

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Table 3 (*continued*)

Characteristics	Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P
Brain metastases				
Yes	1.30 (1.14–1.47)	<0.001	1.29 (1.13–1.47)	<0.001
No/unknown	Reference		Reference	
Lung metastases				
Yes	1.26 (1.18–1.34)	<0.001	1.17 (1.09–1.25)	<0.001
No/unknown	Reference		Reference	
Chemotherapy				
Yes	0.47 (0.44–0.51)	<0.001	0.45 (0.42–0.48)	<0.001
No/unknown	Reference		Reference	
Radiotherapy				
Yes	0.73 (0.66–0.81)	<0.001	0.68 (0.61–0.76)	<0.001
No/unknown	Reference		Reference	

HR, hazard ratio; CI, confidence interval; NOS, not otherwise specified.

Table 4 Post-matching of multifactor Cox and multifactor competition analyses results in patients

Characteristics	Multivariate Cox		Multivariate competing	
	HR (95% CI)	P	SHR (95% CI)	P
Age				
<50 years	0.78 (0.65–0.93)	0.006	0.84 (0.70–1.00)	0.056
≥50 years	Reference		Reference	
Race				
White	0.60 (0.19–1.91)	0.38	0.42 (0.19–0.97)	0.04
Black	0.56 (0.17–1.82)	0.33	0.35 (0.15–0.82)	0.02
Others	0.39 (0.12–1.31)	0.13	0.35 (0.15–0.84)	0.02
Unknown	Reference		Reference	
Gender				
Male	1.05 (0.87–1.25)	0.62	0.96 (0.80–1.14)	0.62
Female	Reference		Reference	
Marital at diagnosis				
Married	1.01 (0.67–1.53)	0.96	1.11 (0.70–1.75)	0.65
Others	0.89 (0.59–1.33)	0.56	1.03 (0.66–1.61)	0.91
Unknown	Reference		Reference	
Year of diagnosis				
2010–2013	1.09 (0.87–1.37)	0.44	0.99 (0.79–1.24)	0.92
2014–2017	0.91 (0.73–1.14)	0.41	0.99 (0.79–1.23)	0.90
2018–2020	Reference		Reference	

Table 4 (*continued*)

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Table 4 (*continued*)

Characteristics	Multivariate Cox		Multivariate competing	
	HR (95% CI)	P	SHR (95% CI)	P
Histology				
Carcinoma, NOS	1.34 (1.00–1.81)	0.05	1.32 (0.97–1.81)	0.08
Adenocarcinoma, NOS	1.30 (1.02–1.65)	0.03	1.20 (0.95–1.53)	0.13
Neuroendocrine tumor	0.48 (0.36–0.64)	<0.001	0.66 (0.51–0.87)	0.003
Others	Reference		Reference	
Grade				
Well	0.80 (0.39–1.64)	0.54	1.10 (0.64–1.87)	0.73
Moderately	0.87 (0.38–1.99)	0.74	1.21 (0.60–2.46)	0.59
Poorly	1.34 (0.89–2.02)	0.16	1.50 (1.08–2.09)	0.02
Undifferentiated	1.82 (0.88–3.76)	0.11	1.86 (1.13–3.06)	0.01
Unknown	Reference		Reference	
Bone metastases				
Yes	1.20 (0.97–1.49)	0.10	1.19 (0.95–1.48)	0.13
No/unknown	Reference		Reference	
Brain metastases				
Yes	1.76 (1.20–2.58)	0.004	1.89 (1.30–2.74)	<0.001
No/unknown	Reference		Reference	
Lung metastases				
Yes	1.15 (0.93–1.41)	0.20	1.11 (0.90–1.36)	0.34
No/unknown	Reference		Reference	
Chemotherapy				
Yes	0.47 (0.39–0.58)	<0.001	0.76 (0.62–0.93)	0.007
No/unknown	Reference		Reference	
Radiotherapy				
Yes	0.73 (0.53–1.01)	0.055	0.79 (0.59–1.06)	0.11
No/unknown	Reference		Reference	

HR, hazard ratio; CI, confidence interval; SHR, subdistribution hazard ratio; NOS, not otherwise specified.

Discussion

CUP refers to metastatic foci diagnosed as malignant tumors via pathological examination, yet the primary site eludes identification despite thorough medical history, physical examination, and pre-treatment tests (10). Factors contributing to the unknown primary site include limitations in detection methods, inadequate pathological tissue sampling, primary site removal, extensive metastasis hindering primary site identification, unique modes of tumor dissemination, diminutive primary site size, spontaneous regression of the primary site, among others (8,11,12). Recent years have witnessed a decline in CUP incidence, potentially attributable to enhanced success rates in identifying primary site tumors (13,14). While liver metastases with known primary sites have been extensively studied (15,16), liver metastases with unknown primary sites remain scarcely explored. Presently, this phenomenon is primarily documented in a limited number of case reports (17). This study, to the best of our knowledge, represents the largest sample size investigation to date,

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Table 5 Univariate and multivariate competing analyses of cancer-specific survival in patients before adjustment

Characteristics	Univariate		Multivariate	
	SHR (95% CI)	P	SHR (95% CI)	P
Age				
<50 years	0.70 (0.62–0.78)	<0.001	0.78 (0.70–0.88)	<0.001
≥50 years	Reference		Reference	
Race				
White	1.71 (1.03–2.84)	0.04	1.91 (1.11–3.29)	0.02
Black	1.56 (0.94–2.61)	0.09	1.78 (1.02–3.07)	0.04
Others	1.56 (0.93–2.61)	0.09	1.72 (0.99–2.99)	0.055
Unknown	Reference		Reference	
Gender				
Male	1.04 (0.98–1.10)	0.16		
Female	Reference			
Marital at diagnosis				
Married	1.02 (0.88–1.18)	0.80		
Others	1.13 (0.97–1.31)	0.11		
Unknown	Reference			
Year of diagnosis				
2010–2013	1.08 (1.01–1.16)	0.03	1.05 (0.98–1.14)	0.18
2014–2017	1.02 (0.95–1.09)	0.58	1.03 (0.96–1.10)	0.42
2018–2020	Reference		Reference	
Histology				
Carcinoma, NOS	1.13 (1.03–1.24)	0.01	1.08 (0.98–1.20)	0.11
Adenocarcinoma, NOS	1.04 (0.96–1.13)	0.32	1.04 (0.96–1.12)	0.39
Neuroendocrine tumor	0.62 (0.57–0.68)	<0.001	0.63 (0.58–0.70)	<0.001
Others	Reference		Reference	
Grade				
Well	0.44 (0.31–0.63)	<0.001	0.58 (0.41–0.82)	0.002
Moderately	0.97 (0.80–1.17)	0.73	1.02 (0.85–1.23)	0.83
Poorly	1.23 (1.09–1.38)	<0.001	1.17 (1.03–1.34)	0.01
Undifferentiated	1.17 (0.89–1.53)	0.27	1.35 (1.00–1.82)	0.054
Unknown	Reference		Reference	
Bone metastases				
Yes	1.17 (1.10–1.24)	<0.001	1.19 (1.11–1.28)	<0.001
No/unknown	Reference		Reference	

Table 5 (*continued*)

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Table 5 (*continued*)

Characteristics	Univariate		Multivariate	
	SHR (95% CI)	P	SHR (95% CI)	P
Brain metastases				
Yes	1.24 (1.12–1.38)	<0.001	1.18 (1.05–1.33)	0.006
No/unknown	Reference		Reference	
Lung metastases				
Yes	1.19 (1.12–1.27)	<0.001	1.10 (1.03–1.18)	0.004
No/unknown	Reference		Reference	
Chemotherapy				
Yes	0.68 (0.64–0.71)	<0.001	0.69 (0.65–0.73)	<0.001
No/unknown	Reference		Reference	
Radiotherapy				
Yes	0.88 (0.82–0.95)	0.002	0.82 (0.75–0.90)	<0.001
No/unknown	Reference		Reference	

SHR, subdistribution hazard ratio; CI, confidence interval; NOS, not otherwise specified.

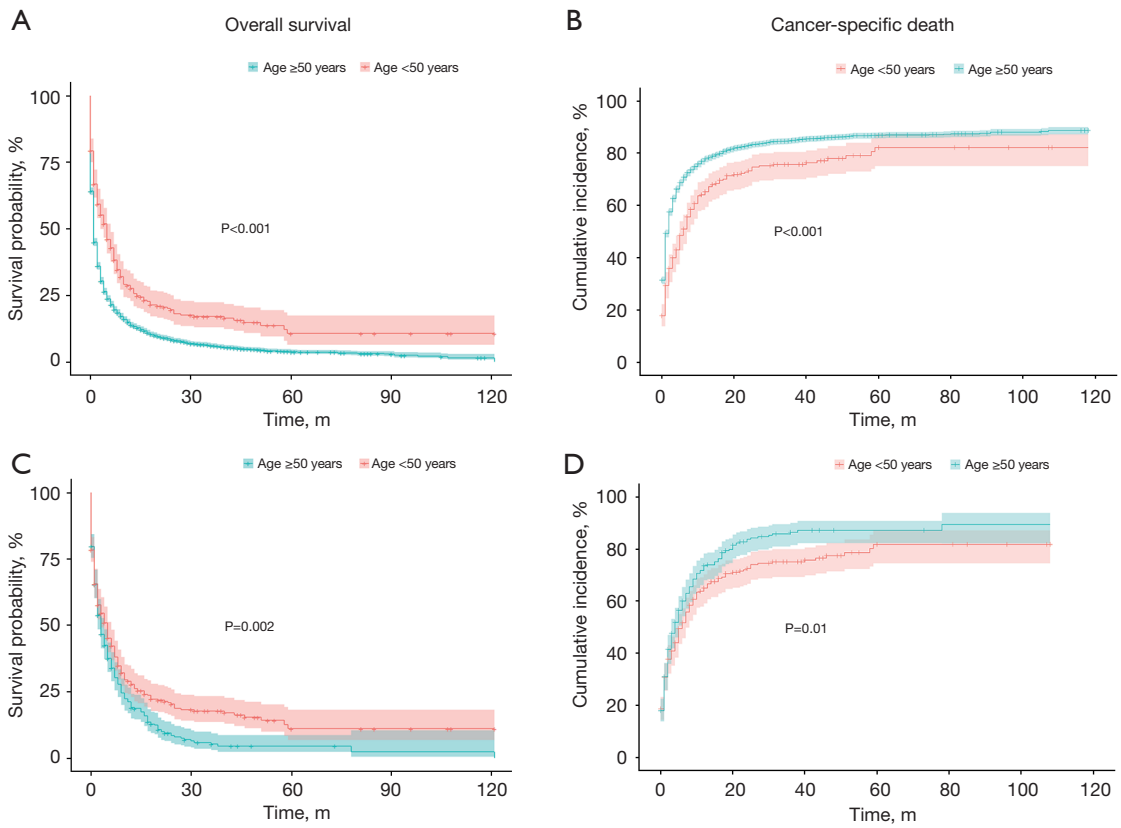

Figure 2 Comparison of overall survival and cancer-specific death analysis of patients in age <50 years and age ≥50 years groups before (A,B) and after (C,D) propensity score matching.

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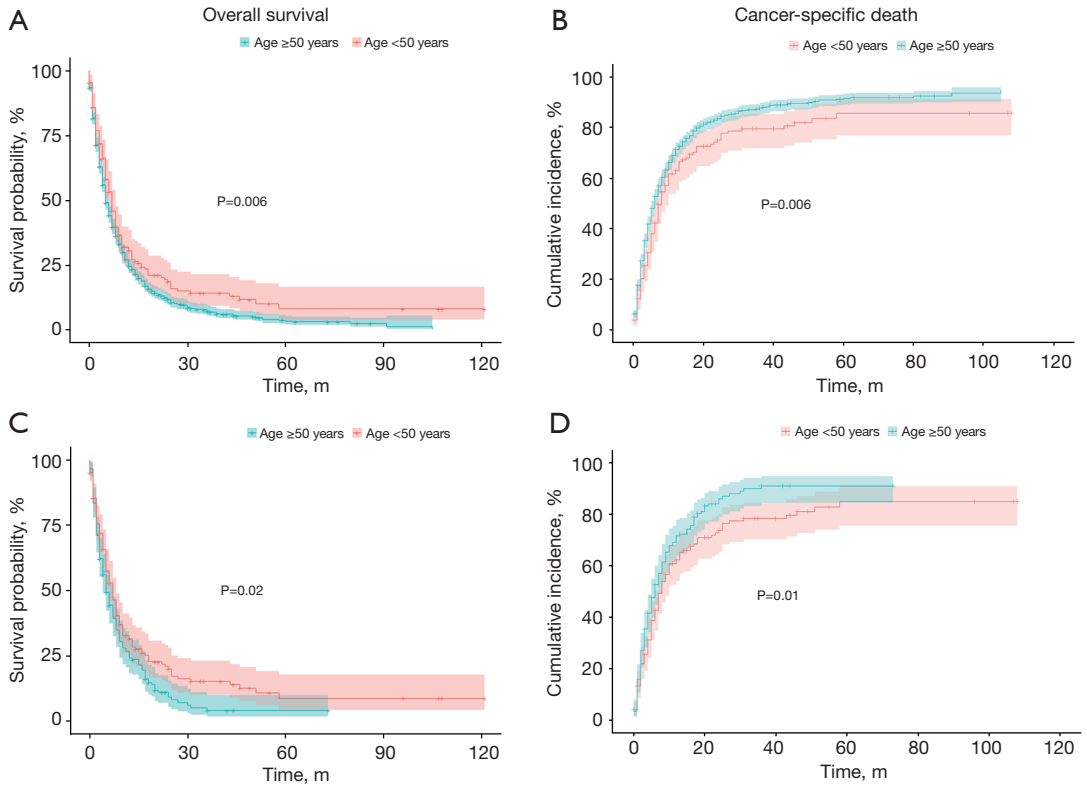

Figure 3 Comparison of overall survival and cancer-specific death between age <50 years and age ≥50 years groups in chemotherapy patients before (A,B) and after (C,D) propensity score matching.

probing into the clinical characteristics and prognosis of patients with CUPL. The survival prognosis for CUP patients is already dismal, and this is further exacerbated when liver metastases are present (18,19). In our study, the 1-year OS rate for patients with liver metastases of unknown primary origin was a mere 14.7%, with a corresponding 1-year CSS rate of 23%. Hence, understanding the clinical characteristics of these patients and identifying viable therapeutic approaches are crucial for improving survival outcomes.

Our findings revealed that the majority of liver metastases of unknown primary origin occurred in age ≥50 years' patients (93.2%), with only a minor proportion (6.8%) aged <50 years. Comparable observations have been reported by others, such as Australian authors noting the rarity of CUP in individuals under 40, with a mean diagnosis age of 75 in 2011, identifying age as a robust risk factor for CUP (10). Our study further underscores age as a common independent prognostic factor influencing both OS and CSS in patients with liver metastases of CUP. Both univariate Cox regression and competing analyses indicated a reduced risk of death in the age <50 years group [HR =0.59, 95% CI: 0.52–0.67; subdistribution HR (SHR) =0.70, 95% CI: 0.62–0.78], and multivariate analyses consistently supported this conclusion (HR =0.72, 95% CI: 0.63–0.82; SHR =0.78, 95% CI: 0.70–0.88). Even after the matching process, age continued to be identified as an independent prognostic factor for OS. This may be attributed to elderly patients' inherent susceptibility to various comorbidities, limited physical tolerance, and reduced accessibility to radiotherapy and chemotherapy, ultimately contributing to a poorer prognosis.

Beyond age, tumor histology and differentiation grade are pivotal factors influencing the prognosis of patients with unexplained liver metastases. Previous studies identified adenocarcinoma as the most prevalent CUP histologic subtype, constituting 50%, with poorly differentiated and undifferentiated carcinoma at 30%, and 15% classified as squamous-cell carcinomas, and 5% as undifferentiated neoplasms (3,6,8,13). Our study aligns with these findings, with adenocarcinoma NOS representing approximately 41% of the total population. Both Cox regression and

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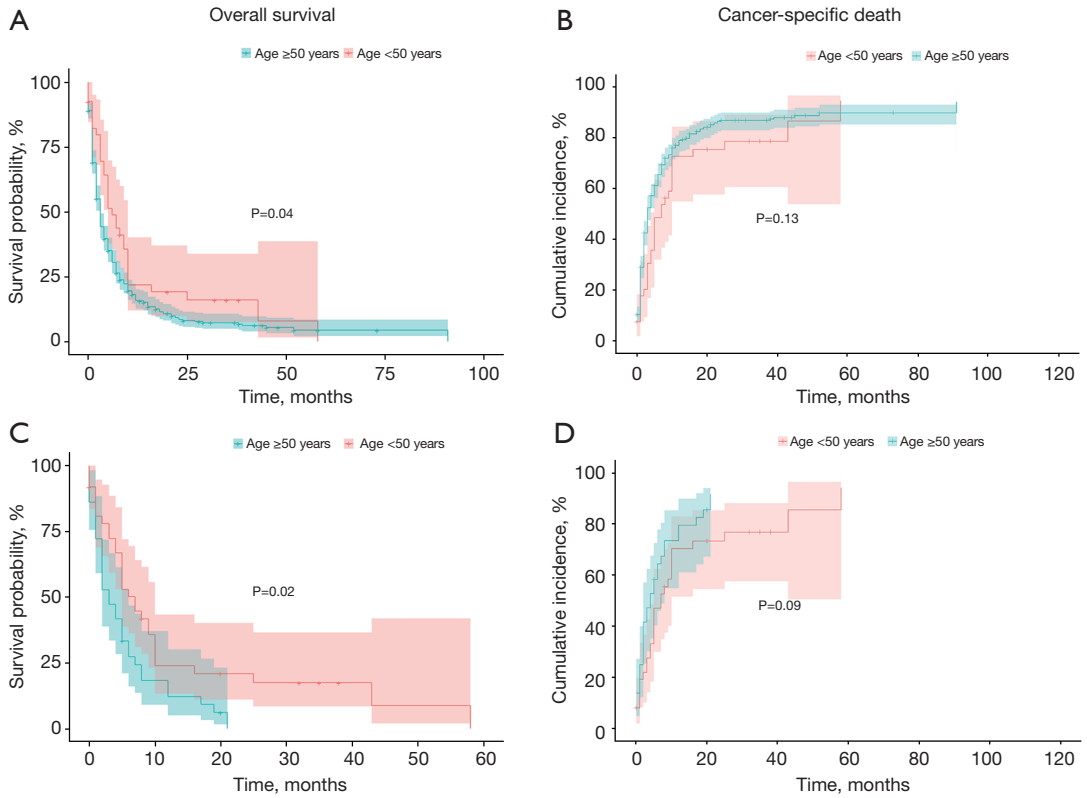

Figure 4 Comparison of overall survival and cancer-specific death between age <50 years and age ≥50 years groups in radiation patients before (A,B) and after (C,D) propensity score matching.

competing analyses results indicated that any tumor, excluding neuroendocrine tumors, predicted a poorer prognosis for patients with liver metastases of CUP.

In the absence of a standard treatment regimen for CUP, general consensus recommends surgical resection if feasible, with postoperative chemotherapy, and for unresectable cases, systemic treatment options may be considered (20-22). Our findings from univariate and multivariate Cox regression, as well as competing risk analyses, suggested that patients with liver metastases receiving radiotherapy and chemotherapy had reduced death risks compared to those without such treatments. Notably, among patients undergoing chemotherapy, the age <50 years group exhibited superior overall and CSS compared to the age ≥50 years group. No significant difference in CSS was observed between younger and older groups among patients receiving radiotherapy. Thus, chemotherapy emerges as a crucial method for improving the prognosis of CUP patients with liver metastases. Other therapeutic avenues, including molecular targeting, immunotherapy, and organ- and target-specific therapies, warrant further investigation.

Acknowledging the limitations of our retrospective study, such as potential selection bias, incomplete treatment data, and lack of information on tumor recurrence in the SEER database, underscores the need for large-scale clinical randomized trials to validate our findings.

Conclusions

In summary, our study unveils that the majority of patients with CUPL are elderly, facing an exceedingly grim survival prognosis. Despite the age <50 years group comprising a small fraction of patients, their overall and CSS outcomes are relatively favorable compared to the age ≥50 years group. Furthermore, survival benefits are associated with chemotherapy, with superior overall and CSS in the age <50 years group receiving chemotherapy compared to their age ≥50 years counterparts.

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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-24-136/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-136/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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