Original Article

Incidence and survival outcomes of secondary liver cancer: a Surveillance Epidemiology and End Results database analysis

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Background: The global incidence and mortality rates of liver cancer, which is the second leading cause of cancer-related deaths worldwide, are increasing. However, information on its epidemiology and clinical prognosis is limited. This study aimed to characterize the epidemiology and prognostic factors of secondary liver cancer to aid in the pretreatment evaluation of the disease.

Methods: Patients diagnosed with secondary liver cancer between 2010 and 2014 in the Surveillance, Epidemiology, and End Results (SEER) database were retrospectively included. Kaplan-Meier analysis and Multivariate Cox regression analysis were performed to screen for significant factors associated with secondary liver cancer.

Results: A total of 85,738 secondary liver cancer patients were identified; in this population, the first primary site was the lung (25.9%), followed by the colorectum, pancreas, stomach, breast, and cecum. Patients with primary tumors of the colorectum, cecum and breast had longer median survival time. Advanced age, male gender, black race, poor differentiation or lack of differentiation, regional lymph node metastases, and presence of distant metastasis were associated with poor prognosis.

Conclusions: In this study, novel findings on the role of the primary site and synchronous distant metastasis to specific organs in patients with secondary liver cancer were described. These findings have significant implications in clinical diagnosis and treatment, and provide a better understanding of secondary liver cancer in the general population.

Keywords: Secondary liver cancer; epidemiology; prognosis; primary site; Surveillance, Epidemiology, and End Results (SEER)

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Introduction

Liver cancer is the fifth and ninth most common cancer in male and female, respectively (1). It is the second leading cause of cancer-related death worldwide (1,2). In 2012, 782,500 newly diagnosed liver cancer cases and 745,500 deaths due to the same were estimated globally (2,3). Moreover, secondary liver cancer is more common than primary liver cancer (4-6).

The liver is one of the most common sites for organ-specific metastasis (7), which is mainly attributable to the organ-specific circulation pattern and distinct anatomy of

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microvessels (8). The liver has a unique dual blood supply system from both the portal vein and the hepatic artery, which increases the possibility of metastatic deposition. In addition, the sinusoidal hepatic endothelial layer is characterized by an incomplete covering of the microvessel structures (9); consequently, the extracellular matrix components are directly accessible to the circulating cells (9,10).

Although the global incidence and mortality rates of liver cancer are increasing, imposing a huge burden on the health care system (3), information regarding the epidemiology and clinical prognosis of secondary liver cancer is still limited. Using data from the Surveillance, Epidemiology, and End Results (SEER) database, we conducted a population-based analysis to comprehensively identify the epidemiological characters and prognostic factors of secondary liver cancer, to potentially help clinicians make better clinical decisions during pretreatment evaluation. We present the following article in accordance with the STORBE reporting checklist (available at http://dx.doi.org/10.21037/tcr-20-3319).

Methods

Data source

As the SEER database is publicly available, and the data used in this study did not include specific patient identifiers, the study did not require a review by the ethics committee. The SEER program is a premier source of cancer statistics in the United States and collects data from 18 population-based central cancer registries while covering 27–30% of the US population (11). SEER*Stat 8.3.5 (National Cancer Institute, MD, USA) software was used to extract the data. We identified 85,738 patients, whose liver metastases were synchronous to the primary tumor as secondary liver cancer patients diagnosed between 2010 and 2014. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Variables

Covariates included demographic variables (age at diagnosis, gender, race) and diagnostic information (primary site, tumor size, grade, lymph nodes stage, and synchronous additional distant metastasis to specific organs). The outcome measures were overall survival (OS, time from the diagnosis of secondary liver cancer to by any cause) and cancer-specific survival (CSS, time from the diagnosis of secondary liver cancer to death by cancer). We used the term "unknown" to represent missing data and treated it as an independent variable during analysis.

Statistical analysis

Kaplan-Meier analysis and log-rank test were used to estimate and compare the outcomes between different primary sites. Multivariate Cox regression models were conducted after adjusting for various covariates to assess the prognostic factors associated with OS and CSS. Hazard ratio (HR) with corresponding 95% confidence interval (95% CI) was used to show the effect of different variables on OS and CSS (12). All tests were two-sided, and $P<0.05$ was considered statistically significant. Statistical analyses were performed using SPSS version 21.0 (IBM Corp, Armonk, NY, USA).

Results

Demographics and clinical characteristics

A total of 85,738 patients with secondary liver cancer were included in our study. As shown in *Table 1*, majority of the secondary liver cancers originated from the digestive system (56.9%), and the six most common primary sites were the lung (25.9%), colorectum (21.4%), pancreas (19.6%), stomach (4.6%), breast (4.4%) and cecum (4.1%). When stratified by race, the first primary site was the lung for White and the colorectum for Black or Others patients. Interestingly, there was a significant number of male cases whose primary site was esophagus or stomach (male: female=10.5:3.7).

Considering that unspecific or unknown primary sites, as well as the shortage of cases could contribute as potential confounding factors, we only showed patient characteristics for those who had secondary liver cancer from the top six primary sites described above (*Table 2*). For patients with breast as the primary site, the proportion below the age of 40 was high. We also observed that patients, whose primary sites were the lung or breast, were more likely to have synchronous distant metastasis, especially bone metastasis.

Survival outcomes

Among the total study population, the median and average OS were 3 months and 7.680±10.467 months, respectively, and that for CSS were 2 months and 5.820±8.015 months,

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Table 1 Relative frequencies of secondary liver cancer patients by primary site, gender, and race

Primary site	Total		Gender				Race							
			Male		Female		White		Black		Others		Unknown	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Esophagus	2,296	2.7	1,976	4.4	320	0.8	2,023	3.0	182	1.6	84	1.3	7	2.7
Stomach	3,915	4.6	2,758	6.1	1,157	2.9	2,797	4.2	626	5.4	472	7.1	20	7.6
Small intestine	1,249	1.5	663	1.5	586	1.4	991	1.5	204	1.7	53	0.8	1	0.4
Cecum	3,542	4.1	1,710	3.8	1,832	4.5	2,696	4.0	651	5.6	186	2.8	9	3.4
Colorectum	18,334	21.4	10,460	23.2	7,874	19.4	13,755	20.5	2,770	23.7	1,754	26.4	55	21.0
Gallbladder/Biliary tract	2,603	3.0	1,089	2.4	1,514	3.7	1,976	2.9	332	2.8	287	4.3	8	3.1
Pancreas	16,841	19.6	9,139	20.2	7,702	19.0	13,186	19.6	2,285	19.6	1,304	19.6	66	25.2
Lung	22,214	25.9	12,234	27.1	9,980	24.6	18,413	27.4	2,376	20.3	1,389	20.9	36	13.7
Breast	3,745	4.4	22	0.0	3,723	9.2	2,757	4.1	679	5.8	294	4.4	15	5.7
Urinary system	2,609	3.0	1,668	3.7	941	2.3	2,101	3.1	322	2.8	180	2.7	6	2.3
Reproductive system	3,603	4.2	809	1.8	2,794	6.9	2,700	4.0	613	5.2	276	4.2	14	5.3
Others	4,787	5.6	2,643	5.9	2,144	5.3	3,753	5.6	643	5.5	366	5.5	25	9.5
Total	85,738	100	45,171	100	40,567	100	67,148	100	11,683	100	6,645	100	262	100

respectively (*Table 3*). The OS and CSS Kaplan–Meier curves showed significant differences in survival outcomes according to primary sites (*Figure 1*). The median CSS of patients with the colorectum as the primary site was 6 months, which was greater than that of patients with other primary sites. Patients whose primary sites were the lung and pancreas had the worst median CSS of 2 months (*Table 3*).

Multivariate prognostic factors

Results of the multivariate analysis indicated that advanced age, male gender, black race, poor differentiation or lack of differentiation, and regional lymph node metastases were associated with poor prognosis (*Table 4*). Patients with the pancreas, lung or stomach as the primary site had a higher risk of poor outcomes. (*Table 4*).

The number of patients who had synchronous distant metastasis to specific organs was limited; hence, we analyzed this variable in specific cohorts. In the cohort of patients under the first six primary sites, the site specific HR for metastasis were: brain, CSS: 1.189, P<0.001; lung, CSS: 1.154, P<0.001; and bone, CSS: 1.096, P<0.001 (*Table 4*). In the cohort of patients with colorectum as the primary site, combined with bone metastasis had the worst CSS (HR: 1.402, P<0.001). In the cohort of patients with pancreas as the primary site, combined with brain metastasis had the worst CSS (HR: 1.61, P=0.007). In the cohort of patients with the lung as the primary site, HR for metastasis showed no significant difference (*Table 5*).

Discussion

Population-based incidence and survival studies can provide valuable information for clinicians, researchers, and public health officials; these can also guide the direction of future research. In this study, we described the incidence, survival outcomes and prognostic factors of secondary liver cancer. Our findings indicate that the most common primary site was the lung, followed by the colorectum and pancreas, consistent with the findings of previous studies (6,13). However, Bosch *et al*. (14) established the breast as the most common primary site. This difference can be mainly attributed to the inclusion criteria set for study participants. Lung and pancreatic metastases are commonly synchronous, but breast metastasis tends to be metachronous (15,16). Moreover, the median disease-free interval before clinical

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Table 2 Characteristics of secondary liver cancer patients from the six most common primary sites

Characteristic	Total, No. (%)	Stomach, No. (%)	Cecum, No. (%)	Colorectum, No. (%)	Pancreas, No. (%)	Lung, No. (%)	Breast, No. (%)
All subjects	68,591 (100.0)	3,915 (100.0)	3,542 (100.0)	1,8334 (100.0)	1,6841 (100.0)	22,214 (100.0)	3,745 (100.0)
Age at diagnosis, years							
<40	16,54 (2.4)	128 (3.3)	62 (1.8)	768 (4.2)	219 (1.3)	140 (0.6)	337 (9.0)
40–59	19,707 (28.7)	1,127 (28.8)	1,005 (28.4)	6,620 (36.1)	4,209 (25.0)	5,120 (23.0)	1,626 (43.4)
60–79	36,284 (52.9)	2,022 (51.6)	1,736 (49.0)	8,201 (44.7)	9,350 (55.5)	13,551 (61.0)	1,424 (38.0)
≥80	10,946 (16.0)	638 (16.3)	739 (20.9)	2,745 (15.0)	3,063 (18.2)	3,403 (15.3)	358 (9.6)
Tumor size, cm							
<2	3,361 (4.9)	101 (2.6)	89 (2.5)	471 (2.6)	650 (3.9)	1,629 (7.3)	421 (11.2)
2–4	21,855 (31.9)	596 (15.2)	981 (27.7)	4,295 (23.4)	7,751 (46.0)	6,967 (31.4)	1,265 (33.8)
5–9	19,141 (27.9)	758 (19.4)	1,401 (39.6)	5,740 (31.3)	4,204 (25.0),	6,127 (27.6)	911 (24.3)
≥10	2,795 (4.1)	220 (5.6)	171 (4.8)	826 (4.5)	323 (1.9)	962 (4.3)	293 (7.8)
Unknown	21,439 (31.3)	2,240 (57.2)	900 (25.4)	7,002 (38.2)	3,913 (23.2)	6,529 (29.4)	855 (22.8)
Grade							
Grade I	1,620 (2.4)	97 (2.5)	192 (5.4)	665 (3.6)	343 (2.0)	195 (0.9)	128 (3.4)
Grade II	14,484 (21.1)	933 (23.8)	1,684 (47.5)	8,847 (48.3)	1,095 (6.5)	918 (4.1)	1,007 (26.9)
Grade III	12,427 (18.1)	1,814 (46.3)	687 (19.4)	2,892 (15.8)	1,693 (10.1)	3,748 (16.9)	1,593 (42.5)
Grade IV	2,023 (2.9)	75 (1.9)	159 (4.5)	501 (2.7)	146 (0.9)	1,110 (5.0)	32 (0.9)
Unknown	38,037 (55.5)	996 (25.4)	820 (23.2)	5,429 (29.6)	13,564 (80.5)	16,243 (73.1)	985 (26.3)
N–stage							
Node negative	2,588 (3.8)	65 (1.7)	270 (7.6)	1,710 (9.3)	228 (1.4)	167 (0.8)	148 (4.0)
Node positive	11,671 (17.0)	248 (6.3)	1,821 (51.4)	5,938 (32.4)	507 (3.0)	2,010 (9.0)	1,147 (30.6)
Unknown	54,332 (79.2)	3,602 (92.0)	1,451 (41.0)	10,686 (58.3)	16,106 (95.6)	20,037 (90.2)	2,450 (65.4)
Additional metastasis							
None	37,828 (55.2)	2,756 (70.4)	2,594 (73.2)	12,431 (67.8)	12,273 (72.9)	6,822 (30.7)	952 (25.4)
Bone	7,313 (10.7)	207 (5.3)	90 (2.5)	506 (2.8)	592 (3.5)	4,792 (21.6)	1,126 (30.1)
Brain	1,477 (2.2)	22 (0.6)	5 (0.1)	52 (0.3)	36 (0.2)	1,329 (6.0)	33 (0.9)
Lung	9,461 (13.8)	490 (12.5)	588 (16.6)	3,721 (20.3)	2,272 (13.5)	2,054 (9.2)	336 (9.0)
Two or Three	7,574 (11.0)	156 (4.0)	101 (2.9)	546 (3.0)	442 (2.6)	5,317 (23.9)	1,012 (27.0)
Unknown	4,938 (7.2)	284 (7.3)	164 (4.6)	1,078 (5.9)	1,226 (7.3)	1,900 (8.6)	286 (7.6)

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Table 3 Survival time of secondary liver cancer patients with the first six primary sites

Primary site	No. (%)	Overall survival			Cancer-specific survival		
		Median	Average	SE	Median	Average	SE
Stomach	3,915 (5.7)	3	6.95	9.529	3	5.36	6.85
Cecum	3,542 (5.2)	7	11.2	12.256	5	9.14	10.087
Colorectum	18,334 (26.7)	8	12.28	12.954	6	9.69	10.676
Pancreas	16,841 (24.6)	2	4.79	7.39	2	3.91	5.627
Lung	22,214 (32.4)	2	4.7	6.763	2	4.18	5.676
Breast	3,745 (5.5)	8	13.23	13.948	4	9.24	11.22
Total	68,591 (100.0)	3	7.68	10.467	2	5.82	8.015

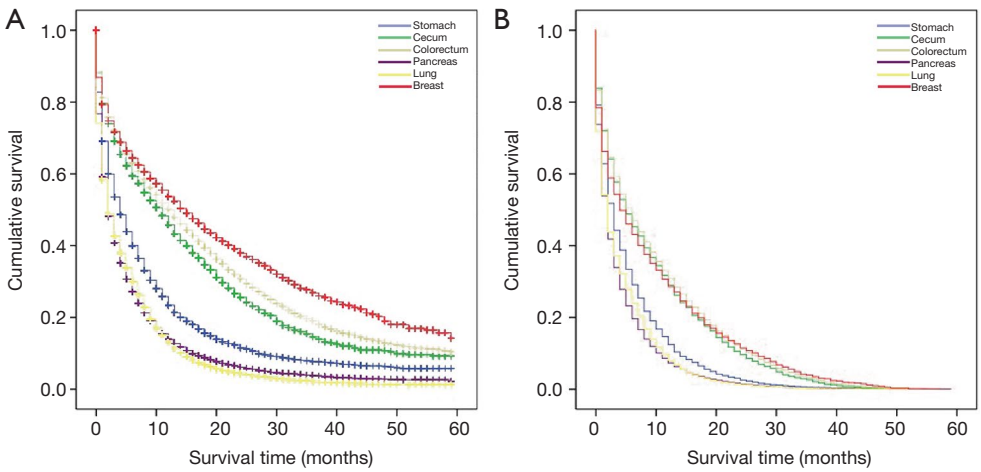

Figure 1 Comparison of survival in secondary liver cancer patients according to specific primary sites. Kaplan-Meier analysis for overall survival (A) and cancer-specific survival (B).

liver metastasis for breast cancer patients is 20.2 months (16).

We found that advanced age, male gender, black race, poor differentiation or lack of differentiation, and regional lymph node metastases were associated with worse prognosis; however, the impact of race and tumor size were not obvious. Tumor size is closely correlated with the cancer stage at diagnosis (17). Generally, patients with small tumor size are asymptomatic, and computed tomography, magnetic resonance imaging, or positron emission tomography are not performed unless metastatic disease is suspected (5,18). Therefore, we speculate that patients with small tumors included in our study were diagnosed at an early stage due to their more severe clinical manifestations, which weakened the association between tumor size and prognosis. Nevertheless, liver function and other clinical indexes were not available during our study; hence, this speculation must be verified through further research.

Previous studies were mostly based on single-institution experience and focused on one specific primary cancer site; therefore, the survival time of secondary liver cancer patients was rarely described systematically with respect to the primary sites. For example, in secondary liver patients deriving from colorectum who undergo primary tumor resection, the mean survival is approximately 6-9 months (19,20). Another study reported that for secondary liver cancer patients deriving from breast cancer, the median OS was 7 months (21). One epidemiological study on secondary liver cancer patients deriving from adenocarcinoma and

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Table 4 Multivariate analyses of factors affecting overall survival and cancer-specific survival in secondary liver cancer patients from the six most common primary sites

Variable	TOTAL			
	Overall survival		Cancer-specific survival	
	HR (95% CI)	P value	HR (95% CI)	P value
Primary site				
Stomach	1.00 (reference)		1.00 (reference)	
Cecum	0.891 (0.844–0.942)	<0.001	0.843 (0.796–0.892)	<0.001
Colorectum	0.773 (0.742–0.805)	<0.001	0.772 (0.74–0.805)	<0.001
Pancreas	1.371 (1.316–1.428)	<0.001	1.224 (1.173–1.277)	<0.001
Lung	1.221 (1.173–1.272)	<0.001	1.087 (1.042–1.134)	<0.001
Breast	0.605 (0.571–0.641)	<0.001	0.749 (0.706–0.795)	<0.001
Age at diagnosis, years				
<40	1.00 (reference)		1.00 (reference)	
40–59	1.354 (1.265–1.449)	<0.001	1.185 (1.105–1.271)	<0.001
60–79	1.866 (1.744–1.995)	<0.001	1.519 (1.418–1.628)	<0.001
≥80	3.067 (2.862–3.288)	<0.001	2.288 (2.13–2.457)	<0.001
Gender				
Male	1.00 (reference)		1.00 (reference)	
Female	0.942 (0.926–0.959)	<0.001	0.953 (0.936–0.971)	<0.001
Race				
White	1.00 (reference)		1.00 (reference)	
Black	1.105 (1.078–1.133)	<0.001	1.064 (1.037–1.091)	<0.001
Others	0.879 (0.851–0.908)	<0.001	0.93 (0.899–0.961)	<0.001
Tumor size, cm				
<2	1.00 (reference)		1.00 (reference)	
2–4	0.998 (0.958–1.04)	0.924	0.998 (0.956–1.042)	0.943
5–9	1.11 (1.064–1.157)	<0.001	1.093 (1.046–1.141)	<0.001
≥10	1.191 (1.125–1.261)	<0.001	1.18 (1.112–1.252)	<0.001
Grade				
Grade I	1.00 (reference)		1.00 (reference)	
Grade II	1.362 (1.273–1.458)	<0.001	1.124 (1.047–1.206)	0.001
Grade III	1.986 (1.856–2.125)	<0.001	1.489 (1.388–1.597)	<0.001
Grade IV	2.056 (1.897–2.229)	<0.001	1.496 (1.376–1.627)	<0.001
N-stage				
Node negative	1.00 (reference)		1.00 (reference)	
Node positive	2.197 (2.072–2.33)	<0.001	1.514 (1.424–1.61)	<0.001

Table 4 (*continued*)

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Table 4 (*continued*)

Variable	TOTAL			
	Overall survival		Cancer-specific survival	
	HR (95% CI)	P value	HR (95% CI)	P value
Additional metastasis				
None	1.00 (reference)		1.00 (reference)	
Bone	1.164 (1.128–1.2)	<0.001	1.096 (1.062–1.131)	<0.001
Brain	1.28 (1.209–1.356)	<0.001	1.189 (1.121–1.261)	<0.001
Lung	1.244 (1.212–1.276)	<0.001	1.154 (1.124–1.185)	<0.001
Two or Three	1.312 (1.273–1.353)	<0.001	1.223 (1.185–1.261)	<0.001

Model adjusted for primary site, age at diagnosis, gender, race, tumor size, grade, N-stage, and additional metastasis.

small cell lung cancer showed the mean OS was 3 months and 4 months, respectively (22). Owing to the bias caused by the inclusion criteria, number of participants, data sources, and the survival time reported in different studies varies greatly, highlighting the need for the current study to help fill in the gaps. In contrast, this bias was reduced in our study, hence providing more objective and accurate findings. Overall, we performed a horizontal comparison among secondary liver cancer patients from the six most common primary sites, and found that patients whose primary sites were the colorectum, breast, and cecum had longer CSS than those whose primary sites were the stomach, lung, and pancreas.

Interestingly, we found that for secondary liver cancer patients deriving from colorectum, bone metastasis was a poor prognostic factor, as compared to metastases in other organs. Bone metastasis is very rare and the prognosis for colorectal cancer is poor (23-25). Moreover, numerous skeletal-related clinical events may occur in patients with bone metastasis, which decreases the patients' functionality and quality of life (26,27). Early secondary liver cancer is asymptomatic, whereas bone metastasis is often symptomatic; therefore, bone metastasis could act as a warning signal during disease screening. We also found that for patients deriving from pancreas, brain metastasis was a poor prognostic factor. It is extremely rare in pancreatic cancer and only a few case reports exist for reference (28). In most of the reported cases, the disease had rapidly progressed, and the patients soon died after palliative treatment (28-30). Moreover, patients benefit poorly from surgical resection of brain metastases (30,31).

A current study reported that circulation patterns, extravasation barriers, and survival on arrival are three key determinants of the capacity of particular tumors to seed specific organs (32). Furthermore, the microenvironment, chemokines, and microRNAs are being widely investigated to reveal the molecular mechanisms of metastatic organ tropism (32-35). Based on our findings, we conclude that there may be interactions between synchronous distant metastases and the primary sites in secondary liver cancer, which influence its incidence and prognosis, and this conclusion provides clinical evidence for basic research.

The present study has some potential limitations. First, the SEER database did not include information on synchronous distant metastasis to specific organs until 2010; therefore, the follow-up period was not long enough. Second, we were limited to the information that the SEER database provided; hence, systemic therapy, other metastatic sites, and physical condition of patients that may relate to prognosis were not considered.

Despite these limitations, our study is the most comprehensive population-based analysis for secondary liver cancer. These findings can help oncologists and hepatologists design personalized treatment and appropriate follow-up strategy, and provide a better understanding of secondary liver cancer for the general population.

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Table 5 Multivariate analyses of factors affecting overall survival and cancer-specific survival in secondary liver cancer patients with the specific primary sites

Variable	Primary site											
	Colorectum				Pancreas				Lung			
	Overall survival		Cancer-specific survival		Overall survival		Cancer-specific survival		Overall survival		Cancer-specific survival	
	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value
Age at diagnosis, years												
<40	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
40–59	1.102 (0.994–1.221)	0.064	1.097 (0.987–1.219)	0.085	1.725 (1.446–2.058)	<0.001	1.52 (1.266–1.825)	<0.001	1.543 (1.266–1.882)	<0.001	1.253 (1.021–1.538)	0.031
60–79	1.702 (1.538–1.883)	<0.001	1.478 (1.332–1.64)	<0.001	2.381 (2–2.836)	<0.001	1.947 (1.624–2.334)	<0.001	1.924 (1.58–2.344)	<0.001	1.559 (1.272–1.91)	<0.001
≥80	3.384 (3.042–3.764)	<0.001	2.473 (2.216–2.759)	<0.001	3.971 (3.324–4.742)	<0.001	3.102 (2.579–3.731)	<0.001	2.735 (2.24–3.34)	<0.001	2.117 (1.723–2.601)	<0.001
Gender												
Male	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Female	1.024 (0.987–1.061)	0.202	1.037 (0.999–1.077)	0.058	0.966 (0.934–0.998)	0.038	0.955 (0.923–0.988)	0.008	0.871 (0.846–0.896)	<0.001	0.898 (0.872–0.924)	<0.001
Race												
White	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Black	1.234 (1.175–1.296)	0.064	1.077 (1.023–1.133)	0.005	1.138 (1.085–1.194)	<0.001	1.121 (1.067–1.177)	<0.001	1.01 (0.965–1.057)	0.656	1.017 (0.97–1.067)	0.473
Others	0.956 (0.898–1.018)	<0.001	0.962 (0.901–1.027)	0.246	0.976 (0.918–1.038)	0.437	1.007 (0.945–1.072)	0.838	0.745 (0.701–0.792)	<0.001	0.822 (0.772–0.876)	<0.001
Tumor size, cm												
<2	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
2–4	0.911 (0.807–1.028)	0.132	0.942 (0.829–1.07)	0.356	1.011 (0.927–1.103)	0.799	0.993 (0.907–1.086)	0.870	1.027 (0.969–1.088)	0.373	1.017 (0.958–1.08)	0.579
5–9	1.08 (0.959–1.217)	0.203	1.073 (0.947–1.217)	0.267	1.101 (1.006–1.204)	0.036	1.107 (1.009–1.214)	0.032	1.14 (1.074–1.209)	<0.001	1.097 (1.032–1.166)	0.003
≥10	1.275 (1.108–1.467)	0.001	1.224 (1.057–1.418)	0.007	1.113 (0.961–1.289)	0.153	1.183 (1.017–1.377)	0.029	1.217 (1.118–1.325)	<0.001	1.178 (1.079–1.287)	<0.001

Table 5 (*continued*)

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Table 5 (*continued*)

Variable	Primary site											
	Colorectum				Pancreas				Lung			
	Overall survival		Cancer-specific survival		Overall survival		Cancer-specific survival		Overall survival		Cancer-specific survival	
	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value
Grade												
Grade I	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Grade II	1.041 (0.939–1.154)	0.443	1.031 (0.927–1.147)	0.575	2.279 (1.934–2.685)	<0.001	1.551 (1.309–1.838)	<0.001	1.273 (1.064–1.524)	0.008	1.071 (0.889–1.29)	0.471
Grade III	1.645 (1.476–1.834)	<0.001	1.459 (1.304–1.633)	<0.001	3.089 (2.636–3.62)	<0.001	1.899 (1.611–2.237)	<0.001	1.703 (1.439–2.015)	<0.001	1.35 (1.133–1.609)	0.001
Grade IV	1.926 (1.667–2.226)	<0.001	1.512 (1.3–1.758)	<0.001	3.059 (2.425–3.858)	<0.001	2.026 (1.598–2.568)	<0.001	1.697 (1.423–2.023)	<0.001	1.257 (1.046–1.51)	0.015
N-stage												
Node negative	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Node positive	1.618 (1.493–1.754)	<0.001	1.189 (1.092–1.294)	<0.001	1.225 (1.01–1.486)	0.039	1.169 (0.959–1.425)	0.122	1.134 (0.945–1.359)	0.176	0.977 (0.811–1.178)	0.808
Additional metastasis												
None	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Bone	1.557 (1.406–1.726)	<0.001	1.402 (1.262–1.557)	<0.001	1.181 (1.08–1.291)	<0.001	1.158 (1.058–1.269)	0.002	1.079 (1.042–1.117)	<0.001	1.055 (1.017–1.094)	0.004
Brain	1.795 (1.334–2.416)	<0.001	1.219 (0.899–1.652)	0.202	1.634 (1.161–2.301)	0.005	1.61 (1.137–2.279)	0.007	1.144 (1.077–1.217)	<0.001	1.115 (1.047–1.187)	0.001
Lung	1.24 (1.185–1.297)	<0.001	1.117 (1.066–1.17)	<0.001	1.302 (1.241–1.365)	<0.001	1.234 (1.175–1.295)	<0.001	1.134 (1.076–1.194)	<0.001	1.102 (1.044–1.164)	<0.001
Two or Three	1.721 (1.562–1.896)	<0.001	1.394 (1.263–1.54)	<0.001	1.503 (1.362–1.658)	<0.001	1.331 (1.202–1.473)	<0.001	1.162 (1.11–1.216)	<0.001	1.153 (1.101–1.208)	<0.001

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Footnote

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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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