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Clinicopathological Characteristics, Survival and Prognostic Factors in Gastrointestinal Large Cell Neuroendocrine Carcinoma

A Retrospective Cohort Study

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Objectives: Gastrointestinal large cell neuroendocrine carcinoma (GILCNEC) has a low incidence but high malignancy and poor prognosis. The main purpose of this study was to thoroughly investigate its clinicopathological features, survival and prognostic factors.

Methods: Information on patients with GILCNEC was extracted from the Surveillance, Epidemiology, and End Result program, and prognostic factors were analyzed by analyzing clinicopathological data and survival functions. Finally, multivariate analysis was applied to identify independent risk factors associated with survival.

Results: A total of 531 individuals were screened in our study from the Surveillance, Epidemiology, and End Result database. The primary sites are mainly from the following: esophagus in 39 (7.3%) patients, stomach in 72 (13.6%) patients, hepatobiliary in 51 (9.6%) patients, pancreas in 97 (18.3%) patients, small intestines in 27 (5.1%), and colorectum in 245 (46.1%) patients. Esophagus, stomach, pancreas, and colorectum large cell neuroendocrine carcinoma (LCNEC) were more common in males ($P = 0.001$). Esophagus LCNEC had inferior overall survival (OS), whereas small intestine LCNEC was associated with better OS. The results of multivariate analysis showed that the American Joint Committee on Cancer Sixth Edition stage, surgery, and radiotherapy were independent prognostic indicators of OS in patients with GILCNEC ($P < 0.05$).

Conclusions: The prognosis of patients with GILCNEC varies depending on the primary tumor site. American Joint Committee on Cancer Sixth Edition stage, surgery, and radiotherapy are independent prognostic factors of patients with GILCNEC. Although surgery and radiotherapy can prolong the survival of patients with GILCNEC, their prognosis remains poor, and further prospectively designed multicenter clinical studies are needed to indicate the decision for clinicians.

Key Words: prognosis, gastrointestinal large cell neuroendocrine carcinoma, GILCNEC, SEER

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Neuroendocrine neoplasms (NENs) are rare heterogeneous tumors originating from secretory cells of the diffuse neuroendocrine system,[1,2] and their incidence is rising at an alarming rate.[3] The gastrointestinal tract is a common site of origin for NENs, accounting for ~2/3 of all patients,[1] with the intestine, pancreas, colorectum, and appendix being the sites of origin with the highest incidence.[4] The Fifth Edition of the World Health Organization (WHO) Classification of Tumors of the Digestive System, published in 2019, divides gastrointestinal NENs into well-differentiated neuroendocrine tumors (NETs) and poorly differentiated neuroendocrine carcinomas (NECs), the latter being further divided into small cell NECs and large cell neuroendocrine carcinomas (LCNECs).[5] In 1991, Travis first identified a specific subtype called pulmonary LCNEC.[6] LCNECs possess more open nuclei, prominent nucleoli, pro-amphophilic cytoplasm, and distinct necrotic areas.[7] Its typical molecular markers are a high proliferative rate based on Ki-67 staining, abnormal p53, and absent Rb staining. They also express high levels of Bcl-2 which has antiapoptotic activity and p21 which is a marker of angiogenesis.[8] There are limited studies on the prognosis of gastrointestinal extrapulmonary LCNEC (gastrointestinal large cell neuroendocrine carcinoma [GILCNEC]), and most of them are single cancer studies and case reports.[9–11] A Dutch registry study showed that the 5-year overall survival (OS) of patients with LCNEC was only 20%.[12]

Studies on the primary tumor site and prognostic factors and clinicopathological in GILCNEC have not been reported. However, there is increasing evidence that GILCNEC has a significantly increased incidence and poor prognosis.[12–14] The main purpose of this work was to assess the effect of the primary tumor site on GILCNEC prognosis and to evaluate influencing the prognosis and predicting treatment response factors by analyzing the clinicopathological features. Ultimately to guide clinical treatment.

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The authors declare no conflicts of interest.

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TABLE 1. Patient Characteristics

Variable	Primary site of tumor (N = 531)												
	Esophagus ï¼Nï¼	(%)	Stomach ï¼Nï¼	(%)	Hepatobiliary ï¼Nï¼	(%)	Pancreas ï¼Nï¼	(%)	Small intestines ï¼Nï¼	(%)	Colorectum ï¼Nï¼	(%)	*P*
Age (y)													
< 65	19	48.72	20	27.78	24	47.06	56	57.73	14	51.85	109	44.49	0.008
≥ 65	20	51.28	52	72.22	27	52.94	41	42.27	13	48.15	136	55.51	—
Sex													
Female	7	17.95	21	29.17	28	54.90	39	40.21	14	51.85	116	47.35	0.001
Male	32	82.05	51	70.83	23	45.10	58	59.79	13	48.15	129	52.65	—
Race													
White	35	89.74	47	65.28	43	84.31	67	69.07	20	74.07	206	84.08	0.005
Black	3	7.69	14	19.44	4	7.84	17	17.53	6	22.22	28	11.43	—
Others	1	2.56	11	15.28	4	7.84	13	13.40	1	3.70	11	4.49	—
Marital status													
Married	25	64.10	37	51.39	37	72.55	50	51.55	9	33.33	135	55.10	0.020
Single	7	17.95	14	19.44	5	9.80	21	21.65	10	37.04	34	13.88	—
Others	7	17.95	21	29.17	9	17.65	26	26.80	8	29.63	76	31.02	—
Tumor size (mm)													
< 50	5	12.82	14	19.44	20	39.22	39	40.21	10	37.04	87	35.51	< 0.001
≥ 50	14	35.90	37	51.39	19	37.25	40	41.24	9	33.33	117	47.76	—
NA	20	51.28	21	29.17	12	23.53	18	18.56	8	29.63	41	16.73	—
Grade													
Well-differentiated (grade I)	0	0.00	0	0.00	1	1.96	1	1.03	1	3.70	3	1.22	< 0.001
Moderately differentiated (grade II)	0	0.00	1	1.39	0	0.00	3	3.09	0	0.00	1	0.41	—
Poorly differentiated (grade III)	22	56.41	30	41.67	24	47.06	39	40.21	12	44.44	95	38.78	—
Undifferentiated (grade IV)	7	17.95	16	22.22	13	25.49	8	8.25	4	14.81	91	37.14	—
NA	10	25.64	25	34.72	13	25.49	46	47.42	10	37.04	55	22.45	—
AJCC Sixth edition													
T													
T0	0	0.00	0	0.00	0	0.00	1	1.03	0	0.00	0	0.00	< 0.001
T1	8	20.51	7	9.72	4	7.84	3	3.09	1	3.70	11	4.49	—
T2	2	5.13	15	20.83	3	5.88	12	12.37	1	3.70	10	4.08	—
T3	5	12.82	2	2.78	12	23.53	29	29.90	6	22.22	69	28.16	—
T4	5	12.82	9	12.50	2	3.92	7	7.22	8	29.63	45	18.37	—
NA	19	48.72	39	54.17	30	58.82	45	46.39	11	40.74	110	44.90	—
N													
N0	13	33.33	15	20.83	17	33.33	18	18.56	5	18.52	39	15.92	< 0.001
N1	11	28.21	20	27.78	5	9.80	30	30.93	11	40.74	50	20.41	—
N2	0	0.00	4	5.56	0	0.00	0	0.00	0	0.00	57	23.27	—
N3	0	0.00	1	1.39	0	0.00	0	0.00	0	0.00	0	0.00	—
NA	15	38.46	32	44.44	29	56.86	49	50.52	11	40.74	99	40.41	—
M													
M0	7	17.95	26	36.11	17	33.33	18	18.56	8	29.63	75	30.61	0.007
M1	19	48.72	19	26.39	8	15.69	30	30.93	8	29.63	77	31.43	—
NA	13	33.33	27	37.50	26	50.98	49	50.52	11	40.74	93	37.96	—
Stage													

I	2	5.13	9	12.50	7	13.73	0	0.00	1	3.70	10	4.08	< 0.001
II	4	10.26	7	9.72	8	15.69	16	16.49	1	3.70	11	4.49	—
III	0	0.00	6	8.33	1	1.96	2	2.06	6	22.22	51	20.82	—
IV	19	48.72	22	30.56	8	15.69	45	46.39	8	29.63	77	31.43	—
NA	14	35.90	28	38.89	27	52.94	34	35.05	11	40.74	96	39.18	—
Bone metastatic													
Yes	1	2.56	3	4.17	3	5.88	9	9.28	2	7.41	15	6.12	0.729
No*	38	97.44	69	95.83	48	94.12	88	90.72	25	92.59	230	93.88	—
Brain metastatic													
Yes	0	0.00	0	0.00	3	5.88	2	2.06	0	0.00	5	2.04	0.327
No*	39	100.00	72	100.00	48	94.12	95	97.94	27	100.00	240	97.96	—
Liver metastatic													
Yes	7	17.95	21	29.17	19	37.25	35	36.08	11	40.74	84	34.29	0.290
No*	32	82.05	51	70.83	32	62.75	62	63.92	16	59.26	161	65.71	
Lung metastatic													
Yes	1	2.56	1	1.39	5	9.80	5	5.15	2	7.41	12	4.90	0.333
No*	38	97.44	71	98.61	46	90.20	92	94.85	25	92.59	233	95.10	—
Surgery													
Yes	5	12.82	34	47.22	37	72.55	31	31.96	19	70.37	192	78.37	< 0.001
No*	34	87.18	38	52.78	14	27.45	66	68.04	8	29.63	53	21.63	—
Radiation													
Yes	15	38.46	20	27.78	5	9.80	13	13.40	1	3.70	31	12.65	< 0.001
No*	24	61.54	52	72.22	46	90.20	84	86.60	26	96.30	214	87.35	—
Chemotherapy													
Yes	30	76.92	45	62.50	28	54.90	59	60.82	10	37.04	160	65.31	0.022
No*	9	23.08	27	37.50	23	45.10	38	39.18	17	62.96	85	34.69	—
Era (y)													
2000-2006	4	10.26	11	15.28	4	7.84	9	9.28	8	29.63	29	11.84	0.086
2007-2013	18	46.15	20	27.78	22	43.14	29	29.90	9	33.33	87	35.51	—
2014-2018	17	43.59	41	56.94	25	49.02	59	60.82	10	37.04	129	52.65	—

*No/unknown.
AJCC indicates American Joint Committee on Cancer; NA, not available.

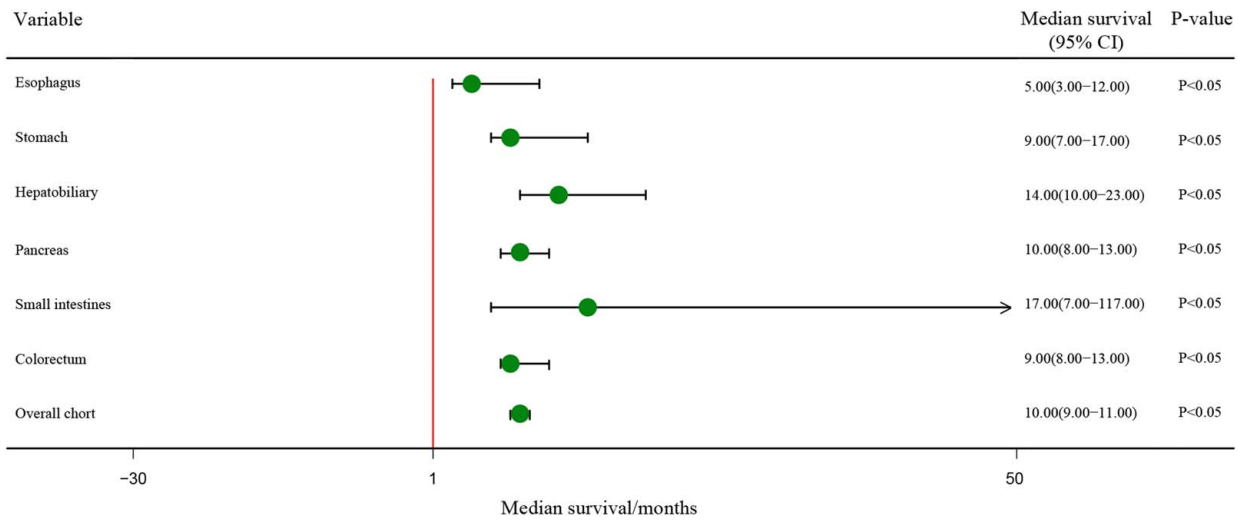

FIGURE 1. Forest plot for median overall survival (OS) based on primary tumor site of large cell neuroendocrine carcinoma (LCNEC). full color online

METHODS

Patient Selection

Clinical information and survival data on patients with GILCNEC diagnosed from 2000 to 2018 was extracted from the Surveillance, Epidemiology, and End Results (SEER) database (http://seer.cancer.gov/) using SEER*Stat software version 8.4.0 (https://seer.cancer.gov/seerstat/). The patient information collected for the SEER data is anonymous and, therefore, this work does not require approval from our Institutional Ethics Review Board. We included patients according to the following criteria: (1) pathologically diagnosed GILCNEC according to the International Classification of Diseases in Oncology, Third Edition, SEER histological and topographical codes. Primary tumor site included: esophagus (C15), stomach (C16), small intestines (C17), colon (C18), rectosigmoid junction (C19.9), rectum (C20.9), liver and intrahepatic bile duct (C22.0-C22.1), gallbladder (C23.9), other and unspecified bile ducts (C24), pancreas (C25) and intestine of unspecified location (C26.0) and (2) histologic code 8013/3 (LCNEC). But the following patients were excluded: (1) age younger than 18 or older than 100 years at diagnosis, (2) having a second primary tumor, (3) not confirmed by pathological histology or only at autopsy, and (4) follow-up data recorded

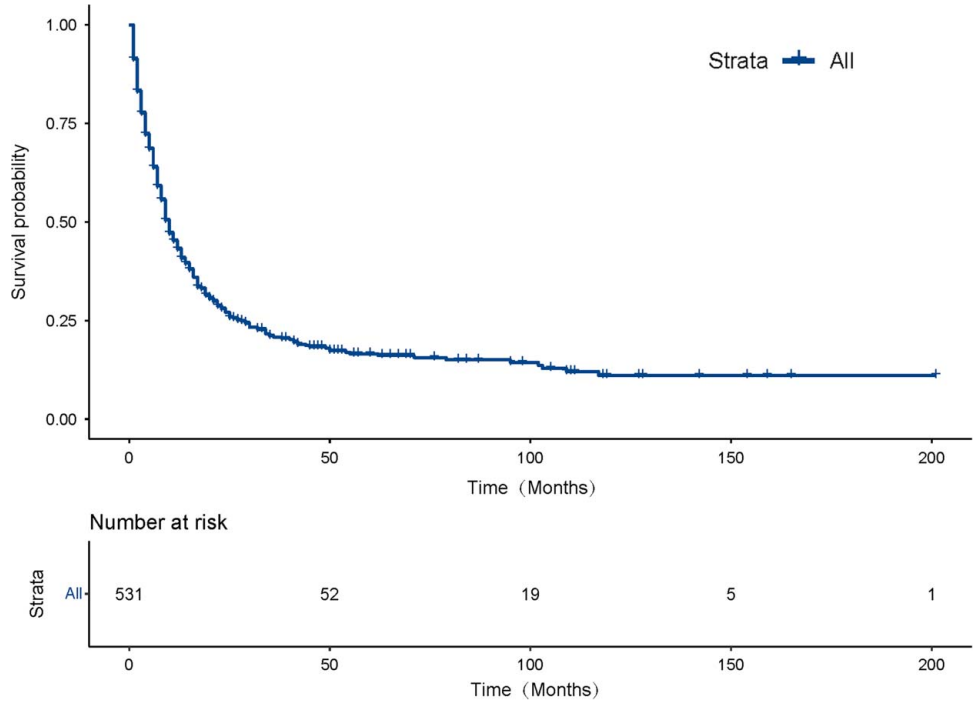

FIGURE 2. OS for the entire gastrointestinal LCNEC cohort. full color online

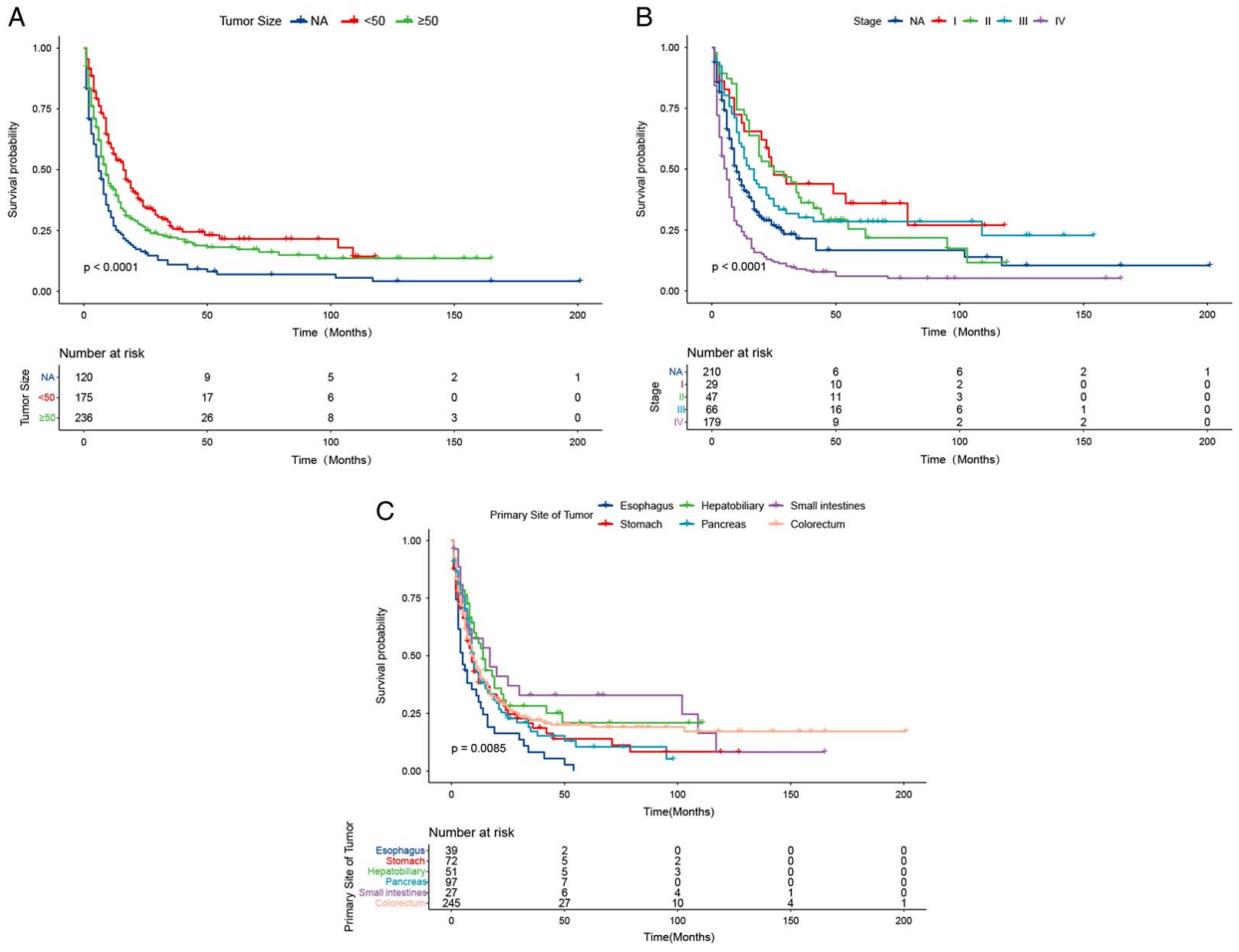

FIGURE 3. OS based on different clinicopathological factors. A, OS based on tumor size. B, OS based on American Joint Committee on Cancer Sixth Edition stage. C, OS based on primary site of tumor. full color online

survival time <1 month or unknown. The specific patient selection process is shown in Supplemental Figure 1 (Supplemental Digital Content 1, http://links.lww.com/AJCO/A523).

Variates and Outcomes

Variables included age, sex, race, marital status, tumor size, American Joint Committee on Cancer (AJCC) Sixth Edition stage, distant metastases information (bone, liver, brain, and lung), surgery, radiotherapy, chemotherapy, and time period at diagnosis.

Survival data (OS) are the primary endpoint, defined as the time point from the date of pathological diagnosis to the date of death from any cause or the last follow-up. The secondary endpoint is the effect of different treatments (surgery, radiotherapy, and chemotherapy) on OS.

Statistical Analyses

Fisher exact or Cross-tabulation χ^2 test was used to analyze baseline clinicopathological features and group differences for proportions. The Kaplan-Meier method was used to plot the survival curves, calculate the median survival time, and determine the difference between the curves using the log-rank test. A stepwise multivariate Cox regression model was used to analyze the variables associated with OS using the forward method and hazard ratios (HRs) and 95% CI were calculated. In this study, a 2-sided P value <0.05 was considered statistically significant. R language (v4.2.1) software was used for all statistical analyses.

RESULTS

Patient Characteristics

This work culminated in the extraction of 531 patients from the SEER database, of whom the median age was 63 years. The distribution of primary tumor site was in the esophagus in 39 (7.3%) patients, in the stomach in 72 (13.6%) patients, in the hepatobiliary in 51 (9.6%) patients, in the pancreas in 97 (18.3%) patients, in the small intestines in 27 (5.1%), and in the colorectum in 245 (46.1%) patients. A higher proportion of elder patients (≥65 y) had esophagus, stomach, hepatobiliary, and colorectum LCNECs compared with younger patients (<65 y; $P = 0.008$). The proportion of patients with LCNECs originating from the esophagus, stomach, pancreas, and colorectum was higher in males than in females ($P = 0.001$). Whites had a higher proportion in the esophagus, stomach, hepatobiliary, pancreas, small intestines, and colorectum LCNECs compared with blacks and other racial groups ($P = 0.005$). Compared with individuals with other marital status, married

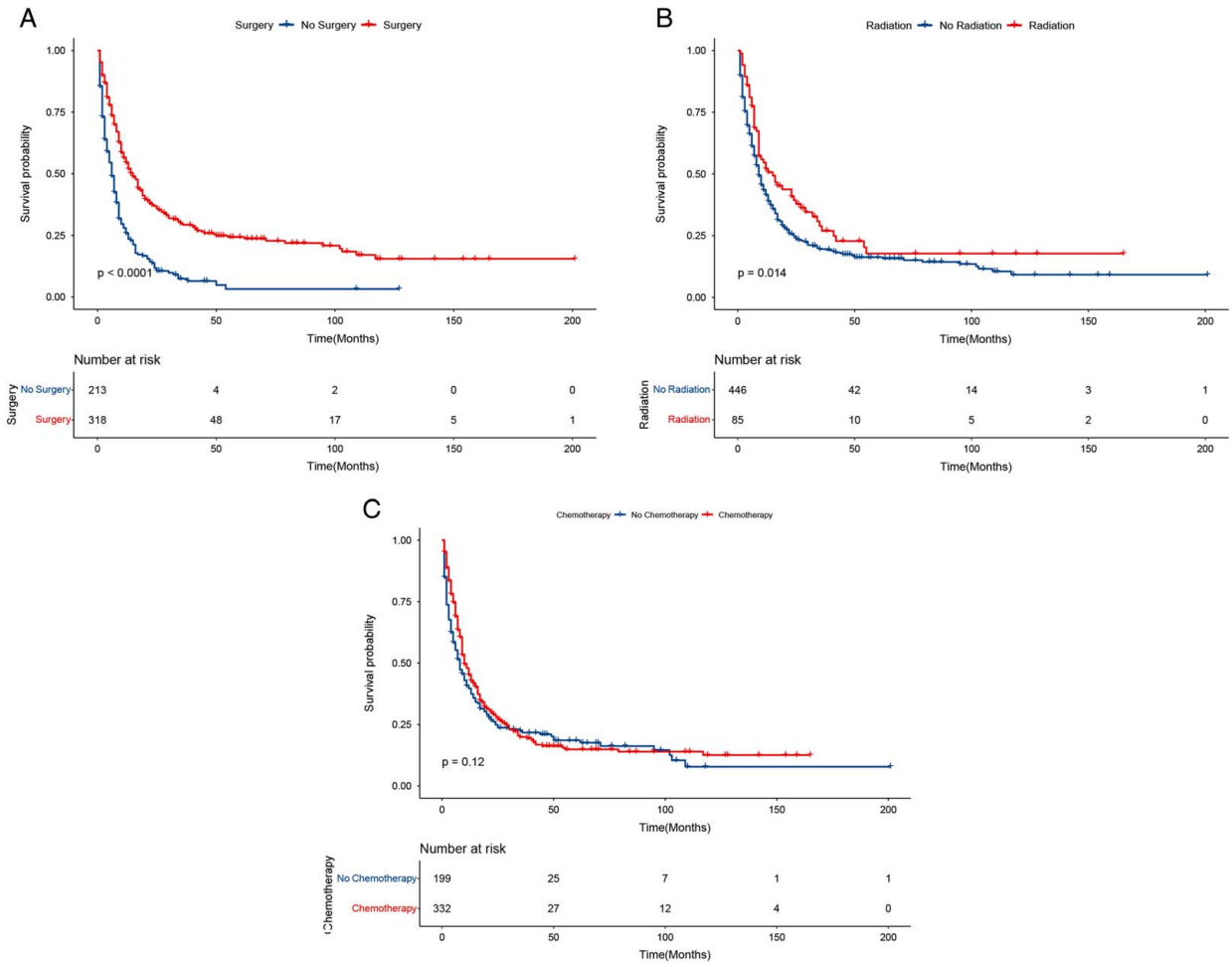

FIGURE 4. OS based on different treatment. A, OS based on surgery performed or not surgery. B, OS based on treated radiation or not receiving radiation. C, OS based on treated chemotherapy or not receiving chemotherapy. full color online

individuals had a higher proportion in the esophagus, stomach, hepatobiliary, pancreas, and colorectum LCNECs ($P = 0.020$). Compared with other sites, the tumor size of patients with esophagus, stomach, and colorectum LCNECs was larger ($P < 0.001$). Stage IV LCNECs were more common in the esophagus, stomach, pancreas, small intestines, and colorectum sites ($P < 0.001$). The different LCNECs in metastasis sites did not show significant differences. However, the results showed that different sites LCNECs were more likely to develop liver metastases. Chemotherapy was the most common treatment in esophagus, stomach, and pancreas LCNECs whereas in the hepatobiliary, small intestines and colorectum LCNECs were surgery. There were no apparent differences in the incidence of GILCNEC at different sites in different periods. The table of clinical characteristics is detailed shown in Table 1.

Analyses of Survival and its Prognostic Factors

The median overall survival (mOS) of 531 patients is 10 months (95% CI: 9.00-11.00 mo). Small intestine LCNEC was associated with the longest mOS and esophagus LCNEC was associated with the shortest mOS. The mOS and OS of all patients with GILCNEC are displayed in Figure 1 and Figure 2, respectively. Patients with tumor size ≥ 50 mm had worse OS compared with those with < 50 mm (Fig. 3A). The survival rate in patients falls progressively as staging progresses (Fig. 3B). Individuals with Esophagus LCNEC had poorer OS, whereas small intestine LCNEC was associated with better OS (Fig. 3C). Patients who received surgery or radiotherapy achieved better OS compared with untreated patients (Fig. 4A, B), whereas patients receiving chemotherapy failed to show a significant survival advantage compared with patients not receiving chemotherapy (Fig. 4C).

In the univariate analysis, sex, tumor size, primary tumor site, AJCC Sixth Edition stage, surgery, and radiotherapy were significantly related to OS in patients with GILCNEC (Table 2). Multivariate analysis demonstrated that stage I, surgery, and radiotherapy were independently correlated with better OS in patients with GILCNEC, whereas stage IV was independently associated with worse OS in patients with GILCNEC (Table 2). Other relevant clinicopathological factors and their effects on OS are summarized in Table 2.

For GILCNEC, the 5-year survival rate is low regardless of the primary tumor site. Among patients with different primary sites, the patients with esophagus LCNEC

TABLE 2. Factors Affecting OS of Gastrointestinal Extrapulmonary Large Cell Carcinoma Based on Univariate and Multivariate Cox Recession Analyses

	Univariate			Multivariate		
Variable	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Age (y)						
< 65	Reference	—	—	—	—	—
≥ 65	0.97	0.80-1.18	0.774	—	—	—
Sex						
Female	Reference	—	—	Reference	—	—
Male	1.23	1.01-1.50	0.040	1.18	0.96–1.46	0.116
Race						
White people	Reference	—	—	—	—	—
Black people	1.21	0.91-1.62	0.186	—	—	—
Others	0.94	0.64-1.36	0.726	—	—	—
Marital status						
Married	Reference	—	—	—	—	—
Single	1.08	0.82-1.41	0.592	—	—	—
Others	0.84	0.67-1.06	0.138	—	—	—
Tumor size (mm)						
< 50	0.50	0.39-0.65	< 0.001	0.75	0.56–1.00	0.050
≥ 50	0.68	0.54-0.87	0.002	0.95	0.72–1.25	0.700
NA	Reference	—	—	Reference	—	—
Primary site						
Esophagus	Reference	—	—	Reference	—	—
Stomach	0.64	0.43-0.96	0.033	1.06	0.69–1.64	0.782
Hepatobiliary	0.46	0.29-0.73	0.001	1.01	0.60–1.68	0.982
Pancreas	0.62	0.42-0.91	0.015	0.70	0.46–1.05	0.084
Small intestines	0.44	0.25-0.76	0.003	0.72	0.41–1.28	0.262
Colorectum	0.56	0.40-0.80	0.001	1.14	0.76–1.72	0.527
AJCC Sixth Edition stage						
I	0.54	0.33-0.87	0.011	0.55	0.34–0.90	0.017
II	0.64	0.45-0.93	0.018	0.82	0.56–1.21	0.315
III	0.69	0.49-0.96	0.026	0.80	0.56–1.14	0.215
IV	1.73	1.38-2.17	< 0.001	1.50	1.17–1.91	< 0.001
NA	Reference	—	—	Reference	—	—
Surgery						
Yes	0.45	0.37-0.55	< 0.001	0.45	0.35–0.59	< 0.001
No*	Reference	—	—	Reference	—	—
Radiation						
Yes	0.71	0.54-0.93	0.014	0.61	0.45–0.82	0.001
No*	Reference	—	—	Reference	—	—
Chemotherapy						
Yes	0.85	0.70-1.04	0.116	—	—	—
No*	Reference	—	—	—	—	—
Era (y)						
2000-2006	Reference	—	—	—	—	—
2007-2013	1.06	0.78-1.43	0.723	—	—	—
2014-2018	1.04	0.77-1.40	0.792	—	—	—

*No/unknown.
AJCC indicates American Joint Committee on Cancer; HR, hazard ratio; NA, not available; OS, overall survival.

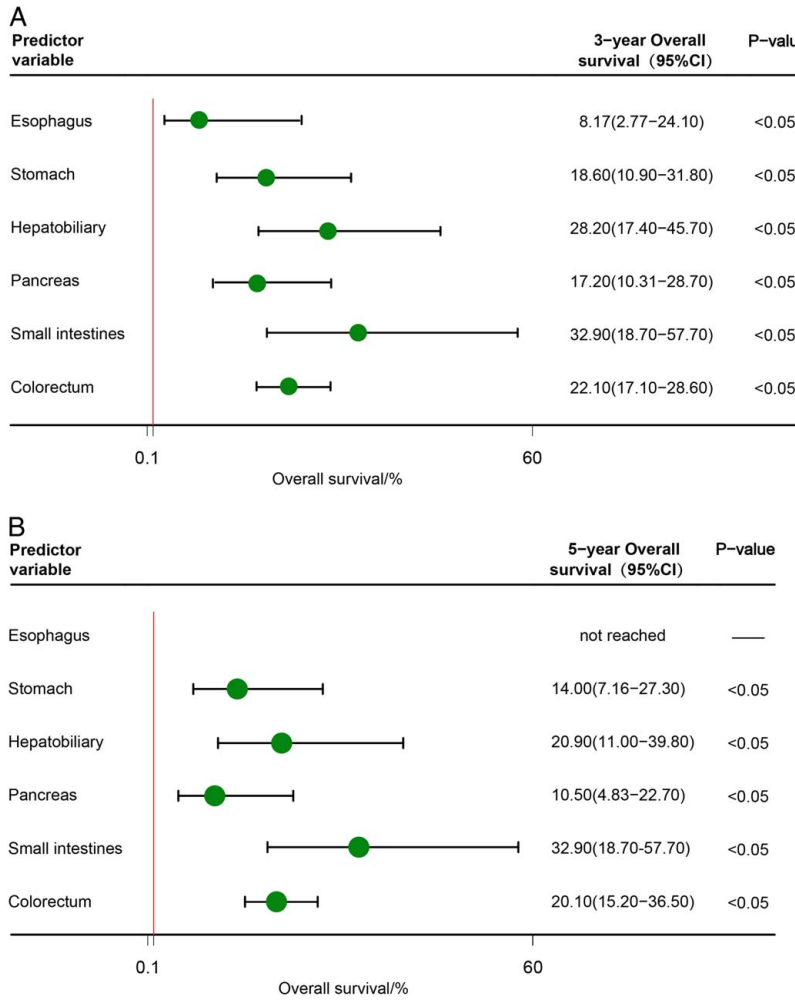

FIGURE 5. Three-year (A) and 5-year (B) survival rates based on primary tumor site. full color online

showed a poor 3-year survival rate, just 8.17%. In contrast, patients with small intestine LCNEC were associated with better OS, and 3 and 5-year survival rates were 32.9% and 32.9%, respectively (Fig. 5). We further studied the interaction plot between different treatment modalities in all patients with GILCNEC. The HR for no treatment was predictably higher than with treatment, but the HR is on the contrary in patients with hepatobiliary LCNEC who received radiotherapy (Fig. 6).

DISCUSSION

LCNEC is a rare malignancy with a poor prognosis.[12,13,15] In the 2004 WHO Classification of Lung Tumors, LCNEC is listed as one of the 4 variants of large cell carcinoma. As understanding of this disease deepens, LCNEC is a more heterogeneous tumor group that shows different genetic conditions in different originating sites (this may, at least in part, be the result of differences in definitional features between organs and diagnostic difficulties). Gastrointestinal and pancreatobiliary tracts also have LCNEC. In the 2022 World Health Organization (WHO) classification of endocrine and NETs, gastrointestinal NECs are defaulted to high grade and can be classified into small cell type (small cell NEC) or large cell type (LCNEC).[16] This study found through SEER data analysis that the median OS for GILCNEC is only 10 months, which aligns well with the latest 2022 WHO NET classification, confirming that LCNEC has a worse prognosis compared with typical carcinoids.

Until now, there are no relevant clinical practice guidelines for the treatment of GILCNEC. Surgical resection is the treatment for early-stage patients, whereas most patients are diagnosed at a mid-late stage. Platinum combined with etoposide or irinotecan is the most commonly used first-line therapy regimen for patients with advanced disease. Studies on the diagnosis, management, treatment, and follow-up of GILCNEC remain scarce, and the results of recent case reports and small retrospective studies suggest a poor prognosis for GILCNEC.[9–11] Before this study, no studies have compared survival outcomes and prognostic factors for GILCNEC based on the primary tumor site.

Our findings suggest that the most common primary site of GILCNEC is the colorectum (46.1%), followed by the pancreas (18.3%), stomach (13.6%), hepatobiliary (9.6%), esophagus (7.3%), and small intestines (5.1%). The primary tumor site in patients with GILCNEC strongly correlates with survival, esophagus LCNEC showing poorer 3-year survival (8.17%), whereas small intestine LCNEC

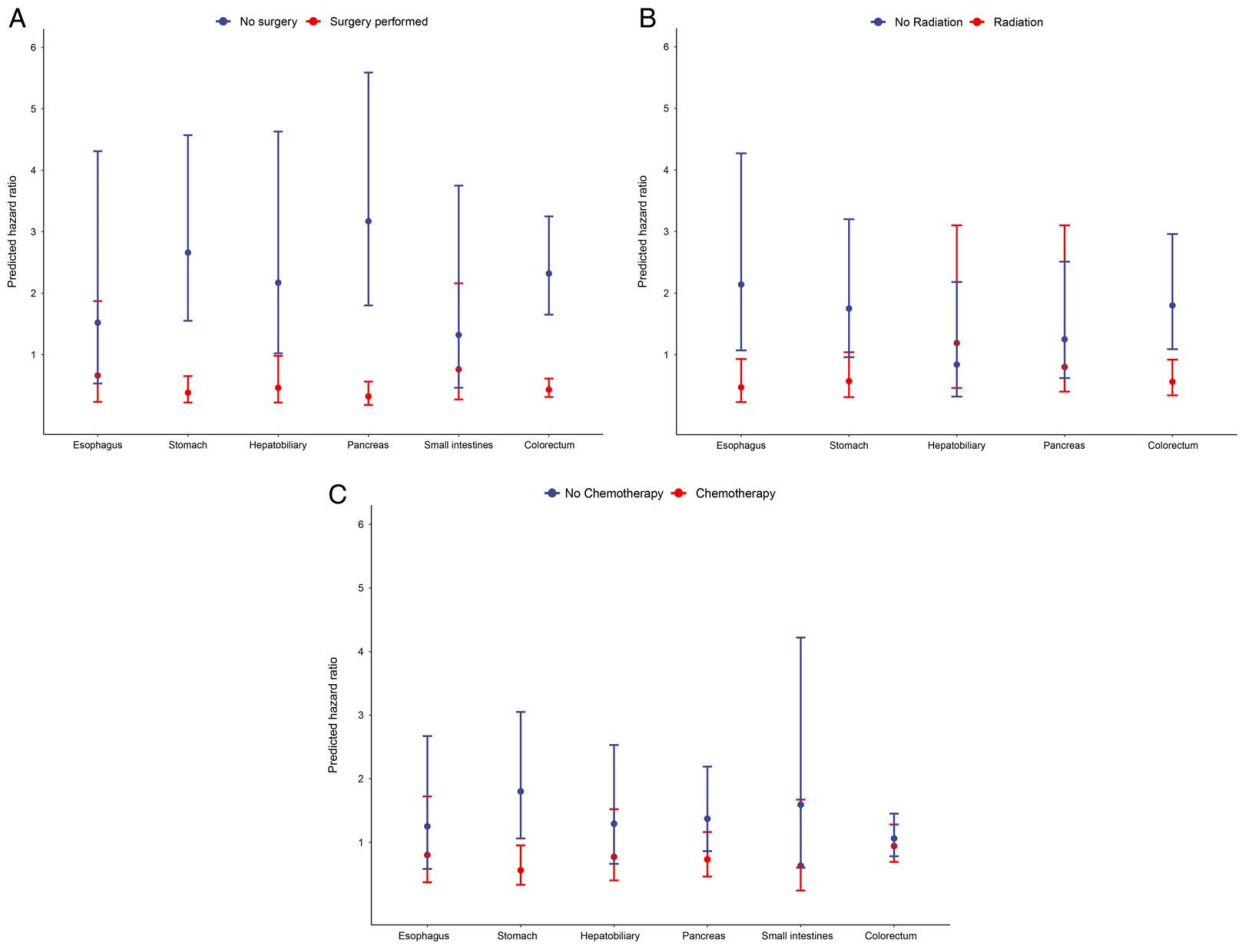

FIGURE 6. Predicted hazard ratios based on the interactions between the primary tumor site and different treatments ([A] surgery; [B] radiation; [C] chemotherapy). full color online

was related to better 3 and 5-year survival rates (32.9% and 32.9%, respectively). In terms of treatment, our study showed that chemotherapy failed to prolong OS statistically significantly in patients with GILCNEC, but surgery and radiotherapy were associated with better OS. This may be due to the different chemotherapy regimens and treatment cycles of patients, which is worthy of further study. In the study of the interaction between the primary tumor site and different treatments, the results showed that the predicted HR was lower in the nonradiotherapy group than in the radiotherapy group for patients with hepatobiliary LCNEC. Possible reasons for this are the inherently highly invasive nature of the tumors at these sites, which manifest as rapid metastases, most often to regional lymph nodes and the liver, leading to a poor prognosis.[17–19] It could be due as well to the low number of patients with hepatobiliary LCNEC receiving radiotherapy.

In our study, a small number of patients with well-differentiated (grade I) and moderately differentiated (grade II) appeared in LCNEC at different locations. As we all know, LCNEC is a high-grade NET. The reason for this may be due to the problem of SEER database recording of patients with GILCNEC, it may also be caused by the previous insufficient understanding and grading standards of LCNEC. Since our inclusion criteria were to include all patients with malignant GILCNEC, we did not exclude patients with these few grade I and grade II LCNEC. As there are very few patients with LCNEC in grade I and grade II, we did not conduct further analysis on patients with LCNEC with different degrees of differentiation.

Currently, surgical resection combined with postoperative adjuvant chemotherapy remains the preferred treatment for early-stage GILCNEC.[20,21] In a retrospective study of 119 patients with surgically resected pancreatic NEC, patients with simultaneous resection of the primary tumor and liver metastases achieved a higher 3-year survival rate compared with nonoperated patients. In addition, patients were able to tolerate more than 4 cycles of platinum combined with etoposide after surgical resection, and their prognosis was improved.[22] In a study of 43 patients with gastric NEC who underwent surgery (including 4 LCNECs), 34 patients received adjuvant chemotherapy after surgery and these patients had an mOS of 44 months, with the best prognosis in patients receiving etoposide, cisplatin, and paclitaxel regimens.[23] In the study of the survival impact of postoperative chemotherapy in 759 high-grade gastroenteropancreatic neuroendocrine cancers from the National Cancer Database, postoperative chemotherapy failed to increase OS benefit in the entire cohort, but improved survival was found in the small intestine subgroup.[24] Whether adjuvant chemotherapy improves GILCNEC survival remains

controversial, and further prospectively designed clinical studies are needed to elucidate the survival benefit of adjuvant chemotherapy in patients undergoing radical surgical resection.

Due to the low incidence, there are few reports on prognostic factors for GILCNEC. Our results suggest that stage I, surgery, and radiotherapy are independent protective factors for survival in patients with GILCNEC, whereas stage IV is an independent risk factor (Table 2). The tumor stage plays an important role in patient prognosis, which is consistent with our results. Our study also fills a gap in this field. Recently, a meta-analysis aimed at studying the role of liquid biopsy in predicting prognosis and treatment response in NETs showed that liquid biopsy is important for identifying tumor progression, and high baseline NETest levels also indicate subsequent disease progression.[25] This suggests that we need to pay more attention to the effect of NETest on the prognosis of gastrointestinal NENs.

In addition, this work also has some limitations. First, our study was a retrospective analysis with an inherent bias. Second, there is no conclusive information on which chemotherapy regimen to use for the treatment of LCNECs at different sites. Third, information on adjuvant radiotherapy or neoadjuvant radiotherapy is also not documented. Fourthly, the 2022 WHO overview of NET pathology classification emphasizes the importance of Ki-67 as a tool for classification and grading. The latest classification indicates that the Ki-67 for GILCNEC should be $>20\%$ (usually 70%).[16] However, the SEER database lacks detailed records of pathological characteristics, and the relationship between Ki-67 and survival prognosis has not been studied.

Nevertheless, our study is also the first and largest study to completely assess the clinicopathological characteristics, survival, and prognostic factors of GILCNEC. We also studied the effect of prognosis based on different primary tumor sites. This study shows that surgery and radiotherapy occupy an irreplaceable position in the treatment of GILCNEC and that active treatment should be administered to patients who can tolerate it.

CONCLUSIONS

Unfortunately, no standardized consensus guidelines to guide the treatment of GILCNEC yet exist. AJCC Sixth Edition stage, surgery, and radiotherapy are independent prognostic factors for patients with GILCNEC. Esophagus LCNEC is associated with a poorer prognosis. However, the 5-year survival rate of patients with GILCNEC is also low regardless of the primary tumor sites, clinicopathological characteristics, and treatment. Accordingly, relevant prospective randomized controlled trials are urgently needed to be carried out to determine the clinical and pathological characteristics of this rare and aggressive tumor and provide clinicians with more reliable and improved treatment options to guide treatment, thereby improving the OS rate of GILCNEC.

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