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Clinicopathological features and survival for gallbladder NEN: a population-based study

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Abstract

Purpose: Gallbladder neuroendocrine neoplasm (GB-NEN) is a relatively rare neoplasm, accounting for 0.5% of all neuroendocrine neoplasm cases and 2.1% of gallbladder cancers. Because of the limited understanding of GB-NEN, the aim of this study was to explore the clinicopathology and survival of GB-NEN patients selected from the Surveillance, Epidemiology, and End Results (SEER) database.

Methods: A total of 248 GB-NEN patients from the SEER database diagnosed between 2004 and 2015 were included. Kaplan–Meier curves were used to examine the survival time. Multivariate Cox proportional hazard models were used to estimate hazard ratios with 95% confidence intervals to analyze the impact of factors on overall survival and cancer-specific survival.

Results: The majority of the GB-NEN patients were women (67.3%), white (77%), and married (61.7%). Most tumors were <2 cm in size (31.0%), G3 stage (25.8%), and distant SEER stage (41.1%). 62.9% and 64.5% of cases showed an absence of lymph node metastasis and tumor metastasis, respectively. Patients who received gallbladder surgery had significantly better survival outcomes ($P < 0.001$). However, patients who received both gallbladder surgery and lymph node resection did not have better survival outcome compared with patients who received only gallbladder surgery. Multivariate Cox proportional hazard models indicated that older age, unmarried status, large tumor size (>5 cm), and distant SEER stage were significant independent predictors for decreased overall survival time and cancer-specific survival time ($P < 0.05$).

Conclusion: Age, marital status, tumor size, and SEER stage were predictors for the survival of GB-NEN patients. Gallbladder surgery was associated with better survival, but the combination of gallbladder surgery and lymphadenectomy had no effect on survival outcomes.

Key Words

- ▶ gallbladder neuroendocrine neoplasm
- ▶ clinicopathological characteristics
- ▶ survival
- ▶ SEER database

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Introduction

Neuroendocrine neoplasms (NENs) are a heterogeneous group of tumors that are derived from diffuse neuroendocrine cells. As a result of improved detection of early-stage disease and possibly stage migration, the incidence and prevalence of NEN are steadily increasing (1, 2). According to the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER)

database, the incidence rate of NEN has increased from 1.09 per 100,000 people in 1973 to 6.98 per 100,000 people in 2012. NEN can be found in various tissues and organs throughout the body, with the highest incidence in gastroenteropancreatic sites, followed by the lungs (1). The incidence of gastroenteropancreatic NEN (GEP-NEN) continues to increase especially in older

adults of 78–84 years of age, with an incidence rate of 3.56 per 100,000 (1, 3). As a result of improvements in therapies, increased overall survival was found in patients with a distant stage of GEP-NEN (1). Regarding treatment, surgery remains effective for localized tumors and systemic treatment options have expanded for patients with metastatic status (4). According to the World Health Organization (WHO) classification of NEN, NEN includes differentiated neuroendocrine tumors, also designated as carcinoid tumors in some systems, and poorly differentiated neuroendocrine carcinoma (5). NEN in the gallbladder is a relatively rare histological tumor type, accounting for 0.5% of all NEN cases (6). The most common histological tumor type of gallbladder cancer (GBC) is adenocarcinoma, representing 76–90% of all GBC cases. By contrast, gallbladder NEN (GB-NEN) only represents 2.1% of GBC cases (7).

The current knowledge of GB-NEN is limited to case reports and small series of studies. A study of ten GB-NEN patients reported that the 1-, 2-, and 3-year survival rates were 20, 10, and 0%, respectively, and the median survival time was 3 months (8). However, data on GB-NEN patients selected from the SEER database showed that the 1-, 2-, 3- and 4-year survival rates were 43–45, 30–33, 28–31, and 22–26%, respectively (7). In a study of biliary neuroendocrine neoplasms, the median survival of GB-NEN patients was 7.9 months and only grade 3 tumors, according to the 2010 WHO classification, were significantly related to poor survival (9).

Because of the rarity of GB-NEN, the survival outcomes, risk factors, and clinicopathological characteristics of GB-NEN patients remain unclear. The aim of this study was to explore the clinicopathological features and survival outcomes of GB-NEN patients using a population-based study based on the SEER database.

Materials and methods

Data source

The data in this study were from the SEER*Stat Database (version 8.3.5). The SEER program consists of 20 cancer registry points, covering 28% of the US population between 1973 and 2015. The SEER database is routinely updated and includes information on patient demographics, clinicopathological characteristics, treatment, and survival. Consent was obtained from each patient after full explanation of the purpose and nature of all procedures. As SEER data is publicly available and all patient data are de-identified, institutional review board

approval and informed consent were not required for this study.

Study population

The strategy to identify GB-NEN cases is shown in Fig. 1. Using the primary site code (C23.9), International Classification of Disease for Oncology, third edition (ICDO-3) (8013/3, 8041/2, 8041/3, 8240/2, 8240/3, 8241/3, 8242/3, 8243/3, 8244/3, 8245/3, 8246/2, 8246/3, 8249/3) and diagnostic confirmation (positive histology), GB-NEN patients from 2004 to 2015 were selected from the database. Only patients with GB-NEN as a primary cancer were included. Patients that were younger than 18 years old and those for whom survival information was not available were excluded. Of the remaining 270 cases, 22 patients that lacked demographic, clinicopathological, or therapy information were also excluded. A total of 248 cases were finally included in this study.

Data extraction

Demographic information (age, sex, race, marital status, time at diagnosis), clinicopathological characteristics (tumor size, grade, SEER stage, lymph node metastasis, tumor metastasis), and therapy information (gallbladder surgery, lymph node surgery) were extracted from the SEER database. The original data from the SEER database was reviewed for sex, race, time at diagnosis, and tumor size information. Patients were divided into two groups according to age: younger than 65 years old vs older than 65 years of age. Because of the similar survival

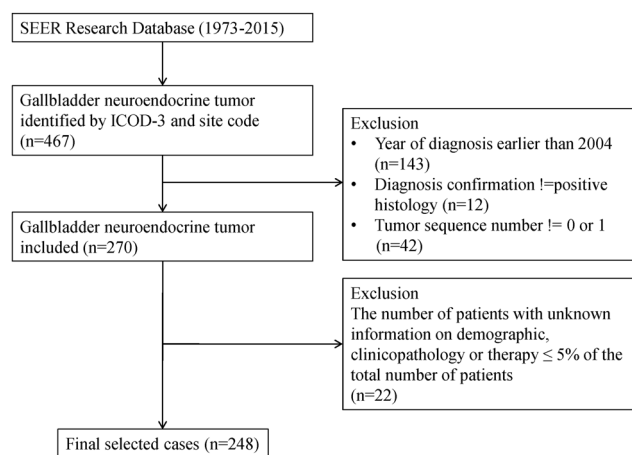


Figure 1 Flowchart displaying the selection procedure of GB-NEN cases in the SEER database.

disadvantages to being unmarried, patients with divorced, separated, widowed, or single status were classified in the unmarried group for comparison with the married group in subsequent analysis. On the basis of the WHO classification of NEN, neuroendocrine carcinoma, small-cell carcinoma (SCC), large-cell neuroendocrine carcinoma (LCNEC) and mixed adenoneuroendocrine carcinoma (MANEC) of the gallbladder, can all be classified within gallbladder neuroendocrine carcinoma (GB-NEC). Carcinoid tumors and atypical carcinoid tumors of the gallbladder are classified within gallbladder neuroendocrine tumors (GB-NETs). Tumor grading was classified according to ICD-O-2 in the SEER database as G1 (well differentiated), G2 (moderately differentiated), G3 (poorly differentiated), or G4 (undifferentiated). According to the Collaborative Stage Data Collection System, TNM staging based on the Cancer Staging Manual (6th edition) of the American Joint Committee on Cancer was not applicable to GB-NEN. Staging was instead performed using the SEER Summary Stage 2000 (localized, regional, distant, or unknown). Lymph node metastatic status was classified as non-metastatic, metastatic, and unknown status (N0, N1, and unknown, respectively). Tumor metastatic status was classified as M0 (no metastasis) or M1 (metastasis). GB-NEN primary site therapy was categorized into two groups: the surgically treated patient group and the non-surgically treated patient group. As described in the SEER database, the surgery group included local tumor excision, simple/partial surgical removal of

gallbladder, total surgical removal of gallbladder, and radical surgery. Lymph node surgery was divided into two groups: the surgically treated patient group and the non-surgically treated patient group. More details about data and variables can be found in the SEER database (<http://seer.cancer.gov>).

Statistical analyses

Overall survival (OS) was defined as the period from the date of diagnosis to the date of death from various causes. Cancer-specific survival (CSS), as the primary endpoint, was determined as the date of diagnosis to the date of cancer-specific death. The Kaplan–Meier method along with the log-rank test was performed for survival analysis. Multivariate Cox proportional hazard models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for OS and CSS. Statistical analysis was performed using SAS 9.2 software (SAS Institute Inc.). Two-tailed *P* values less than 0.05 were considered statistically significant.

Results

A total of 248 GB-NEN cases from the SEER database diagnosed between 2004 and 2015 were included in this study. The general demographic characteristics of patients are shown in [Table 1](#). The majority of GB-NEN

Table 1 General characteristics of gallbladder neuroendocrine neoplasm patients.

Variables	Total patients, <i>n</i> (%)	LCNEC	SCC	Carcinoid tumor	Neuroendocrine carcinoma	MANEC	Atypical carcinoid tumor
Age at diagnosis, years							
≤65	131 (52.8)	7 (33.3)	30 (50.0)	51 (72.9)	38 (43.2)	4 (50.0)	1 (100.0)
>65	117 (47.2)	14 (66.7)	30 (50.0)	19 (27.1)	50 (56.8)	4 (50.0)	0
Gender							
Male	81 (32.7)	10 (47.6)	17 (28.3)	29 (41.4)	23 (26.1)	2 (25.0)	0
Female	167 (67.3)	11 (52.4)	43 (71.7)	41 (58.6)	65 (73.9)	6 (75.0)	1 (100.0)
Race							
White	191 (77.0)	17 (81.0)	47 (78.3)	55 (78.6)	64 (72.7)	7 (87.5)	1 (100.0)
Black	37 (14.9)	2 (9.5)	11 (18.3)	12 (17.1)	11 (12.5)	1 (12.5)	0
Asian/American Indian	20 (8.1)	2 (9.5)	2 (3.3)	3 (4.3)	13 (14.8)	0	0
Marital status							
Married	153 (61.7)	19 (90.5)	32 (53.3)	46 (65.7)	51 (58.0)	5 (62.5)	0
Unmarried ^a	95 (38.3)	2 (9.5)	28 (46.7)	24 (34.3)	37 (42.0)	3 (37.5)	1 (100.0)
Year at diagnosis							
2004–2007	69 (27.8)	2 (9.5)	17 (28.3)	25 (35.7)	25 (28.4)	0	0
2008–2011	74 (29.8)	6 (28.6)	17 (28.3)	24 (34.3)	27 (30.7)	0	0
2012–2015	105 (42.2)	13 (61.9)	26 (43.4)	21 (30.0)	36 (40.9)	8 (100.0)	1 (100.0)

^aUnmarried included single, divorced, widowed, and separated.

LCNEC, large-cell neuroendocrine carcinoma; MANEC, mixed adenoneuroendocrine carcinoma; SCC, small-cell carcinoma.

patients were 65 years of age or younger (52.8%), women (67.3%), white (77%), married (61.7%), and diagnosed in 2012–2015 period of time (42.2%). Among the 248 GB-NEN cases, there were 88 cases with neuroendocrine carcinoma, 70 cases with carcinoid tumor, 60 cases with SCC, 21 cases with LCNEC, 8 cases with MANEC and 1 case with an atypical carcinoid tumor.

The clinicopathological features are presented in Table 2. Where known, patients had a higher proportion of smaller tumor sizes (<2 cm) (31.0%) and G3 stage (25.8%). Regarding SEER stage, most cases were of distant stage (41.1%), followed by localized (31.5%) and regional stage (27.4%). An increased number of GB-NEN patients showed a lack of lymph node and tumor metastases. The majority of patients (70.6%) underwent primary site surgery, that is, gallbladder surgery. Only a small proportion of patients had lymph node surgery (24.6%).

Survival analysis was performed using the Kaplan–Meier method for both CSS (Fig. 2) and OS (Fig. 3) based

on SEER stage, pathological grade, tumor size, status of lymph node metastasis, status of tumor metastasis, and tumor histological type (GB-NEC, GB-NET). The survival time was similar for OS and CSS. Patients with G1/G2 tumors, no lymph node metastasis, no tumor metastasis and GB-NET had longer survival times than patients with G3/G4 tumors, lymph node metastasis, tumor metastasis and GB-NEC. With the increased severity of SEER stage, the survival rate of patients gradually decreased. Furthermore, patients with a smaller tumor size showed better survival outcome. All differences were statistically significant ($P < 0.001$). We also found that patients who received gallbladder surgery had a significantly better outcome in both CSS and OS ($P < 0.001$) (Fig. 4). Among the patients who had gallbladder surgery, we analyzed whether combined lymph node surgery had an effect on survival. However, no increasing survival time was found in the combined treatment group compared with patients who only had gallbladder surgery.

Table 2 Clinicopathologic characteristics of gallbladder neuroendocrine neoplasm patients.

Variables	Total patients, n (%)	LCNEC	SCC	Carcinoid tumor	Neuroendocrine carcinoma	MANEC	Atypical carcinoid tumor
Grade							
G1	31 (12.5)	0	0	24 (34.3)	7 (8.0)	0	0
G2	5 (2.0)	0	0	2 (2.9)	3 (3.4)	0	0
G3	64 (25.8)	8 (38.1)	15 (25.0)	0	37 (42.0)	4 (50.0)	0
G4	38 (15.3)	11 (52.4)	10 (16.7)	0	14 (15.9)	3 (37.5)	0
Unknown	110 (44.3)	2 (9.5)	35 (58.3)	44 (62.8)	37 (30.7)	1 (12.5)	1 (100.0)
N stage							
N0	156 (62.9)	14 (66.7)	22 (36.7)	67 (95.7)	50 (56.8)	2 (25.0)	1 (100.0)
N1	73 (29.4)	4 (19.0)	33 (55.0)	2 (2.9)	28 (31.8)	6 (75.0)	0
Unknown	19 (7.7)	3 (14.3)	5 (8.3)	1 (1.4)	10 (11.4)	0	0
M stage							
M0	160 (64.5)	14 (66.7)	25 (41.7)	67 (95.7)	48 (54.6)	5 (62.5)	1 (100.0)
M1	88 (35.5)	7 (33.3)	35 (58.3)	3 (4.3)	40 (45.4)	3 (37.5)	0
Tumor size (cm)							
≤2	77 (31.0)	1 (4.8)	6 (10.0)	55 (78.6)	14 (15.9)	0	1 (100.0)
2–5	47 (19.0)	6 (28.6)	15 (25.0)	1 (1.4)	20 (22.7)	5 (62.5)	0
>5	46 (18.6)	9 (42.8)	15 (25.0)	0	19 (21.6)	3 (37.5)	0
Unknown	78 (31.4)	5 (23.8)	24 (40.0)	14 (20.0)	35 (39.8)	0	0
SEER stage							
Localized	78 (31.5)	2 (9.5)	3 (5.0)	62 (88.6)	10 (11.4)	0	1 (100.0)
Regional	68 (27.4)	10 (47.6)	18 (30.0)	5 (7.1)	30 (34.1)	5 (62.5)	0
Distant	102 (41.1)	9 (42.9)	39 (65.0)	3 (4.3)	48 (54.5)	3 (37.5)	0
Surgery at primary site							
No	73 (29.4)	5 (23.8)	33 (55.0)	1 (1.4)	33 (37.5)	1 (12.5)	0
Yes	175 (70.6)	16 (76.2)	27 (45.0)	69 (98.6)	55 (62.5)	7 (87.5)	1 (100.0)
Surgery at other site							
No	228 (91.9)	16 (76.2)	57 (95.0)	68 (97.1)	81 (92.0)	5 (62.5)	1 (100.0)
Yes	20 (8.1)	5 (23.8)	3 (5.0)	2 (2.9)	7 (8.0)	3 (37.5)	0
LN surgery							
No	187 (75.4)	16 (76.2)	48 (80.0)	55 (78.6)	64 (72.7)	3 (37.5)	1 (100.0)
Yes	61 (24.6)	5 (23.8)	12 (20.0)	15 (21.4)	24 (27.3)	5 (62.5)	0

LCNEC, large-cell neuroendocrine carcinoma; MANEC, mixed adenoneuroendocrine carcinoma; SCC, small-cell carcinoma.

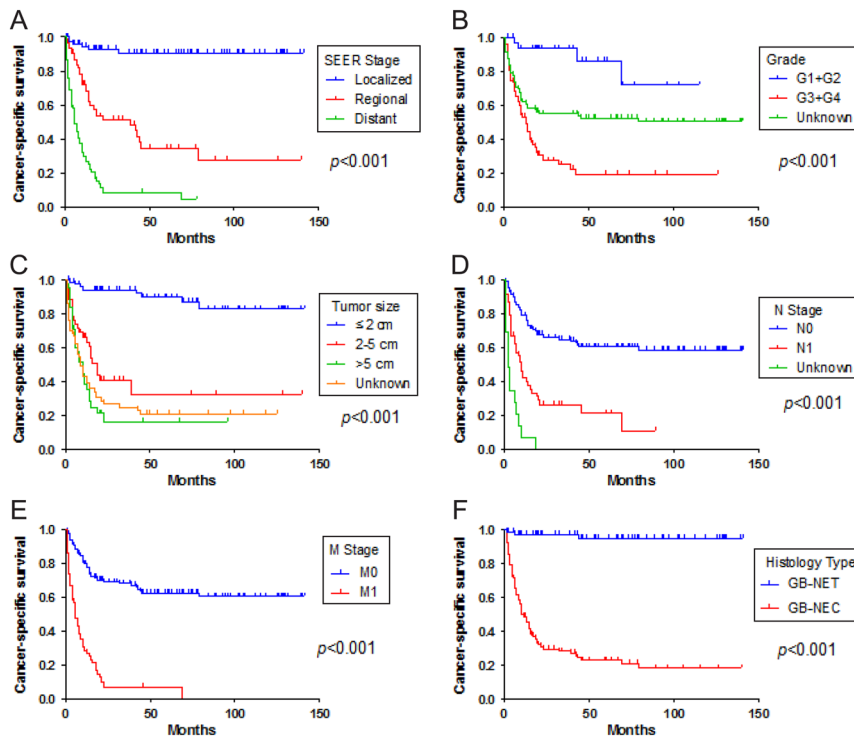


Figure 2 Kaplan-Meier curves of cancer-specific survival according to SEER stage (A), grade (B), tumor size (C), lymph node metastasis (D), tumor metastasis (E), and histological type (F).

Multivariate Cox proportional hazard models were then used to analyze risk factors impacting the prognosis of GB-NEN patients (Table 3). Older age, unmarried status, primary tumors greater than 5 cm, and extensive SEER stage were regarded as significant risk factors for decreased OS. Similar risk factors were identified for decreased CSS. In addition, gallbladder surgery and a histological type of GB-NET were associated with prolonged OS and CSS, respectively.

Discussion

GB-NEN is a rare primary neoplasm of the gallbladder, accounting for 0.5% of all NEN cases and 2% of all GBC cases (6, 7). For example, a study of 435 GBC patients included only 13 GB-NEN cases (3%) (10). Given that only case reports of a small sample of GB-NEN cases have been published, the biological behavior and survival prognosis of GB-NEN cases have remained unclear. We used data from the SEER database to explore the clinicopathological features and survival of GB-NEN.

Joel *et al.* reported the first GB-NEN case in 1929 (7). A retrospective study of 25 GB-NEN patients found that the mean age was 64 years old (ranging from 40 to 71 years) and 68% of the cases were women (11). In a single-center GB-NEN study of ten patients, the average age was

59 years, and eight cases were in women (8). Of the 248 patients included in the study, female patients accounted for a higher proportion. The majority of the cases was of white ethnicity and married social status.

A few case reports have been published on the different histologic types of GB-NEN, including neuroendocrine carcinoma, LCNEC, SCC, MANEC, carcinoid tumors, and atypical carcinoid tumors (12, 13, 14, 15, 16, 17, 18, 19). A previous study of GB-NEN cases from the SEER database between 2000 and 2005 reported that among 105 GB-NEN cases, 1% were LCNEC, 30.5% were SCC, 32.4% were carcinoid tumors, 34.3% were neuroendocrine carcinoma, and 1.9% were MANEC (7). In this study, among the 248 GB-NEN cases included between 2004 and 2015, 8.5% were LCNEC, 24.2% were SCC, 28.2% were carcinoid tumors, 35.5% were neuroendocrine carcinoma, and 3.2% were MANEC. Neuroendocrine carcinoma and carcinoid tumors were more common than other types of GB-NEN. SCC and LCNEC are poorly differentiated neuroendocrine carcinoma types and SCC cases are more frequently observed than LCNEC. For example, one report analyzed the clinicopathological characteristics of 36 SCC cases (20). However, only eight LCNEC cases of GB-NEN were reported from 2001 to 2016 (13).

In a previous study on GB-NEN between 1973 and 2005, 2.4, 7.3, 26.3, and 63.4% of cases were classified as G1, G2, G3, and G4, respectively (7). While in our study,

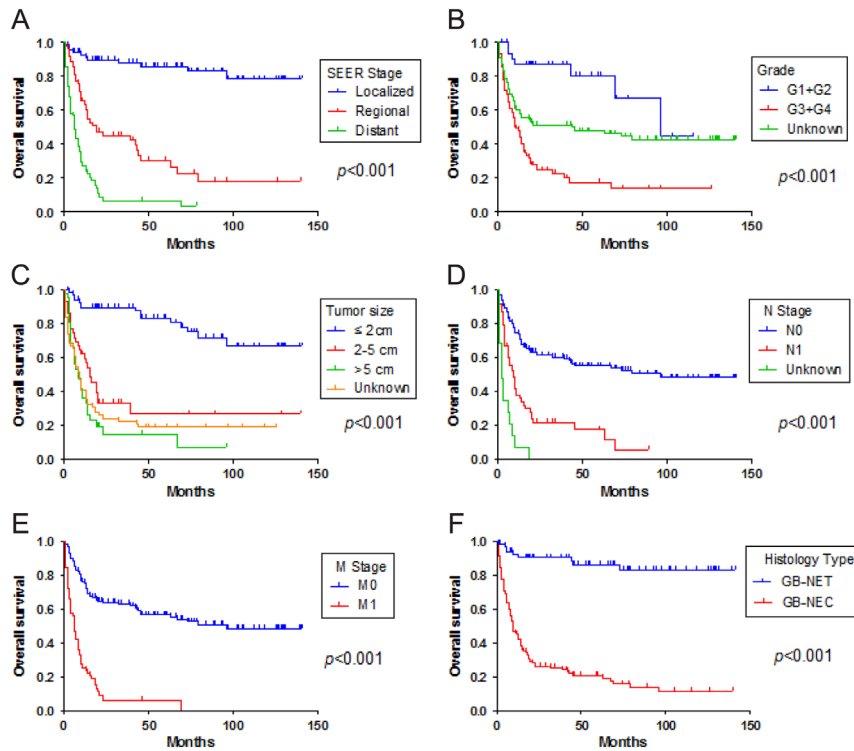


Figure 3

Kaplan–Meier curves of overall survival according to SEER stage (A), grade (B), tumor size (C), lymph node metastasis (D), tumor metastasis (E), and histology (F).

22.5% were G1, 3.6% were G2, 46.4% were G3, and 27.5% were G4, indicating a marked increase in G1 cases and a significantly reduced number of G4 cases compared with the previous study. We also found that the number of diagnosed GB-NEN cases increased in more recent years. Among the total patient group, 27.8, 29.8, and 42.2% of cases were diagnosed during 2004–2007, 2008–2011,

and 2012–2015, respectively. This trend may result from the increased awareness of physical examination and the advancement of examination technology, such as X-ray computed tomography, magnetic resonance imaging, and PET-CT. With the improvements in diagnostic ability, more GB-NEN cases of early grade (G1 and G2) tumors are being detected.

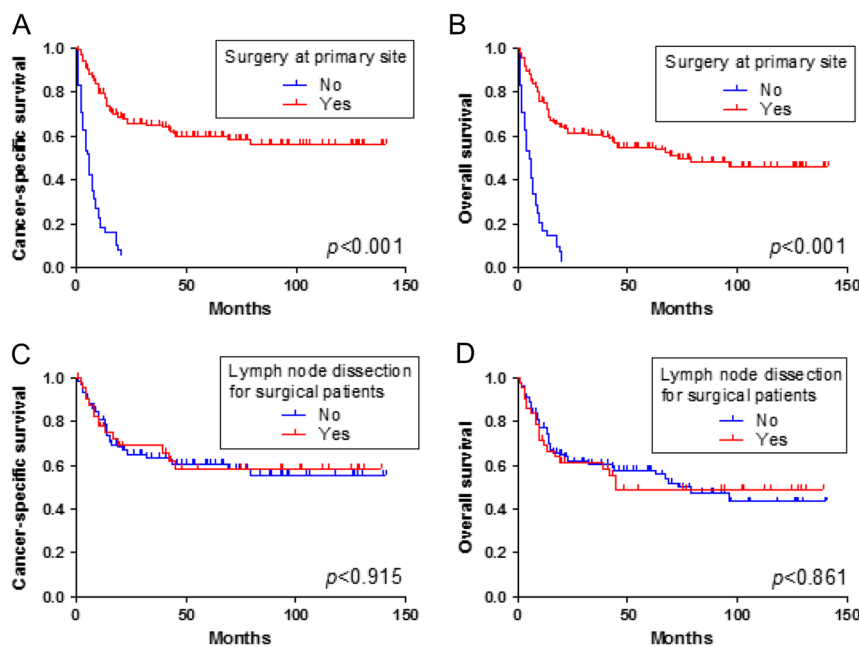


Figure 4

Kaplan–Meier curves of overall survival and cancer-specific survival according to surgery at the primary site (A and B) and lymph node dissection for surgical patients (C and D).

Table 3 Multivariate cox proportional hazards regression analysis for gallbladder neuroendocrine neoplasm patients.

Variables		Cancer-specific survival		Overall survival	
		HR (95% CI)	P	HR (95% CI)	P
Age at diagnosis, years	≤65	1.00	–	1.00	–
	>65	1.65 (1.14–2.40)	0.008	1.78 (1.26–2.52)	0.001
Marital status	Married	1.00	–	1.00	–
	Unmarried ^a	1.89 (1.27–2.81)	0.002	1.91 (1.33–2.73)	<0.001
Tumor size (cm)	≤2	1.00	–	1.00	–
	2–5	1.83 (0.84–4.01)	0.129	1.50 (0.79–2.84)	0.215
	>5	2.95 (1.37–6.39)	0.006	2.15 (1.13–4.09)	0.020
	Unknown	4.84 (2.29–10.21)	<0.001	3.32 (1.82–6.06)	<0.001
SEER stage	Localized	1.00	–	1.00	–
	Regional	4.50 (1.62–12.49)	0.004	6.06 (3.05–12.06)	<0.001
	Distant	9.42 (3.32–26.73)	<0.001	10.60 (5.15–21.82)	<0.001
N stage	N0	1.00	–	NA	–
	N1	1.03 (0.68–1.57)	0.881		
	Unknown	2.16 (1.19–3.91)	0.011		
Histological category ^b	GB-NEC	1.00	–	NA	–
	GB-NET	0.22 (0.06–0.86)	0.030		
Surgery at primary site	No	NA	–	1.00	–
	Yes			0.58 (0.37–0.90)	0.014

^aUnmarried included single, divorced, widowed, and separated; ^bGB-NEC included neuroendocrine carcinoma, large-cell neuroendocrine carcinoma, small-cell carcinoma, and mixed adenoneuroendocrine carcinoma of the gallbladder and GB-NET included carcinoid tumors and atypical carcinoid tumors of the gallbladder. Bold indicates statistical significance.

Several studies have examined the risk factors for the prognosis of NEN at various sites. Cao *et al.* found that age, sex, T stage, M stage, and histological type were independent prognostic factors for gastric NEN (21). Zhang *et al.* showed that lymph node metastasis and distant metastasis were independent predictors of OS for NEN of the gastroesophageal junction (22). Lee *et al.* identified 43 patients with biliary NEN, including 11 GB-NEN cases, and the only factor related to poor prognosis was G3 staging according to the WHO classification (9). Copy number variations of somatic SNVs and small insertions and deletions in primary and metastatic GB-NEN tissues were identified by whole-genome sequencing, which could be valuable prognostic factors or indicators of the treatment response (23). However, to the best of our knowledge, no study has examined the survival prognosis for GB-NEN. In this study, the Kaplan–Meier method and multivariate Cox proportional hazard models were performed to evaluate the predictors of survival for GB-NEN. Advanced SEER stage, aggressive grade, increased tumor size, lymph node metastasis, and distant metastasis were statistically significantly related to decreased survival time. In addition, older age, unmarried status, primary tumors greater than 5 cm, and progressive SEER stage were regarded as independent significant risk factors for survival. Gallbladder surgery was a significant factor for OS. GB-NET was a risk factor for decreased cancer-specific survival time. The prognosis is different between

neuroendocrine carcinoma and neuroendocrine tumor (5); this was taken into consideration in the Kaplan–Meier method and multivariate analysis. It was found that the classification GB-NET was associated with a better survival outcome. The classification GB-NET was also a factor for increased cancer-specific survival time. These predictors will be useful for physicians to estimate the prognosis for GB-NEN patients.

Surgery is currently considered the most important method to treat GB-NEN. The lesion can be removed by surgery and can be examined to define the histological type and provide clinical characteristics for postoperative treatment. Because there are few reports on the biological characteristics and clinicopathological features of GB-NEN, there are currently no standardized surgical strategies and guidelines for GB-NEN. However, radical surgery results in a significant improvement in the prognosis of GBC (24, 25), which can provide a reference for the treatment of GB-NEN. For carcinomas confined to the mucosa, cholecystectomy can be performed. For progressive tumors without distant metastasis, radical resection of the gallbladder, peripheral lymph node dissection, and partial hepatectomy are recommended. For cases that cannot be cured by surgery, patient quality of life can be improved by palliative surgery. In addition, preoperative comprehensive treatment can be used to reduce the tumor burden and to actively seek surgical treatments (24). In this study, we found that patients undergoing gallbladder

surgery had better survival than patients without surgical treatment. However, among cases that received gallbladder surgery, the further addition of lymph node surgery had no effect on survival. A previous study on pancreatic NEN also showed that extended lymphadenectomy was not associated with better OS (26).

This study has several limitations. First, data on patient postoperative complications, recurrence and neoadjuvant chemotherapy are not available to the public in the SEER database. Because these factors may affect the prognosis of GB-NEN, the predictive model in this study should be modified if these factors are available. Second, although this study contained the largest number of GB-NEN patients to date, GB-NEN studies of larger sample size are needed to confirm our findings. In future research on GB-NEN, stratification analysis may be used to further analyze the prognostic factors. In addition, the information in the SEER database comes from various registries. Notably, SEER quality improvement methods have been developed using appropriate statistical procedures that provide measures to evaluate the performance of SEER registries.

In conclusion, we found that age, marital status, tumor size, and SEER stage are predictors for the survival of GB-NEN patients. Surgical treatment of gallbladder tumors is associated with increased survival time, but surgery combined with lymphadenectomy has no effect on survival outcomes.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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