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SYSTEMATIC REVIEWS

# Gallbladder neuroendocrine carcinoma diagnosis, treatment and prognosis based on the SEER database: A literature review

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# Abstract

# BACKGROUND

Gallbladder neuroendocrine carcinoma (GB-NEC) has a low incidence rate; therefore, its clinical characteristics, diagnosis, treatment and prognosis are not well explored.

# AIM

To review recent research and analyze corresponding data in the Surveillance Epidemiology and End Results (SEER) database.

# **METHODS**

Data of GB-NEC (n = 287) and gallbladder adenocarcinoma (GB-ADC) (n = 19484) patients from 1975 to 2016 were extracted from the SEER database. Survival analysis was performed using Kaplan-Meier and Cox proportional hazards regression. P < 0.05 was considered statistically significant. We also reviewed 108 studies retrieved from PubMed and Reference Citation Analysis (https://www. referencecitationanalysis.com/). The keywords used for the search were: "(Carcinoma, Neuroendocrine) AND (Gallbladder Neoplasms)".

# RESULTS

The GB-NEC incidence rate was 1.6% (of all gallbladder carcinomas), male to female ratio was 1:2 and the median survival time was 7 mo. The 1-, 2-, 3- and 5year overall survival (OS) was 36.6%, 17.8%, 13.2% and 7.3% respectively. Serum chromogranin A levels may be a specific tumor marker for the diagnosis of GB-NEC. Elevated carcinoembryonic antigen, carbohydrate antigen (CA)-19-9 and CA-125 levels were associated with poor prognosis. Age [hazard ratio (HR) = 1.027, 95% confidence interval (CI): 1.006–1.047, P = 0.01] and liver metastasis (HR = 3.055, 95% CI: 1.839–5.075, *P* < 0.001) are independent prognostic risk factors for OS. Patients with advanced GB-NEC treated with surgical resection combined with radiotherapy and/or chemotherapy may have a better prognosis than those treated with surgical resection alone. There was no significant difference in OS between GB-NEC and GB-ADC.



#### CONCLUSION

The clinical manifestations and prognosis of GB-NEC are similar to GB-ADC, but the treatment is completely different. Early diagnosis and treatment are the top priorities.

Key Words: Clinical features; Diagnosis; Gallbladder neuroendocrine tumor; Pathology; Treatment

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**Core tip:** A literature review based on the Surveillance Epidemiology and End Results database was conducted to find the clinical manifestations, diagnosis, treatment, and prognosis of gallbladder neuroendocrine carcinoma. We tried to clarify the direction of further research on this tumor.

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# INTRODUCTION

Neuroendocrine neoplasms (NENs) have been reported in nearly every tissue. According to the International Agency for Research on Cancer – World Health Organization, neuroendocrine tumors (NETs) are composed of cells with distinctive phenotype characterized by the expression of general and specific neuroendocrine biomarkers. NETs account for about 0.5% of all newly diagnosed malignancies[1]. Gallbladder neuroendocrine carcinoma (GB-NEC) is extremely rare. Yao *et al*[2] reported that GB-NEC accounted for only 0.5% of all NENs and for 2.1% of all gallbladder malignancies. Since GB-NEC has a low incidence rate, many clinical questions related to it are yet to be fully explored in literature. After reviewing the relevant literature, we found the following problems: (1) The epidemiological characteristics, clinical features, treatment and prognosis of GB-NEC are still unclear; (2) Most studies compared the prognosis of GB-NEC to that of adenocarcinoma; however, the results reported are still contradictory. In most of the studies, the sample sizes were small and as such, the results may not be objective; and (3) Most of the studies only focused on the clinical manifestations and prognosis of GB-NEC. Few articles explored the pathogenesis and mechanism of GB-NEC. In this study, the authors attempt to address the three problems stated above.

# MATERIALS AND METHODS

#### Patients and literature

The Surveillance Epidemiology and End Results (SEER) database was searched and screened according to the following criteria: (1) Site and morphology; diagnostic confirmation = positive histology; (2) Type of reporting source = autopsy only; death certificate only; (3) Site and morphology site recode ICD-0-3/WHO 2008 = gallbladder; and (4) cause of death; follow-up; survival month = complete dates are available. Finally, 19 842 patients with pathologically confirmed gallbladder malignancy from 1975 to 2016 were obtained. Among them, there were 19 484 cases of gallbladder adenocarcinoma and 287 cases of GB-NEC. Among the patients with GB-NEC, there were 29 cases of large cell NEC and 109 cases of small cell NEC. In addition, we searched PubMed and *Reference Citation Analysis* (https://www.referen cecitationanalysis.com/) for the following keywords and obtained 217 articles describing GB-NEC: Key words = (carcinoma, neuroendocrine) AND (gallbladder neoplasms). These described: (1) Mixed GB-NEC; (2) other biliary NEC; (3) metastatic tumor; and (4) NENs not carcinoma were ruled out, giving a final total of 108 articles for review (Figure 1).

#### Variables and outcome

Patients' variables and follow-up data were obtained from SEER database, including gender, age, race, pathological differentiation degree of tumor, pathological classification, and tumor metastasis. All patients had complete follow-up data on postoperative survival status, and the primary outcome of this study was OS.

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Figure 1 Retrieval from SEER database and literature. SEER: Surveillance Epidemiology and End Results; WHO: World Health Organization; GB-NEC: Gallbladder neroendocrine carcinoma; GB-ADC: Gallbladder adenocarcinoma.

## Statistical analysis

<sup>2</sup>and independent sample *t* tests and univariate ANOVA were used to compare baseline data of patients between GB-ADC and GN-NEC. Univariate<sup>2</sup> test and multivariate Cox regression analysis was used to investigate the independent risk factors influencing the prognosis of GB-NEC patients. Kaplan-Meier curve and log-rank test were used to explore survival analysis between different groups of patients. All analysis was performed using SPSS Statistics version 24.0 (IBM Corp., Armonk, NY, USA). P < 0.05 was considered statistically significant.

# RESULTS

#### Epidemiology and classification of GB-NEC

GB-NEC account for 2%–2.5% of all gallbladder tumors and the male to female ratio ranges between 1:4 and 1:2[2-4]. In our study, a total of 19 771 patients diagnosed with gallbladder malignancy from 1975 to 2016 were selected from the SEER database and analyzed. In this cohort, GB-NEC accounted for 1.4% of all gallbladder malignancies. The male to female ratio was 1:2, the average age was 68 years and the median survival time was 7 mo. GB-NEC had a significantly lower degree of tumor differentiation compared to GB-ADC. The proportion of poorly differentiated and undifferentiated tumors was 57.8% *vs* 33% (*P* < 0.001) (Table 1).

In order to avoid ambiguity in clinical practice, the WHO 2019 classification is currently used. The WHO criteria classifies NETs into three levels instead of discretely classifying NEC. However, NEC are still classified into small and large cell types. The final classification of NEC is not based on the degree of tumor differentiation, but rather on the mitotic rate and tumor genetic characteristics<sup>[4]</sup>. In most mixed NENs, both neuroendocrine and non-neuroendocrine components are poorly differentiated. The neuroendocrine component has proliferation indices in the same range as other NECs; however, this conceptual category allows for the possibility of one or both components being well differentiated. When feasible, each component should therefore be graded separately<sup>[5]</sup>. As such, most previous studies on NEC have reported no clear distinction between NET and NEC. The clinicopathological characteristics of NEC and NET remain ambiguous. In this paper, we focus on GB-NEC (Table 2).

# Origin of GB-NEC

NETs of the gastrointestinal tract usually originate from hormone-producing cells known as amine precursor uptake and decarboxylation (APUD) cells[6]. However, normal gallbladder mucosa does not have APUD cells; therefore, several hypotheses exist to explain the origin of GB-NECs.

#### Intestinal or gastric metaplasia of gallbladder epithelium

As early as 1975, Mlaitio found that patients with gallbladder stones experienced repeated inflammation



Table 1 Clinicopathological features of GB-NEC and GB-ADC			
Clinical variable	GB-NEC ( <i>n</i> = 287)	GB-ADC ( <i>n</i> = 19 484)	<i>P</i> value
Age, mean (range), yr	68 (32-98)	70 (11-104)	0.175
Race, <i>n</i> (%)			0.372
Black	35 (12.2%)	2187 (11.2%)	
White	227 (79.1%)	15121 (77.6%)	
Other	25 (8.7%)	2127 (10.9%)	
Sex, n (%)			0.239
Female	192 (66.9%)	13679 (70.2%)	
Male	95 (33.1%)	5805 (29.8%)	
Grade, <i>n</i> (%)			< 0.001
I	9 (3.1%)	2220 (11.4%)	
Ш	7 (2.4%)	5853 (30.0%)	
Ш	98 (34.1%)	5980 (30.7%)	
IV	68 (23.7%)	445 (2.3%)	
Unknown	105 (36.6%)	4986 (25.6%)	
Survival time, median, 95%CI (mo)	8 (6.6-9.4)	7 (6.8-7.2)	0.079
Histologic type, <i>n</i> (%)			
Neuroendocrine carcinoma	149 (51.9%)		
Large cell neuroendocrine carcinoma	29 (10.1%)		
Small cell neuroendocrine carcinoma	109 (38.0%)		
SEER Combined Mets at DX-liver, <i>n</i> (%)	53 (18.5%)		

Grade: Grade I: well differentiated; differentiated; NOS Grade II: Moderately differentiated; moderately differentiated; intermediate differentiation; Grade IIL: Poorly differentiated; Differentiated Grade IV: Undifferentiated: Anaplastic Surveillance Epidemiology and End Results Combined Mets at DX-liver: The tumor metastasized to the liver. GB-NEC: Gallbladder neuroendocrine carcinoma; GB-ADC: Gallbladder adenocarcinoma; SEER: Surveillance Epidemiology and End Results.

> that leads to metaplasia of the normal epithelial cells of the gallbladder. Cells with endocrine function including goblet cells and enterochromaffin gradually replace the normal cells. If the hypothesis holds, in principle, gallbladder stones and cholecystitis are highly correlated with GB-NECs. Unfortunately, due to the rarity of GB-NEC, no large sample size analysis of the hypothesis exists[7].

#### Pluripotent cells hypothesis

This hypothesis is based on a demonstration of shared immunoreactivity patterns between tumor components and common characteristics (featuring both neuroendocrine and glandular differentiation) observed in electron micrographs[8-12].

#### Adenocarcinoma transformation theory

In addition to the aforementioned hypotheses, some scholars have proposed that GB-NEC is derived from the transformation of adenocarcinoma. The rationale is that endocrine carcinoma and adenocarcinoma sometimes coexist. However, currently evidence to support the hypothesis is insufficient[13-16].

# Clinical manifestations and diagnosis of GB-NEC (immunohistochemistry, biomarkers and imaging)

About half of GB-NEC patients present with upper right quadrant discomfort or pain on initial doctor's visit, accompanied with atypical manifestations such as weight loss, anorexia, jaundice, fever, nausea and vomiting. At the time of diagnosis, patients often have distant metastases (often liver metastasis) with lymph node involvement, thus disqualifying them from surgical resection. Most studies have not found any specific tumor markers for GB-NECs. There have been sporadic reports of carbohydrate antigen (CA)-125, CA-19-9, carcinoembryonic antigen (CEA) and serum chromogranin A (CgA) being elevated in GB-NEC. GB-NECs can be divided into functional and nonfunctional types. Functional NETs may secrete histamine, vasodilator factors or substances contributing to carcinoid syndrome. Although the syndrome is rarely reported in GB-NEC, it makes the diagnosis of GB-NEC difficult. Lin et



# Table 2 2019 World Health Organization and 2017 international Agency for Research on Cancer classification and grading criteria for neuroendocrine neoplasms of the gastrointestinal tract and hapatopancreatobiliary organs

Terminology	Differentiation	Grade	Mitotic¹ rate (mitoses/2 mm²)	Ki-67 index	Molecular differences
NET GI	Well-differentiated NET (carcinoid)	Low	< 2	< 3%	Mutations in MEN1, DAXX .ATRX
NET G2		Intermediate	2-20	3% - 20%	Mutations in MEN1, DAXX .ATRX
NET G3		High	> 20	> 20%	Mutations in MEN1, DAXX .ATRX
NEC <sup>2</sup>	Poorly differentiated NEC	High	> 20	> 20%	Mutations in TP53 or RB1
Mixed NENs <sup>2</sup>	Well or poorly differentiated	Variable <sup>3</sup>	Variable	Variable	

<sup>1</sup>Mitotic rates arc expressed as number of mitoses/2 mm<sup>2</sup> as determined by counting in 50 fields of 0.2 mm<sup>2</sup> (in a total area of 10 mm<sup>2</sup>); The Ki-67 proliferation index is determined by counting at least 500 cells in regions of highest labeling (hot-spots) which arc identified at scanning magnification; The Grade is based on whichever of the two proliferation indexes place the neoplasm in the higher grade category [6].

<sup>2</sup>NEC including {NEC, small-cell lype [SCNEC; NEC; large cell typc (LCNEC)]}; Mixed NENs including [mixed neuroendorine-non-neuroendorine neoplasms (MiNENs)]; Mixed adenoneuroendocrine carcinomas (MANECs).

<sup>3</sup>Vriablc means: Changeable.

NET: Neuroendocrine tumors; NEC: Neuroendocrine carcinoma.

al[17] reported a patient with GB-NEC complicated by Cushing's syndrome. The disease is predominantly diagnosed by postoperative pathology and immunohistochemistry. It is worth noting that some reports have reported a relationship between elevated tumor markers (such as CEA) and prognosis, as well as liver invasion[18]. Patient clinicopathological characteristics are summarized in Table 3. Imaging has limited diagnostic value for GB-NEC. On ultrasound, a solid, nonuniform, hypoechoic lesion is detected. On plain computed tomography (CT), the lesions may appear hypodense. With contrastenhanced CT, uneven enhancement, cystic degeneration and necrosis may be observed. The gallbladder regional lymph nodes as well as those of the hepatic hilum may be enlarged. The scan may also show annular enhancement. On plain magnetic resonance imaging (MRI), all lesions show a low signal on T1weighted imaging (T1WI) and a high signal on T2-weighted imaging (T2WI). The signal of the lesions is lower in T1WI and higher in T2WI. With enhanced MRI, uneven enhancement is observed. GB-NEC has no particularly distinguishing features on imaging. It mostly has a wide-basal shape with a clear boundary. Cystic degeneration and necrosis are common. Both CT and MRI are necessary to assess involvement of adjacent organs. Lymph node involvement and metastasis are useful for preoperative staging and selection of treatment options (Figures 2 and 3).

#### Treatment of GB-NEC

Surgery: GB-NEC surgical resection refers to the surgical options available for gallbladder cancer. Basic cholecystectomy is limited to patients classified as stage T1a[19]. Some surgeons have reported cholecystectomy combined with wedge resection (negative margins) to be sufficient for T1b malignant gallbladder tumors[20,21]. However, Liu et al[22] in their case report considered basic cholecystectomy with bed cautery to be sufficient for T1bN0M0 GB-NEC. Further research is required given that theirs' was a case report. For GB-NEC classified as T2-4 without lymph node involvement, surgical resection may improve prognosis. When patient have lymph node metastasis, lymph node dissection may improve prognosis however the scope lymph node resection D1/D2 remains controversial[23]. For advanced gallbladder cancer, most clinical guidelines recommend systemic comprehensive treatment such as radiotherapy and chemotherapy[24] (Table 4).

Radiotherapy and chemotherapy: Although surgery remains the only curative approach, most patients experience recurrence and resection is not an option for some [23]. As such, the National Comprehensive Cancer Network guidelines recommend adjuvant chemotherapy, concurrent chemoradiotherapy or observation for resected gallbladder carcinoma staged T2 or higher[24]. Generally speaking, neuroendocrine carcinoma histology is similar to that of small cell lung cancer; therefore, platinum-etoposide chemotherapy is recommended as a more effective regimen for extrapulmonary NETs[25,26]. To date, no uniform radiotherapy and chemotherapy protocol exists for BG-NEC. We reviewed and summarized reported effective regimens for GB-NEC (Table 5).

#### Disease outcome, prognosis, risk factors and comparison with GB-ADC

Prognosis and associated risk factors of GB-NEC are unknown due the low incidence rate of GB-NEC. Some researchers have compared GB-NEC and GB-ADC prognosis. Some suggest that GB-ADC has a



Table 3 Clinical manifestations and laboratory tests of GB-NEC			
Clinical features of GB-NEC	Immunohistochemical	Biomarker	
Discomfort or pain in the upper abdomen[4,7,10,18, 22,33-43]	CgA synaptophysin, CD5 (most frequent)[4,17,22,33,34,44-47]	CA-125[4,18]	
Physical examination found[34,39]	cytokeratin 7 (CK7 cytoplasmic positivity)[4,33,37,38,40,41,44, 48,49]	CA-199[ <mark>4,10,18</mark> ]	
Weight loss[27,45,48]	TTF-1[33,38,41,48]	CEA[4,18,36,46]	
Poor appetite[4,18,33,50]	Cytokeratin[4,18,38,48]	Blood CgA[45,49]	
Jaundice[4,27]	CD117[38]	soluble IL-2 receptor (sIL-2R)[34]	
Fever[40]	loss of Rbl expression with intense pl6 labeling[38]	NSE[4,17,34]	
Carcinoid syndrome[7,17]	EMA[10,49]		
Abnormal liver function[41]	CA199[ <mark>42]</mark>		
nausea and vomiting[36]	P53[10]		

Immunohistochemical positive markers are described in the second column. Elevated tumor markers in serum are depicted in the third column. GB-NEC: Gallbladder neuroendocrine carcinoma; CgA: Chromogranin A.

Table 4 Application of surgical treatment of GB-NEC			
Tumor stage	Treatment		
T1aN0M0	Cholecystectomy		
T1bNOMO	Cholecystectomy + gallbladder bed cautery/wedge resection <sup>1</sup>		
T2-T3NOMO	Cholecystectomy + wedge resection/cholecystectomy + resection of liver segments (IVb + V/> 3 segments)/hepatectomy + pancreaticoduodenectomy		
T1-T3N1MO	Cholecystectomy + resection of liver segments + lymph node resection $(D1/D2^2)$ /hepatectomy+pancre- aticoduodenectomy + lymph node resection $(D1/D2)$		
IVA and IVB (advanced stage)	Systemic comprehensive therapy		

<sup>1</sup>Wedge resection: Wedge resection of the liver parenchyma of the gallbladder fossa. The specific amount of liver parenchyma to be removed has not yet been determined. In our center, liver parenchyma of 2 cm at the margin of gallbladder fossa is generally removed.

<sup>2</sup>D1 and D2: D1: Dissection of lymph nodes around the hepatic ligament; D2: Extended dissection of lymph nodes beyond the hepatic ligament. GB-NEC: Gallbladder neuroendocrine carcinoma.

> better prognosis<sup>[27]</sup> while others think no significant difference exists<sup>[28]</sup>. Consequently, we analyzed and summarized data from the SEER database to determine independent prognostic factors for GB-NEC; compare GB-NEC prognosis to that of GB-ADC; and determine the effect of postoperative adjuvant therapy on patient survival.

> The primary outcome was patient survival (death). Variables of interest included: race, sex, pathology, tumor grade, liver metastasis and age. Determination of potential and independent prognostic factors (in relation to OS) was via univariate and multivariate analysis respectively. We found that age [hazard ratio (HR) = 1.027, 95% confidence interval (CI): 1.006-1.047, P = 0.01] and liver metastasis (HR = 3.055, 95% CI: 1.839-5.075, P < 0.001) were independent prognostic factors for GB-NEC. However, race and gender only influence incidence but not OS (Table 6).

> We screened six patients who underwent only surgical resection and 16 who underwent resection coupled with adjuvant therapy (radiotherapy and/or chemotherapy) to analyze and compare survival. Due to the limitation of the database, specific chemotherapy regime and the clinical data of patients could not be ascertained due to Health insurance Portability and Accountability compliance. TNM staging for all patients was Stage III and above. Based on Kaplan-Meier analysis, postoperative adjuvant radiotherapy and or chemotherapy may prolong patient survival (Figure 3A). We also compared prognosis between the different pathological subtypes of GB-NEC. There was no significant difference in survival was found between small cell GB-NEC (n = 29), large cell GB-NEC (n = 109) and GB-NEC (*n* = 149).

> In respect to GB-NEC and GB-ADC, we found that the 5-year OS was 7.3% and 9.7% in GB-NEC and GB-ADC, respectively. There was a significant difference in OS between the two irrespective of stage (Figure 3B–D).

Table 5 Currently effective chemoradiotherapy regiments that have been tried			
Ref.	Chemoradiotherapy regiments		
Moris et al[44]	XELOX and Zometaf		
Chen <i>et al</i> [36], Meoni <i>et al</i> [45], Furrukh <i>et al</i> [46], Abutaka <i>et al</i> [49]	CBP and ETP		
Tidjane et al[39]	ETP+CP four cycles + 5-fluorouracil + oxaliplatin		
Okuyama et al[34]	Intravenous CP (60 mg/m <sup>2</sup> ) and DXT (60 mg/m <sup>2</sup> ) every 3 wk for four cycles, followed by intravenous CBP (120 mg/m <sup>2</sup> ) and DXT (60 mg/m <sup>2</sup> ) every 3 wk for three cycles		
Duffy <i>et al</i> [3]	VP-16 150 mg/dL; CP 50 mg/dL		
Chen <i>et al</i> [4]	Radiotherapy with 10 MV-X-ray and 3D-CRT, (50 Gy/25f)		
Shimono <i>et al</i> [10]	3D-CRT ( $40  Gy/20$ fractions per 4 wk and to give $10  Gy/20$ fractions per 4 wk, respectively, resulting in a total dose of $50  Gy$ ) + CP + ETP and CAV followed by CP + ETP alone		
Shimono <i>et al</i> [10]	Three cycles of CP (50 mg/body) + ETP (80 mg/body) as systemic chemotherapy		

CBP: Carboplatin; ETP: Etoposide (VP-16); CP: Cisplatin; 3D-CRT: 3D conformal radiotherapy; DXT: Docetaxel; CAV: Etoposide; cyclophosphamide, adriamycin, and vincristine.

#### Table 6 Univariate and multivariate Cox regression analysis of prognostic factors for overall survival

Variables	Univariate <i>P</i> value	Multivariate P value	HR (95%CI)
Race	0.842	NA	NA
Histology	0.931	NA	NA
Grade	0.123	NA	NA
Liver metastasis	> 0.001	> 0.001	3.055 (1.839-5.075)
Age	0.004	0.01	1.027 (1.006-1.049)

HR: Hazard ratio; CI: Confidence interval; NA: Not available.



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Figure 2 Neuroendocrine carcinoma of gallbladder under magnetic resonance imaging and pathological section. A: Gallbladder neuroendocrine carcinoma invading the liver magnetic resonance imaging T2 AX FAST; B: Poorly differentiated neuroendocrine carcinoma of the gallbladder, with some high-grade intraepithelial neoplasia of the gallbladder epithelium, canceration (< 5%).

# DISCUSSION

Currently, GB-NECs are not well understood by clinicians because of its low incidence rate. To address this challenge, we reviewed the literature (case reports and reviews) and analyzed data in the SEER database so as to provide more insight into GB-NEC diagnosis, pathology, treatment and prognosis. We also wanted to compare GB-NEC to GB-ADC. In the course of our analysis, we used the SEER database



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Figure 3 Overall survival of GB-NEC and GB-ADC patients. A: Stage III-IV surgery versus surgery combined chemotherapy and or radiotherapy; B: GB-NEC versus GB- small cell NEC/GB-large cell NEC; C: GB-NEC versus GB-ADC; D: Stage III-IV GB-NEC versus GB-ADC. LCNC: Large cell neuroendocrine carcinoma; SCNC: Small cell neuroendocrine carcinoma; NEC: Neuroendocrine carcinoma; GB-NEC: Gallbladder NEC; GB-ADC: Gallbladder adenocarcinoma.

to perform analysis on GB-NEC and GB-ADC data with larger sample sizes compared with previous studies

The observed GB-NEC incidence was lower than we anticipated, < 2%. The male to female ratio was 1:2 and the average age of onset was 68 years (incidence is higher in older women). GB-NEC had an median OS of 7 mo. GB-NEC has a lower degree of tumor differentiation compared to GB-ADC. The proportion of poorly differentiated and undifferentiated tumors was 57.8% versus 33% (P < 0.001) in GB-NEC and GB-ADC, respectively. GB-NEC was highly malignant with an aggressive progression profile. Systemic metastasis was common, even in early stages. Most patients were diagnosed at an aggressive stage[4,29-32], and 19.7% had already developed liver metastasis at the time of diagnosis. One explanation is that the gallbladder lacks a peritoneal layer on its hepatic adjacent side. Instead, the boundary between the gallbladder and the liver is the cystic plate, which is a continuation of Glisson's capsule[26]. For this reason, gallbladder cancers that invade the muscularis (T1b-T2) have a propensity to invade the liver and the correlation between the metastasis foci and Glisson system needs verification.

Clinical manifestations are not specific and about half of the patients present with right upper quadrant abdominal pain and discomfort. Presentation with carcinoid syndrome may be somewhat specific; however, its incidence in GB-NEC is low. Serum CgA may be a sensitive biomarker for GB-NEC. CA-125, CA-19-9, CEA, soluble IL-2 receptor and nonspecific enolase are elevated in some patients but none of them is specific. Some studies have suggested that CA-125 is associated with liver metastasis and poor prognosis. We however could not verify these findings due database-related limitations. Imaging examination has limited value in GB-NEC however its useful for treatment planning. Diagnosis of GB-NEC is mostly based on pathology and immunohistochemistry. The neoplasm must originate from the gallbladder instead of invasion of NEC from the liver or other organs [7]

Radical resection is the only curative approach. Selection of surgical resection is based on recommended surgical methods for gallbladder cancer. Patients with Stage III can be considered for surgery and postoperative adjuvant therapy. Except for T1aN0M0, specific surgical procedures are



controversial. Patients with T2N0M0 may only require basic cholecystectomy and gallbladder bed cautery. Based on the nearly 20% incidence rate of liver metastasis, performing a wedge resection of the liver would be preferable since the difficulty level of wedge resection is not significantly different from gallbladder cautery to hepatobiliary surgeons around the world.

# CONCLUSION

GB-NEC has a low incidence rate, high degree of malignancy and poor prognosis. The incidence is significantly higher in older women. GB-NEC is difficult to diagnose and most patients have advanced disease at the time of diagnosis. Therefore, the focus should be placed on investigating the pathogenesis and treatment rather than the atypical clinical manifestations of GB-NEC.

# **ARTICLE HIGHLIGHTS**

## Research background

Neuroendocrine neoplasms (NENs) have been reported in nearly every tissue. According to the International Agency for Research on Cancer - World Health Organization, neuroendocrine tumors (NETs) are composed of cells with distinctive phenotype characterized by the expression of general and specific neuroendocrine biomarkers. NETs account for about 0.5% of all newly diagnosed malignancies. Gallbladder neuroendocrine carcinoma (GB-NEC) is extremely rare; thus, many clinical questions related to it are yet to be fully explored.

## Research motivation

To investigate GB-NEC, we reviewed recent research and analyzed corresponding data in the Surveillance Epidemiology and End Results (SEER) database.

## Research objectives

We found the following problems. (1) The epidemiological characteristics, clinical features, treatment and prognosis of GB-NEC are still unclear; (2) Most studies compared the prognosis of GB-NEC to that of adenocarcinoma; however, the results reported are still contradictory. In most of the studies, the sample sizes were small and as such, the results may not be objective; and (3) Most studies only focused on the clinical manifestations and prognosis of GB-NEC. Few articles explored the pathogenesis and mechanism of GB-NEC. So in this study, we attempted to address the three problems stated above.

# Research methods

Data of GB-NEC (n = 287) and gallbladder adenocarcinoma (GB-ADC) (n = 19 484) patients from 1975 to 2016 were extracted from the SEER database. Survival analysis was performed using Kaplan-Meier and Cox proportional hazards regression. P < 0.05 was considered statistically significant. We also reviewed 108 studies retrieved from PubMed and Reference Citation Analysis (https://www.referencecitationanalysis.com/). The keywords used for the search were: "(carcinoma, neuroendocrine) AND (gallbladder neoplasms)".

# Research results

The GB-NEC incidence rate was 1.6% (of all gallbladder carcinomas), male to female ratio was 1:2 and the median survival time was 7 mo. The 1-, 2-, 3- and 5-year overall survival (OS) was 36.6%, 17.8%, 13.2% and 7.3%, respectively. Serum chromogranin A levels maybe a specific tumor marker for the diagnosis of GB-NEC. Elevated carcinoembryonic antigen, carbohydrate antigen (CA)-19-9 and CA-125 levels were associated with poor prognosis. Age and liver metastasis were independent prognostic risk factors for OS. Patients with advanced GB-NEC treated with surgical resection combined with radiotherapy and/or chemotherapy may have a better prognosis than those treated with surgical resection alone. There was no significant difference in OS between GB-NEC and GB-ADC.

# **Research conclusions**

GB-NEC has a low incidence rate, high degree of malignancy and poor prognosis. The incidence is significantly higher in older women. GB-NEC is difficult to diagnose and most patients have advanced disease at the time of diagnosis. Therefore, the focus should be on investigating the pathogenesis and treatment rather than the atypical clinical manifestations of GB-NEC.

# Research perspectives

Many researchers pay too much attention to the differences between GB-ADC and GB-NEC. In our study, except for blood biomarkers, there were no significant differences between the above two



diseases. Therefore, focus should be on investigating the pathogenesis and treatment rather than the atypical clinical manifestations of GB-NEC.

# FOOTNOTES

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## REFERENCES

- Taal BG, Visser O. Epidemiology of neuroendocrine tumours. Neuroendocrinology 2004; 80 Suppl 1: 3-7 [PMID: 1 15477707 DOI: 10.1159/000080731]
- 2 Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, Abdalla EK, Fleming JB, Vauthey JN, Rashid A, Evans DB. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 2008; 26: 3063-3072 [PMID: 18565894 DOI: 10.1200/JCO.2007.15.4377]
- 3 Duffy A, Capanu M, Abou-Alfa GK, Huitzil D, Jarnagin W, Fong Y, D'Angelica M, Dematteo RP, Blumgart LH, O'Reilly EM. Gallbladder cancer (GBC): 10-year experience at Memorial Sloan-Kettering Cancer Centre (MSKCC). J Surg Oncol 2008; 98: 485-489 [PMID: 18802958 DOI: 10.1002/jso.21141]
- Chen C, Wang L, Liu X, Zhang G, Zhao Y, Geng Z. Gallbladder neuroendocrine carcinoma: report of 10 cases and comparision of clinicopathologic features with gallbladder adenocarcinoma. Int J Clin Exp Pathol 2015; 8: 8218-8226 [PMID: 26339390]
- 5 Rindi G, Klimstra DS, Abedi-Ardekani B, Asa SL, Bosman FT, Brambilla E, Busam KJ, de Krijger RR, Dietel M, El-Naggar AK, Fernandez-Cuesta L, Klöppel G, McCluggage WG, Moch H, Ohgaki H, Rakha EA, Reed NS, Rous BA, Sasano H, Scarpa A, Scoazec JY, Travis WD, Tallini G, Trouillas J, van Krieken JH, Cree IA. A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal. Mod Pathol 2018; 31: 1770-1786 [PMID: 30140036 DOI: 10.1038/s41379-018-0110-y
- 6 Alawad M, Gupta R, Haseeb MA, Brunicardi FC. Clinicopathologic and Molecular Features of Mixed Neuroendocrine Non-Neuroendocrine Neoplasms of the Gallbladder. Gastroenterology Res 2020; 13: 269-278 [PMID: 33447306 DOI: 10.14740/gr1323]
- 7 Eltawil KM, Gustafsson BI, Kidd M, Modlin IM. Neuroendocrine tumors of the gallbladder: an evaluation and reassessment of management strategy. J Clin Gastroenterol 2010; 44: 687-695 [PMID: 20375728 DOI: 10.1097/MCG.0b013e3181d7a6d4]
- 8 Paniz Mondolfi AE, Slova D, Fan W, Attiyeh FF, Afthinos J, Reidy J, Pang Y, Theise ND. Mixed adenoneuroendocrine carcinoma (MANEC) of the gallbladder: a possible stem cell tumor? Pathol Int 2011; 61: 608-614 [PMID: 21951672 DOI: 10.1111/j.1440-1827.2011.02709.x]
- lida Y, Tsutsumi Y. Small cell (endocrine cell) carcinoma of the gallbladder with squamous and adenocarcinomatous components. Acta Pathol Jpn 1992; 42: 119-125 [PMID: 1314006 DOI: 10.1111/j.1440-1827.1992.tb03086.x]
- 10 Shimono C, Suwa K, Sato M, Shirai S, Yamada K, Nakamura Y, Makuuchi M. Large cell neuroendocrine carcinoma of the gallbladder: long survival achieved by multimodal treatment. Int J Clin Oncol 2009; 14: 351-355 [PMID: 19705247 DOI: 10.1007/s10147-008-0843-6]
- 11 Laitio M. Goblet cells, enterochromaffin cells, superficial gastric-type epithelium and antral-type glands in the gallbladder. Beitr Pathol 1975; 156: 343-358 [PMID: 1220670 DOI: 10.1016/s0005-8165(75)80044-8]
- Harada K, Sato Y, Ikeda H, Hsu M, Igarashi S, Nakanuma Y. Notch1-Hes1 signalling axis in the tumourigenesis of biliary 12 neuroendocrine tumours. J Clin Pathol 2013; 66: 386-391 [PMID: 23423517 DOI: 10.1136/jclinpath-2012-201273]
- Nishikura K, Watanabe H, Iwafuchi M, Fujiwara T, Kojima K, Ajioka Y. Carcinogenesis of gastric endocrine cell



carcinoma: analysis of histopathology and p53 gene alteration. Gastric Cancer 2003; 6: 203-209 [PMID: 14716513 DOI: 10.1007/s10120-003-0249-0]

- 14 Li Y, Yau A, Schaeffer D, Magliocco A, Gui X, Urbanski S, Waghray R, Owen D, Gao ZH. Colorectal glandularneuroendocrine mixed tumor: pathologic spectrum and clinical implications. Am J Surg Pathol 2011; 35: 413-425 [PMID: 21317713 DOI: 10.1097/PAS.0b013e3182093657]
- Bergsland EK, Roy R, Stephens P, Ross JS, Olshen A. Genomic profiling to distinguish poorly differentiated 15 neuroendocrine carcinomas arising in different sites. J Clin Oncol 2016; 34: 4020-4020 [DOI: 10.1200/JCO.2016.34.15 suppl.4020
- 16 de Mestier L, Cros J, Neuzillet C, Hentic O, Egal A, Muller N, Bouché O, Cadiot G, Ruszniewski P, Couvelard A, Hammel P. Digestive System Mixed Neuroendocrine-Non-Neuroendocrine Neoplasms. Neuroendocrinology 2017; 105: 412-425 [PMID: 28803232 DOI: 10.1159/000475527]
- Lin D, Suwantarat N, Kwee S, Miyashiro M. Cushing's syndrome caused by an ACTH-producing large cell neuroendocrine 17 carcinoma of the gallbladder. World J Gastrointest Oncol 2010; 2: 56-58 [PMID: 21160818 DOI: 10.4251/wjgo.v2.i1.56]
- 18 Chu H, Zhang C, Shi Y, Wu W, Hu Z, Zhang J, Huang D. Gallbladder neuroendocrine carcinoma: A single center experience. Medicine (Baltimore) 2020; 99: e21912 [PMID: 32899024 DOI: 10.1097/MD.00000000021912]
- Goetze TO, Paolucci V. Immediate re-resection of T1 incidental gallbladder carcinomas: a survival analysis of the German 19 Registry. Surg Endosc 2008; 22: 2462-2465 [PMID: 18247090 DOI: 10.1007/s00464-008-9747-9]
- Krell RW, Wei AC. Gallbladder cancer: surgical management. Chin Clin Oncol 2019; 8: 36 [PMID: 31431029 DOI: 20 10.21037/cco.2019.06.06]
- Javle M, Zhao H, Abou-Alfa GK. Systemic therapy for gallbladder cancer. Chin Clin Oncol 2019; 8: 44 [PMID: 31484490 21 DOI: 10.21037/cco.2019.08.14]
- 22 Liu W, Chen W, He X, Qu Q, Hong T, Li B. Cholecystectomy with gallbladder bed cautery might be sufficient for T1bN0M0 neuroendocrine carcinoma of gallbladders: Cases report and literature review. Medicine (Baltimore) 2017; 96: e8778 [PMID: 29381978 DOI: 10.1097/MD.00000000008778]
- 23 Benson AB, D'Angelica MI, Abrams TA, Are C, Bloomston PM, Chang DT, Clary BM, Covey AM, Ensminger WD, Iver R, Kelley RK, Linehan D, Malafa MP, Meranze SG, Park JO, Pawlik T, Posey JA, Scaife C, Schefter T, Sigurdson ER, Tian GG, Vauthey JN, Venook AP, Yen Y, Zhu AX, Hoffmann KG, McMillian NR, Sundar H. Hepatobiliary cancers, version 2.2014. J Natl Compr Canc Netw 2014; 12: 1152-1182 [PMID: 25099447 DOI: 10.6004/jnccn.2014.0112]
- 24 Moertel CG, Kvols LK, O'Connell MJ, Rubin J. Treatment of neuroendocrine carcinomas with combined etoposide and cisplatin. Evidence of major therapeutic activity in the anaplastic variants of these neoplasms. Cancer 1991; 68: 227-232 [PMID: 1712661 DOI: 10.1002/1097-0142(19910715)68:2<227::aid-cncr2820680202>3.0.co;2-i]
- Mitry E, Baudin E, Ducreux M, Sabourin JC, Rufié P, Aparicio T, Lasser P, Elias D, Duvillard P, Schlumberger M, 25 Rougier P. Treatment of poorly differentiated neuroendocrine tumours with etoposide and cisplatin. Br J Cancer 1999; 81: 1351-1355 [PMID: 10604732 DOI: 10.1038/sj.bjc.6690325]
- Yan S, Wang Y, Chen X, Zhang Y, Huang Z, Zhao J, Zhou J, Li Z, Bi X, Luo Z, Cai J, Zhao H. Clinical Analysis of 15 26 Cases of Gallbladder Neuroendocrine Carcinoma and Comparison with Gallbladder Adenocarcinoma Using a Propensity Score Matching. Cancer Manag Res 2020; 12: 1437-1446 [PMID: 32161496 DOI: 10.2147/CMAR.S227501]
- 27 Do MY, Jang SI, Kang HP, Kim EJ, Lee KJ, Park GE, Lee SJ, Lee DK, Woo SM, Cho JH. Comparison of the Clinical Features and Outcomes of Gallbladder Neuroendocrine Carcinoma with Those of Adenocarcinoma: A Propensity Score-Matched Analysis. Cancers (Basel) 2021; 13 [PMID: 34572940 DOI: 10.3390/cancers13184713]
- 28 Lee KJ, Cho JH, Lee SH, Lee KH, Park BK, Lee JK, Woo SM, Ryu JK, Kim YS, Kim JW, Lee WJ. Clinicopathological characteristics of biliary neuroendocrine neoplasms: a multicenter study. Scand J Gastroenterol 2017; 52: 437-441 [PMID: 27924650 DOI: 10.1080/00365521.2016.1261938]
- Kim J, Lee WJ, Lee SH, Lee KB, Ryu JK, Kim YT, Kim SW, Yoon YB, Hwang JH, Han HS, Woo SM, Park SJ. Clinical 29 features of 20 patients with curatively resected biliary neuroendocrine tumours. Dig Liver Dis 2011; 43: 965-970 [PMID: 21856258 DOI: 10.1016/j.dld.2011.07.010]
- Blumgart LH, Hann LE. Surgical and Radiologic Anatomy of the Liver, Biliary Tract, and Pancreas. Surgery of the 30 Liver, Biliary Tract and Pancreas (Fourth Edition). 2007; 1: 3-29 [DOI: 10.1016/B978-1-4160-3256-4.50009-0]
- Deehan DJ, Heys SD, Kernohan N, Eremin O. Carcinoid tumour of the gall bladder: two case reports and a review of 31 published works. Gut 1993; 34: 1274-1276 [PMID: 8406168 DOI: 10.1136/gut.34.9.1274]
- Fischer L, Kleeff J, Esposito I, Hinz U, Zimmermann A, Friess H, Büchler MW. Clinical outcome and long-term survival 32 in 118 consecutive patients with neuroendocrine tumours of the pancreas. Br J Surg 2008; 95: 627-635 [PMID: 18306152] DOI: 10.1002/bjs.6051]
- 33 Siddamreddy S, Meegada S, Syed A, Sarwar M, Muppidi V. Gallbladder Neuroendocrine Carcinoma: A Rare Endocrine Tumor. Cureus 2020; 12: e7487 [PMID: 32368420 DOI: 10.7759/cureus.7487]
- Okuyama Y, Fukui A, Enoki Y, Morishita H, Yoshida N, Fujimoto S. A large cell neuroendocrine carcinoma of the gall 34 bladder: diagnosis with 18FDG-PET/CT-guided biliary cytology and treatment with combined chemotherapy achieved a long-term stable condition. Jpn J Clin Oncol 2013; 43: 571-574 [PMID: 23532186 DOI: 10.1093/jjco/hyt033]
- 35 Du H, Zhang H, Xu Y, Wang L. Neuroendocrine tumor of the gallbladder with spectral CT. Quant Imaging Med Surg 2014; 4: 516-518 [PMID: 25525590 DOI: 10.3978/j.issn.2223-4292.2014.08.04]
- 36 Chen H, Shen YY, Ni XZ. Two cases of neuroendocrine carcinoma of the gallbladder. World J Gastroenterol 2014; 20: 11916-11920 [PMID: 25206300 DOI: 10.3748/wjg.v20.i33.11916]
- Zou RQ, Hu HJ, Li FY. Primary Small Cell Neuroendocrine Carcinoma of the Gallbladder with Lymph Node Metastasis. J 37 Gastrointest Surg 2021; 25: 2142-2144 [PMID: 33547583 DOI: 10.1007/s11605-021-04941-2]
- 38 Lee SM, Sung CO. Neuroendocrine Carcinomas of the Gallbladder: A Clinicopathologic and Immunohistochemical Analysis of 34 Resected Cases. Am J Surg Pathol 2020; 44: 1308-1321 [PMID: 32739935 DOI: 10.1097/PAS.00000000001536]
- Tidjane A, Boudjenan N, Bengueddach A, Kadri A, Ikhlef N, Benmaarouf N, Tabeti B. Pure large cell neuroendocrine 39 carcinoma of the gallbladder, is surgical relentlessness beneficial? Int Cancer Conf J 2021; 1-7 [PMID: 33425643 DOI:



#### 10.1007/s13691-020-00461-z]

- 40 Wang P, Chen J, Jiang Y, Jia C, Pang J, Wang S, Chang X. Neuroendocrine Neoplasms of the Gallbladder: A Clinicopathological Analysis of 13 Patients and a Review of the Literature. Gastroenterol Res Pract 2021; 2021: 5592525 [PMID: 34122537 DOI: 10.1155/2021/5592525]
- 41 Peters C, Lewin E, Wu T, Nakanishi Y. "Pure" High-Grade Large Cell Neuroendocrine Carcinoma Arising from Low- and High-Grade Dysplasia of the Gallbladder: Case Report and Review of the Literature. J Gastrointest Cancer 2019; 50: 967-971 [PMID: 30043226 DOI: 10.1007/s12029-018-0148-6]
- 42 Chu H, Shi Y, Liu J, Huang D, Zhang J, Dou C. Update in clinical management for gallbladder neuroendocrine carcinoma. Medicine (Baltimore) 2021; 100: e25449 [PMID: 33832150 DOI: 10.1097/MD.00000000025449]
- 43 Hari DM, Howard JH, Leung AM, Chui CG, Sim MS, Bilchik AJ. A 21-year analysis of stage I gallbladder carcinoma: is cholecystectomy alone adequate? HPB (Oxford) 2013; 15: 40-48 [PMID: 23216778 DOI: 10.1111/i.1477-2574.2012.00559.x
- Moris D, Tsilimigras DI, Lim J, Camastra D, Nanavati A, Knechtle SJ, Barbas AS. Neuroendocrine carcinomas of the 44 gallbladder: Lessons learnt from cases at opposite ends of the spectrum. J BUON 2018; 23: 1922-1926 [PMID: 30610822]
- Meoni G, Antonuzzo L, Messerini L, Giommoni E, Muto A, Petreni P, Vannini A, Lunghi A, Molinara E, Di Costanzo F. 45 Gallbladder neuroendocrine neoplasm: a case report and critical evaluation of WHO classification. Endocr J 2014; 61: 989-994 [PMID: 25088492 DOI: 10.1507/endocrj.ej14-0191]
- Furrukh M, Qureshi A, Saparamadu A, Kumar S. Malignant neuroendocrine tumour of the gallbladder with elevated 46 carcinoembryonic antigen: case report and literature review. BMJ Case Rep 2013; 2013 [PMID: 23661652 DOI: 10.1136/bcr-2013-008778]
- 47 Chakrabarti D, Qayoom S, Ghosh A, Gupta R. Neuroendocrine carcinoma of the gall bladder in a young lady presenting with upper abdominal heaviness: a common complaint and a rare diagnosis. BMJ Case Rep 2019; 12 [PMID: 30954965 DOI: 10.1136/bcr-2019-229684]
- 48 Liu W, Chen W, Chen J, Hong T, Li B, Qu Q, He X. Neuroendocrine carcinoma of gallbladder: a case series and literature review. Eur J Med Res 2019; 24: 8 [PMID: 30717775 DOI: 10.1186/s40001-019-0363-z]
- Abutaka A, El-Matbouly M, Helmy I, Elmoghazy W, Sulieman I, Ben Gashir M, Soofi M, Khalaf H, Elaffandi A. Repeat 49 liver resection for pure large cell neuroendocrine carcinoma of the gallbladder: a favorable outcome. World J Surg Oncol 2019; 17: 126 [PMID: 31325969 DOI: 10.1186/s12957-019-1666-9]
- Aiello P, Aragona F, Territo V, Caruso AM, Patti R, Buscemi S, Di Vita G. Concomitant small cell neuroendocrine 50 carcinoma of gallbladder and breast cancer. Case Rep Surg 2014; 2014: 945921 [PMID: 25328753 DOI: 10.1155/2014/945921]





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