**Name of Journal:** *World Journal of Clinical Cases*

**Manuscript NO:** 75096

**Manuscript Type:** SYSTEMATIC REVIEWS

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

Cai XC *et al*. Gallbladder NEC literature review

Xing-Chen Cai, Sheng-Dong Wu

**Xing-Chen Cai, Sheng-Dong Wu,** Department of Hepato-Pancreato-Billiary Surgery, Ningbo Medical Center Lihuili Hospital, The Affiliated Hospital of Ningbo University, Ningbo 315300, Zhejiang Province, China

**Author contributions:** Wu SD contributed to the article framework guidance and revision; and Cai XC contributed to the data acquisition, statistical analysis and article writing.

**Corresponding author: Sheng-Dong Wu, Doctor,** Department of Hepato-Pancreato-Billiary Surgery, Ningbo Medical Center Lihuili Hospital, The Affiliated Hospital of Ningbo University, No. 818 Fenghua Road, Ningbo 315300, Zhejiang Province, China. b407167953@163.com

**Received:** January 18, 2022

**Revised:** April 21, 2022

**Accepted: July 11, 2022**

**Published online:**

**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* = 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)”.

***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 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

Cai XC, Wu SD. Gallbladder neuroendocrine carcinoma diagnosis, treatment and prognosis based on the SEER database: A literature review. *World J Clin Cases* 2022; In press

**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.

**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. (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.referencecitationanalysis.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.

***Statistical analysis***

χ2 and independent sample *t* tests and univariate ANOVA were used to compare baseline data of patients between GB-ADC and GN-NEC.  Univariate χ2 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[4]. 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[5]. 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 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 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 contrast-enhanced 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 T1-weighted 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 better prognosis[27] while others think no significant difference exists[28]. 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–3D).

**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 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. (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.

**REFERENCES**

1 **Taal BG**, Visser O. Epidemiology of neuroendocrine tumours. *Neuroendocrinology* 2004; **80 Suppl 1**: 3-7 [PMID: 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]

4 **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]

9 **Iida 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]

12 **Harada K**, Sato Y, Ikeda H, Hsu M, Igarashi S, Nakanuma Y. Notch1-Hes1 signalling axis in the tumourigenesis of biliary neuroendocrine tumours. *J Clin Pathol* 2013; **66**: 386-391 [PMID: 23423517 DOI: 10.1136/jclinpath-2012-201273]

13 **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 glandular-neuroendocrine mixed tumor: pathologic spectrum and clinical implications. *Am J Surg Pathol* 2011; **35**: 413-425 [PMID: 21317713 DOI: 10.1097/PAS.0b013e3182093657]

15 **Bergsland EK**, Roy R, Stephens P, Ross JS, Olshen A. Genomic profiling to distinguish poorly differentiated 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]

17 **Lin D**, Suwantarat N, Kwee S, Miyashiro M. Cushing's syndrome caused by an ACTH-producing large cell neuroendocrine 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.0000000000021912]

19 **Goetze TO**, Paolucci V. Immediate re-resection of T1 incidental gallbladder carcinomas: a survival analysis of the German Registry. *Surg Endosc* 2008; **22**: 2462-2465 [PMID: 18247090 DOI: 10.1007/s00464-008-9747-9]

20 **Krell RW**, Wei AC. Gallbladder cancer: surgical management. *Chin Clin Oncol* 2019; **8**: 36 [PMID: 31431029 DOI: 10.21037/cco.2019.06.06]

21 **Javle M**, Zhao H, Abou-Alfa GK. Systemic therapy for gallbladder cancer. *Chin Clin Oncol* 2019; **8**: 44 [PMID: 31484490 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.0000000000008778]

23 **Benson AB**, D'Angelica MI, Abrams TA, Are C, Bloomston PM, Chang DT, Clary BM, Covey AM, Ensminger WD, Iyer 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]

25 **Mitry E**, Baudin E, Ducreux M, Sabourin JC, Rufié P, Aparicio T, Aparicio T, Lasser P, Elias D, Duvillard P, Schlumberger M, 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]

26 **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 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, Lee 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]

29 **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 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]

30 **Blumgart LH**, Hann LE. Surgical and Radiologic Anatomy of the Liver, Biliary Tract, and Pancreas. Surgery of the Liver, Biliary Tract and Pancreas (Fourth Edition). 2007; **1**: 3-29 [DOI: 10.1016/B978-1-4160-3256-4.50009-0]

31 **Deehan DJ**, Heys SD, Kernohan N, Eremin O. Carcinoid tumour of the gall bladder: two case reports and a review of published works. *Gut* 1993; **34**: 1274-1276 [PMID: 8406168 DOI: 10.1136/gut.34.9.1274]

32 **Fischer L**, Kleeff J, Esposito I, Hinz U, Zimmermann A, Friess H, Büchler MW. Clinical outcome and long-term survival 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]

34 **Okuyama Y**, Fukui A, Enoki Y, Morishita H, Yoshida N, Fujimoto S. A large cell neuroendocrine carcinoma of the gall 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]

37 **Zou RQ**, Hu HJ, Li FY. Primary Small Cell Neuroendocrine Carcinoma of the Gallbladder with Lymph Node Metastasis. *J 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.0000000000001536]

39 **Tidjane A**, Boudjenan N, Bengueddach A, Kadri A, Ikhlef N, Benmaarouf N, Tabeti B. Pure large cell neuroendocrine carcinoma of the gallbladder, is surgical relentlessness beneficial? A case report and literature review. *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.0000000000025449]

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/j.1477-2574.2012.00559.x]

44 **Moris D**, Tsilimigras DI, Lim J, Camastra D, Nanavati A, Knechtle SJ, Barbas AS. Neuroendocrine carcinomas of the gallbladder: Lessons learnt from cases at opposite ends of the spectrum. *J BUON* 2018; **23**: 1922-1926 [PMID: 30610822]

45 **Meoni G**, Antonuzzo L, Messerini L, Giommoni E, Muto A, Petreni P, Vannini A, Lunghi A, Molinara E, Di Costanzo F. 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]

46 **Furrukh M**, Qureshi A, Saparamadu A, Kumar S. Malignant neuroendocrine tumour of the gallbladder with elevated 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]

49 **Abutaka A**, El-Matbouly M, Helmy I, Elmoghazy W, Sulieman I, Ben Gashir M, Soofi M, Khalaf H, Elaffandi A. Repeat 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]

50 **Aiello P**, Aragona F, Territo V, Caruso AM, Patti R, Buscemi S, Di Vita G. Concomitant small cell neuroendocrine carcinoma of gallbladder and breast cancer. *Case Rep Surg* 2014; **2014**: 945921 [PMID: 25328753 DOI: 10.1155/2014/945921]

**Footnotes**

**Conflict-of-interest statement:** All authors report no relevant conflicts of interest for this article.

**PRISMA 2009 Checklist statement:** The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review started:** January 18, 2022

**First decision:** April 11, 2022

**Article in press:**

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** China

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

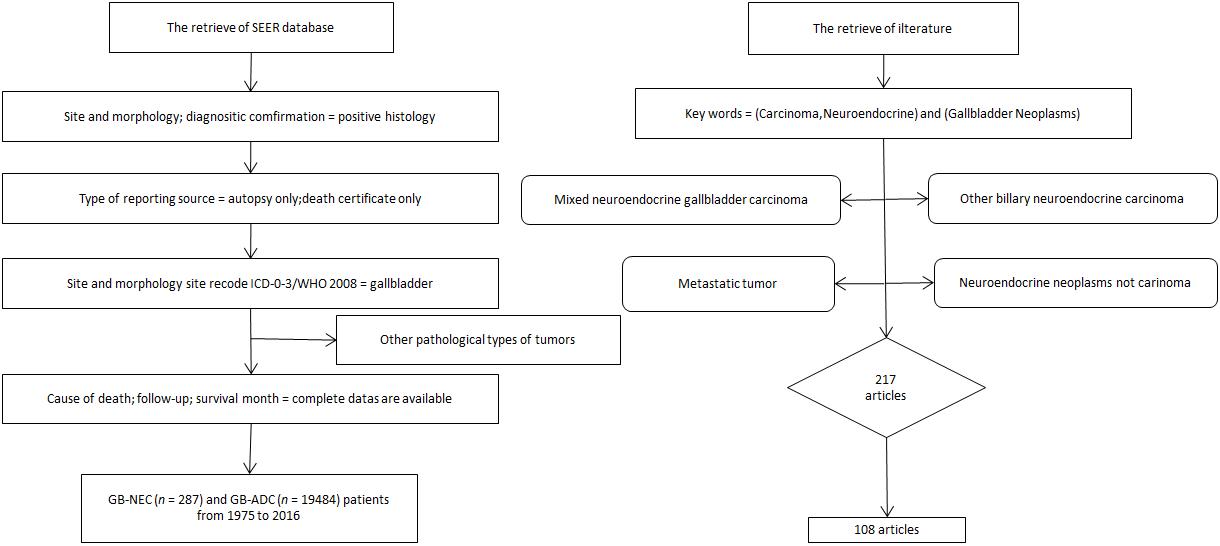
Grade C (Good): C

Grade D (Fair): D

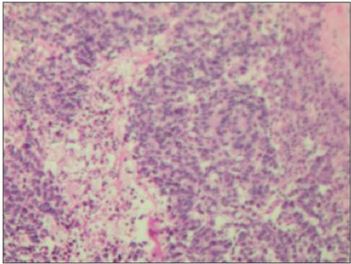
Grade E (Poor): 0

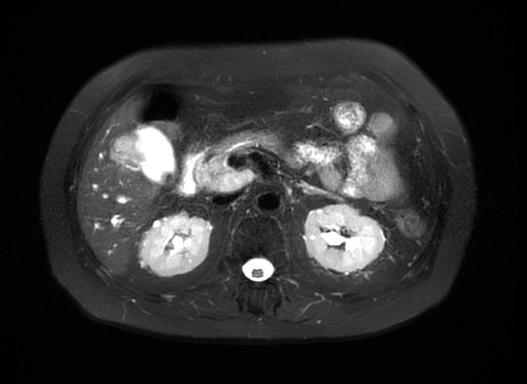
**P-Reviewer:** Dauyey K, Kazakhstan; Hosoya S, Japan **A-Editor:** Liu X, China **S-Editor:** Ma YJ **L-Editor:** Kerr C **P-Editor:**

**Figure Legends**

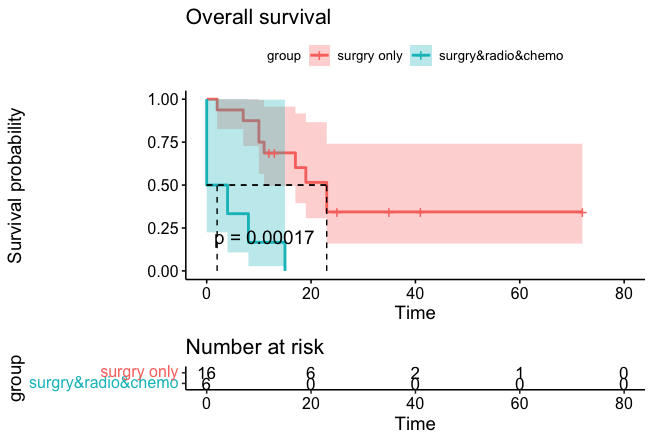
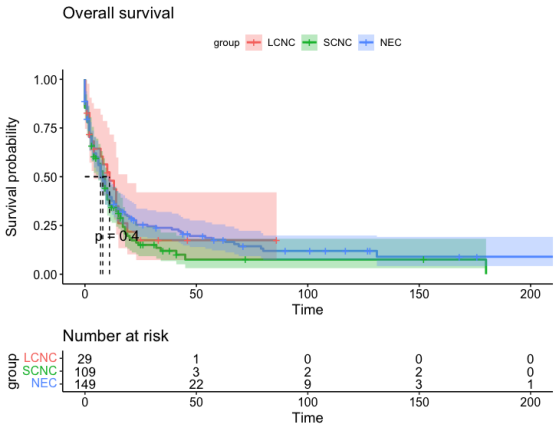


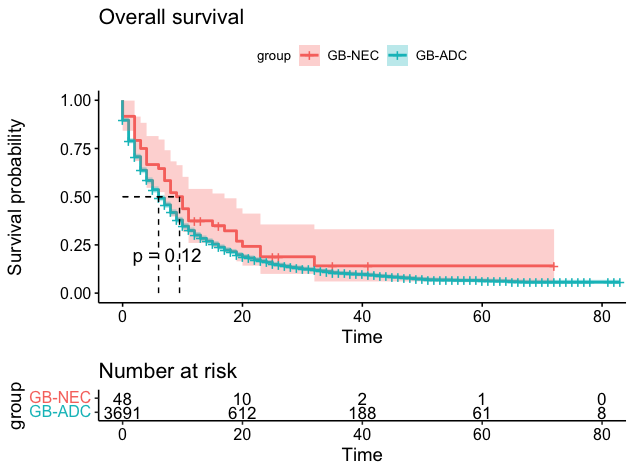
**Figure 1 Retrieval from SEER database and literature.** SEER: surveillance epidemiology and end results; WHO: World Health Organization; GB-NEC: Gallbladder neroendocrine carcinoma; GB-ADC: gallbladder adenocarcinoma.



A B

**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%).



A B



C D

**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.

**Table 1 Clinicopathological features of GB-NEC and GB-ADC**

|  |  |  |  |
| --- | --- | --- | --- |
| **Clinical variable** | **GB-NEC (*n* = 287)** | **GB-ADC (*n* = 19 484)** | ***P* value** |
| Age, mean (range), yr | 68 (32-98) | 70 (11-104) | 0.175 |
| Race, *n* (%) |  |  | 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, *n* (%) |  |  | < 0.001 |
| I | 9(3.1%) | 2220(11.4%) |  |
| II | 7(2.4%) | 5853(30.0%) |  |
| III | 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, *n* (%) |  |  |  |
| 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, *n* (%) | 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.

**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 Gl | 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 |
| NEC2 | Poorly differentiated NEC | High | > 20 | > 20% | Mutations in TP53 or RB1 |
| Mixed NENs2 | Well or poorly differentiated | Variable3 | Variable | Variable |  |

1Mitotic rates arc expressed as number of mitoses/2 mm2 as determined by counting in 50 fields of 0.2 mm2 (in a total area of 10 mm2); 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].

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

3Vriablc means: changeable.

NET: neuroendocrine tumors; NEC: neuroendocrine carcinoma.

**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,*3*7*,*38,40,41,44, 48,49] | CA-199[4,10,18] |
| 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[42] |  |
| 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 |
| T1b NO MO | cholecystectomy + gallbladder bed cautery/wedge resection1 |
| T2-T3NO MO | cholecystectomy + wedge resection/cholecystectomy + resection of liver segments (IVb + V/> 3 segments)/hepatectomy + pancreaticoduodenectomy |
| T1-T3 N1 MO | Cholecystectomy + resection of liver segments + lymph node resection (D1/D22)/hepatectomy+pancreaticoduodenectomy + lymph node resection (D1/D2) |
| IVA and IVB (advanced stage) | Systemic comprehensive therapy |

1Wedge 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.

2D1 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.

**Table 5 Currently effective chemoradiotherapy regiments that have been tried**

|  |  |
| --- | --- |
| Moris *et al*[44] | XELOX and Zometaf[44] |
| Chen *et al*[36], Meoni *et al*[45], Furrukh *et al*[46], Abutaka *et al*[49] | CBP and ETP[36,45,46,49] |
| Tidjane *et al*[39] | ETP+CP four cycles + 5-fluorouracil + oxaliplatin[39] |
| Okuyama *et al*[34] | Intravenous CP (60 mg/m2) and DXT (60 mg/m2 ) every 3 wk for four cycles, followed by intravenous CBP (120 mg/m2 ) and DXT (60 mg/m2 ) every 3 wk for three cycles[34] |
| Chen *et al*[4] | VP-16 150 mg/dl[3]; CP 50 mg/dl[3]), radiotherapy with 10 MV-X-ray and 3D-CRT,(50 Gy/25f)[4] |
| Shimono *et al*[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 [10] |
| Shimono *et al*[10] | Three cycles of CP (50 mg/body) + ETP (80 mg/body) as systemic chemotherapy[10] |

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 *P*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.