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

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Abstract

BACKGROUND

Gallbladder neroendocrine carcinoma (GB-NEC) has a very low incidence rate, as such, its clinical characteristics, diagnosis, treatment and prognosis are not well explored.

AMI

To review recent research and analyze corresponding data in the Surveillance Epidemiology and End Results (SEER) program of the United States National Cancer institute.

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 values < 0.05 were considered statistically significant. We also reviewed 108 studies retrieved from Pubmed. The kewords 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) was36.6%, 17.8%, 13.2% and 7.3% respectively. Serum CgA levels maybe a specific tumor marker for the diagnosis of GB-NEC. Elevated CEA, CA19-9 and CA-125 Levels are associated with poor prognosis. Age (HR 1.027, 95%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 statistical difference in OS between GB-NEC and GB-ADC.

CONCLUSION

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

Key Words: Clinical features; diagnosis; gallbladder neuroendocrine tumor; pathology; treatment

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Core Tip: A literature review based on SEER database was conducted to find the clinical manifestations, diagnosis , treatment , and prognosis of gallbladder neuroendocrine carcinoma. Tried to clarify the direction of further research on this tumor.

INTRODUCTION

Neuronedocrine neoplasms (NEN) have been reported in nearly every tissue. According to the international Agency for Research on Cancer - World Health Organization (IARC-WHO), neuroendocrine tumors (NET) are composed of cells with distinctive phenotype characterized by the expression of general and specific nueroendocrine biomarkers. NETs account for about 0.5% of all newly diagnosed malignancies[1]. Gallbladder neuroendocrine carcinoma (GB-NEC) is extremely rare. Yao et la reported that GB-NEC accounted for only 0.5% of all NENs and for 2.1% of all gallbladder malignancies[2]. Since GB-NEC has a very 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. Majority of the studies only focus on the clinical manifestation 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.

METHODS :

PATIENTS AND LITERATURE:

SEER DATABASE IS SEARCHED AND SCREENED ACCORDING TO THE FOLLOWING CRITERIA:1.SITE AND MORPHOLOGY;DIAGNOSITIC COMFIRMATION = POSITIVE HISTOLOGY 2.TYPE OF REPORTING SOURCE=AUTOPSY ONLY ;DEATH CERTIFICATE ONLY 3.SITE AND MORPHOLOGY SITE RECODE ICD-0-3/WHO 2008=GALLBLADDER 4.CAUSE OF DEATH ;FOLLOW-UP ;SURVIVAL MONTH =COMPLETE DATES ARE AVAILABLE ,FINALLY, 19771 PATIENTS WITH PATHOLOGICALLY

CONFIRMED GALLBLADDER MALIGNANCY FROM 1975 TO 2016 WERE OBTAINED. AMONG THEM, THERE WERE 19484 CASES OF GALLBLADDER ADENOCARCINOMA AND 287 CASES OF GALLBLADDER NEUROENDOCRINE CARCINOMA. AMONG THE PATIENTS WITH GALLBLADDER NEUROENDOCRINE CARCINOMA, THERE WERE 29 CASES OF LARGE CELL NEUROENDOCRINE CARCINOMA AND 109 CASES OF SMALL CELL NEUROENDOCRINE CARCINOMA. IN ADDITION WE SEARCHED PUBMED FOR THE FOLLOWING KEYWORDS AND OBTAINED 217 LITERATURES DESCRIBING GB-NEC : KEY WORDS=(CARCINOMA,NEUROENDOCRINE) AND(GALLBLADDER NEOPLASMS).AMONG THEM THE LITERATURE WHICH DISCRIBE1. MIX NEUROENDOCRINE GALLBLADDER CARCINOMA 2.OTHER BILIARY NEUROENDOCRINE CARCINOMA 3.MEASTATIC TUMOR 4.NEUROENDOCRINE NEOPLASMS NOT CARCINOMA WILL BE RULED OUT, IN THE END A TOTAL OF 108 ARTICLES WERE REVIEWED.AS SHOWN IN THE FLOW - CHART 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:

CHI-SQUARE AND INDEPENDENT SAMPLE T TESTS AND UNIVARIATE ANOVA TESTS WERE USED TO COMPARE BASELINE DATA OF PATIENTS BETWEEN GB-ADC AND GN-NEC. UNIVARIATE CHI-SQUARE TEST AND MULTIVARIATE COX REGRESSION ANALYSIS WAS USED TO INVESTIGATE THE INDEPENDENT RISK FACTORS INFLUENCING THE PROGNOSIS OF GB-NEC PATIENTS.K-M 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. RELEASED 2016. IBM SPSS STATISTICS FOR WINDOWS, VERSION 24.0. ARMONK, NY: IBM CORP.). 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 to 1:2[2-4]. In our study, a total of 19771 patients diagnosed with gallbladder malignancy from 1975 to 2016 were selected from the SEER database and analyzed. In this cohort, GB-NEC accounted for 1.6% of all gallbladder malignancies. The male to female ratio was 1:2, the average age was 68 years old 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 MiNENs, 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

Neuroendocrine tumors 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 researched and found that patients with gallbladder stones experienced repeated onslaughts of inflammation which 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 higly 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 CA-125, CA19-9, CEA and serum CgA being elevated in GB-NEC. GB-NECs can be divided into functional and non-functional 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. Jin et la reported a patient with GB-NEC complicated by Cushing's syndrome[17]. 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 wel as liver invasion[18]. Patient clinicopathological characteristics are summarized in table 3. Imaging has very limited diagnostic value for GB-NEC. On ultrasound, a solid, non-uniform, hypoechoic lesion is detected. On plain CT, the lesions may appear hypodense. With contrast enhanced CT, uneven enhancment, 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 sho annular enhancement。On pain MRI imaging, all lesion show a low signal on T1WI and a high signal on T2WI. The signal of the lesions in lower on the T1WI and higher on T2WI. With enhanced MRI, uneven enchancement is observed. GB-NEC has no particularly distinguishing features on imaging. It mostly has a wide-basal shap with a clear boundary. Cystic denegeration and necrosis are common observations. 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 1 & 2)

Treatment of GB-NEC

Surgery

GB-NEC surgical resection basically refers to the surgery options available for gallbladder cancer treatment. 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* in their case report considered basic cholecystectomy with bed cautery to be sufficient for T1bN0M0 GB-NEC[22]. Further research is required given 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]. Details in 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 (NCCN) guidelines recommend adjuvant chemotherapy, concurrent CRT or observation for resected gallbladder carcinoma staged T2 or higher[24]. Generally speaking, neuroendocrine carcinoma histology is similar to small cell lung cancer, therefore chemotherapy is recommended as first-line regimen for extrapulmonary neuroendocrine tumors, platinum-etoposide[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: 1. the independent prognostic factors for GB-NEC. 2. compare GB-NEC prognosis to GB-ADC. 3. impact 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 overall survival) was *via* univariate and multivariate analysis respectively. We found that age (HR 1.027, 95%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 overall survival (Table 6).

We screened 6 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 HIPAA 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 1.1). We also compared prognosis between the different pathological sub-types 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 respetively. There was significant difference in OS between the two irrespetive of stage (Figures 1.2 - 1.4)

Conclusion&discussion:

Currently, GB-NECs are not well understood by clinicians given its very low incidence rate. To address this challenge, we aimed to review reported literature (case reports and reviews) as well as analyze 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. The in the course of our analysis, we used the SEER database to perform analysis on GB-NEC and GB-ADC data with relatively larger sample sizes compared with previous studies.

The observed GB-NEC incidence was much lower than we anticipated, less than 2%. The male to female ratio was 1:2 and the average age of onset was 68 years (incidence is higher in elderly women). GB-NEC had an median OS of 7 mo . GB-NEC patients GB-NEC has a lower degree of tumor differentiation compared to GB-ADC. The porpotion of poorly defferentiated and undifferentiated tumors is 57.8% *vs* 33% (P<0.001) in GB-NEC and GB-ADC respectively. GB-NEC is highly malignant with an aggressive progression profile. Systemic metastasis is common, even in early stages. Most patients are diagnosed at an aggressive stage[4, 29, 30]. 19.7% of patients 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 Gillison system need further verification.

Clinical manifestation are not specific however 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 very low. Serum CgA may be a sensitive biomarker for GB-NEC. CA-125, CA-19-9, CEA, soluble IL-2 receptor and NSE are elevated in some patients but none of them were specific. Some studies have suggested that CA-125 was 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 planing. Diagnosis of GB-NEC is mostly based on pathology and immunohistochemistry (IHC) tests. 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 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, a high degree of malignancy and poor prognosis. The incidence is significantly higher in elderly females. GB-NEC is difficult to diagnose and most patients are with advanced disease at the time of diagnosis. Therefore, focus should be placed on investing the pathogenesis and treatment rather than the atypical clinical manifestations of GB-NEC.

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