Int J Clin Exp Pathol 2015;8(7):8218-8226
www.ijcep.com /ISSN:1936-2625/IJCEP0009917

Original Article

Gallbladder neuroendocrine carcinoma: report of 10 cases and comparision of clinicopathologic features with gallbladder adenocarcinoma

Chen Chen[1], Lin Wang[1], Xi Liu[2], Guanjun Zhang[2], Yaling Zhao[3], Zhimin Geng[1]

Departments of [1]Hepatobiliary Surgery, [2]Pathology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710061, China; [3]Department of Epidemiology and Biostatistics, School of Public Health, Xi'an Jiaotong University, Health Science Center, Xi'an 710061, China

Received May 5, 2015; Accepted June 23, 2015; Epub July 1, 2015; Published July 15, 2015

Abstract: Few cases of neuroendocrine carcinoma (NEC) of the gallbladder (GB-NEC) have been reported. Data obtained from the 10 patients with GB-NEC treated in our hospital between January 2008 and December 2012 were retrospectively analyzed and compared with those of 377 patients with gallbladder adenocarcinoma. GB-NEC accounted for 2.2% of all gallbladder cancers. The patients (8 females and 2 males) were 59.0 ± 10.0 years old. Four patients presented mixed adenocarcinoma, while six had pure NEC. Immunohistochemical examinations showed a positive rate of 100% for CgA, NSE, and CK; the positive rates for Syn, EMA, and CD56 were 88.9, 87.5, and 75%, respectively. TNM grades II, IVA, and IVB were found in 1, 2, and 7 patients, respectively. GB-NEC patients showed significantly higher N2 lymphatic metastasis rates than gallbladder adenocarcinoma patients (70.0 vs. 34.0%; $P < 0.05$). Two patients were treated with radical resection and the remaining 8 with palliative operation. The 1-, 2-, and 3-year survival rates were 20, 10, and 0%, respectively (median survival time, 3.0 m); the 1-, 2-, 3-, and 5-year survival rates for all gallbladder adenocarcinoma patients were 38.0, 31.0, 30.1, and 28.4%, respectively (median survival time, 6.0 m), the difference was statistically significant ($P = 0.038$). The results demonstrate that GB-NEC was mainly found in aged females and shows high malignancy. Its prognosis is poorer than that of gallbladder adenocarcinoma, and surgical resection combined with TACE, radiotherapy, and chemotherapy could increase patient survival.

Keywords: Gallbladder carcinoma, neuroendocrine carcinoma, gallbladder adenocarcinoma, clinical feature, surgery

Introduction

Neuroendocrine carcinomas (NECs), also known as APUD (Amine Precursor Uptake Decarboxylation) tumors, originate from disseminated neuroendocrine cells. NECs account for less than 1% of all malignant tumors. Most NECs are found in gastrointestinal (66%) and respiratory (31%) tracts [1]. In the gastrointestinal tract, most NECs are found in the rectum, jejuno-ileum, and pancreas [2], and NEC of the gallbladder (GB-NEC) is very rare [3]. Modlin et al reported that NECs of the extrahepatic duct and gallbladder only account for 0.2-2% and 0.2% of all gastrointestinal tract NECs [4, 5]. As GB-NEC cases are very rare, only very few studies have investigated the mechanisms and treatments of this NEC subtype. In recent years, GB-NEC has attracted increasing attention with the understandings and diagnosis of this tumor. From January 2008 to December 2012, 464 patients with gallbladder carcinoma were surgically treated at the Department of Hepatobiliary Surgery of our hospital, and 10 (accounting for 2.2% of all gallbladder carcinomas) of them were diagnosed with NEC according to postoperative pathological and immunohistochemical examinations. In the present study, clinical data from these 10 patients were analyzed to summarize the clinical presentations, disease progression, effects of surgical treatment, and long-term outcomes of GB-NEC.

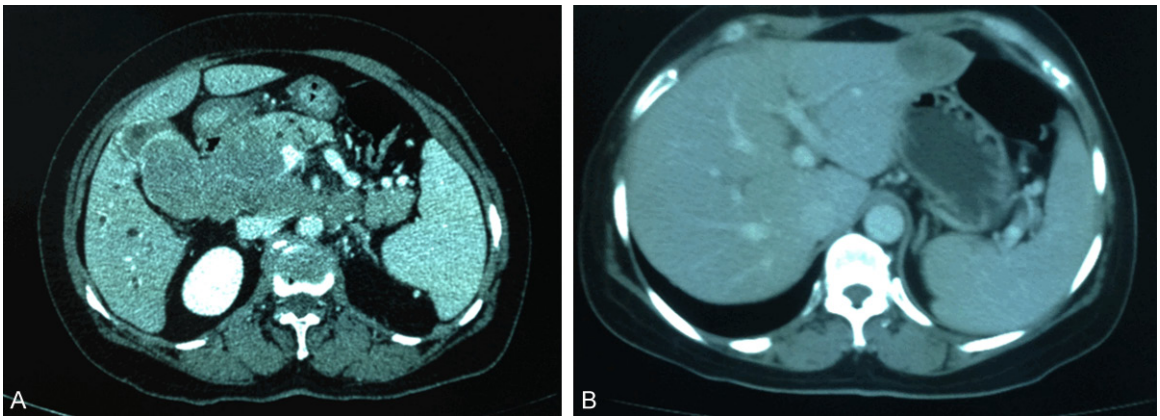

Figure 1. A: Enhanced CT scan showing malignant mass in the gallbladder, with portal and retroperitoneal lymph node metastases and main portal vein invasion. B: Liver metastasis was found at 6-month after radical resection for Patient 8, CT scan showing metastatic lesion at the left lateral lobe.

Patients and methods

Methods

Data were retrospectively analyzed, from 10 patients with GB-NEC and 377 patients with gallbladder adenocarcinoma that had been treated between January 2008 and December 2012 at the Department of Hepatobiliary Surgery, First Affiliated Hospital of Xi'an Jiaotong University. General characteristics, clinical presentations, imaging data, laboratory examination results, pathological findings, surgical procedures, and survival were compared between the patients with GB-NEC and those with gallbladder adenocarcinomas.

Imaging and laboratory examinations

Imaging examinations included abdominal ultrasound and enhanced CT scanning. Morning fasting venous blood was collected from all patients; after centrifugation, serum was collected before surgery and the levels of tumor biomarkers including CA-125, CA-199, carcinoembryonic antigen (CEA), and neuron-specific enolase (NSE) were measured within 6 hours using a chemiluminescence kit (E170, Roche, Switzerland). CA-125 > 35.00 U/ml, CA-199 > 37.00 U/ml, CEA > 3.40 ng/ml, or NSE > 15.20 ng/ml was considered positive.

Surgical procedures

According to surgical findings (including invasive range of tumor, lymphatic metastasis, and distant metastasis), radical resection, extensive radical resection, and palliative operation were performed, respectively, for patients with TNM grade II, III, and IV tumors. For radical resection, cholecystectomy, wedge resection of the liver, and dissection of lymph nodes at the hepatoduodenal ligament were performed.

Pathological examination

The extent of disease was determined using the TNM classification of extrahepatic bile duct tumors according to the American Joint Committee on Cancer/International Union Against Cancer guidelines (AJCC/UICC), 7th edition [6]. Immunohistochemical examination of NSE, chromogranin A (CgA), synaptophysin (Syn), cytokeratin (CK), epithelial membrane antigen (EMA), and CD56 were performed by the immunohistochemical streptavidin-perosidase (SP) method. GB-NEC was diagnosed based on the WHO classification published in 2010 [7].

Follow-up of the patients

All patients were followed up by telephone, mail, or outpatient visits. Patient data were analyzed to the last follow-up before June 1, 2014. Patient survival was calculated from the time of surgery to the time of death or most recent follow-up.

Statistical analysis

SPSS 13.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Continuous variables were expressed as mean ± standard deviation and analyzed using the *t*-test. Categorical variables were analyzed

Table 1. General characteristics, stage, and surgical procedures for the 10 patients with GB-NEC

ID	Sex	Age	T	N	M	TNM stage	Surgical procedure	Margin
1	F	65	3	2	0	IVB	Radical resection	R1
2	M	68	4	2	0	IVB	Palliative resection of gallbladder cancer, T-tube drainage	R2
3	F	59	3	2	0	IVB	Palliative resection of gallbladder cancer, liver radiofrequency ablation	R2
4	F	71	4	1	0	IVA	Cholecystectomy, U-tube drainage	R2
5	F	63	3	2	1	IVB	Cholecystectomy, T-tube drainage	R2
6	M	53	4	2	1	IVB	Palliative resection of gallbladder cancer, left lobectomy, partial gastrectomy, gastroenterostomy, common bile duct exploration, and T-tube drainage	R2
7	F	58	4	2	0	IVB	Palliative resection of gallbladder cancer, radiofrequency ablation of metastases, and T-tube drainage	R2
8	F	49	2	0	0	II	Radical resection, resection of liver metastases, and TACE	R0
9	F	67	4	1	0	IVA	Cholecystectomy, Y-tube drainage	R2
10	F	40	4	2	0	IVB	Subtotal cholecystectomy, cholangioenterostomy	R2

Table 2. Pathology and adjuvant therapy of the 10 patients with NEC of the gallbladder

ID	Tumor position	Tumor size (cm)	Morphology	Combination with adenocarcinoma	Differentiation of adenocarcinoma	Intravascular tumor thrombi	Chemo-therapy	Radio-therapy	Survival (d)
1	Fundus	3 × 1.5 × 1.3	Infiltrative	Yes	Undifferentiated	No	No	No	170
2	Fundus	3.5 × 2.8 × 1.8	Infiltrative	No	NA	Yes	No	No	86
3	Body	4 × 3 × 3	Protruding	No	NA	No	No	Yes	92
4	Neck	1.5 × 2 × 1.3	Infiltrative	Yes	II	No	No	No	110
5	Body	6 × 4.5 × 3.5	Infiltrative	No	NA	Yes	No	No	105
6	Body	6 × 4 × 1.5	Protruding	Yes	III	No	No	No	55
7	Fundus	2.5 × 1.5 × 1	Protruding	No	NA	No	No	No	90
8	Neck	2 × 2.5 × 1.2	Infiltrative	No	NA	No	Yes	No	700
9	Body	6 × 5 × 4	Protruding	Yes	III	Yes	No	No	90
10	Fundus	4.5 × 3 × 1.5	Infiltrative	No	NA	No	Yes	Yes	380

using the χ^2 test. Survival curves were generated using the Kaplan-Meier method and compared using the log-rank test. A value of $P < 0.05$ was considered statistically significant.

Results

General characteristics and clinical presentations

Among the 10 included patients with GB-NEC, 8 (80.0%) were females and 2 (20.0%) males. The mean patient age was 59.0 ± 10.0 (ranging from 40 to 71) years. The clinical presentations of the patients were similar to common gallbladder adenocarcinoma. The main presentations were: epigastric pain (5/10, 50.0%), jaundice (2/10, 20.0%), epigastric mass (2/10, 20.0%), emaciation (2/10, 20.0%), poor appetite (1/10, 10.0%), and weakness (1/10, 10.0%). In addition, 8 (80%), 3 (30%), and 1 (10%) patients also had cholecystolithiasis, hypertension, and type 2 diabetes, respectively.

Imaging data

Ultrasound examination was performed for all 10 patients, and CT scanning was performed for 8 of them. Both ultrasound data and CT scans revealed space occupying lesions in the gallbladder; the imaging results were similar to those obtained with common gallbladder carcinoma patients (**Figure 1**).

Tumor biomarkers

Serum levels of tumor biomarkers were measured for all 10 patients. The results showed positive rates of 57.1% (4/7), 25.0% (2/8), and 12.5% (1/8) for CEA, CA-19-9, and CA-125, respectively. In addition, serum NSE levels were measured for 2 of the 10 patients, and both samples were positive.

Treatments

Surgical treatments were performed for all 10 patients, and the surgical procedures are listed in **Table 1**. Radical resection was carried out in 2 patients (R1 for 1 patient, and R0 for the other); the remaining 8 patients received palliative surgery.

Postoperative radiotherapy and chemotherapy were performed in 3 patients (**Table 2**). 3-D radiotherapy with 10 MV-X-ray and DT4000 cGy/20f was performed for Patient 3. Liver metastasis was found for Patient 8 at 6-month after radical resection (**Figure 1B**), and resection of the liver metastases was performed twice followed by 3 cycles of transhepatic arterial chemoembolization (TACE). Eight cycles of chemotherapy were performed for Patient 10 at 11-month after palliative surgery (VP-16 150 mg/d1-3; CDDP 50 mg/d1-3) and radiotherapy with 10 MV-X-ray and 3D-CRTDT 50 Gy/25f was performed.

Pathological results

Pathological examination showed that the tumors in 4 patients (40.0%) were combined with adenocarcinoma with different differentiation characteristics (2 poorly differentiated, 1 with moderate differentiation, and 1 undifferentiated), while the remaining 6 patients (60.0%) had pure NEC. The NECs in all 10

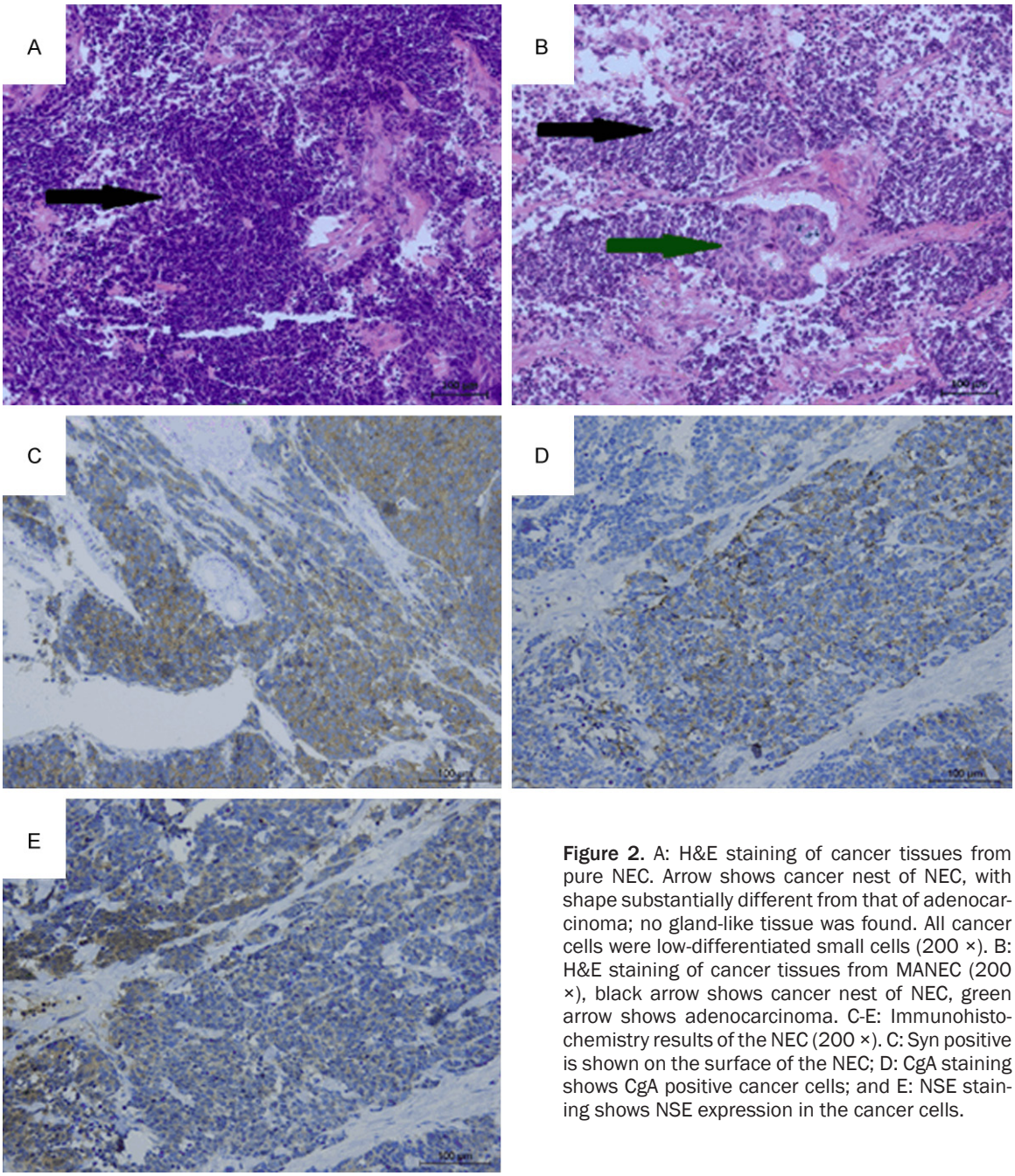

Figure 2. A: H&E staining of cancer tissues from pure NEC. Arrow shows cancer nest of NEC, with shape substantially different from that of adenocarcinoma; no gland-like tissue was found. All cancer cells were low-differentiated small cells (200 ×). B: H&E staining of cancer tissues from MANEC (200 ×), black arrow shows cancer nest of NEC, green arrow shows adenocarcinoma. C-E: Immunohistochemistry results of the NEC (200 ×). C: Syn positive is shown on the surface of the NEC; D: CgA staining shows CgA positive cancer cells; and E: NSE staining shows NSE expression in the cancer cells.

patients were poorly differentiated small cell carcinoma, among which 3 (30.0%) were accompanied with intravascular tumor thrombi (**Table 2**; **Figure 2**).

The main NEC biomarkers were evaluated by immunohistochemistry and positive rates for CgA (10/10), NSE (10/10), and CK (9/9) were 100%; positive rates for Syn, EMA, and CD56 were 88.9% (8/9), 87.5% (7/8), and 75% (3/4), respectively (**Figure 2**).

Nine of the 10 patients (90.0%) showed TNM stage IV tumor. This percentage was higher compared with the 63.7% (240/377) gallbladder adenocarcinoma patients that had stage IV tumors; however, the difference was not statistically significant. Nine of the 10 NEC patients (90.0%) had lymphatic metastases, representing a higher rate than what obtained in patients with gallbladder carcinomas (73.7%, 278/377); however, the difference was not statistically significant ($P > 0.05$). Seven of the 10 patients

Table 3. Comparision of clinical features between GB-NEC and gallbladder adenocarcinoma

		N		*P* value
		Adenocarcinoma	NEC	
Age		61.9 ± 10.6	59.0 ± 10.0	0.667
Sex	Male	111	3	1.000
	Female	266	7	
Symptom				
Cholecystolithiasis	No	158	5	0.633
	Yes	219	4	
Jaundice	No	279	7	1.000
	Yes	98	3	
Epigastric pain	No	92	3	0.973
	Yes	285	7	
Emaciation	No	259	9	0.274
	Yes	118	1	
Epigastric mass	No	259	8	0.155
	Yes	18	2	
Surgery	Radical resection	153	2	0.327
	Palliative resection	224	8	
Margin	R0	152	1	0.096
	R1/R2	225	9	
T	T1-T3	254	4	0.090
	T4	123	6	
N	N0-N1	249	3	< 0.05
	N2	128	7	
M	M0	276	7	0.732
	M1	101	3	
TNM stage	I-III	137	1	0.104
	IV	240	9	
Pathological differentiation	Poorly differentiated	173	10	< 0.05
	Moderately and highly differentiated	204	0	

(70.0%) with NEC had N2 lymphatic metastases, which was significantly higher than what observed in gallbladder carcinoma patients (34.0%, 128/377; $P < 0.05$) (**Table 3**).

Follow-up results

The minimal and longest postoperative survival times were 1.8 m and 23.3 m, respectively, with a median survival time of 3.0 m. The 1-, 2-, and 3-year cumulative survival rates were 20, 10, and 0%, respectively. For the patients with gallbladder adenocarcinoma treated during the same period, the follow-up rate was 83.8%, and median survival time of 6.0 m was obtained; the 1-, 2-, 3-, and 5-year survival rates were 38.0, 31.0, 30.1, and 28.4%, respectively. **Figure 3** shows the Kaplan-Meier survival curves of the patients with different follow-up outcomes and pathological classifications. Log-rank test indicated that the difference was statistically significant ($P = 0.038$). Furthermore, we found that survival time in the 10 patients varied considerably according to the different treatment options received. 3 patients who received postoperative radiotherapy and chemotherapy survived for 3.0, 23.3, and 12.7 m, respectively, median and mean survival times were 12.7 and 13.0 m, respectively; while for the remaining 7 patients that only received surgical treatments, median and mean survival times of 3 and 3.5 m were found, respectively.

Discussion

GB-NEC is very rare in clinical practices, and only few case reports have been published to

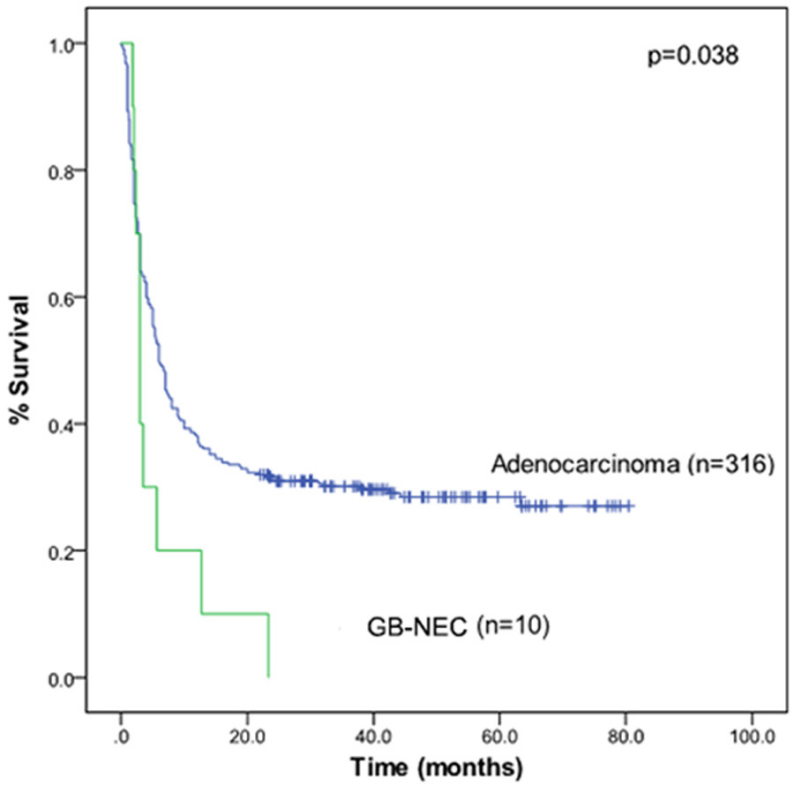

Figure 3. Survival curves of GB-NEC and gallbladder adenocarcinoma.

date. Two studies with relatively large sample sizes were from Korea, with 6 and 12 patients, respectively [8, 9]. Ten patients with GB-NEC were included in the present study, making it one of the largest in China. According to the statistics of Surveillance, Epidemiology and End Result (SEER), GB-NEC accounts for 0.5% of all NEC and 2.1% of all gallbladder tumors [5]. In a study performed by Duffy et al [10], data from 435 patients with gallbladder cancers treated at the Memorial Sloan-Kettering Cancer Center (MSKCC) between 1995 and 2005 showed that 3% of them had NEC. In the present study, 10 patients were found with GB-NEC between 2007 and 2012, which accounted for 2.2% of all gallbladder cancers, which is similar to the findings published by SEER and MSKCC.

Most researchers agree that aged female patients are with higher risk of developing GB-NEC, an idea supported by the findings of the present study. Ahn et al [11] revealed that some functional GB-NEC could be found with specific presentations. However, the findings described here showed that clinical presentations and signs of GB-NEC were of no specificity as compared to gallbladder adenocarcinomas; most of them were non-functional NEC, in accordance with previous studies [12-14].

Commonly used tests including ultrasound examination, CT scanning, MRI, and tumor biomarkers do not effectively distinguish GB-NEC from other gallbladder carcinomas; thus, pathological and immunohistochemical examinations should be performed. Currently, the most commonly used immunological biomarkers for NEC include neuro-specific enolase (NSE), chromogranin A (CgA) and synaptophysin (Syn). In the present study, positive rates for NSE, CgA and Syn were 100% (10/10), 100% (10/10) and 88.9% (8/9).

As a highly malignant tumor, NEC progresses rapidly and induces early liver invasion and lymphatic metastasis. According to the pathological results of 41 gallbladder NEC cases (between 1973 and 2004) reported by SEER, 2.4% were highly differentiated tumors, 7.3% moderately differentiated tumors, and 89.7% poorly or undifferentiated tumors [5]. However, all the 10 gallbladder NEC cases described in the present study were poorly differentiated small cell NEC, and the level of malignancy was higher than what found for gallbladder adenocarcinoma cases treated during the same period. In addition, TNM staging showed that 90.0% of the 10 NECs were stage IV, which was not significantly different from the rates obtained for gallbladder adenocarcinoma cases treated during the same period; however, 70.0% of the gallbladder NEC cases had N2 lymphatic metastases, a rate significantly higher than that obtained in gallbladder adenocarcinoma patients treated during the same period ($P < 0.05$).

Surgery is the mostly used and preferred treatment method for GB-NEC. The surgical proce-

dures vary from simple cholecystectomy to extensive radical resection (including local lymph node dissection and resection of metastases) [15]. In a study performed by MSKCC researchers, data from 13 patients with GB-NEC were analyzed, and a median patient survival time of 9.8 months was found, which was not significantly different from the median survival time obtained for the 435 patients with gallbladder carcinomas (10.3 months) [10]. In another study performed by Fujii et al, the 1- and 2-year survival rates of the 53 included patients with small cell gallbladder cancers were 28 and 0%, respectively [16]. In the present study, we found survival times from 1.8 m to 23.3 m (median, 3.0 m) for the 10 patients, while the 1-, 2-, and 3-year survival rates were 20, 10, and 0%, respectively; however, the median survival time of the 377 gallbladder adenocarcinoma patients treated during the same period was 6.0 m, with 1-, 2-, 3-, and 5-year survival rates of 38.0, 31.0, 30.1, and 28.4%, respectively, the difference was statistically significant. These findings suggested a poorer prognosis for GB-NEC patients compared with patients with gallbladder adenocarcinoma, this could be associated with the higher percentage of patients with advanced stage and lymphatic metastases.

Because GB-NEC cases are generally with high malignancy, and most NEC are highly invasive with high risk of lymphatic metastasis, most patients are diagnosed at late stages, which decrease the rate of radical resection. In the present study, only 2 of the 10 patients were treated with radical resection; however, adjuvant therapies including radiotherapy and chemotherapy also resulted in encouraging effects in patients with GB-NEC. Indeed, the median survival time of the 3 patients that received TACE, radiotherapy, and chemotherapy after surgical treatment was 12.7 m, while that of the remaining 7 patients solely treated with surgery was only 3.0 m; however, the difference was not statistically significant, which may be due to the small sample size. In a study performed by Elahi et al [17], the survival time of a patient with highly differentiated GB-NEC was 46 months after postoperative chemotherapy with combined application of gemcitabine, cisplatinum, docetaxel, and sunitinib. In addition, Okuyama et al [18] found that combined application of cis-platinum and docetaxel resulted in patient survival time of 22 months. These findings and ours indicate that adjuvant therapy using radiotherapy and chemotherapy might substantially benefit the patients with GB-NEC. However, as only very limited number of patients with GB-NEC has been treated, no universally accepted preferred radiotherapy or chemotherapy strategy is available to date.

In conclusion, GB-NEC is a special type of gallbladder carcinoma with low incidence rate. This disease has no specific clinical presentation, pathological and immunohistochemical examinations are needed for definite diagnosis. The malignancy rates of GB-NEC are generally high, and local invasion and lymphatic metastases can be found at early stage; the prognosis of GB-NEC is poorer than gallbladder adenocarcinoma. Combining surgical resection, radiotherapy, and chemotherapy could help increase patient survival. However, with a very low incidence and only few studies focused on this disease, no universally accepted treatment is available, and further studies with larger sample size are needed.

Acknowledgements

This study was supported by Shaanxi Province Natural Science Fund Project (2014JM4177).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Zhimin Geng, Department of Hepatobiliary Surgery, The First Affiliated Hospital of Xi'an Jiaotong University, 277 West Yanta Road, Xi'an 710061, P. R. China. Tel: +86-29-85323890; Fax: +86-29-85323473; E-mail: gengzhimin@mail.xjtu.edu.cn

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