Clinicopathological Characteristics of Extrahepatic Biliary Neuroendocrine Neoplasms in the Gallbladder, Extrahepatic Biliary Tract, and Ampulla of Vater: A Single-Center Cross-Sectional Study

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Abstract

Background

Significant changes were made in the grading and staging systems for neuroendocrine neoplasms (NENs) in 2017. Therefore, a clinical report to comprehensively update the clinicopathological characteristics, therapeutic approaches, and prognosis of these patients should be drafted.

Methods

We retrospectively reviewed a database of 16 patients who developed NENs or mixed endocrine non-endocrine neoplasms (MiNENs) after curative resection. Among them, eight had ampulla of Vater (AoV) tumors, and eight had non-AoV tumors. One patient had NEN Grade 1, five had NEN Grade 2, and five had NEN Grade 3 (G3); all had poorly differentiated neuroendocrine carcinoma. Five patients had MiNEN or combined carcinoma.

Results

The mean age was 57.88 years. The overall survival rates after curative surgery at 1, 3, and 5 years were 87.1, 80.4, and 71.4%, respectively. The 1-, 3-, and 5-year disease-free survival rates were 87.1%, 79.8%, and 71.8%, respectively. In univariate analysis, age >65 years, mitotic count (>20/10 high-power fields), Ki-67 index >20%, and presence of stones were significant prognosticators, whereas only the mitotic count was statistically significant in the multivariate analysis. Age >65 years ($p=0.039$), a Ki-67 index >20% ($p=0.03$), presence of stones ($p=0.021$), G3 stage disease, MiNEN ($p=0.002$), or perineural invasion ($p<0.001$) were more frequently observed in the non-AoV group than in the AoV group.

Conclusion

High mitosis count had a greater effect on extrahepatic biliary NEN than the tumor-node-metastasis staging system. Patients with AoV tumors had better prognostic predictor factors compared to those with non-AoV tumors.

Background

The incidence rate of neuroendocrine neoplasms (NENs) is currently increasing by 6% annually [1]. NENs mostly occur in the gastrointestinal tract (66%) or the bronchopulmonary system (31%) but can also occur in the ovary, testes, hepatobiliary system, and pancreas [1]. The extrahepatic bile ducts are rare primary sites of NENs, accounting for only 0.2–2% of all such malignancies [2, 3]. According to the 2017 World Health Organization (WHO) classification, NENs are classified as Grade 1 (mitotic count <2 per 10 high-power fields [HPFs] and/or 2% Ki-67 index), Grade 2 (G2) (mitotic count 2–20 per 10 HPFs and/or 3–20% Ki-67 index), or Grade 3 (G3), combined with well-differentiated neuroendocrine carcinoma ([NEC], mitotic count >20 per 10 HPFs and/or >20% Ki-67 index), poorly differentiated NEC including small-cell carcinoma and large-cell carcinoma, or mixed endocrine non-endocrine neoplasm (MiNEN) [4]. The different clinicopathological features, prognoses, and molecular alterations of NEC suggest that NEC is a separate disease entity from well-differentiated neuroendocrine tumors [4]. All NENs possess malignant potential. Extrahepatic biliary NENs, except those in the ampulla of Vater (AoV), are difficult to diagnose preoperatively and difficult to distinguish

from cholangiocarcinomas. There is no standard treatment for extrahepatic biliary NENs since their natural history and prognostic factors remain unclear; however, aggressive multimodal treatments, such as surgery with chemotherapy, are currently the only treatment to improve the survival rate [5, 6]. In this study, we report the clinicopathological characteristics and surgical outcomes of patients with extrahepatic biliary NENs (AoV, gallbladder [GB], and extrahepatic biliary tract) who underwent curative resection with or without adjuvant treatment.

Methods

A total of 16 patients diagnosed with NENs or MiNENs underwent curative resection with or without adjuvant treatment between 2010 and 2020 at Pusan National University Hospital (Pusan, Korea). One patient was classified as having NEN Grade 1 (G1), five had G2, and five had G3, based on the 2017 WHO classification, and they all had poorly differentiated small cell-type NEC. Five patients had MiNEN or combined carcinoma. Patient data were retrospectively reviewed after approval was obtained from the relevant institutional review board. The requirement for obtaining informed consent from patients was waived due to the retrospective nature of the study.

Procedures

The type of surgery performed by the surgeon was dependent on the tumor location. Pancreatoduodenectomy was performed to resect tumors located in the AoV and distal common bile duct. Extended cholecystectomy (including 4b and 5 segments of the liver) was performed to resect tumors located in the GB. Radical bile duct resection with Roux-en-Y hepaticojejunostomy was performed to resect mid-distal common bile duct tumors. Lymphadenectomy was routinely performed from the left celiac trunk around the hepatoduodenal ligament, including the retropancreatic region. If metastasis or direct invasion was suspected, additional tissues were resected.

Histopathology

Histopathological diagnosis was determined based on the following diagnostic criteria: (1) positive immunohistochemical staining of multiple proteins, including for chromogranin A and synaptophysin, or a cluster of differentiation, which indicates the presence of neural cell adhesion molecules, and (2) histopathologic presence of high-grade and small-cell cytologic features, very high cellularity with hyperchromatic nuclei, absence of very small nucleoli with scant cytoplasm, high nuclear-cytoplasmic ratio, and a round- or fusiform-shaped cells (based on the classification of squamous cell carcinomas as NENs by the WHO [5, 7-10]).

Adjuvant treatment

Adjuvant chemotherapy was administered to treat lymph node (LN) metastasis, lymphovascular invasion (LVI), or perineural invasion (PNI) among patients with G1 and G2 NENs and for patients with poorly differentiated NECs or MiNENs. The chemotherapy regimen included topotecan and cisplatin, and these were not administered when patients refused chemotherapy. In patients with dominant adenocarcinoma in combined

adenoneuroendocrine carcinoma, gemcitabine and cisplatin or 5-fluorouracil and leucovorin were administered. Combined chemoradiation therapy was also administered to patients in the adenocarcinoma-dominant group.

Follow-up

Tumor marker tests and abdominal and chest computed tomography (CT) were performed every 6 months to identify distant metastases. If recurrence was suspected, additional magnetic resonance imaging (MRI) or positron emission tomography (PET)-CT was performed along with biopsy, when possible. If performing a biopsy was not possible, recurrence was evaluated using imaging tests. Patients with recurrent disease underwent palliative chemotherapy with local treatment for metastatic lesions.

Statistical analysis

The categorical variables of the AoV and non-AoV groups were compared, and differences were analyzed using log-rank tests. A two-tailed Fisher's exact test was used to compare the categorical variables. Statistical significance was set at $p < 0.05$. Age, tumor size, and LN ratio were compared using Student's t-test and Mann-Whitney U test. Overall survival (OS) was compared using the log rank test. All tests were performed using the Statistical Package for the Social Sciences (SPSS) version 20.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Demographic characteristics of patients

The female-to-male ratio was 1.7 to 1, and the mean age was 57.88 ± 13.27 (range, 36 to 74) years. Six patients presented with symptoms, whereas the rest (62.5%) were incidentally diagnosed during health screening or evaluation for other diseases. Preoperative biopsy could be performed in seven (43.8%) patients, all of whom had tumors located in the AoV, except one patient with tumors in the GB.

Pancreaticoduodenectomy was performed on nine patients, whereas extended cholecystectomy was performed on six patients. The complete resection rate (R0) was 93.8%. Among the patients, 68.8% underwent adjuvant chemotherapy (Table 1). The median follow-up period after surgery was 72 months. The 1-, 3-, and 5-year postoperative OS rates were 87.1%, 80.4%, and 71.4%, respectively. The 1-, 3-, and 5-year disease-free survival (DFS) rates were 87.1%, 79.8%, and 71.8%, respectively (Fig. 1).

Table 1
Patient demographics

Variables	
Sex (male:female)	7:9
Age (range) in years	57.88 ± 13.27 (36–74)
Comorbidities	11 (68.8%)
Symptoms	6 (37.5%)
Abdominal discomfort	4 (25%)
Jaundice	2 (12.5%)
None	10 (62.5%)
Location	
Ampulla of Vater	8 (50%)
Non-ampulla of Vater	8 (50%)
Gallbladder	6
Extrahepatic bile duct	2
Histology	
G1/G2	6
G3/MiNEN/combined	10
Preoperative biopsy	7 (43.8%)
Operative method	
Pancreaticoduodenectomy	9
Extended cholecystectomy	6
Radical bile duct resection	1
Complete resection rate (R0)	15 (93.8%)
Adjuvant chemotherapy	11 (68.8%)
MiNEN, mixed endocrine non-endocrine neoplasm	

Results of statistical analysis

In univariate analysis, advanced age (>65 years), mitotic count > 20/10 HPFs, Ki-67 labeling index >20%, and presence of stones were strongly positively correlated with patient survival and disease recurrence. According to multivariate analysis, patients with a mitotic count >20/10 HPFs was a significant predictor for poor OS and DFS (hazard ratio = 17.48, p = 0.033 and hazard ratio = 17.66, p = 0.033). However, the presence of T status

(T3, 4), LN metastasis, LVI, and/or PNI was not significantly associated with prognosis. Mitotic count was the only independent risk factor for survival and disease recurrence in all patients (Table 2).

Table 2
Univariate and multivariate analyses for overall and disease-free survival rates

Variable	Overall survival			Disease-free survival				
	Univariate	Multivariate		Univariate	Multivariate			
	P	HR	95% CI	P	P	HR	95% CI	P
Age >65	0.018	0.491	0.018–13.08	0.671	0.033	0.525	0.020–13.56	0.698
Sex (female)	0.437	-	-	-	0.489	-	-	-
Tumor location (non-AoV)	0.717	-	-	-	0.797	-	-	-
Mitosis >20	0.009	17.48	1.269–240.79	0.033	0.010	17.66	1.267–246.06	0.033
Ki-67 >20	0.044	0.000	NA	0.975	0.059	-	-	-
Presence of stone	0.040	10.76	0.853–135.60	0.066	0.039	10.89	0.861–137.87	0.065
Histologic grade (G3,MiNEN/combined)	0.065	-	-	-	0.081	-	-	-
T status (T3,T4)*	0.069	-	-	-	0.068	-	-	-
LN metastasis	0.456	-	-	-	0.446	-	-	-
LVI	0.657	-	-	-	0.672	-	-	-
PNI	0.4667	-	-	-	0.548	-	-	-
Adjuvant chemotherapy	0.886	-	-	-	0.956	-	-	-
AoV, ampulla of Vater; MiNEN, mixed endocrine non-endocrine neoplasm; LN, lymph node; LVI, lymphovascular invasion; PNI, perineural invasion								
*According to the American Joint Committee on Cancer, 7th edition.								

Advanced age (>65 years), Ki-67 labeling index >20%, poor histologic grade (G3 or MiNEN/combined), presence of stone, and PNI were significantly more common in the non-AoV group than in the AoV group (Table 3).

Table 3
Comparison between the AoV and Non-AoV groups

Variables	AoV (n = 8)	Non-AoV (N = 8)	P
Age			0.039
≤65	7 (87.5%)	3 (37.5%)	
>65	1 (12.5%)	5 (62.5%)	
Sex			0.614
Male	4 (50%)	3 (37.5%)	
Female	4 (50%)	5 (62.5%)	
Comorbidities			0.590
Yes	3 (37.5%)	2 (25.0%)	
No	5 (62.5%)	6 (75.0%)	
Symptoms			1.000
Yes	5 (62.5%)	5 (62.5%)	
No	3 (37.5%)	3 (37.5%)	
Mitosis			1.000
≤20	6 (75.0%)	6 (75.0%)	
>20	2 (25.0%)	2 (25.0%)	
Ki-67			0.003
≤20	4 (50%)	3 (37.5%)	
>20	4 (50%)	5 (62.5%)	
Stone			0.021
Yes	0 (0.0%)	4 (50%)	
No	8 (100%)	4 (50%)	
Histologic grade			0.002
G1/G2	6 (75.0%)	0 (0.0%)	
G3/MiNEN/Combined	2 (25.0%)	8 (100%)	
T status*			1.000

AoV, ampulla of Vater; MiNEN, mixed endocrine non-endocrine neoplasm; LN, lymph node; LVI, lymphovascular invasion; PNI, perineural invasion

*According to the American Joint Committee on Cancer, 7th edition.

Variables	AoV (n = 8)	Non-AoV (N = 8)	P
T1, 2	5 (62.5%)	5 (62.5%)	
T3, 4	3 (37.5%)	3 (37.5%)	
LN metastasis			0.614
Yes	5 (62.5%)	4 (50%)	
No	3 (37.5%)	4 (50%)	
LVI			0.590
Yes	5 (62.5%)	6 (75.0%)	
No	3 (37.5%)	2 (25.0%)	
PNI			<0.001
Yes	0 (0.0%)	7 (87.5%)	
No	8 (100%)	1 (12.5%)	
AoV, ampulla of Vater; MiNEN, mixed endocrine non-endocrine neoplasm; LN, lymph node; LVI, lymphovascular invasion; PNI, perineural invasion			
*According to the American Joint Committee on Cancer, 7th edition.			

Outcomes

One patient in the AoV group with synchronous single hepatic metastasis, multiple small bowel gastrointestinal stromal tumors, and papillary thyroid cancer had G2 lesions. He exhibited no recurrence for 18 months postoperatively without adjuvant treatment. Recurrence was observed in three patients postoperatively. One patient with a G2 lesion achieved complete remission after undergoing palliative chemotherapy (Sutent®, sunitinib malate, Pfizer) and lived for 96 months without recurrence. One patient with poorly differentiated NEC developed hepatic metastasis 27 months after surgery and received radiofrequency ablation and chemotherapy (etoposide and cisplatin). The patient died at 66 months and exhibited progression after recurrence. One patient with combined adenoneuroendocrine carcinoma (small-cell type, 90%) developed carcinoma peritonei 7 months postoperatively and died 10 months after recurrence following the administration of adjuvant chemotherapy (etoposide and cisplatin). In the non-AoV group, three patients exhibited recurrence. One patient with GB tumors had poorly differentiated NEC. Six months after surgery, the patient experienced recurrence and died 3 months later. No treatment was administered after the surgery. One patient with GB tumor had MiNEN (adenosquamous, 60%; poorly differentiated NEC, 40%). He received adjuvant concurrent chemoradiation therapy (CCRT) (5-fluorouracil and leucovorin-based) after surgery but did not complete the scheduled course due to complications. Nine months after surgery, the tumors recurred in the liver, and partial liver resection was performed. The patient exhibited no evidence of recurrence for 4 months. There was a patient with biliary tract tumor with recurrence in the liver and bone 11 months postoperatively; the patient died 1 month after recurrence. This patient was diagnosed with combined adenoneuroendocrine

carcinoma (adenocarcinoma, 80%; poorly differentiated NEC, 20%), and CCRT (gemcitabine and cisplatin) was performed after surgery.

Discussion

Two significant changes were made in the revised WHO grading system in 2017. The first change was a new subset of well-differentiated NENs, particularly G3 NEN lesions that are well differentiated but have a high ki-67 index (>20%) and have a proportion of cells with a mitotic rate >20 per 10 HPFs. The second was change in the terminology for mixed adenoneuroendocrine carcinoma to MiNEN. MiNEN must comprise at least 30% of non-endocrine components besides adenocarcinomas, such as squamous or acinar cell carcinoma [10]. In our study, we had one patient with G1, five with G2, and five with pure poorly differentiated carcinoma (small-cell type, G3). We observed two patients with combined carcinoma, which made up <30% of the tumor burden, and three patients with MiNEN. In each, the final category was poorly differentiated small-cell type carcinoma.

A nationwide study of 4951 patients with NEN reported that 1.8% of all NENs were of biliary origin [11]. They are difficult to diagnose preoperatively due to their low incidence. Several diagnostic imaging techniques (CT, MRI, PET-CT, single-photon emission CT) have been used to evaluate patients with NENs, but they each have limitations, especially in cases of extrahepatic bile duct NENs [11]. Endoscopic ultrasound or endoscopic ultrasound-guided biopsy has been shown as being effective in preoperative diagnosis, but it is confined to specific circumstances, such as in patients with tumors of AoV origin or those with direct liver invasion [12]. Even in patients with tumors of AoV origin, the biopsy confirmation rate for submucosal lesions is relatively low, ranging from 14–66%. Furthermore, reaching a definitive diagnosis using the mitotic count preoperatively is difficult for the same reason (i.e., due to its low availability and accuracy) [11]. In our study, six patients were diagnosed with NENs preoperatively by biopsy; however, accurate grading was not possible.

Managing NENs is complicated; therefore, histologic grading and staging of the lesion are essential for proper decision-making. Burns et al. demonstrated that complete resection of resectable locoregional NENs achieved excellent outcomes [13]. However, some authors have reported that no rational surgical strategy exists for several reasons, including the rarity of the disease, lack of predictive prognostic factors, inability to identify progression, and limited understanding of the biology of the lesion [5]. Two patients with GB and AoV lesions who were included in our study underwent hepatopancreatoduodenectomy. They remained recurrence-free for 144 and 24 months, respectively. Our outcomes indicate that surgery for patients with locoregional NENs may improve the odds of survival if complete resection is possible.

The incidence rate of LN metastases is approximately 50% [14], resulting in recommendations as to the procedure of choice for NEN treatment, such as LN dissection being made. Nodal involvement was not a significant factor for long-term survival. Because a more advanced stage does not predict a worse prognosis, the American Joint Committee on Cancer TNM and European Neuroendocrine Tumor Society staging systems are limited in predicting prognosis. However, surgical resection combined with regional node resection must be performed for treatment and staging [15]. Nine patients had LN metastases in our study, and there was no significant difference among them in terms of long-term survival. There was no prognostic difference between AoV and non-AoV lesions.

The prognosis of gastroenteropancreatic neuroendocrine tumors is generally better stage-for-stage compared to adenocarcinoma in similar sites. Poor prognostic factors include advanced age, incomplete surgical resection, tumor spread, and high-grade or poorly differentiated histology [11, 16]. In our analysis, advanced age (>65 years), mitotic count (>20/10 HPFs), Ki-67 index >20%, and presence of stones had significant prognostic value for OS rates. DFS-related factors were advanced age (>65 years), increased mitotic count (>20/10 HPFs), and presence of stones. The mitotic count was the only clinically significant value according to multivariate analysis. Interestingly, in contrast to AoV lesions, non-AoV lesions had pathologically different classifications according to the WHO guidelines. They were all poorly differentiated carcinomas or adenocarcinomas combined with cancer. NENs are slow-growing in nature, and its early detection during health screening or during evaluation for other diseases may not be possible. Detection seems to be reliable for lesions with or without AoV. Stones and advanced age (>65 years) were more frequent in patients with non-AoV tumors than in patients with AoV tumors (62.5% and 50%, respectively). A high Ki-67 index (>20%) and PNI were also more common in non-AoV patients than in AoV patients (Table 3). In our study, one patient underwent R1 resection for a non-AoV lesion remaining in the adenocarcinoma portion of the remnant bile duct and died 12 months postoperatively.

Diagnosing NENs preoperatively remains difficult despite developments in imaging studies. Cholangiocarcinoma, in particular, presents significantly similar characteristics and morphology to NENs when evaluated using various modalities, including ultrasound, CT, or MRI. Preoperative tissue confirmation may be helpful, and endoscopic ultrasound-guided biopsy is considered more useful than endoscopic biopsy alone in obtaining an accurate preoperative diagnosis [17]. Moreover, preoperative biopsy did not indicate whether the tumor was a NEN or NEC. In our study, preoperative biopsy confirmation was possible in six and one patients in the AoV and non-AoV groups, respectively. Chromogranin A is elevated in 90% of gut NENs and is associated with tumor burden and recurrence. Therefore, serum chromogranin A could be an effective biomarker for the diagnosis of NENs before surgery. However, testing for it is not cost-effective due to the rarity of extrahepatic biliary NENs [18].

No definite treatment guideline for NENs has been drafted to date; however, complete surgical resection is required for long-term survival, similar to that observed for other hepatobiliary malignant tumors. Our experience indicates that aggressive adjuvant treatment helps to prevent NENs, such as NEC or MiNEN; however, its efficacy remains controversial. The roles of adjuvant radiotherapy and chemotherapy in the management of NEC or MiNEN remain unclear. Traditional radiotherapy is generally ineffective for treating NENs [19].

The limitations of studies on NENs are generally due to the rarity of the disease. In this study, we found several possible predictive factors for survival and disease recurrence; however, not all of them could be demonstrated due to the small number of patients. This is the reason that large-scale multicenter studies are required.

Conclusions

In cases of extrahepatic biliary NEN, early detection of tumors and adequate surgery and aggressive adjuvant treatment for high-risk patients are important to achieve long-term survival and prevent disease recurrence. A high mitotic count (>20/10 HPFs) is a useful predictor of recurrence or for selecting high-risk patients.

List Of Abbreviations

AoV ampulla of Vater

CCRT concurrent chemoradiation therapy

CT computed tomography

DFS disease-free survival

GB gallbladder

G1 Grade 1

G2 Grade 2

G3 Grade 3

HPF high-power field

LN lymph node

LVI lymphovascular invasion

MinENs mixed endocrine non-endocrine neoplasms

MRI magnetic resonance imaging

NEC neuroendocrine carcinoma

NENs neuroendocrine neoplasms

OS overall survival

PET positron emission tomography

PNI perineural invasion

SPSS Statistical Package for the Social Sciences

WHO World Health Organization

Declarations

Ethics approval and consent to participate

This retrospective study was performed in accordance with relevant guidelines and regulations, and approved by the Pusan National University Institutional Review Board at Clinical Trial Center (Institutional review board number: 2109-004-107)

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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None declared

Authors' contributions

YMP, BGN and HIS were responsible for conceptualization, data curation, formal analysis. SK,SBH, NKL, DUK, SYH and SJL were responsible for investigation, methodology, and project administration. All authors were responsible for the resources. HIS supervised this study. YMP was responsible for writing – original draft. YMP and HIS were responsible for writing – review & editing. All authors read and approved the final version of the manuscript.

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Figures

1A

1B

Figure 1

Overall and disease-free survival rates of patients with neuroendocrine tumors. (a) The 1-, 3-, and 5-year overall survival rates were 87.1%, 80.4%, and 71.4%, respectively. (b) The 1-, 3-, and 5-year disease-free survival rates were 87.1%, 79.8%, and 71.8%, respectively.