Session I

A Case of Primary Extrahepatic Bile Duct Neuroendocrine Carcinoma

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1. Case presentation

64세 남자가 1달 전부터 시작된 황달을 주소로 내원하였다. 타 병원 CT에서 distal CBD mass가 확인되어 본원에 내원하여 MRCP, PET-CT 및 ERCP를 통한 조직검사를 하였고, 조직검사 결과는 chronic inflammation with atypical glands로 나왔으나, 임상적으로 악성종양이 의심되어 진단 및 치료적 목적으로 수술적 절제를 시행하였다.

2. Diagnosis

수술 검체는 CD56, synaptophysin, chromogranin-A에서 양성 소견이 확인되었고, ki-67 index가 60% 정도 10 HPF 당 20개의 mitosis가 확인되어 최종 병리 결과는 neuroendocrine carcinoma (WHO classification G3), small cell type으로 확인 되었다. Resection margin은 carcinoma의 involvement는 없었으며, lympho-vascular invasion 및 perineural invasion은 확인되었다.

3. Therapy and Clinical course

Neuroendocrine carcinoma의 가장 중요한 치료는 수술적 절제로 알려져 있으며, 진단 및 치료적으로 PPPD가 시행된 상태이며, lympho-vascular invasion 및 perineural invasion이 동반된 상태로, adjuvant chemotherapy로 etoposide-cisplatin으로 6차례 항암치료를 시행하였고, 현재 외래에서 재발의 증거 없이 추적 관찰 중에 있다.

4. Conclusion

담도에서의 neuroendocrine tumor는 전체 소화기계 neuroendocrine tumor 중 1% 미만의 드문 종양으로, WHO classification이 중요한 예후인자로 알려져 있다. 저자들은 수술이후 확진된 neuroendocrine carcinoma의 경험을 보고하는 바이다.

Key words: biliary neuroendocine tumor, neuroendocrine carcinoma

REFERENCES

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2. NCCN clinical practive guidelines in oncology: Neuroendocrine tumor (ver 3.2017)
3. Garcia-Carbonero R, Sorbye H, Baudin E, Raymond E, Wiedenmann B, Niederle B, ... & Caplin M (2016). ENETS consensus guidelines for high-grade gastroenteropancreatic neuroendocrine tumors and neuroendocrine carcinomas. Neuroendocrinology 103(2):186-194

M/64

C.C) Jaundice

P.I) 내원 1달 전부터 발생한 jaundice로 타 병원에서 시행한 검사에서 distal CBD mass 확인되어 본원 내원함.

P.Hx) HT / DM / Hepa / Tbc + / + / - / -

S.Hx) smoking : current smoker (40 pack-years)

alcohol : 소주 2병/회, 2회/주

Review of System

[Constitutional systems]
General weakness/Fatigue/Weight loss/Weight gain/Chilling/Fever (-/-/-/-/-/-)

[HEENT]
Headache/Dizziness/Sore throat (-/-/-)

[Cadiovascular & Respiratory]
Chest pain/Dyspnea/Palpitation (-/-/-) Cough/Sputum/Wheeze/Hemoptysis (-/-/-/-)

[Gastrointestinal]
Anorexia/Nausea/Vomiting/Diarrhea/Constipation (-/-/-/-/-) Abdominal pain (-)

[Genitourinary]
Dysuria/Frequency/Urgency/Hematuria (-/-/-/-)

[Musculoskeletal]
Arthralgia/Joint swelling/Stiffness (-/-/-)

PHYSICAL EXAMINATION

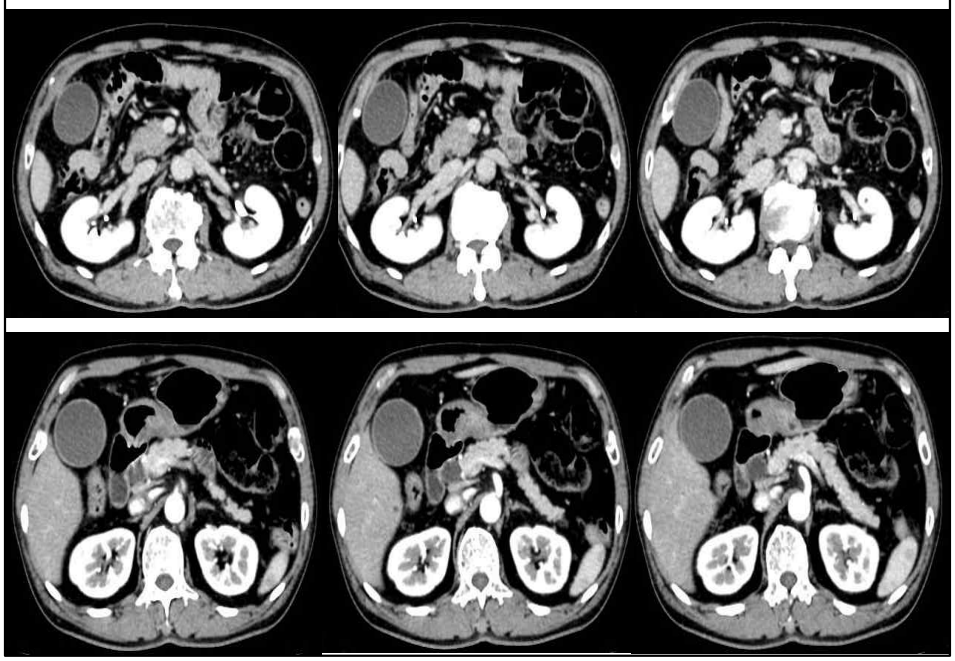
- **GA / GC**
  - Not ill appearance
  - good condition
- **HEENT**
  - Not anemic conjunctivae
  - **Icteric sclera**
  - Not dehydrated tongue
  - Not engorged neck v.
  - No CLN, SCLN enlargement
- **Chest**
  - CBS /s r
  - RHB /s m
- **Abdomen**
  - Not distended
  - Whole abd. T/RT -/-
  - Audible BS
- **Extremities**
  - No Pitting edema

Lab finding (17.04.26)

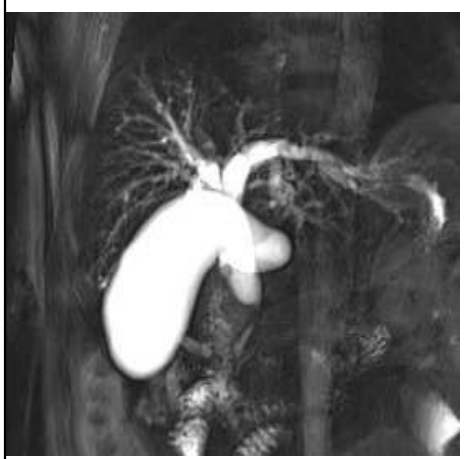
CBC	
WBC	8,300 /mm^3
neutrophil	55.8 %
Hb	13.7 g/dL
PLT	277 10^3/mm^3
Amy/Lip	48.0/15.4 IU/L
GGT	**2,183** IU/L
CRP	**1.02** mg/dL
CA19-9 /CEA	**235.4** U/mL /3.0 /ng/mL

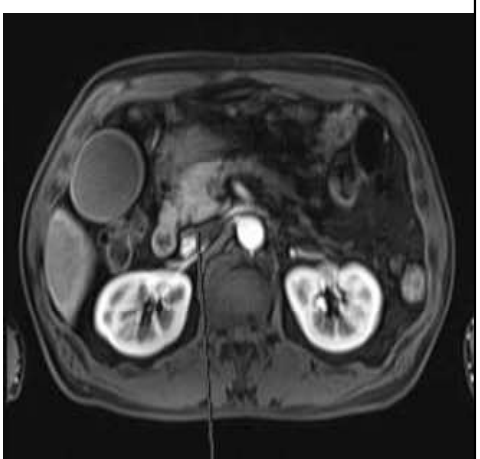
Biochemistry	
AST/ALT	**89/92** IU/L
ALP/LDH	**314**/192 IU/L
TB/DB	**13.41/12.10** mg/Dl
TP/Alb	6.2/3.5 gm/dL
BUN/Cr	9.9/0.63 gm/dL
TC/UA	**399**/3.4 gm/dL
Ca/P	9.2/2.9 gm/dL
Na/K	138.3/4.40 mEq/L

17.04.24 abd. CT - LMC

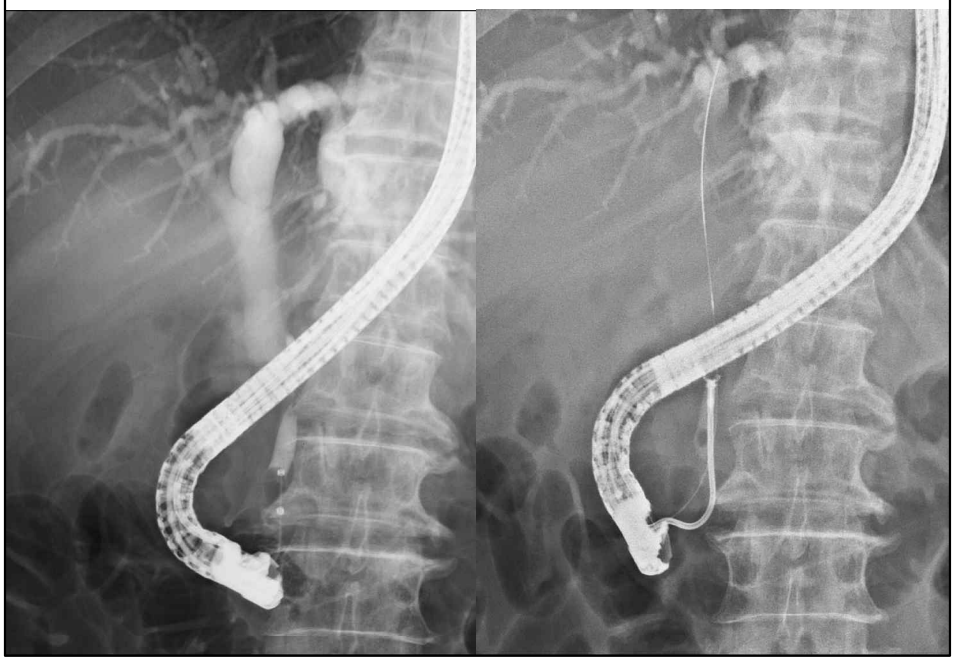


17.04.26 mrcp

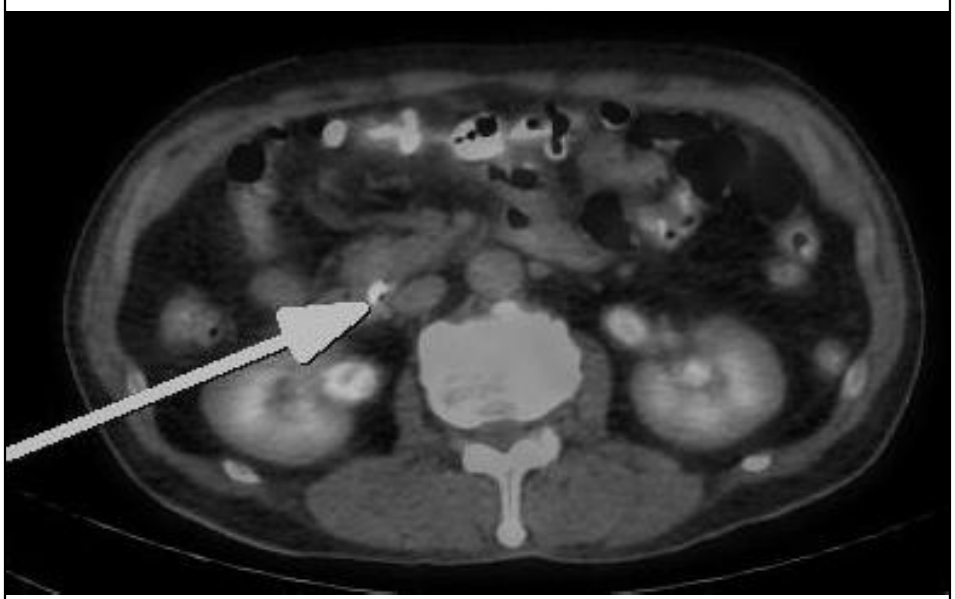




17.04.27 ERCP

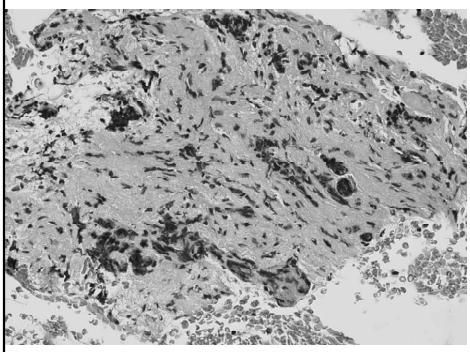


17.04.28 PET-CT

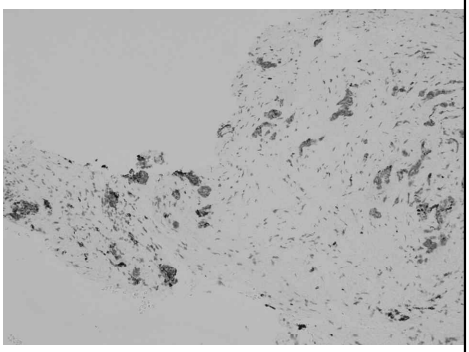


• Distal CBD (SUV 2.7)에서 mild focal uptake이 관찰

Biopsy result



H & E stain, x 400

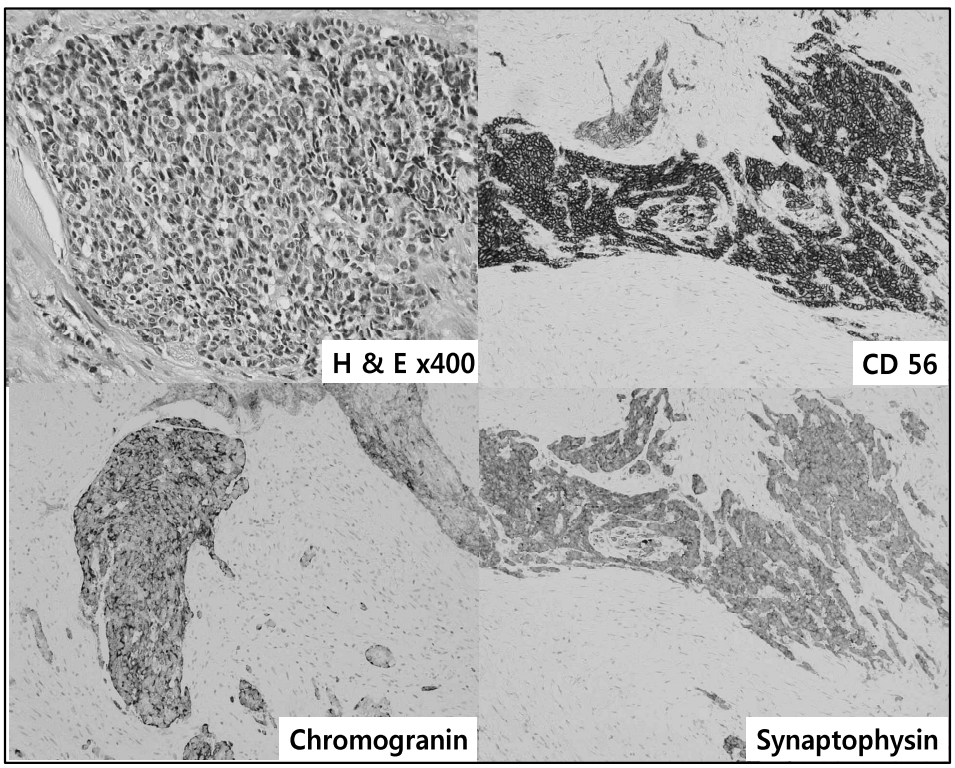


Ki - 67

Common bile buct, distal, biopsy :

Chronic inflammation with atypical glands, suggestive of reactive atypia of ductal epithelium

1) CK7 (focal+), CK20 (-), CEA (-), p53 (focal weak+), Ki-67 (about 20%), Smad4 (focal loss) panCK (focal+), LCA (-)
2) If clinically malignancy is suspected, rebiopsy is recommended.



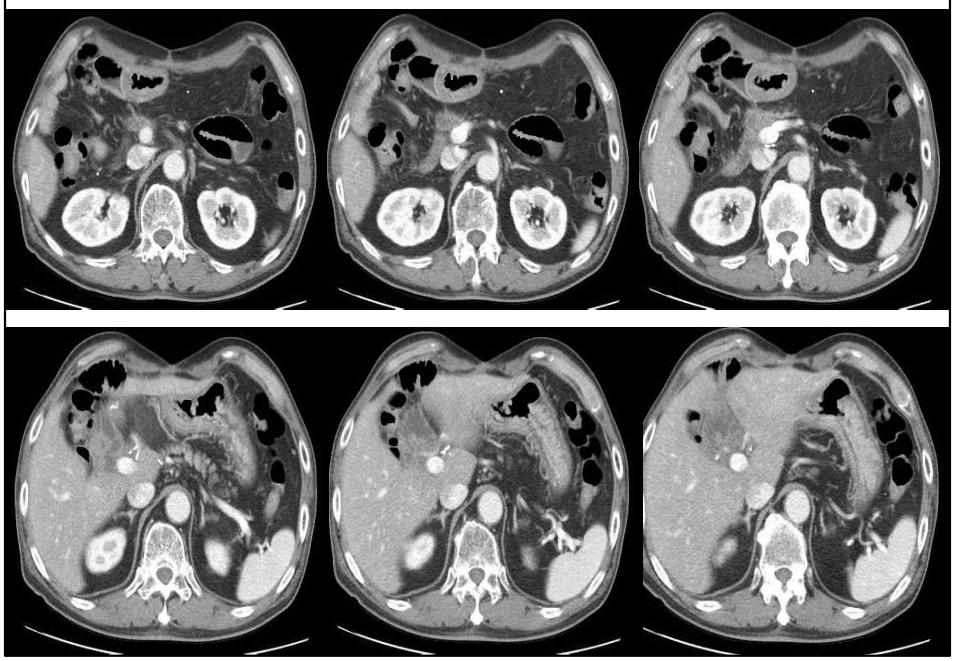
17.05.15 PPPD

- Common bile duct, pylorus preserving pancreaticoduodenectomy :
  1. Histologic type: **Neuroendocrine carcinoma, small cell type**
     [CD56(+)/synaptophysin(+)/chromogranin-A(+)/p53(-)/CK7(+)/CK19(+)/CK20(-)/CDX2(+)
     Smad4(-)/CEA(-)]
  2. Tumor size: 2.0x1.1 cm
  3. Tumor Site: Common bile duct
  4. Histologic grade: **G3 by WHO 2010**
     - **Mitosis: 20/10 HPFs, Ki-proliferation index: about 60%**
  5. Microscopic Tumor Extension : Tumor invades beyond the wall of the bile duct (pT2)
  6. Margins
     Pancreatic margin
     radial resection margin - uninvolved by invasive carcinoma
     proximal shave resection margin - uninvolved by invasive carcinoma
     Common bile duct margin - uninvolved by invasive carcinoma
     Intestinal margin (proximal and distal) - uninvolved by invasive carcinoma
  7. Lymph-Vascular invasion: **present, mild**
  8. Perineural invasion: **present, moderate**
  9. Metastasis to regional lymph nodes: no tumor (0/20)
     [pancreaticobiliary 0/18, duodenal 0/2]
  10. Associated finding :
      1) chronic pancreatitis
- Lymph node, #12, dissection :
- No tumor (0/1).

Progression

- 2017.06.09 #1 aEP
- 2017.06.30 #2 aEP
- 2017.07.24 #3 aEP
- 2017.08.21 #4 aEP
- 2017.09.18 #5 aEP
- 2017.10.16 #6 aEP

17.11.06 abd. CT



Case Review

Neuroendocrine Tumor

Neuroendocrine tumor

- **Enterochromaffin cell**
  - Play a crucial role in gastrointestinal regulation, particularly **intestinal motility and secretion**
  - Highest proportion in small intestine, and rarely within the biliary ducts.
- **Biliary NET**
  - extremely rare (1% of all GI NET)

Distribution of NECs (NOS), carcinoids, and SCCs by gastrointestinal site

Anatomic site	NEC (NOS)	Carcinoid	SCC
GB	56	119	54
EHBD	10	31	17
Ampulla of Vater	40	110	7
Stomach	302	2,035	147
Duodenum	128	1281	8
Jejunum	34	449	1
Ileum	163	3,418	3
Other small intestine	118	2306	1
Cecum	245	1219	69
Appendix	29	967	0
Ascending colon	127	288	33
Hepatic flexure of colon	49	81	8
Transverse colon	57	113	15
Splenic flexure of colon	20	41	4
Descending colon	19	96	10
Sigmoid colon	90	663	32
Overlapping lesion of colon	7	30	9
Colon, NOS	36	188	8
Rectosigmoid junction	51	546	17
Gastrointestinal system (total)	1581	13 981	443

The total number of neoplasms in the entire gastrointestinal system is recorded last (SEER 1973-2005).

Annals of Diagnostic Pathology 13(2009):378–383

Diagnosis & staging

- Neuroendocrine Gastroenteropancreatic tumor
  - **Chromogranin A, synaptophysin :** Common phenotype with immunoreactivity
  - **CD 56, NSE :** offen positive
  - **Ki-67 :** mandatory to grade the tumor according to WHO classification

Grade	Gastroenteropancreatic (GEP) NETs
Low Grade (G1)	<2 mitoses/10 HPF AND/OR <3% Ki-67 index
Intermediate Grade (G2)	2–20 mitoses/10 HPF AND/OR 3–20% Ki-67 index
High Grade (G3)	>20 mitoses/10 HPF AND/OR >20% Ki-67 index

Treatment

- **Surgical resection**
  - **Only curative** approach for NET
  - Localized metastatic disease to the liver : potentially resetable
  - not to operate on G3 pancreatic NEC : widely metastasized at the timepoint of diagnosis

- **Medical therapy**
  - Somatostatin analogs : functioning NETs, Non-functioning G1/G2 NETs (first line therapy)
  - mTOR inhibitor (Everolimus) : G1/2
  - Tyrosine kinase inhibitors(sunitinib, pazopanib) : pancreatic NET
  - Metastatic NEC G3 : systemic chemotherapy (etopo - cis)
    - ➔ Noestablished second-line : temozolomide ± (capecitabine ± bevacizumab)

2017년 대한소화기암학회 신경내분비종양연구회

Clinicopathological characteristics of biliary neuroendocrine neoplasms: a multicenter study

Kyong Joo Lee[a]*, Jae Hee Cho[b]*, Sang Hyub Lee[c], Kwang Hyuk Lee[d], Byung Kyu Park[e], Jun Kyu Lee[f], Sang Myung Woo[g], Ji Kon Ryu[c], Jong Kyun Lee[d], Yeon Suk Kim[b], Jae Woo Kim[a] and Woo Jin Lee[g]

Table 1. Clinicopathological features of biliary neuroendocrine neoplasms.

	Gallbladder ($n=11$)	EHBD ($n=5$)	Ampulla of Vater ($n=27$)
Median age, years	62 (range, 31–84)	74 (range, 54–84)	60 (range, 29–77)
Sex			
Male	6 (54.5%)	4 (80%)	15 (55.6%)
Female	5 (45.5%)	1 (20%)	12 (44.4%)
Symptoms			
Abdominal pain	8 (72.7%)	2 (40%)	7 (25.9%)
Jaundice	2 (18.2%)	2 (40%)	7 (25.9%)
Weight loss	1 (9.1%)	0	1 (3.7%)
Incidental diagnosis	2 (18.2%)	1 (20%)	9 (33.3%)
Coexistence			
Diabetes mellitus	1 (9.1%)	0	2 (7.4%)
Gallbladder stone	0	0	1 (3.7%)
Choledocholithiasis	1 (9.1%)	0	0
Initial metastasis			
Liver	7 (73.6%)	0	5 (18.5%)
Lymph nodes	2 (18.2%)	0	1 (3.7%)
WHO classification (2010)			
NEN G1	0	1 (20%)	13 (48.1%)
NEN G2	0	0	4 (14.8%)
NEC G3	11 (100%)	4 (80%)	10 (37.1%)
Initial treatment			
Operation	7 (63.6%)	5 (100%)	21 (77.8%)
Endoscopic resection	0	0	3 (11.1%)
Chemotherapy	3 (27.3%)	0	1 (3.7%)
Conservative care	1 (9.1%)	0	2 (7.4%)
Curative resection (R0)	3 (27.3%)	3 (60%)	16 (59.3%)

EHBD: extrahepatic bile duct; WHO: World Health Organization; NEN: neuroendocrine neoplasm; NEC: neuroendocrine carcinoma; MANEC: mixed adenoneuroendocrine caricoma.

Table 2. Prognostic factors affecting overall survival in biliary neuroendocrine neoplasms.

Characteristic	HR	p^a	HR	95% CI	p^b
Age					
<60	1		1		
≥60	0.65	0.418	0.82	0.26–2.56	0.738
Sex					
Female	1		1		
Male	2.57	0.041	2.07	0.57–7.47	0.264
Tumor location					
Ampulla of Vater	1		1		
Extrahepatic bile duct	5.11	0.001	1.94	0.45–8.31	0.368
Gallbladder	3.77	0.033	2.86	0.72–11.36	0.136
Presence of metastasis					
No	1		1		
Yes	2.46	0.039	2.2	0.53–9.03	0.274
WHO classification (2010)					
NEN G1 & G2	1		1		
NEC G3	34.17	0.001	27.1	2.81–260.68	0.004
Curative resection (R0)					
No	1		1		
Yes	0.79	0.575	0.38	0.07–1.88	0.235
Chemotherapy					
No	1		1		
Yes	0.299	0.006	1.19	0.27–5.2	0.813

NET G3 / NEC

	Grade-concordant (Mitotic G2/Ki67 G2) PanNETs (n = 53)	Grade-discordant (Mitotic G2/Ki67 G3) PanNETs (n = 19)	Poorly Differentiated NECs (n = 43)
Median survival (95% confidence interval) (mo)	67.8 (51.8-93.8)	54.1 (30.5-117.9)	11 (6-18)
2-y survival (mean ± SD) (%)	86.7 ± 5.1	74.9 ± 11	22.5 ± 6.9
5-y survival (mean ± SD) (%)	62.4 ± 8.3	29.1 ± 16	16.1 ± 6.3
P	0.2	0.002	

Am J Surg Pathol 2015;39:683-690.

Neuroendocrine neoplasm	Morphology (differentiation)	Grading G1–G3 (Ki–67 index in %)	Abbreviation
Neuroendocrine tumor Grade 1	Well-differentiated	G1 (≤2%)	NET G1
Neuroendocrine tumor Grade 2	Well-differentiated	G2 (3–20%)	NET G2
Neuroendocrine tumor Grade 3	Well-differentiated	G3 (>20%)	NET G3
Neuroendocrine carcinoma	Poorly-differentiated (large or small cell)	G3 (>20%)	NEC

	NET G3	NEC	*P*
Number of patients	12	113	
OR, *n* (%)	2 (17)	39 (35)	0.18
SD, *n* (%)	1 (8)	25 (22)	0.24
PD, *n* (%)	6 (50)	30 (27)	0.09
NA, *n* (%)	3 (25)	19 (17)	0.36
DCR (%)	3 (33%)	64 (68%)	0.036
Median PFS (95% CI), months	2.4 (1.1–3.8)	5.0 (4.0–6.1)	0.049
Median OS (95% CI), months	NR	16.4 (13.4–19.5)	0.003

Endocr Relat Cancer. 2015 Aug;22(4):657-64

- **Well-differentiate/high grade (2017 NCCN guideline)**
  - Not all high-grade neuroendocrine cancers are poorly differentiated.
  - NETs with ki-67 >20% : well-differentiated (ki-67 20-50%)
    - ➔ poorly respond to "etoposide/cisplatin"
    - ➔ favorably repond to treatment for well-differentiated NETs

Adjuvant / Neoadjuvant CTx

- **14 pancreas high grade NEC /s meta**
  - Resection 이후 adjuvant CTx => 13 recur (DFS 7 months)
  - Neoadjuvant CTx : no evidence, considered

Ann Surg Oncol. 2016;23:1721-1728.

- **25 GB NET** (19 NEC, 6 mixed adenoneuroendocrine carcinoma)
  - 2 ED (adjuvant carbo-etopo)
  - 9 LAD (6 neoadujvant; 5 op – R0 (f/u 7 months)
    - ➔ 3 recur /DFS 5 months)
  - 14 meta

J Gastrointest Cancer 2018 Feb 13.

Ki 67

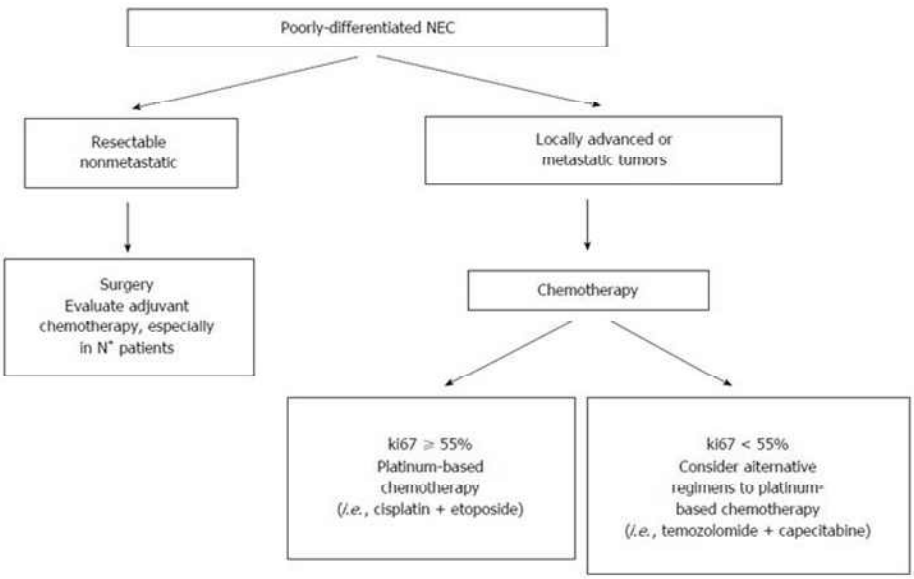
- 252 NEC palliative CTx PR/CR rate, OS
  - Ki 67 <55%: 15%, 14 months
  - Ki 67 >55%: 42%, 10 months

Ann Oncol. 2013 Jan;24(1):152-60.

- 25 NEC EP failed : Temozolomide + capecitabine
  - CR/PR : 8 patients , OS : 22 months
  - PD : 8 patients, OS : 7 months
  - Ki 67 <60% : more favorable response

Cancer 2011;117: 4617-4622

Ki 67



World J Gastroenterol. Dec 7, 2016;22(45):9944-9953