

## Case Report

# Ampullary Large-Cell Neuroendocrine Carcinoma, a Diagnostic Challenge of a Rare Aggressive Neoplasm: A Case Report and Literature Review

Eleni Karlafti <sup>1,2,\*</sup>, Maria Charalampidou <sup>3,\*</sup>, Georgia Fotiadou <sup>3</sup>, Ioanna Abba Deka <sup>4</sup>, Georgia Raptou <sup>4</sup>, Filippos Kyriakidis <sup>5</sup>, Stavros Panidis <sup>3</sup>, Aristeidis Ioannidis <sup>3</sup>, Adonis A. Protopapas <sup>2</sup>, Smaro Netta <sup>3</sup> and Daniel Paramythiotis <sup>3</sup>

- <sup>1</sup> Emergency Department, University Hospital of Thessaloniki AHEPA, Aristotle University of Thessaloniki, 546 21 Thessaloniki, Greece
  - <sup>2</sup> First Propaedeutic Department of Internal Medicine, University Hospital of Thessaloniki AHEPA, Aristotle University of Thessaloniki, 546 21 Thessaloniki, Greece; adoprot@hotmail.com
  - <sup>3</sup> First Propaedeutic Surgical Department, University Hospital of Thessaloniki AHEPA, Aristotle University of Thessaloniki, 546 21 Thessaloniki, Greece; geofotiadou@gmail.com (G.F.); st.panidis@gmail.com (S.P.); ariioann@yahoo.gr (A.I.); smaronetta@gmail.com (S.N.); danosprx1@hotmail.com (D.P.)
  - <sup>4</sup> Pathology Department, University Hospital of Thessaloniki AHEPA, Aristotle University of Thessaloniki, 546 21 Thessaloniki, Greece; ampou\_nt@hotmail.com (I.A.D.); graptou@auth.gr (G.R.)
  - <sup>5</sup> Theganio Cancer Hospital of Thessaloniki, 546 39 Thessaloniki, Greece; filipposkyr1@hotmail.gr
- \* Correspondence: linakarlafti@hotmail.com (E.K.); mcharalampidou@outlook.com (M.C.)



**Citation:** Karlafti, E.; Charalampidou, M.; Fotiadou, G.; Abba Deka, I.; Raptou, G.; Kyriakidis, F.; Panidis, S.; Ioannidis, A.; Protopapas, A.A.; Netta, S.; et al. Ampullary Large-Cell Neuroendocrine Carcinoma, a Diagnostic Challenge of a Rare Aggressive Neoplasm: A Case Report and Literature Review. *Diagnostics* **2022**, *12*, 1797. <https://doi.org/10.3390/diagnostics12081797>

Academic Editor: Alexander Haug

Received: 17 June 2022

Accepted: 19 July 2022

Published: 25 July 2022

**Publisher's Note:** MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



**Copyright:** © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

**Abstract:** Ampullary large-cell neuroendocrine carcinomas (LCNECs) are extremely rare, and available data are limited on case reports. They present with jaundice, non-specific abdominal pain, or weight loss, imitating adenocarcinoma. Their incidence increases due to the improved diagnostic techniques. However, preoperative diagnosis remains challenging. We report the case of a 70-year-old man with a history of metabolic syndrome, cholecystectomy, and right hemicolectomy, presenting with jaundice. Laboratory results showed increased liver biochemistry indicators and elevated CA 19-9. Esophagogastroduodenoscopy revealed an ulcerative tumor on the ampulla of Vater, and the biopsy revealed neuroendocrine carcinoma. Although computed tomography (CT) detected enlarged regional lymph nodes, the positron emission tomography (PET) showed a hyperactive lesion only in this area. Pylorus-preserving pancreatoduodenectomy with R0 resection was performed. Pathologic evaluation of the 3.1 × 1.9 cm tumor revealed an LCNEC with immunohistochemical positivity at Synaptophysin, EMA, CD56, and cytokeratin CK8/18. The Ki-67 index was 45%. Two out of the nine dissected lymph nodes were occupied by the neoplasm. The patient was discharged home free of symptoms, and adjuvant chemotherapy with carboplatin + etoposide was initiated. A comprehensive review of the reported cases showed that the preoperative biopsy result was different from the final diagnosis in few cases, regarding the subtypes. Conventional radiology cannot identify small masses, and other methods, such as endoscopy, magnetic resonance cholangiopancreatography (MRCP), and FDG-PET scan, might aid the diagnosis. Diagnosis is based on histology and immunohistochemical markers of the surgical specimens. The treatment of choice is pancreatoduodenectomy, followed by adjuvant chemotherapy. However, recurrence is frequent, and the prognosis remains poor.

**Keywords:** neuroendocrine carcinoma; neuroendocrine neoplasm; large cell; ampulla of Vater

## 1. Introduction

Periampullary neoplasms include pancreatic, duodenal, distal common bile duct (CBD), and ampullary neoplasms. Ampullary carcinomas arise within the ampulla of Vater [1].

Neuroendocrine neoplasms (NENs) of the gastrointestinal tract (GEP-NENs) are a rare and diverse group. Besides common-shared characteristics, they are also characterized by site-specific distinctions regarding the clinical and pathological course and long-term prognosis [2,3]. Arising from the diffuse neuroendocrine system, they are usually less aggressive than their non-endocrine counterparts [4].

Ampullary NENs are even more uncommonly reported, accounting for less than 0.3% of all gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) [5,6]. Therefore, available data are based on few case series and retrospective reviews, and ampullary neuroendocrine neoplasms are often discussed together due to the anatomic proximity with those arising from the duodenum or the pancreas, which are more often described [7,8]. In addition, their clinical picture imitates adenocarcinoma (ADC) [9], which is also the most common malignancy in that area [10]. Thus, preoperative diagnosis is difficult.

According to the 2019 WHO classification of tumors of the digestive system, NENs were classified into well-differentiated neuroendocrine tumors (NETs), poorly differentiated neuroendocrine carcinomas (NECs), and mixed neuroendocrine–non-neuroendocrine neoplasms (MiNENs). There have been only few case reports of MiNEN in the ampulla of Vater [11–14]. Well-differentiated and poorly differentiated NENs reflect two genetically and biologically different entities [15].

NETs were further classified into low-, intermediate-, and high-grade (G1–G2) based on the mitotic rate and the Ki-67 index. Ki-67 labeling reflects high proliferative activity, which has been shown to have a prognostic value. Therefore, G1 NETs are characterized by a low mitotic rate (<2 mitoses/2 mm<sup>2</sup>) and Ki-67 index < 3%, G2 NETs have shown a medium mitotic rate and Ki-67 index, while G3 NETs have a mitotic rate over 20 mitoses/2 mm<sup>2</sup> and Ki-67 index > 20%. NECs have, by definition, a high mitotic rate (>20 mitoses/2 mm<sup>2</sup>) and Ki-67 index > 20% and are classified as large-cell neuroendocrine carcinoma (LCNEC) and small-cell neuroendocrine carcinoma (SCNEC) [16].

Periampullary neuroendocrine carcinoma (NEC) usually presents with jaundice, bleeding, non-specific abdominal pain, and less commonly with weight loss. Presentation with acute pancreatitis is rare [9].

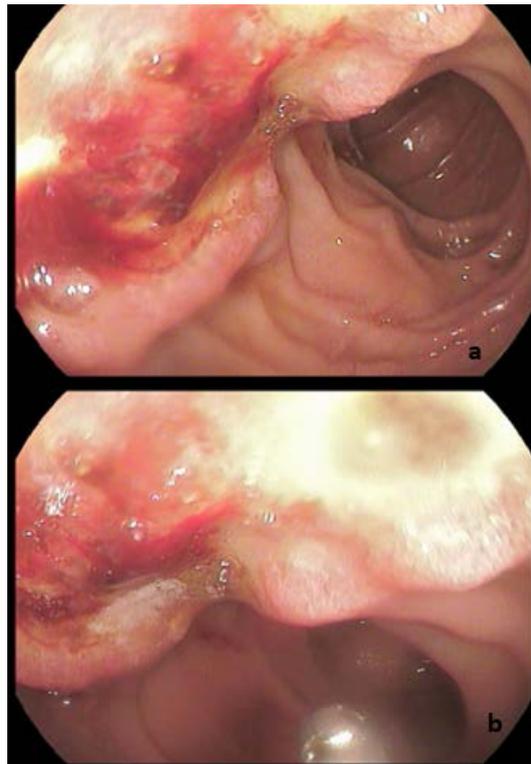
We provide herein a case report of a large-cell neuroendocrine carcinoma (LCNEC) of the ampulla of Vater, as well as a thorough literature review to consolidate our knowledge. However, the most effective treatment strategies and their exact prognosis remain unclear due to these tumors' low incidence.

## 2. Case Report

A 70-year-old man presented to the Emergency Department of our hospital because of jaundice, during the last month. His medical history includes colon polyps, right hemicolectomy (two years before he was diagnosed with an adenoma with low-grade dysplasia in caecum), cholecystectomy, inguinal hernia repair, type 2 diabetes mellitus, hypertension, and dyslipidemia. Vital signs on presentation were within normal limits. Abdominal examination revealed reduced bowel movements.

On his admission, the blood biochemistry tests showed a total bilirubin concentration of 14 mg/dL (normal values 0.1–1.2) and elevated levels of liver enzymes (aspartate aminotransferase (AST), 51 IU/L (0–32); alanine aminotransferase (ALT), 78 IU/L (0–32);  $\gamma$ -glutamyltranspeptidase, 628 IU/L (10–60); alkaline phosphatase (ALP), 457 U/L (40–129)). Chest and abdominal radiography were unremarkable. Abdominal ultrasonography disclosed a dilated biliary tree.

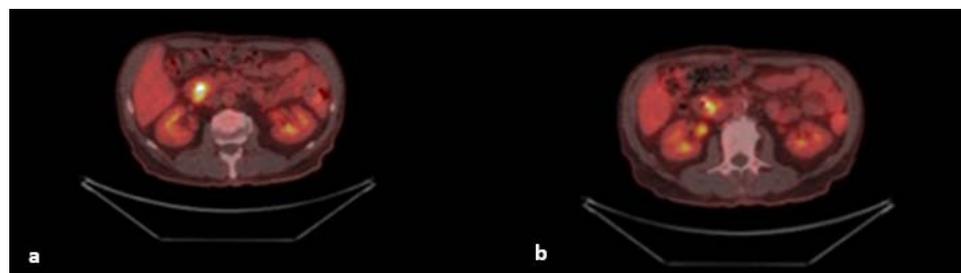
An esophagogastroduodenoscopy (EGD) was scheduled for further assessment and revealed a sizable ulcerative polypoid tumor in the ampulla of Vater (Figure 1). To minimize the patient's symptoms, endoscopic retrograde cholangiopancreatography was performed with plastic stent placement in both the major pancreatic and the bile duct. The patient's jaundice and liver biochemistry tests were then improved (total bilirubin, 1.7 mg/dL).



**Figure 1.** (a,b) Gastroduodenal endoscopy showed a large ulcerative ampullary lesion.

Further laboratory tests showed the following results: carbohydrate antigen 19-9 (CA19-9), 259 IU/mL; carcinoembryonic antigen (CEA), 3.54 ng/mL; cancer antigen 125 (CA 125), 9.79 IU/mL; alpha-fetoprotein (aFP), 1.6 ng/mL; prostatic-specific antigen (PSA), 2.17 ng/mL. The blood CEA, CA 125, aFP, and PSA levels were within the normal limits.

An abdominal contrast-enhanced computed tomography scan (CECT) showed cholangiectasis, a dilated common bile duct (1.4 cm), a dilated major and accessory pancreatic duct, and an indistinct and thickened duodenum wall between the ampulla of Vater and the heterogeneous appearing head of the pancreas. Enlarged lymph nodes with necrosis were found in porta hepatis (1.9 cm) and behind the third part of the duodenum (1.3 cm). A PET scan showed a hyperactive lesion in the ampulla with a high standardized uptake value (SUV max 10.6) (Figure 2).



**Figure 2.** (a,b) Axial fused PET/CT images show the lesion on the ampullary area. Increased uptake along the common bile duct stent. Focally increased radiopharmaceutical uptake in the intestinal propellers.

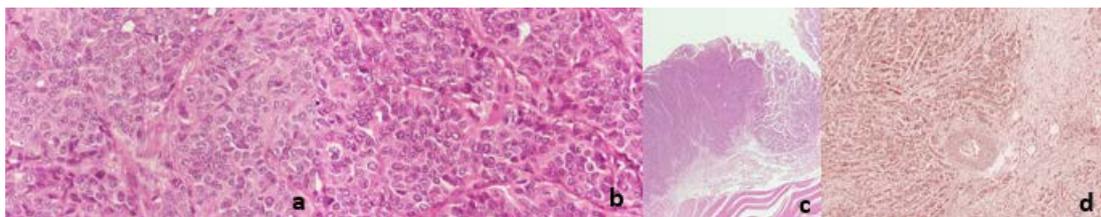
The surgical resection of the tumor was decided. In the context of preoperative control, a colonoscopy was performed to check for colon polyps and due to the past medical history

of caecum tumor. A perianal abscess was incidentally found and treated with surgical incision and drainage.

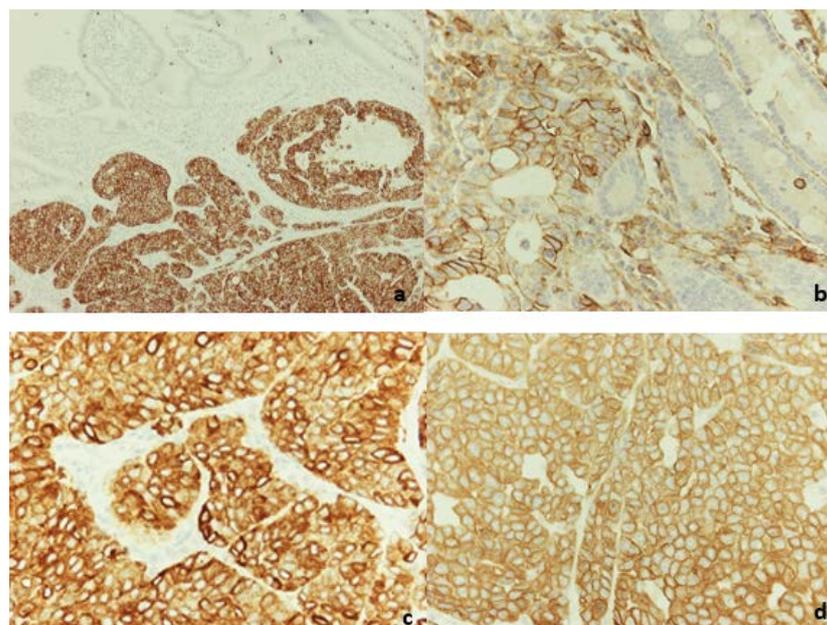
The patient underwent pylorus-preserving pancreaticoduodenectomy (Traverso-Longmire/modified Whipple) with pancreatojejunostomy and dissection of the lymph nodes.

Macroscopic examination revealed a tumor measuring  $3.1 \times 1.9$  cm located at the ampulla of Vater. A total of nine lymph nodes were dissected.

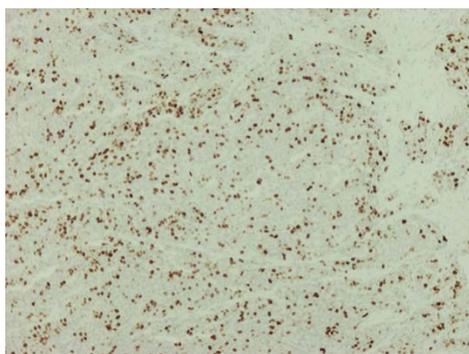
Regarding microscopic examination, sections of the tumor showed large, mostly uniform, oval tumor cells with irregular nuclei, finely granular chromatin, and indistinct nucleoli. The neoplastic cells showed little pleomorphism (Figure 3a). They were composed of organoid nests or trabeculi, separated by thin fibrovascular septae. In a few nests, tumor cells showed peripheral palisading, often with a minor component of pseudoglandular formation (Figure 3b). The majority of those formations contained small foci of necrosis. The surface of the neoplasm was ulcerative (Figure 3c). The neoplastic cells were infiltrating the pancreatic parenchyma (Figure 3d). Two out of the nine dissected lymph nodes were occupied by the neoplasm. Surgical margins were clear of tumor cells. The neoplasm was characterized by the expression of synaptophysin, CD56, CK8/18, and EMA (Figure 4). With the marker of cell proliferation Ki67/MIB1, the percentage of positive nuclei was up to 45% (Figure 5).



**Figure 3.** (a) (HE, 40 $\times$ ) Large tumor cells with irregular nuclei, finely granular chromatin, and indistinct nucleoli. (b) (HE, 40 $\times$ ) Tumor architecture includes organoid nests or trabeculi separated by thin fibrovascular septae. (c) (HE, 2 $\times$ ) The exterior surface of the neoplasm shows ulceration. (d) (HE, 40 $\times$ ) Left side of the image shows infiltration of the neoplasm, meanwhile the right side shows involved pancreatic parenchyma.



**Figure 4.** (a) Synaptophysin, 10 $\times$ , (b) CD56, 40 $\times$ , (c) EMA, 40 $\times$ , (d) CK8/18, 40 $\times$ .



**Figure 5.** Ki67/MIB1, 10 $\times$ .

The final diagnosis was large-cell neuroendocrine carcinoma of the ampulla of Vater. Based on the TNM classification, the patient's stage was T3 N1 M0 (pStage IIIA). An uneventful postoperative course was observed, and the patient was discharged free of symptoms on day 11 after the surgery. A course of chemotherapy with carboplatin 200 mg + etoposide 100 mg was initiated to treat NEC. Surveillance with physical examination and chest/abdominal/pelvic CT is recommended every 12 weeks for the first year and then every 6 months [17].

### 3. Discussion

GEP-NENs are rare and are mainly well-differentiated. Poorly differentiated carcinomas (SCNEC and LCNEC) are uncommon [18]. The incidence of GEP-NECs was 4.6 cases per 1 million in 2012 [19]. The large-cell subtype constitutes about 60% of GEP-NEC cases, thus being more common than the small-cell subtype [20].

The incidence of NENs increases, which could be due to the better quality of endoscopic and radiological diagnostic techniques, and those tumors can be detected at an earlier stage before they cause specific symptoms [3,21–23].

Recent literature emphasizes more in the histopathological subtypes than the TNM staging system to predict the tumor's aggressiveness and decide on a treatment plan [24].

We found 19 cases of NENs reported in the literature in a two-year time period, from May 2020 until April 2022 (Table 1) [9,14,25–36].

There were only two cases of SCNECs [25,27] and one case of LCNEC [26] reported. Like our case, at least three NEN cases [14,31] had elevated carbohydrate antigen 19-9 (CA19-9) levels, although none of them was a poorly differentiated NEC. This field was not answered in the case of the LCNEC. Elevated CA19-9 in serum reflects a poor prognosis and aggressiveness in cases of pancreatic NENs [37]. Although it is also correlated with poor prognosis in ampullary adenocarcinomas (ADCs) [38,39], it has not yet been analyzed in patients with ampullary NENs.

In a population-based study of 20,836 patients with GEP-NENs examining sex differences, it was shown that females were more likely to have NET histological subtype (vs. NEC) and better overall survival (OS) than males. It was suggested that this might be the result of biological differences, which is concordant with preclinical studies examining the favorable effect of estrogen and progesterone receptors' expression in patients with GEP-NENs [40].

**Table 1.** Summary of the literature review of cases of ampullary neuroendocrine neoplasms from May 2020 until April 2022.

	Author	Sex	Age	Clinical Presentation	Tumor Markers in Serum	Distant Metastases on Imaging
1	Kleinschmidt et al. [9]	F	56	right upper quadrant pain	NA	NA
2	Ito et al. [25]	M	65	jaundice	(−)	(−)
3	Jung et al. [26]	M	64	NA	NA	Liver
4	Li et al. [27]	M	57	jaundice, weight loss	(−)	(−)
5	Shiratori et al. [28]	M	60	(−)	(−)	(−)
6	Noorali et al. [29]	F	40	epigastric pain, pruritus	NA	(−)
7	Noorali et al. [29]	M	58	epigastric pain, weight loss	NA	NA
8	Xiao et al. [30]	F	50	pruritus	NA	Umbilical sac
9	Zahid et al. [31]	F	42	jaundice, pruritus	CA19-9 slightly elevated	(−)
10	Guerrero et al. [32]	F	69	epigastric pain	NA	(−)
11	Matli et al. [33]	M	71	abdominal pain, weight loss	NA	NA
12	Matli et al. [33]	F	83	nausea, vomiting	(−)	Liver, left lung, and left shoulder
13	Malhotra et al. [34]	M	33	nausea, vomiting, dyspepsia	NA	(−)
14	Fujii et al. [35]	M	53	presyncope secondary to anemia	(−)	(−)
15	Wang et al. [14]	M	81	jaundice	CA19-9 elevated	(−)
16	Wang et al. [14]	M	69	jaundice	(−)	(−)
17	Wang et al. [14]	M	67	abdominal pain	CA19-9 elevated	(−)
18	Wang et al. [14]	M	72	jaundice, abdominal pain	(−)	(−)
19	Choi et al. [36]	F	46	anemia	(−)	(−)

Table 1. Cont.

	Endoscopic Findings	Ki-67 Index	Tumor Size	Immunohistochemistry
1	NA (ERCP/EUS)	3–20%	22 mm	Synaptophysin, Cytokeratin
2	Unexposed tumor (ERCP)	40–50%	11 mm	Synaptophysin, Chromogranin A, p53, and Rb1
3	NA	NA	NA	Synaptophysin
4	NA	40%	50 mm	Synaptophysin, CD56, Cytokeratin
5	Tumor within the submucosal layer (EUS)	2%	10 mm	Synaptophysin, Chromogranin A
6	Ulcerative vegetative 22 * 17 mm lesion around the ampulla (EGD)	4%	NA	Synaptophysin, Chromogranin A
7	Gastritis with a small polyp in the antrum (EGD)	15%	NA	Synaptophysin, Chromogranin A, CEA
8	21 × 17 mm polypoid ampullary mass (EGD)	NA	11 mm	Synaptophysin, CD56
9	Ulcerated, tumorous-looking ampulla (ERCP)	NA	NA	Synaptophysin, Chromogranin A
10	Well-defined, homogeneous, hypoechoic 19 × 9 mm lesion (EUS)	4%	17 mm	NA
11	Single intramural mass in the area of papilla (EUS)	NA	NA	Synaptophysin
12	NA (EUS)	NA	NA	Synaptophysin, Chromogranin A, Cytokeratin
13	Mass lesion causing intra-luminal bulge at the ampulla (EGD)	NA	25 mm	Synaptophysin, chromogranin A, S-100
14	Bleeding from an erosion	2.50%	11 mm	Synaptophysin
15	NA	30%	NA	Synaptophysin, CD56
16	NA (Duodenal endoscopy)	50%	NA	Synaptophysin, Chromogranin A, CD56
17	Irregular ulcer in the ampulla with a crater-like bulge around	70%	NA	Synaptophysin, Chromogranin A, CD56
18	NA	70%	NA	Synaptophysin, CD56
19	Firm, bulging fibrotic ampullary mass with diffuse edema (EGD)	1%	24 mm	Synaptophysin, Chromogranin A, S-100, NSE

Table 1. Cont.

	WHO Classification	Metastatic Lymph Nodes	Adjuvant Chemotherapy	Recurrence/Outcome (Months)
1	NET G1	1/15	NA	NA
2	SCNEC	(−)	(irinotecan + cisplatin), (etoposide + cisplatin)	(+)/Death (18)
3	LCNEC	NA	NA	(+) eyelid metastasis/NA
4	SCNEC	1	(−)	(+)/Death (14)
5	NET G1	(−)	NA	(−)/Survival (12)
6	NET G2	NA	NA	(+) liver metastasis/NA
7	NET G2	NA	NA	(−)/Survival (84)
8	NET G1	4/19	NA	NA
9	NET G3	NA	NA	(−)/Survival (6)
10	CoGNET	(−)	NA	(−)/Survival (24)
11	NET	NA	NA	NA
12	NET G1	NA	(everolimus + lanreotide), temodar, PRRT	NA
13	NA	NA	NA	NA
14	NET G1	(−)	(−)	(−)/Survival (89)
15	MiNEN	NA	(−)	(−)/Death (postoperative complication)
16	MiNEN	NA	(oxaliplatin + 5-fluorouracil + leucovorin), (etoposide + nedaplatin), (irinotecan + nedaplatin)	(+) liver metastasis/Death (29)
17	MiNEN	NA	capecitabine + oxaliplatin	(+) liver metastasis/Death (22)
18	MiNEN	NA	cisplatin + etoposide (hepatic arterial chemoembolization)	(+) liver metastasis/Survival (1)
19	CoGNET	4/18	(−)	(−)/Survival (36 months)

NA: not answered; M: male; F: female; CA19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; EUS: endoscopic ultrasound; EGD: esophagogastroduodenoscopy; ERCP: endoscopic retrograde cholangiopancreatography; NSE: neuron-specific enolase; NET: neuroendocrine tumor; G1: grade 1; G2: grade 2; G3: grade 3; MiNEN: mixed neuroendocrine–non-neuroendocrine carcinomas; CoGNET: composite gangliocytoma/neuroma and neuroendocrine tumor; LCNEC: large-cell neuroendocrine carcinoma; SCNEC: small-cell neuroendocrine carcinoma; PRRT: peptide receptor radionuclide therapy.

Surface changes of NENs during endoscopy, such as depression, erosion, or ulceration, usually indicate aggressive disease [41]. Conventional radiology can detect a highly vascularized mass and dilated main pancreatic duct (MPD) and common bile duct (CBD) [42]. Since abdominal computed tomography (CT) scan cannot usually identify small ampullary tumors, additional methods, such as endoscopic resonance cholangiopancreatography (ERCP) and magnetic resonance cholangiopancreatography (MRCP), might also aid the diagnosis [43]. In addition, the use of endoscopic ultrasound (EUS) might define the locoregional staging of ampullary NENs [44,45]. However, despite the advancements in imaging technology, preoperative diagnosis of NECs is still challenging [24].

Further imaging is necessary to rule out distant metastases [46]. Although GEP-NETs are slow-growing and have low glycolytic activity, FDG-PET scan might aid in revealing distant metastases and recurrent lesions of highly proliferative tumors, such as NECs [4,47]. A prospective study showed that FDG-PET scan had only 58% sensitivity in diagnosing neuroendocrine tumors. However, it has a high prognostic value, thus predicting the more aggressive carcinomas [48]. Furthermore, in contrast to cases of pulmonary NECs, imaging of the brain is only recommended in symptomatic patients with NECs of the gastrointestinal tract since available data have indicated that central nervous system (CNS) metastases are less common [49,50]. The use of somatostatin receptors is not proven; however, positive imaging could indicate a well-differentiated tumor [49,50]. Since NETs of the Vater's ampulla and their metastases often express somatostatin receptors, somatostatin receptor scan (SRS) can detect them with an 86% sensitivity [8,43]. However, although somatostatin receptors are often expressed in NET G3, SRS cannot detect the usually somatostatin-receptor-negative NECs [46]. In addition, mutations in the P53 tumor-suppressor gene and deletion of the Rb gene are often present in NECs, indicating an extremely malignant tumor, thus making those markers useful for the differential diagnosis between NET G3 and NECs [16].

Diagnosis of NECs is often complicated and is based on biopsy specimens [49]. Immunohistochemical markers for neuroendocrine differentiation, such as synaptophysin and chromogranin A, are essential to set the diagnosis. However, in poorly differentiated NECs, chromogranin A may be absent, while synaptophysin may be focal or even absent in the small-cell NEC subtype [51]. The absence of both synaptophysin and chromogranin A is exceptional, and in this case, the differential diagnosis of other tumors must be considered [15].

Neuron-specific enolase (NSE) and CD56 marker are in many cases positive in GEP-NENs but have low specificity [51]. While periampullary adenocarcinomas commonly express MUC1 and cytokeratin 7, 2 markers, they are unusual among GEP-NENs [52].

Histologically, LCNECs, like well-differentiated NETs, have a trabecular or organoid growth pattern, rosette formations, salt- and pepper-like chromatin, or peripheral palisading, also keeping features of poorly-differentiated NECs with high mitotic activity and large necrotic areas. However, unlike SCNEC, they have enlarged nucleoli and a lower nuclear-to-cytoplasmic ratio [53–55].

It has been proposed that NECs either originate from multipotent stem cells, such as non-neuroendocrine adenocarcinomas, or arise from well-differentiated NENs. However, the first possibility is more likely, as well and poorly differentiated NENs have separate components [49].

Ampullary LCNECs in the literature are limited to 24 case reports before ours, as identified by our review to date (Table 2) [11,18,24,26,56–68]. Only 14 cases were pure LCNECs [24,26,56,57,59–63,66], while the other 11 had other components [11,18,26,59,60,65,66,68]. Many of these patients had early recurrence with metastases, especially in the liver [24,56,58,60–66,68].

**Table 2.** Summary of the large-cell neuroendocrine carcinomas reported in the English literature.

	Date of Publication	Author	Sex	Age	Clinical Presentation	Tumor Markers in Serum
1.	2003	Cavazza et al. [56]	F	74	jaundice, anorexia, pruritus	tissue polypeptide antigen, CEA
2.	2004	Hartel et al. [57]	F	44	jaundice, pruritus	(–)
3.	2004	Cheng et al. [58]	F	55	epigastric pain	NA
4.	2005	Nassar et al. [59]	M	61	NA	NA
5.	2005	Nassar et al. [59]	M	75	NA	NA
6.	2005	Nassar et al. [59]	M	84	NA	NA
7.	2005	Nassar et al. [59]	F	50	NA	NA
8.	2005	Nassar et al. [59]	M	77	NA	NA
9.	2005	Nassar et al. [59]	M	80	NA	NA
10.	2005	Nassar et al. [59]	M	55	NA	NA
11.	2005	Nassar et al. [59]	F	68	NA	NA
12.	2006	Huang et al. [60]	M	59	jaundice, anorexia	NA
13.	2006	Selvakumar et al. [61]	M	48	jaundice, anorexia, weight loss	NA
14.	2006	Jun et al. [62]	M	56	anorexia, pruritus	NA
15.	2008	Liu et al. [18]	F	70	jaundice	(–)
16.	2010	Stojic et al. [63]	M	60	epigastric pain, nausea, vomiting, anorexia, jaundice, fever, and weight loss	NA
17.	2010	Sunose et al. [64]	F	73	jaundice, fatigue	NA
18.	2012	Huang et al. [65]	M	52	jaundice, anorexia, epigastric pain	CEA
19.	2012	Beggs et al. [66]	M	52	obstructive jaundice	NA
20.	2014	Zhang et al. [67]	M	69	jaundice, pruritus	CA19-9
21.	2017	Mahansaria et al. [11]	NA	NA	NA	(–)
22.	2017	Imamura et al. [68]	M	81	(–)	CEA, CA 19-9
23.	2020	Jung et al. [26]	male	64	NA	NA
24.	2021	Sonmez et al. [24]	male	78	jaundice, epigastric pain	NA
	Distant Metastases on Imaging	Endoscopic Findings	Biopsy	Ki-67 Index	Mitotic Rate	Maximum Tumor Diameter (mm)
1.	(–)	Ulceration of the Vater papilla and 3 cm stenosis of the common bile duct	poorly differentiated carcinoma	NA	90/10HPF	NA
2.	(–)	Ulcerated tumor of the main duodenal papilla	NA	NA	4/HPF	16
3.	(–)	Ulcerated polypoidal lesion in the ampullary region	poorly differentiated carcinoma with neuroendocrine features	60%	50/10HPF	18
4.	NA	NA	NA	NA	NA	NA
5.	NA	NA	NA	NA	NA	NA

Table 2. Cont.

	Distant Metastases on Imaging	Endoscopic Findings	Biopsy	Ki-67 Index	Mitotic Rate	Maximum Tumor Diameter (mm)
6.	NA	NA	NA	NA	NA	NA
7.	NA	NA	NA	NA	NA	NA
8.	NA	NA	NA	NA	NA	NA
9.	NA	NA	NA	NA	NA	NA
10.	NA	NA	NA	NA	NA	NA
11.	NA	NA	NA	NA	NA	NA
12.	(−)	Enlarged ampulla of Vater with an intact mucosal surface	carcinoid tumor	NA	NA	28
13.	(−)	Prominent ampulla	NA	NA	9-11/HPF	20
14.	NA	NA	NA	NA	NA	NA
15.	(−)	Swollen duodenal papilla	poorly differentiated endocrine carcinoma	90%	NA	10
16.	(−)	15 mm ulcerated tumor in the region of the papilla of Vater	NA	41%	36/10HPF	30
17.	(−)	Enlarged ampulla covered with normal mucosa	(−)	NA	NA	25
18.	NA	Stricture at the ampulla of Vater	NA	NA	20/10HPF	16
19.	NA	Ulcerated irregular ampulla of Vater	poorly differentiated adenocarcinoma	NA	NA	NA
20.	(−)	NA	LCNEC + ADC	NA	60/10HPF	15
21.	NA	NA	NA	50%	NA	40
22.	NA	14 mm irregular protruding tumor lesion at the ampulla (duodenal endoscopy)	poorly differentiated adenocarcinoma	89%	32/10HPF	NA
23.	Liver	NA	NA	NA	NA	NA
24.	NA	'bulging' tumor appearance invading the orifice of the papilla	NET	80%	NA	15
	Other Components	Immunohistochemistry	Number of Metastatic Lymph Nodes	Adjuvant Chemotherapy	Recurrence/Outcome (Months)	
1.	(−)	Synaptophysin, Chromogranin A, Cytokeratin, NSE	NA	(−)	(+) liver, L2-L3 vertebral, fluid of peritoneal cavity metastases/died (8)	
2.	(−)	Synaptophysin, Chromogranin A, CEA, Cytokeratins (AE 1 1 3 and cytokeratin 7)	2	NA	NA	
3.	5% vague ADC	Synaptophysin, Chromogranin A, CD117	2/23	(−)	(+) liver, mesentery, peritoneum metastases/died (6)	
4.	Adenoma	NA	1	NA	(+)/died (15)	
5.	(−)	NA	1	NA	(+)/died (30)	
6.	Adenoma	NA	3	NA	(+)/died (13)	

Table 2. Cont.

	Other Components	Immunohistochemistry	Number of Metastatic Lymph Nodes	Adjuvant Chemotherapy	Recurrence/Outcome (Months)
7.	(−)	NA	5	NA	(+)/died (16)
8.	Adenoma	NA	1	NA	(−)/alive (17)
9.	(−)	NA	1	NA	(+)/died (16)
10.	(−)	NA	4	NA	(−)/alive (10)
11.	(−)	NA	4	NA	(+)/died (4)
12.	(−)	Synaptophysin, Chromogranin A, NSE	5/18	cisplatin + cyclophosphamide	(+) liver peritoneum metastases/died (10)
13.	(−)	Synaptophysin, Chromogranin A, Pancytokeratin	2/13	NA	(+) liver metastases/alive (6)
14.	NA	NA	NA	(−)	(+) liver metastases, pancreatojejunostomy site/alive (2)
15.	ADC	Synaptophysin, Chromogranin A, Cytokeratin, CD56	(−)	NA	(−)/alive (1)
16.	(−)	Synaptophysin, PGP 9.5, NSE, Cytokeratin, CK8, Somatostatin, p27, HDAC1, HDAC2, HDAC3	3/19	etoposide + cisplatin	(+) liver metastases/alive (11)
17.	ADC, signet-ring cell carcinoma, SCC	Synaptophysin, Chromogranin A, CD56	NA	(−)	(+) liver, bone metastases/died (13)
18.	pancreatic hepatoid microcarcinoma	Synaptophysin, Chromogranin A, Cytokeratin 7, CAM 5.2	(−)	NA	(+) liver metastases/alive (15)
19.	(−)	Synaptophysin	1	cisplatin + etoposide + mannitol	(+) liver/alive (20)
20.	intestinal type adenoma	Synaptophysin	(−)	(−)	(−)/alive (33)
21.	ADC pancreatobiliary type	Synaptophysin, Chromogranin A, NSE, S-100, MUC 1+, MOC31+	4/39	(−)	(+)/NA
22.	papillary adenoma	Synaptophysin, Chromogranin A	(−)	(−)	(+) liver metastases/died (11)
23.	(−)	Synaptophysin	NA	NA	(+) eyelid metastases/NA
24.	(−)	NA	(−)	(−)	(+) liver metastases/died (8)

Abbreviations: NA: not answered; M: male; F: female; CA19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; EGD: esophagogastroduodenoscopy; SCC: squamous cell carcinoma; NSE: neuron-specific enolase; NET: neuroendocrine tumor; ADC: adenocarcinoma; LCNEC: large-cell neuroendocrine carcinoma; HPF: high-power field.

The literature's rate of lymph node involvement varies from 46% to 88% for NETs of the Vater's ampulla [7]. In a retrospective cohort study, more patients with ampullary NETs had increased tumor grade and positive lymph nodes than patients with duodenal or pancreatic NETs. Tumor size was more prominent in patients with ampullary NETs than in duodenal NETs and smaller than in pancreatic NETs. In addition, the median overall survival (OS) was worse in patients with ampullary NETs undergoing surgical resection (5-year OS about 62%) compared to duodenal NETs or pancreatic head NETs (5-year OS about 75%). However, SCNECs and MiNENs were excluded from this study [7].

Therefore, the treatment of choice for poorly differentiated NECs is pancreaticoduodenectomy (PD) with R0 resection, accompanied by lymphadenectomy. In contrast, other procedures, such as endoscopic local resection and surgical ampullectomy, are discussed in

the presence of severe comorbidities [69]. Two operation techniques are performed: the classic Whipple operation or the Traverso and Longmire pylorus-preserving pancreatoduodenectomy (PPPD), which seems to be as effective as the classic Whipple [70]. It has been suggested that PD should be performed by experienced surgeons to manage postoperative complications better [42].

Poorly differentiated GEP-NECs have an aggressive progression and tend to develop widespread metastases. Especially, the ampulla of Vater is highly vascularized, which also explains the high rate of distant metastases of ampullary tumors [9]. Therefore, adjuvant chemotherapy should follow surgical excision.

Due to histology and biological behavior similarities, GEP-NENs are treated according to treatment approaches for small-cell lung cancer (SCLC) recommendations. Adjuvant chemotherapy is recommended, while neoadjuvant chemotherapy is still not well-described [71]. Platinum-based chemotherapy, like cisplatin/etoposide or cisplatin/carboplatin combination, is recommended as a first-line treatment for patients with poorly differentiated NECs, if the patient has adequate organ function and clinical status [17,72–74]. However, platinum-based chemotherapy had a substantially lower response rate in NECs with a Ki-67 index < 55% [49]. The use of temozolomide- (TMZ), irinotecan-, or oxaliplatin-based schedules as second-line treatment is still uncertain [72]. On the other hand, it has been proposed in the literature that adjuvant chemotherapy provides a survival benefit in patients with resected ampullary adenocarcinoma. However, it is still not common practice for these patients [75].

It has also been suggested that neoadjuvant chemotherapy could benefit patients with esophageal NENs. However, available data about other non-pancreatic gastrointestinal NENs are still limited [76].

We reported a patient with a rare ampullary large-cell neuroendocrine carcinoma (LCNEC) that had obstructive jaundice and elevated CA19-9 levels. The tumor was pictured in the PET scan as a hyperactive lesion in the ampulla of Vater, was treated with PPPD in our surgical department, and is now receiving the fourth cycle of adjuvant chemotherapy.

#### 4. Conclusions

Overall, pure ampullary neuroendocrine large-cell carcinomas are extremely rare entities. On the other hand, they can also sporadically coexist with non-neuroendocrine neoplasms, more frequently adenocarcinomas. Currently available data suggest Whipple's procedure and adjuvant chemotherapy based on the treatment of gastroenteropancreatic and non-gastroenteropancreatic LCNECs. Further issues that will need to be addressed in the future are the targeted neoadjuvant chemotherapy and the use of endoscopic surgical resection of eligible neuroendocrine neoplasms.

**Author Contributions:** Management of the patient, E.K., I.A.D., G.R., F.K., S.P., A.I., A.A.P., S.N. and D.P.; investigation, E.K., M.C., G.F. and F.K.; resources, E.K., M.C., G.F., I.A.D. and A.A.P.; data curation, M.C., G.F., I.A.D., G.R., S.P., A.I., A.A.P. and D.P.; writing—original draft preparation, M.C., G.F. and I.A.D.; writing—review and editing, E.K., M.C., G.F., G.R., F.K., S.N. and D.P.; supervision, D.P.; project administration, E.K. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Informed consent has been obtained from the patient to publish this paper and is available on demand.

**Conflicts of Interest:** The authors declare no conflict of interest.

## References

1. Braasch, J.W.; Camer, S.J. Periampullary Carcinoma. *Med. Clin. N. Am.* **1975**, *59*, 309–314. [\[CrossRef\]](#)
2. Yang, M.; Zeng, L.; Ke, N.-W.; Tan, C.-L.; Tian, B.-L.; Liu, X.-B.; Xiang, B.; Zhang, Y. World Health Organization grading classification for pancreatic neuroendocrine neoplasms: A comprehensive analysis from a large Chinese institution. *BMC Cancer* **2020**, *20*, 906. [\[CrossRef\]](#) [\[PubMed\]](#)
3. Dasari, A.; Shen, C.; Halperin, D.M.; Zhao, B.; Zhou, S.; Xu, Y.; Shih, T.; Yao, J.C. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients with Neuroendocrine Tumors in the United States. *JAMA Oncol.* **2017**, *3*, 1335–1342. [\[CrossRef\]](#) [\[PubMed\]](#)
4. Andreasi, V.; Partelli, S.; Muffatti, F.; Manzoni, M.F.; Capurso, G.; Falconi, M. Update on gastroenteropancreatic neuroendocrine tumors. *Dig. Liver Dis.* **2020**, *53*, 171–182. [\[CrossRef\]](#)
5. Hatzitheoklitos, E.; Büchler, M.W.; Friess, H.; Poch, B.; Ebert, M.; Mohr, W.; Imaizumi, T.; Beger, H.G. Carcinoid of the ampulla of Vater. Clinical characteristics and morphologic features. *Cancer* **1994**, *73*, 1580–1588. [\[CrossRef\]](#)
6. Schmocker, R.K.; Wright, M.J.; Ding, D.; Javed, A.A.; Cameron, J.L.; Lafaro, K.; Burns, W.R.; He, J.; Wolfgang, C.L.; Burkhart, R.A. Duodenal, ampullary, and pancreatic neuroendocrine tumors: Oncologic outcomes are driven by tumor biology and tissue of origin. *J. Surg. Oncol.* **2020**, *123*, 416–424. [\[CrossRef\]](#)
7. Ruff, S.M.; Standring, O.; Wu, G.; Levy, A.; Anantha, S.; Newman, E.; Karpeh, M.S.; Nealon, W.; Deutsch, G.B.; Weiss, M.J.; et al. Ampullary Neuroendocrine Tumors: Insight into a Rare Histology. *Ann. Surg. Oncol.* **2021**, *28*, 8318–8328. [\[CrossRef\]](#)
8. Carter, J.T.; Grenert, J.P.; Rubenstein, L.; Stewart, L.; Way, L.W. Neuroendocrine Tumors of the Ampulla of Vater: Biological behavior and surgical management. *Arch. Surg.* **2009**, *144*, 527–531. [\[CrossRef\]](#)
9. Kleinschmidt, T.K.; Christein, J. Neuroendocrine carcinoma of the ampulla of Vater: A case report, review and recommendations. *J. Surg. Case Rep.* **2020**, *2020*, rjaa119. [\[CrossRef\]](#)
10. Acharya, A.; Markar, S.R.; Sodergren, M.H.; Malietzis, G.; Darzi, A.; Athanasiou, T.; Khan, A.Z. Meta-analysis of adjuvant therapy following curative surgery for periampullary adenocarcinoma. *Br. J. Surg.* **2017**, *104*, 814–822. [\[CrossRef\]](#)
11. Mahansaria, S.S.; Agrawal, N.; Arora, A.; Bihari, C.; Appukuttan, M.; Chattopadhyay, T.K. Ampullary Mixed Adenoneuroendocrine Carcinoma: Surprise Histology, Familiar Management. *Int. J. Surg. Pathol.* **2017**, *25*, 585–591. [\[CrossRef\]](#)
12. Ginori, A.; Bello, G.L.; Vassallo, L.; Tripodi, S.A. Amphicrine Carcinoma of the Ampullary Region. *Tumori J.* **2015**, *101*, e70–e72. [\[CrossRef\]](#)
13. Huang, Z.; Xiao, W.-D.; Li, Y.; Huang, S.; Cai, J.; Ao, J. Mixed adenoneuroendocrine carcinoma of the ampulla: Two case reports. *World J. Gastroenterol.* **2015**, *21*, 2254–2259. [\[CrossRef\]](#)
14. Wang, Y.; Zhang, Z.; Wang, C.; Xi, S.-H.; Wang, X.-M. Mixed neuroendocrine-non-neuroendocrine neoplasm of the ampulla: Four case reports. *World J. Clin. Cases* **2022**, *10*, 2268–2274. [\[CrossRef\]](#)
15. Pavel, M.; Öberg, K.; Falconi, M.; Krenning, E.P.; Sundin, A.; Perren, A.; Berruti, A. Gastroenteropancreatic neuroendocrine neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* **2020**, *31*, 844–860. [\[CrossRef\]](#)
16. Nagtegaal, I.D.; Odze, R.D.; Klimstra, D.; Paradis, V.; Rugge, M.; Schirmacher, P.; Washington, K.M.; Carneiro, F.; Cree, I.A.; the WHO Classification of Tumours Editorial Board. The 2019 WHO classification of tumours of the digestive system. *Histopathology* **2020**, *76*, 182–188. [\[CrossRef\]](#)
17. Shah, M.H.; Goldner, W.S.; Benson, A.B.; Bergsland, E.; Blaszkowsky, L.S.; Brock, P.; Chan, J.; Das, S.; Dickson, P.V.; Fanta, P.; et al. Neuroendocrine and Adrenal Tumors, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *J. Natl. Compr. Cancer Netw.* **2021**, *19*, 839–868. [\[CrossRef\]](#)
18. Liu, S.-H.; Tsay, S.-H. Coexistence of Large Cell Neuroendocrine Carcinoma and Adenocarcinoma of the Ampulla of Vater. *J. Chin. Med. Assoc.* **2008**, *71*, 536–540. [\[CrossRef\]](#)
19. Das, S.; Dasari, A. Epidemiology, Incidence, and Prevalence of Neuroendocrine Neoplasms: Are There Global Differences? *Curr. Oncol. Rep.* **2021**, *23*, 43. [\[CrossRef\]](#)
20. Dasari, A.; Mehta, K.; Byers, L.A.; Sorbye, H.; Yao, J.C. Comparative study of lung and extrapulmonary poorly differentiated neuroendocrine carcinomas: A SEER database analysis of 162,983 cases. *Cancer* **2017**, *124*, 807–815. [\[CrossRef\]](#)
21. Hallet, J.; Law, C.H.L.; Cukier, M.; Saskin, R.; Liu, N.; Singh, S. Exploring the rising incidence of neuroendocrine tumors: A population-based analysis of epidemiology, metastatic presentation, and outcomes. *Cancer* **2014**, *121*, 589–597. [\[CrossRef\]](#)
22. Korse, C.M.; Taal, B.G.; van Velthuysen, M.-L.F.; Visser, O. Incidence and survival of neuroendocrine tumours in the Netherlands according to histological grade: Experience of two decades of cancer registry. *Eur. J. Cancer* **2013**, *49*, 1975–1983. [\[CrossRef\]](#)
23. Milione, M.; Parente, P.; Grillo, F.; Zamboni, G.; Mastracci, L.; Capella, C.; Fassan, M.; Vanoli, A. Neuroendocrine neoplasms of the duodenum, ampullary region, jejunum and ileum. *Pathologica* **2021**, *113*, 12–18. [\[CrossRef\]](#)
24. Sönmez, R.E. Aggressive clinical course of large cell neuroendocrine carcinoma of ampulla of Vater. *Nothorn Clin. Istanbul.* **2019**, *8*, 97–100. [\[CrossRef\]](#)
25. Ito, H.; Wada, Y.; Takami, Y.; Ryu, T.; Ureshino, H.; Imamura, H.; Sasaki, S.; Ohno, A.; Hijioka, M.; Kaku, T.; et al. A case of small cell neuroendocrine carcinoma of the ampulla of Vater. *Surg. Case Rep.* **2020**, *6*, 150. [\[CrossRef\]](#)
26. Jung, S.K.; Yang, S.-W.; Hong, E.K.; Park, W.S. A Metastatic Neuroendocrine Eyelid Carcinoma Originating from the Ampulla of Vater. *Ophthalmic Plast. Reconstr. Surg.* **2020**, *36*, e95–e96. [\[CrossRef\]](#)
27. Li, X.; Li, D.; Sun, X.; Lv, G. Mixed adenoneuroendocrine carcinoma (MANEC) of the ampulla of Vater in a Chinese patient: A case report. *J. Int. Med. Res.* **2020**, *48*, 300060520947918. [\[CrossRef\]](#)

28. Shiratori, Y.; Nakamura, K.; Suzuki, K.; Fukuda, K. Endoscopic papillectomy for an ampullary neuroendocrine tumor. *Clin. J. Gastroenterol.* **2020**, *13*, 1144–1149. [[CrossRef](#)] [[PubMed](#)]
29. Noorali, S.; Haghighi, S. Treatment of ampullary neuroendocrine tumor by Capecitabine (Xeloda®) and Temozolomide (Temodal®). *Gastroenterol. Hepatol. Bed Bench.* **2021**, *14*, 85–88. [[PubMed](#)]
30. Xiao, K.; Swierczynski, S.; Xiao, G. Small, low-grade ampullary neuroendocrine tumor presenting with metastasis and multiple synchronous tumors in a patient with neurofibromatosis type 1: A case report with literature review. *J. Surg. Case Rep.* **2021**, *2021*, rjab076. [[CrossRef](#)] [[PubMed](#)]
31. Zahid, A.; Ali, D.; Zubair, M.; Ahmed, I.; Fatima, T.; Afzal, M.F. Neuroendocrine tumour of the ampulla of Vater: A rare neoplasm at an atypical site. *J. Pak. Med. Assoc.* **2020**, *71*, 1486–1488. [[CrossRef](#)]
32. Guerrero, V.L.; Costa, A.G.; Monzonis, A.R.; González, N.B.; Borobia, F.G. Surgical management strategy in ampullary tumors with low malignant potential: Presentation of a patient with a gangliocytic paraganglioma. *Cir. Esp. (Engl. Ed.)* **2021**, *99*, 621–623. [[CrossRef](#)]
33. Matli, V.V.K.; Wellman, G.; Jaganmohan, S.; Koticha, K. Ampullary and Pancreatic Neuroendocrine Tumors: A Series of Cases and Review of the Literature. *Cureus* **2022**, *14*, 21657. [[CrossRef](#)]
34. Malhotra, A.; Venugopal, S.; Ravindra, S. Unique spheroid deposits of amyloid in an ampullary neuroendocrine tumour. *Indian J. Pathol. Microbiol.* **2022**, *65*, 226–228. [[CrossRef](#)]
35. Fujii, M.; Okamoto, Y.; Fujioka, S.; Yoshioka, M.; Shiode, J. Neuroendocrine tumor of the ampulla of Vater showing chronological endoscopic changes. *Clin. J. Gastroenterol.* **2022**, *15*, 205–209. [[CrossRef](#)]
36. Choi, H.; Choi, J.W.; Ryu, D.H.; Park, S.; Kim, M.J.; Yoo, K.C.; Woo, C.G. Ampullary gangliocytic paraganglioma with lymph node metastasis: A case report with literature review. *Medicine (Baltimore)* **2022**, *101*, e29138. [[CrossRef](#)]
37. Luo, G.; Jin, K.; Cheng, H.; Liu, C.; Guopei, L.; Lu, Y.; Yang, C.; Xu, J.; Wang, W.; Gao, H.; et al. Carbohydrate antigen 19-9 as a prognostic biomarker in pancreatic neuroendocrine tumors. *Oncol. Lett.* **2017**, *14*, 6795–6800. [[CrossRef](#)]
38. Yoen, H.; Kim, J.H.; Hur, B.Y.; Ahn, S.J.; Jeon, S.K.; Choi, S.-Y.; Lee, K.B.; Han, J.K. Prediction of tumor recurrence and poor survival of ampullary adenocarcinoma using preoperative clinical and CT findings. *Eur. Radiol.* **2020**, *31*, 2433–2443. [[CrossRef](#)]
39. Schiergens, T.S.; Renz, B.W.; Reu, S.; Neumann, J.; Al-Sayegh, R.; Nieß, H.; Ilmer, M.; Kruger, S.; Boeck, S.; Heinemann, V.; et al. Prognostic Value of Preoperative Serum Carcinoembryonic Antigen and Carbohydrate Antigen 19-9 After Resection of Ampullary Cancer. *J. Gastrointest. Surg.* **2017**, *21*, 1775–1783. [[CrossRef](#)]
40. Abdel-Rahman, O.; Fazio, N. Sex-Based Differences in Prognosis of Patients with Gastroenteropancreatic-Neuroendocrine Neoplasms. *Pancreas* **2021**, *50*, 727–731. [[CrossRef](#)]
41. Kim, B.N.; Sohn, D.K.; Hong, C.W.; Han, K.S.; Chang, H.J.; Jung, K.H.; Lim, S.-B.; Choi, H.S.; Jeong, S.-Y.; Park, J.-G. Atypical endoscopic features can be associated with metastasis in rectal carcinoid tumors. *Surg. Endosc.* **2008**, *22*, 1992–1996. [[CrossRef](#)]
42. Milanetto, A.C.; Pasquali, C.; Da Broi, M.; Brambilla, T.; Capretti, G.; Zerbi, A. Ampullary neuroendocrine neoplasms: Surgical experience of a rare and challenging entity. *Langenbecks Arch. Surg.* **2018**, *403*, 581–589. [[CrossRef](#)]
43. Taghizadeh-Hesary, F.; Moradi, A.; Malekzadeh, M. Long-term complete remission of a patient with high grade neuroendocrine carcinoma of ampulla of Vater. *BMJ Case Rep.* **2018**, *2018*, bcr2018224845. [[CrossRef](#)]
44. O'Toole, D.; Palazzo, L. Endoscopy and Endoscopic Ultrasound in Assessing and Managing Neuroendocrine Neoplasms. *Front. Horm. Res.* **2015**, *44*, 88–103. [[CrossRef](#)]
45. de Mestier, L.; Lorenzo, D.; Fine, C.; Cros, J.; Hentic, O.; Walter, T.; Panis, Y.; Couvelard, A.; Cadiot, G.; Ruszniewski, P. Endoscopic, transanal, laparoscopic, and transabdominal management of rectal neuroendocrine tumors. *Best Pract. Res. Clin. Endocrinol. Metab.* **2019**, *33*, 101293. [[CrossRef](#)]
46. Ito, T.; Masui, T.; Komoto, I.; Doi, R.; Osamura, R.Y.; Sakurai, A.; Ikeda, M.; Takano, K.; Igarashi, H.; Shimatsu, A.; et al. JNETS clinical practice guidelines for gastroenteropancreatic neuroendocrine neoplasms: Diagnosis, treatment, and follow-up: A synopsis. *J. Gastroenterol.* **2021**, *56*, 1033–1044. [[CrossRef](#)]
47. Zhang, P.; Yu, J.; Li, J.; Shen, L.; Li, N.; Zhu, H.; Zhai, S.; Zhang, Y.; Yang, Z.; Lu, M. Clinical and Prognostic Value of PET/CT Imaging with Combination of <sup>68</sup>Ga-DOTATATE and <sup>18</sup>F-FDG in Gastroenteropancreatic Neuroendocrine Neoplasms. *Contrast Media Mol. Imaging* **2018**, *2018*, 2340389. [[CrossRef](#)]
48. Binderup, T.; Knigge, U.; Loft, A.; Federspiel, B.; Kjaer, A. 18F-Fluorodeoxyglucose Positron Emission Tomography Predicts Survival of Patients with Neuroendocrine Tumors. *Clin. Cancer Res.* **2010**, *16*, 978–985. [[CrossRef](#)]
49. Sorbye, H.; Strosberg, J.; Baudin, E.; Klimstra, D.S.; Yao, J.C. Gastroenteropancreatic high-grade neuroendocrine carcinoma. *Cancer* **2014**, *120*, 2814–2823. [[CrossRef](#)]
50. Krug, S.; Teupe, F.; Michl, P.; Gress, T.M.; Rinke, A. Brain metastases in patients with neuroendocrine neoplasms: Risk factors and outcome. *BMC Cancer* **2019**, *19*, 362. [[CrossRef](#)] [[PubMed](#)]
51. Perren, A.; Couvelard, A.; Scoazec, J.-Y.; Costa, F.; Borbath, I.; Fave, G.D.; Gorbounova, V.; Gross, D.; Grossman, A.; Jensen, R.T.; et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Pathology-Diagnosis and Prognostic Stratification. *Neuroendocrinology* **2017**, *105*, 196–200. [[CrossRef](#)] [[PubMed](#)]
52. Vanoli, A.; Albarello, L.; Uncini, S.; Fassan, M.; Grillo, F.; Di Sabatino, A.; Martino, M.; Pasquali, C.; Milanetto, A.C.; Falconi, M.; et al. Neuroendocrine Tumors (NETs) of the Minor Papilla/Ampulla. *Am. J. Surg. Pathol.* **2019**, *43*, 725–736. [[CrossRef](#)] [[PubMed](#)]
53. Hiroshima, K.; Mino-Kenudson, M. Update on large cell neuroendocrine carcinoma. *Transl. Lung Cancer Res.* **2017**, *6*, 530–539. [[CrossRef](#)] [[PubMed](#)]

54. Hirabayashi, K.; Zamboni, G.; Nishi, T.; Tanaka, A.; Kajiwara, H.; Nakamura, N. Histopathology of gastrointestinal neuroendocrine neoplasms. *Front. Oncol.* **2013**, *3*, 2. [[CrossRef](#)]
55. Raiker, R.; Chauhan, A.; Hasanein, H.; Burkeen, G.; Horn, M.; Veedu, J.; Vela, C.; Arnold, S.; Kolesar, J.; Anthony, L.; et al. Biliary tract large cell neuroendocrine carcinoma: Current evidence. *Orphanet J. Rare Dis.* **2019**, *14*, 266. [[CrossRef](#)]
56. Cavazza, A.; Gallo, M.; Valcavi, R.; De Marco, L.; Gardini, G. Large Cell Neuroendocrine Carcinoma of the Ampulla of Vater. *Arch. Pathol. Lab. Med.* **2003**, *127*, 221–223. [[CrossRef](#)]
57. Hartel, M.; Wente, M.N.; Bergmann, F.; Schmidt, J.; Büchler, M.W.; Friess, H. Large-cell neuroendocrine carcinoma of the major duodenal papilla: Case report. *Gastrointest. Endosc.* **2004**, *60*, 838–841. [[CrossRef](#)]
58. Cheng, S.-P.; Yang, T.-L.; Chang, K.-M.; Liu, C.-L. Large cell neuroendocrine carcinoma of the ampulla of Vater with glandular differentiation. *J. Clin. Pathol.* **2004**, *57*, 1098–1100. [[CrossRef](#)]
59. Nassar, H.; Albores-Saavedra, J.; Klimstra, D.S. High-Grade Neuroendocrine Carcinoma of the Ampulla of Vater. *Am. J. Surg. Pathol.* **2005**, *29*, 588–594. [[CrossRef](#)]
60. Huang, S.-S.; Jan, Y.-J.; Cheng, S.-B.; Yeh, D.-C.; Wu, C.-C.; Liu, T.-J.; P'Eng, F.-K. Large Cell Neuroendocrine Carcinoma of the Ampulla of Vater: Report of a Case. *Surg. Today* **2006**, *36*, 1032–1035. [[CrossRef](#)]
61. Selvakumar, E.; Vimalraj, V.; Rajendran, S.; Balachandar, T.G.; Kannan, D.G.; Jeswanth, S.; Ravichandran, P.; Sundaram, A.; Surendran, R. Large cell neuroendocrine carcinoma of the ampulla of Vater. *Hepatobiliary Pancreat Dis. Int.* **2006**, *5*, 465–467.
62. Jun, S.R.; Lee, J.M.; Han, J.K.; Choi, B.I. High-grade Neuroendocrine Carcinomas of the Gallbladder and Bile Duct. *J. Comput. Assist. Tomogr.* **2006**, *30*, 604–609. [[CrossRef](#)]
63. Stojic, Z.; Brasanac, D.; Bilanovic, D.; Mitrovic, O.; Stevanovic, R.; Boricic, I. Large-cell neuroendocrine carcinoma of the ampulla of Vater. *Med. Oncol.* **2009**, *27*, 1144–1148. [[CrossRef](#)]
64. Sunose, Y.; Ogawa, T.; Itoh, H.; Andoh, T.; Tomizawa, N.; Tanaka, T.; Sakamoto, I.; Arakawa, K.; Ikeya, T.; Takeyoshi, I. Large Cell Neuroendocrine Carcinoma of the Ampulla of Vater with Adenocarcinoma and Squamous Cell Carcinoma Components. *Jpn. J. Clin. Oncol.* **2010**, *41*, 434–439. [[CrossRef](#)]
65. Chen, T.-C.; Huang, S.-C.; Chang, H.-C.; Yeh, T.-S.; Ng, K.-F. Hepatoid microcarcinoma of the pancreas: A case report and review of the literature. *Chang. Gung Med. J.* **2012**, *35*, 285. [[CrossRef](#)]
66. Beggs, R.E.; Kelly, M.E.; Eltayeb, O.; Crotty, P.; McDermott, R.; Ridgway, P. Large Cell Neuroendocrine Carcinoma of the Ampulla of Vater. *JOP J. Pancreas* **2012**, *13*, 470–475. [[CrossRef](#)]
67. Zhang, L.; DeMay, R.M. Cytological features of mixed adenoneuroendocrine carcinoma of the ampulla: Two case reports with review of literature. *Diagn. Cytopathol.* **2014**, *42*, 1075–1084. [[CrossRef](#)]
68. Imamura, N.; Nanashima, A.; Hiyoshi, M.; Fujii, Y. Report of two cases of large cell neuroendocrine carcinoma of duodenal ampulla with contrasting outcomes following pancreaticoduodenectomy according to the use of adjuvant chemotherapy. *Int. J. Surg. Case Rep.* **2017**, *31*, 132–138. [[CrossRef](#)]
69. Dumitrascu, T.; Dima, S.; Herlea, V.; Tomulescu, V.; Ionescu, M.; Popescu, I. Neuroendocrine tumours of the ampulla of Vater: Clinico-pathological features, surgical approach and assessment of prognosis. *Langenbecks Arch. Surg.* **2012**, *397*, 933–943. [[CrossRef](#)]
70. Diener, M.K.; Knaebel, H.-P.; Heukauf, C.; Antes, G.; Büchler, M.W.; Seiler, C.M. A Systematic Review and Meta-analysis of Pylorus-preserving Versus Classical Pancreaticoduodenectomy for Surgical Treatment of Periapillary and Pancreatic Carcinoma. *Ann. Surg.* **2007**, *245*, 187–200. [[CrossRef](#)]
71. Russo, G.L.; Pusceddu, S.; Proto, C.; Macerelli, M.; Signorelli, D.; Vitali, M.; Ganzinelli, M.; Gallucci, R.; Zilembo, N.; Platania, M.; et al. Treatment of lung large cell neuroendocrine carcinoma. *Tumor Biol.* **2016**, *37*, 7047–7057. [[CrossRef](#)]
72. Garcia-Carbonero, R.; Rinke, A.; Valle, J.W.; Fazio, N.; Caplin, M.; Gorbounova, V.; O'Connor, J.; Eriksson, B.; Sorbye, H.; Kulke, M.; et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Neoplasms: Systemic Therapy-Chemotherapy. *Neuroendocrinology* **2017**, *105*, 281–294. [[CrossRef](#)]
73. Moertel, C.G.; Kvols, L.K.; O'Connell, M.J.; Rubin, J. Treatment of neuroendocrine carcinomas with combined etoposide and cis-platin. Evidence of major therapeutic activity in the anaplastic variants of these neoplasms. *Cancer* **1991**, *68*, 227–232. [[CrossRef](#)]
74. Mitry, E.; Baudin, E.; Ducreux, M.; Sabourin, J.-C.; Rufié, P.; Aparicio, T.; Lasser, P.; Elias, D.; Duvillard, P.; Schlumberger, M.; et al. Treatment of poorly differentiated neuroendocrine tumours with etoposide and cisplatin. *Br. J. Cancer* **1999**, *81*, 1351–1355. [[CrossRef](#)]
75. Kamarajah, S.K.; Bednar, F.; Cho, C.S.; Nathan, H. Survival Benefit of Adjuvant Chemotherapy after Pancreatoduodenectomy for Ampullary Adenocarcinoma: A Propensity-Matched National Cancer Database (NCDB) Analysis. *J. Gastrointest. Surg.* **2020**, *25*, 1805–1814. [[CrossRef](#)]
76. Lania, A.; Ferrau, F.; Rubino, M.; Modica, R.; Colao, A.; Faggiano, A. Neoadjuvant Therapy for Neuroendocrine Neoplasms: Recent Progresses and Future Approaches. *Front. Endocrinol.* **2021**, *12*, 651438. [[CrossRef](#)]