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Original Research

Carcinoid tumors of the duodenum and the ampulla of Vater: Current diagnostic and therapeutic approach in a series of 8 patients. Case series

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ABSTRACT

Aim: To describe the specific characteristics of duodenal/perivaterian carcinoids and to analyze the diagnostic/therapeutic approach.

Material and methods: Eight patients were included in our study. Symptoms on admission included dyspepsia, upper gastrointestinal (GI) bleeding and anemia. All patients underwent upper GI endoscopy and gastrointestinal peptides (gastrin) and neuroendocrine markers (Chromogranin-A, CgA) measurement. Imaging studies were performed in all patients, including OCTREOSCAN, while in patients with ACs MRCP or ERCP was also performed, when necessary. Definite diagnosis was confirmed by histopathologic examination.

Results: Polypoid masses (carcinoids) were revealed at duodenal bulb and ampulla of Vater, in 5 and 3 patients, respectively. Serum gastrin was moderately increased in 4 patients, while in one patient it was more than 1000 pg/ml. Serum CgA was moderately increased in one patient, in whom OCTREOSCAN detected a solitary hepatic metastasis. Two patients with DC, of less than 1 cm of diameter, were treated by endoscopic polypectomy, while all the other patients underwent surgery. The patient with hepatic metastasis and positive OCTREOSCAN received also Octreotide LAR, resulting in stabilization of disease. No recurrence or metastases were observed during follow-up (range : 1.5–9.6 years).

Conclusions: In DC tumors <1 cm endoscopic excision with close follow-up is an adequate treatment, while in tumors >1 cm and in AC, surgical resection is the treatment of choice. In metastatic tumors, resection of the primary lesion with administration of somatostatin analogues may stabilize the disease and improve patient's quality of life.

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1. Introduction

Carcinoids are rare, slow growing malignancies, predominantly arising from the Gastrointestinal (GI) tract. They are originated from a variety of different neuroendocrine cell types and are usually identified histologically by their affinity for silver salts and by positive reactions to neuroendocrine markers like neuron-specific enolase (NSE), synaptophysin and chromogranin. Appendix and the small bowel are the most frequent locations of carcinoid tumors within the GI tract, while carcinoids of the duodenum (DC) and

especially of the ampulla of Vater (AC) are rare tumors, accounting for less than 2% and 0.3% of all gastrointestinal carcinoids, respectively.^{1,2} According to the traditional classification, proposed by Williams et al.,³ DC and AC belong to foregut carcinoids together with those of the respiratory tract, stomach and pancreas. However, a new classification, which takes into account not only their embryological origin, but also histologic variations of carcinoids, has recently been adopted by many authors.⁴ According to this new classification system, neuroendocrine tumors of the duodenum and uppermost jejunum (including those of the ampullary region) are classified as well-differentiated endocrine tumors, well-differentiated endocrine carcinomas and poorly differentiated endocrine carcinomas.

In this paper, we present our experience with 8 patients with carcinoids located in the duodenum ($n = 5$) and the ampulla of Vater ($n = 3$). Clinical and pathologic features of these two rare entities are compared and our diagnostic and therapeutic approach is analyzed. The relevant literature is briefly reviewed.

Abbreviations: DC, Duodenal carcinoids; AC, Ampulla of vater carcinoids; US, Ultrasonography; CT, Computed tomography; EUS, Endoscopic ultrasonography.

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2. Material and methods

Among a total number of 114 patients with carcinoid tumors of all origins, including 103 patients with carcinoids of the GI tract/pancreas (Table 1), we present 8 cases in which carcinoids were located in the duodenum ($n = 5$) and the ampulla of Vater ($n = 3$). These patients had been treated in the Section of Neuroendocrinology, First Department of Propaedeutic Internal Medicine of Athens University Medical School, "Laiko" Hospital, Athens Greece, during the last 10 years. Five patients were females, aged from 36 to 67 years (median, 51 years) and three were males, aged from 62 to 77 years (median, 68.3 years). The diagnosis was based upon histopathological features and immunohistochemical markers, after biopsies taken during upper GI endoscopy or Endoscopic Retrograde Cholangio-Pancreatography (ERCP). The following immunohistochemical markers were used: NSE (Dako M0873, dilution 1:50), Chromogranin-A (Dako A 0430, dilution 1:100) and Synaptophysin (Dako M0776, dilution 1:10).

After confirmation of diagnosis and endoscopic or surgical treatment, all patients were evaluated several times per year with clinical, biochemical and radiographic assessments. The follow-up protocol included:

- 1) Measurement of 24 h secretion of urinary 5-hydroxy-indole-acetic acid (5-HIAA), and serum Chromogranin-A (CgA), every three months.
- 2) Measurement of serum neurohormonal peptides such as gastrin, somatostatin and pancreatic polypeptide (PP), when necessary.
- 3) Liver biochemistry tests every six months and in patients with hepatic metastases every four months.
- 4) Abdominal ultrasonography (US) every six months or every four months in patients with metastases and also endoscopic ultrasonography (EUS), when necessary.
- 5) Abdominal Computed Tomography (CT) scan once a year in all patients, and Magnetic Resonance Imaging (MRI) or Magnetic Resonance Cholangio-Pancreatography (MRCP), when necessary.
- 6) Somatostatin-Receptor-Scintigraphy (OCTREOSCAN), once a year in all patients.
- 7) Upper GI endoscopy, once a year in all patients.

The follow-up period ranged between 1.5 years and 9.6 years (mean, 4.2 years) and it is still in progress.

3. Results

3.1. Clinical features

Three out of five patients with DC were females and 2 were males, while 2 patients with AC were females and 1 was male. Four (4/5, 80%) of the patients with DC were referred to us, because of ulcer-like symptoms, while the other patient was admitted to our hospital for upper GI bleeding. On the contrary, one patient with AC presented with weakness and shortness of breath during the last 8 months due to a severe anemia (hematocrit, 18%), one patient referred to us because of painless jaundice of 4 weeks duration, while the other patient was admitted for malaena and painless jaundice of sudden onset. The latter patient had also a history of von Recklinghausen's disease. There were no clinical signs of "carcinoid syndrome" in any of the previous patients. The clinical features of all patients at the time of presentation, are summarized in Table 2.

3.2. Laboratory findings

On admission, one patient with DC and two patients with AC had anemia. Liver function tests were normal in all patients with

DC, while in all patients with AC, γ GT and alkaline phosphatase (ALP) were significantly elevated. Also, in the two patients with AC who presented with jaundice, a mild elevation of the aminotransferases (AST, ALT) and increased serum bilirubin levels (up to 8.5 mg/dl) were found. Serum amylase and clotting parameters were normal in all patients.

Serum gastrin levels were significantly elevated in one patient (>1000 ng/L, normal values < 108 ng/L) and slightly increased in three patients (range, 158–395 ng/L, mean, 273 ng/L) with DC, while it was within normal limits in all patients with AC. Serum PP was moderately elevated (135 pmol/L, normal values: <100 pmol/L) in the patient with high values of serum gastrin, while it was normal in all the other patients. Serum somatostatin levels were normal in all patients. Serum and urine neuroendocrine markers were measured; serum CgA was found moderately increased in seven patients (mean, 266 ng/ml) and significantly elevated (>800 ng/ml) in one patient with DC. In this last patient, urinary 5-HIAA was found increased (19 mg%, normal values < 9 mg%) while the imaging studies revealed a solitary hepatic metastasis. Urinary 5-HIAA was normal in all the other patients (Table 3).

3.3. Endoscopic – imaging findings

On upper GI endoscopy, solitary polypoid lesions (up to 1 cm in 3 patients, 1.5 cm in one patient and more than 2 cm in one patient) were found in the bulb of the duodenum in patients with DC (Fig. 1). On the contrary, in one patient with AC an ulcerated, bleeding tumor with a diameter of 4 cm was revealed in the ampulla of Vater (Fig. 2), while in the remaining 2 patients with AC, the endoscopy raised the suspicion of a submucosal tumor of the ampullary region. In these two patients, upper abdominal US demonstrated a dilatation of the extrahepatic and intrahepatic bile ducts, while in all the other patients US was without pathological findings. The biliary ductal dilatation in the previous two patients was confirmed by the abdominal CT scan or the MRCP (Fig. 3). These two patients underwent an ERCP, which revealed tumors of the ampulla of Vater (Fig. 4).

Based on the histological confirmation of the diagnosis, all the previous patients underwent a Somatostatin-Receptor-Scintigraphy, which showed no abnormalities in seven patients, while in the remaining patient with DC, a solitary hepatic metastasis was revealed (Fig. 5). Of note, in this patient, CT scan and US, performed at the same time, were without pathological findings.

3.4. Treatment

3.4.1. Endoscopic – surgical treatment

Endoscopic (snare) polypectomy was performed in 2 patients, who had polypoid lesions in the bulb < 1 cm. In these patients the infiltration of the regional lymph nodes was excluded by endoscopic ultrasonography (EUS), performed prior to polypectomy. In 2 patients with DC of diameter of 1.5 cm and 2.4 cm, respectively, as well as in the patient with a DC and diameter of the mass ~ 1 cm, who had already a hepatic metastasis, surgical local excision with regional lymph-node dissection was performed. Liver metastasectomy was not possible due to tumor location at the confluence of the hepatic veins/inferior vena cava.

On the contrary, in all three patients with AC a pancreaticoduodenectomy (Whipple procedure) with regional lymph-node resection was performed. During the operation, in the woman with AC and von Recklinghausen's disease, a second mass, of hard consistency, measuring 3.5×3.5 cm was found in the jejunum, approximately 15 cm distal to the ligament of Treitz, which was also resected. Postoperative course was uneventful in all patients, without any significant postoperative complication.

Table 1
Carcinoid tumors of the GI tract, treated in the section of neuroendocrinology, "Laikon" Hospital.

Tumor Location	No of Patients	%
Stomach	16	15.5
Duodenum and Ampulla of Vater	8	7.8
Pancreas	4	3.9
Small Intestine	31	30
Appendix	34	33
Colon and Rectum	10	9.8
Total	103	100

Table 2

Clinical features of patients at the time of presentation.

Patient	Sex - Age	Tumor	Upper GI Bleeding	Ulcer-Like Symptoms	Anemia	Jaundice	Von Recklinhausen
1	F 42	DC	–	+	–	–	–
2	F 49	DC	+	–	+	–	–
3	F 67	DC	–	+	–	–	–
4	M 66	DC	–	+	–	–	–
5	M 77	DC	–	+	–	–	–
6	M 62	AC	–	–	–	+	–
7	F 51	AC	–	–	+	–	–
8	F 36	AC	+	–	+	+	+

DC: Duodenal carcinoids, AC: Ampullary carcinoids, PTS: Patients, GI: Gastrointestinal.

3.4.2. Medical treatment

In the patient with DC, who had already hepatic metastasis at the time of diagnosis and positive OCTREOSCAN a long-acting somatostatin analogue was administered (Octreotide LAR [Long-Acting-Release, NOVARTIS_R], 30 mg intramuscularly, every 28 days, initiated just after surgical resection of the primary lesion). This patient is still treated with somatostatin analogues (3.2 years, after surgery). No adverse effects have been reported.

3.5. Pathologic findings

Size of DC and AC ranged from 0.6 to 2.4 cm, and from 1.0 to 4.0 cm in greatest dimension, respectively. Regional lymph-node metastases were found in the patient with metastatic DC, and in two patients with AC. Microscopically, all tumors, either DC or AC, were composed of medium size cells with eosinophilic cytoplasm and central round nuclei with mild nuclear atypia. Involvement of muscularis propria was apparent in two cases of AC. These tumors showed a small number of mitoses (1–2 per 10 HPF) The AC of the patient with von Recklinghausen's disease contained psammoma bodies. At immunohistochemistry, all DC and AC tumors expressed chromogranin, while 4/5 of DC and 2/3 of AC expressed NSE and synaptophysin. Four out of 5, DC tumors were positive for gastrin, while only the AC tumor of the patient with von Recklinghausen's disease expressed somatostatin.

Finally, it should be pointed out that the second tumor of the patient with von Recklinghausen's disease was a Gastrointestinal Stromal Tumor (GIST), showing strong immunoreactivity for S-100

protein and CD 34 and weak immunoreactivity for smooth muscle actin. According to the new classification of neuroendocrine tumors of duodenum and upper jejunum, tumors of 4 patients with DC and of 1 patient with AC were well-differentiated endocrine tumors, while 2 patients and 1 patient with AC and DC, respectively had well-differentiated endocrine carcinomas. Pathological findings and immunohistochemical features of our patients are summarized in Table 4.

3.6. Follow-up

Follow-up data are available in all patients. The follow-up period ranged between 1.5 and 9.6 years. One patient with AC died 5.3 years after diagnosis, however his death was not attributable to the neoplasm. All the other patients, even the patient with the metastatic carcinoid are still alive. All patients remained asymptomatic. Liver biochemistry tests in patients with AC returned to normal after surgical treatment and remained within normal limits. Serum gastrin and PP in one patient with DC decreased significantly (<300 pg/ml and <108 pmol/L, respectively) after endoscopic treatment. However, serum gastrin remained moderately increased (200–300 pg/m) during the follow-up period. Serum CgA decreased significantly in the patient with hepatic metastasis, after surgical treatment and administration of somatostatin analogues, but never returned to normal limits. On the contrary, urinary 5-HIAA levels at the same patient were normalized two months after the initiation of medical treatment. Serum CgA, which was moderately raised in all the other patients at the time of diagnosis,

Table 3

Laboratory findings of patients in our series.

PT	Tumor	Hct%	Biochemical tests	Gastrin (pg/ml)	Somatostatin	PP (pmol/L)	Serum CgA (ng/ml)	Urinary 5-HIAA (mg%)
1	DC	36	Normal	158	Normal	Normal	256	Normal
2	DC	25	Normal	1095	Normal	135	481	Normal
3	DC	39	Normal	266	Normal	Normal	858	19
4	DC	42	Normal	395	Normal	Normal	163	Normal
5	DC	40	Normal	65	Normal	Normal	245	Normal
6	AC	45	TBIL = 7.2 mg/dL AST = 75 IU/L ALT = 89 IU/L γGT = 456 IU/L ALP = 853 IU/L	Normal	Normal	Normal	195	Normal
7	AC	18	TBIL = Normal AST = Normal ALT = Normal γGT = 389 ALP = 658 IU/L	Normal	Normal	Normal	204	Normal
8	AC	36	TBIL = 8.5 mg/dL AST = 62 IU/L ALT = 94 IU/L γGT = 368 IU/L ALP = 693 IU/L	Normal	Normal	Normal	320	Normal

Hct: Hematocrit, TBIL: Total Bilirubin, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, γGT: γ-glutamyl transpeptidase, ALP: Alkaline phosphatase, PP: Pancreatic polypeptide, CgA: Chromogranin-A, 5-HIAA: 5-Hydroxy-indole-acetic acid.



Fig. 1. Upper GI endoscopy, showing a carcinoid in the bulb of the duodenum.

returned and remained within normal limits after endoscopic or surgical treatment. Except from the patient with the DC who had already hepatic metastasis at the time of diagnosis, no metastases occurred in any of the other patients during the follow-up period. Also, a stabilization of the metastatic lesion was demonstrated by OCTREOSCAN, in the patient with the metastatic tumor, during the follow-up period. The selected treatment and the follow-up of our patients is summarized in Table 5.

4. Discussion

Carcinoid tumors of the duodenum and especially those located at the ampulla of Vater are rare clinical entities. Stamm et al.⁵ identified five major types of duodenal neuroendocrine tumors. Gastrin-producing tumors (Type I) are the most frequent and are

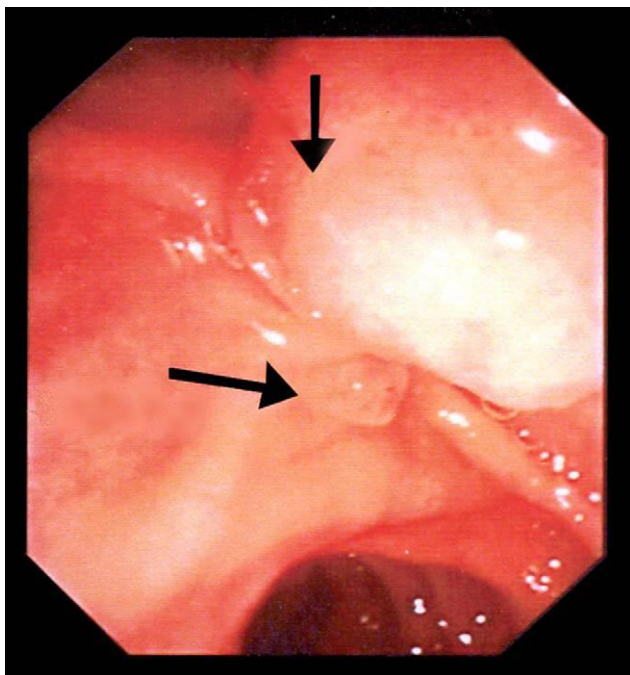


Fig. 2. Endoscopy, revealing an ampullary carcinoid (4 cm diameter) [vertical arrow]. The horizontal arrow shows the ampulla of Vater.



Fig. 3. MRCP of a patient with an ampullary carcinoid, showing biliary ductal dilatation.

located predominantly in the proximal duodenum. In one third of the patients these tumors are associated with Zollinger–Ellison syndrome and Multiple Endocrine Neoplasia type I (MEN-I). Somatostatin-producing tumors (Type II) are second in frequency, occur preferentially at the ampulla of Vater and are often associated with von Recklinghausen's disease. Gangliocytic paragangliomas (Type III) are usually located at the ampulla of Vater or in the periampullary region. Type IV is rare and contains tumors that produce serotonin, calcitonin and PP. These lesions are found outside the ampulla and lack signs and symptoms of infiltrative growth. Poorly differentiated endocrine carcinomas (Type V) are extremely rare and highly malignant neoplasms, usually located at the ampulla of Vater. The patients of our series with DC had Type I tumors, while all of our patients with AC had Type II tumors.

Abdominal pain is thought to be the predominant symptom in tumors located in the bulb of the duodenum, while painless jaundice is the leading symptom in tumors of the ampullary region, occurring in approximately two-thirds of patients. It has been reported that 25% of patients with AC had a history of von Recklinghausen's disease.^{6–8} One out of three (33%) of our patients with AC had a similar history. Perrone⁹ suggested that neurogenic and carcinoid tumors in patients with neurofibromatosis occur as a result of transformation of an endodermal–ectodermal complex, which is near the ampulla of Vater. Hough et al.¹⁰ have proposed that patients with von Recklinghausen's disease and abdominal pain or jaundice should be evaluated for the possibility of an



Fig. 4. ERCP revealing an ampullary carcinoid after sphincterotomy.



Fig. 5. Posterior view of an OCTREOSCAN, revealing a solitary hepatic metastasis in a patient with duodenal carcinoid.

ampullary neuroendocrine tumor. None of our patients, even the patient with the solitary hepatic metastasis, complained of the typical symptoms of carcinoid syndrome (flushing, diarrhea, bronchospasm).

Upper GI endoscopy is thought to be the most useful method for the pre-operative diagnosis of these tumors. In most cases of polypoid lesions located in the duodenal bulb endoscopic biopsy reveals the presence of a carcinoid tumor. On the contrary, AC are usually located in the submucosa, the duodenal mucosa is intact, and endoscopic biopsies are negative. In these cases, as occurred in two of our patients, deeper biopsies after papillotomy during ERCP, are necessary to achieve histologic diagnosis preoperatively.

Serum and urine neuroendocrine markers (such as CgA and 5-HIAA) may have diagnostic value.^{11–13} CgA may also have prognostic significance and can be used during the follow-up of patients. In our series, CgA was moderately increased in seven patients and significantly raised in the patient with metastatic tumor, at the time of their presentation. Urinary 5-HIAA, a serotonin metabolite, is usually elevated in metastatic carcinoid tumors¹⁴ especially when they are located in the small intestine and proximal colon. In our study, it was increased only in the patient with the metastatic tumor, while it was within normal limits in all the other patients.

A large variety of carcinoid tumors and their metastases can express a high density of specific somatostatin receptors, particularly of the subtypes 2 and 5 for which octreotide, a somatostatin analogue, has a high affinity.¹⁵ Thus, these lesions, can be visualized in vivo using gamma camera pictures obtained after injection of ¹¹¹In labeled Octreotide [¹¹¹In-DTPA⁰-D-Phe¹]octreotide-¹¹¹In-penreotide, OCTREOSCAN^R]. The efficacy of OCTREOSCAN, not only to detect but also to predict a therapeutic effect of somatostatin analogues in these tumors, has been shown by several groups.¹⁶ In our series, OCTREOSCAN revealed an unexpected metastasis in one

patient with DC, which was previously unrecognized by other conventional imaging methods. (US, CT, MRI).

Carcinoid tumors of the duodenum can show immunohistochemical evidence of multiple hormone production, while in many cases these hormones like gastrin, pancreatic polypeptide or somatostatin can be detected in the serum.^{17,18} However, only gastrin secretion is clinically significant in a small proportion of patients who have Zollinger–Ellison syndrome.¹⁹ In larger series with DC, only 5% of patients had documented Zollinger–Ellison syndrome, although 56% secreted gastrin in serum. In our series, gastrin was expressed in 80% of patients with DC and serum gastrin was elevated in all these patients, while it was normal in all three patients with AC. Furthermore, in one of these patients gastrin levels were more than 1000 pg/ml. However, this patient had no clinical or other evidence of Zollinger–Ellison syndrome. On the other hand, several studies have shown that more than 50% of AC tumors express somatostatin, which may be explained by the fact that somatostatin-producing cells have been identified in ampullary ducts.²⁰ In our study, only one patient with AC expressed somatostatin, while serum somatostatin levels were normal in this patient, as well as in all the other patients with AC.

The optimal treatment for these tumors is radical excision either endoscopically or surgically. In small polypoid lesions (smaller than 1 cm) located in the bulb of the duodenum, an endoscopic polypectomy could be an efficient therapeutic approach. Local lymph-node metastases should be excluded before therapeutic intervention by endoscopic ultrasonography (EUS). Careful endoscopic follow-up is necessary to exclude local recurrence of the tumor. Two of our patients underwent endoscopic polypectomy. Neither local recurrence nor distal metastases were detected in these patients, during the follow-up period. The remaining three patients with DC underwent local excision with lymph node dissection, as the tumor size was greater than 1 cm. Surgical excision of the primary lesion was performed even in the patient who had already hepatic metastasis at the time of presentation, in order to reduce the intensity of his symptoms and stabilize the disease. The latter was also achieved in the same patient (3.2 years after the initiation of treatment), by the administration of Somatostatin analogues (Octreotide LAR 30 mg IM every 28 days), as an additional treatment. Somatostatin analogues are nowadays the treatment of choice in metastatic carcinoid tumors, where they can achieve not only control of symptoms, but also stabilization of the disease and even tumor shrinkage in some cases.²¹

The treatment of ampullary carcinoid tumors remains controversial. Although most authors agree that surgery is the treatment of choice, the optimal operation for these tumors is under debate. Wide local excision with lymph-node dissection has been suggested for tumors smaller than 2 cm, as there seems to be no difference in prognosis compared with a more radical procedure.²² However, regional lymph node involvement has been reported in 53% of patients with tumors smaller than 2 cm.²³ In our series, lymph node involvement has been found in two patients with tumor size of 1 and 1.2 cm, respectively.²³ Furthermore, metastases

Table 4

Pathologic findings and immunohistochemical features in our series.

Patient	Tumor	Tumor Size	Classification	CgA	NSE	Synaptophysin	Gastrin	Somatostatin
1	DC	0.6 cm	Well-differentiated endocrine tumor	+	–	+	–	–
2	DC	0.8 cm	Well-differentiated endocrine tumor	+	+	–	+	–
3	DC	1.0 cm	Well-differentiated endocrine carcinoma	+	+	+	–	–
4	DC	2.4 cm	Well-differentiated endocrine tumor	+	+	+	–	–
5	DC	1.5 cm	Well-differentiated endocrine tumor	+	+	+	+	–
6	AC	1.0 cm	Well-differentiated endocrine carcinoma	+	+	–	–	–
7	AC	4.0 cm	Well-differentiated endocrine tumor	+	–	+	–	–
8	AC	1.2 cm	Well-differentiated endocrine carcinoma	+	+	+	–	+

NSE: Neuronal specific enolase, CgA: Chromogranin-A.

Table 5

Treatment and follow-up in our series.

Patient	Tumor	Treatment	Metastases/local recurrence	Serum Peptides	Neuroendocrine Markers	Present Status of PTS	Duration of Follow-up (years)
1	DC	Endoscopic polypectomy	–	N	N	ANED	9.6
2	DC	Endoscopic polypectomy	–	Gastrin: 200–300, PP: 100–110	N	ANED	4.6
3	DC	Surgical local excision + Octreotide LAR	Stabilization of hepatic metastasis	N	Serum CgA: 300–400, Urine 5-HIAA: N	AWD	3.2
4	DC	Surgical local excision	–	N	N	ANED	1.5
5	DC	Surgical local excision	–	N	N	ANED	3.2
6	AC	Pancreatico-duodenectomy	–	N	N	DNED	5.3
7	AC	Pancreatico-duodenectomy	–	N	N	ANED	3.5
8	AC	Pancreatico-duodenectomy	–	N	N	ANED	3.1

ANED: Alive no evidence of disease, AWD: Alive with disease, DNED : Died no evidence of disease.

have been reported in 15% of patients with smaller (0.5–0.9 cm) tumors.²⁴ Therefore, a more radical surgical approach, like pancreaticoduodenectomy (Whipple operation) appears to be more appropriate treatment for the ampullary carcinoids, irrespective of tumor size.^{25,26} Preferentially, this procedure should be performed by experienced pancreatic surgeons, in specialized centres. All of our patients with AC underwent a Whipple's operation. Two of them are alive with no evidence of disease, 3.5 and 3.1 years after surgery, while the other patient died 4.3 years after the operation due to a myocardial infarction. It should be noted that all the tumors of this study were well-differentiated and this may explain at least in part the relatively good long-term outcome. Therapeutic results could be worse for poor-differentiated tumors.

Burke et al.²⁷ have shown that, tumor size greater than 2 cm, infiltration of the muscularis propria and mitotic activity are significant risk factors for metastases in DC. However, one of our patients with tumor size of approximately 1 cm had already distal metastases at the time of diagnosis. For AC tumors, most authors have found that tumor size has no prognostic implication, while mitotic activity may predict outcome.²⁸ One of our patients with tumor size of 4 cm and low mitotic activity is still alive without any evidence of disease, 3.5 years after a Whipple's operation.

Conflict of interest

None declared.

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Ethical approval

Not applicable.

Author contribution

Study design: Nikou CC, Toubanakis C, Moulakakis KG. Data Collection: Pavlatos S, Kosmidis C, Mallas E, Safioleas P. Data analysis-editing: Sakorafas GH, Safioleas MC, Nikou CC. Literature research: Moulakakis KG, Pavlatos S, Sakorafas GH.

References

- Laufer JM, Zhang T, Modlin IM. Current status of gastrointestinal carcinoids. *Aliment Pharm Ther* 1999;**13**:271–87.
- Safioleas MC, Moulakakis KG, Kontzoglou K, Stamoulis J, Nikou GC, Toubanakis C, et al. Carcinoid tumors of the appendix. Prognostic factors and evaluation of indications for right hemicolectomy. *Hepatogastroenterology* 2005;**52**:123–7.
- Williams ED, Sandler M. The classification of carcinoid tumors. *Lancet* 1963;**1**:238–9.
- Solcia E, Rindi G, Paolotti D, La Rossa S, Capella C, Fiocca R. Clinicopathological profile as a basis for classification of the endocrine tumors of the gastroenteropancreatic tract. *Ann Oncol* 1999;**10** (Suppl. 2):S9–15.
- Stamm B, Hedinger CE, Saremaslani P. Duodenal and ampullary carcinoid tumors: Report of 12 cases with pathological characteristics, polypeptide content and relation to the MEN-I syndrome and von Recklinghausen's disease (neurofibromatosis). *Virchows Arch A* 1986;**408**:475–89.
- Makhlouf H, Burke A, Sobin L. Carcinoid tumors of the ampulla of Vater: a comparison with duodenal carcinoid tumors. *Cancer* 1999;**85**:1241–9.
- Klein A, Clemens J, Cameron J. Periampullary neoplasms in von Recklinghausen's disease. *Surgery* 1989;**206**:815–9.
- Burke AP, Sobin LH, Shekitka KM, Federspiel BF, Helwig EB. Somatostatin-producing duodenal carcinoids in patients with von Recklinghausen's neurofibromatosis: a predilection of black patients. *Cancer* 1990;**65**:1591–5.
- Perrone T. Duodenal gangliocytic paraganglioma and carcinoid. *Am J Pathol* 1986;**10**:147–8.
- Hough DR, Chan A, Davidson H. von Recklinghausen's disease associated with gastrointestinal carcinoid tumors. *Cancer* 1983;**51**:2206–8.
- Vinik AI, Silva MP, Woltering EA, Go VL, Warner R, Caplin M. Biochemical testing for neuroendocrine tumors. *Pancreas* 2009;**38**:876–89.
- O'Toole D, Groissman A, Groiss D, Delle Fave G, Barkmanova J, O'Connor J, et al. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: biochemical markers. *Neuroendocrinology* 2009;**90**:194–202.
- Nikou GC, Lygidakis NJ, Toubanakis C, Pavlatos S, Tseleni-Balafouta S, Giannatou E, et al. Current diagnosis and treatment of gastrointestinal carcinoids in a series of 101 patients: the significance of serum chromogranin-A, somatostatin receptor scintigraphy and somatostatin analogues. *Hepatogastroenterology* 2005 May–Jun;**52**(63):731–41.
- Ferolla P, Faggiano A, Mansueti G, Avenia N, Cantelmi MG, Gionenali P, et al. The biological characterization of neuroendocrine tumors: the role of neuroendocrine markers. *J Endocrinol Invest* 2008;**31**:277–86.
- Kwekkeboom DJ, Krenning EP, Lebtahi R, Komminoth P, Kos-Kudla B, de Herder WW, et al. ENETS consensus guidelines for the standards of care in neuroendocrine tumors: somatostatin receptor imaging with (111)In-pentetreotide. *Neuroendocrinology* 2009;**90**:184–9.
- Koopmans KP, Neels ON, Kema IP, Elsinga PH, Links TP, de Vries EG, et al. Molecular imaging in neuroendocrine tumors: molecular uptake mechanisms and clinical results. *Crit Rev Oncol Hematol* 2009;**71**:199–213.
- Dayal Y, Tallberg K, Nunnumacher G, DeLellis R, Wolfe H. Duodenal carcinoids in patients with and without neurofibromatosis: A comparative study. *Am J Surg Pathol* 1986;**10**:348–57.
- Lee MW, Silva F, Price J. Gastrin-secreting tumor of the duodenum (G-cell apudoma) associated with secondary biliary cirrhosis. *Cancer* 1982;**49**:2596–601.
- Wengrower D, Fich A. Primary duodenal carcinoid. *Am J Gastroenterol* 1987;**82**:1069–70.
- Stommer P. Somatostatin immunoreactive cells of vater's ampulla and the peripapillary duodenum. *Leber Magen Darm* 1986;**16**:307–11.
- Garland J, Buscombe JR, Bouvier C, Bouloux P, Chapman MH, Chow AC, et al. Sandostatin LAR (long-acting octreotide acetate) for malignant carcinoid syndrome: A 3-years experience. *Aliment Pharm Ther* 2003 Feb;**17**(3):437–44.
- Hatzitheoklitos E, Buchler MW, Friess H, Poch B, Ebert M, Mohr W, et al. Carcinoid of the ampulla of Vater: clinical characteristics and morphologic features. *Cancer* 1994;**73**:1580–8.
- Ricci JL. Carcinoid of the ampulla of Vater. *Cancer* 1993;**71**:686–90.
- Walton GF, Gibbs ER, Spencer GO, Laws HL. Carcinoid tumors of the ampulla of Vater. *Am Surgeon* 1997;**63**:302–4.
- Karatzas G, Kouraklis A, Karayiannakis P, Patapis P, Givalos N, Kaperonis E. Ampullary carcinoid and jejunal stromal tumor associated with von Recklinghausen's disease presenting as gastrointestinal bleeding and jaundice. *Eur J Surg Oncol* 2000;**26**:428–9.
- Papalambros E, Archimandritis A, Pikoulis E, Nikou G, Leppaniemi A, Alexiou D, et al. Carcinoid of the ampulla of Vater: presentation of a new case. *Int Surg* 2000;**85**:64–6.
- Burke AP, Federspiel BH, Sobin LH, Shekitka KM, Helwig EB. Carcinoids of the duodenum: A histologic and immunohistochemical study of 65 tumors. *Am J Surg Pathol* 1989;**13**:828–37.
- Liu K, Mergener K, Feldman JM, Goufried MR. Carcinoids of the ampulla of Vater: a unique subset of gastrointestinal carcinoids. *Mod Pathol* 1997;**11**:59A.