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Review

Carcinoid of the Pancreas: Clinical Characteristics and Morphological Features

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The classical carcinoid tumour (WHO) of the pancreas is extremely rare and its diagnosis may puzzle physicians and pathologists. Here, 29 previously published cases of pancreatic carcinoid tumours, including one new case, are reviewed. Literature research was done using MedLine from 1966 to 1995. Pancreatic carcinoids produce an atypical carcinoid syndrome. Skin flushing was reported in only 34%. The main symptom was pain, followed by diarrhoea and weight loss. Elevated urinary 5-HIAA levels were found in 85% (17/20). The immuncytochemical sensitivity for serotonin was 100% (11/11). The diagnosis of pancreatic carcinoid tumour is based on the typical endocrine histological features together with increased serotonin metabolism. Generally, the slow growth rate and late invasion of adjacent organs render local resection possible, but the high incidence of distant metastases (69%) prevents long-term survival in the majority of patients. The possible role of the Octreoscan, a new radionuclide imaging technique, is discussed with regard to this tumour entity. Copyright © 1996 Elsevier Science Ltd

Key words: pancreas, carcinoid tumour, APUD-cells, serotonin, somatostatin receptor, radionuclide imaging, pancreatectomy, review

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INTRODUCTION

THE TERM carcinoid was first used by Oberdorfer [1] in 1907 to describe carcinoma-like tumours of apparently benign histological appearance occurring in the small intestine. Their argentaffinity was shown by Gosset and Masson [2] in 1914. In 1954, Thorson and coworkers [3] were the first to describe the carcinoid syndrome consisting of valvular disease of the right side of the heart, skin flushing, patchy cyanosis, diarrhoea and bronchoconstriction. According to their embryological origin, these tumours are classified into foregut carcinoids (respiratory tract, pancreas, stomach, proximal duodenum), midgut carcinoids (jejunum, ileum, appendix, Meckel's diverticulum, ascending colon) and hindgut carcinoids (transverse and descending colon, rectum) [4]. This distinction is useful because carcinoid tumours from different areas have different clinical manifestations, humoral products and immunohistochemical features, e.g. foregut and hindgut carcinoids are often argentaffin-negative, whereas midgut carcinoids are always argentaffin-positive. However, modern classifications are based on precise characterisation with specific hormones.

The appendix is the most common site of carcinoids within the gastrointestinal tract, followed by the distal small bowel, rectum and stomach [5–9]. A carcinoid tumour of the pancreas is an exceedingly rare clinical entity. With regard to the biochemical or histochemical evidence of increased serotonin metabolism, 28 cases of primary pancreatic carcinoid tumour have been reported in the literature [10–33]. Here, we review the literature, paying special attention to the clinical presentation, morphological findings, treatment and prognosis of this disease. We also present details of one new case, which is included in the review of the data.

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REVIEW OF CASES OF PANCREATIC CARCINOID TUMOURS

Patient characteristics, signs and symptoms

The most frequent symptoms in patients suffering from carcinoid tumour of the pancreas are abdominal pain, 19/29 (66%), and diarrhoea, 15/29 (52%). Flushing, the pathognomonic finding in carcinoid tumours, was present in 10/29

Table 1. Reported carcinoids of the pancreas

[Ref.]	Sex	Age	Symptoms F	D	N	P	W	C	Localisation in the pancreas	Tumour size (cm)	Metastases Distant	Regional	5-HIAA elevated (urine)	Serotonin elevated (plasma)	Treatment Surgical	Non-surgical	Follow-up
[10]	F	38				X			Head	4 × 4					Whipple		
[11]	F	48	X	X		X	X	X	Tail	2	Bones, liver	X	X	X	No treatment		Died after 12 months
[12]	M	32		X		X			Tail		Liver	X			No treatment		Died after 7 months
[13]	M	70	X				X	X			Lung, liver		X			Cyclophosphamide Prednisone	Died after 18 months
[14]	F	60		X			X	X		3 × 3 × 3	Liver	X	X		Exploratory laparotomy	Actinomycin-D	Died after 2 months
[15]	M	35	X	X		X	X	X	Tail	4 × 3 × 3	Liver, spleen	X	X			Methysergide	Died after 6 months
[16]	F	29				X			Tail	2 × 2					Distal pancreatectomy		
[17]	F	59		X		X	X		Body	4	Liver	X	X		Exploratory laparotomy		
[17,18]	F	64		X	X	X	X				LN		X	X	Exploratory laparotomy		
[18]	M	58				X	X		Body		Liver	X	X		Exploratory laparotomy	Cyproheptadine	
[19]	M	23		X		X	X	X	Body/tail		Liver, lung, bones LN					Cyclophosphamide Vincristine Methothrexate	Died after 4 months
[20]	F	78				X			Tail	9 × 2 × 2					Distal pancreatectomy		
[21]	F	48			X	X			Body/tail		Liver			X	Distal pancreatectomy		
[22]	F	41	X								Liver, breast		NL		Exploratory laparotomy		

[23]	—	—	X	X					Liver		X		No data			
[23]	—	—							Liver		X		No data			
[24]	F	23		X	X			Tail	10 × 10 × 12				Distal pancreatectomy	Bromocriptine	Well after 24 months	
[25]	F	22	X	X		X	X			Liver, LN		X		Ivalon	Died after 7 months	
[26]	—	63				X	X	Tail		Bones		X	X	Radiochemotherapy 5-FU, Streptozotocin	Well after 34 months	
[27]	F	46				X				Liver		NL	X	Pancreatectomy	Somatostatin	
[27]	F	63	X	X						Liver		NL	X	Pancreatectomy	Somatostatin 5-FU	
[28]	—	63		X			X	Body/tail	8 × 6			X		Distal pancreatectomy		
[29]	F	55	X		X	X		Tail	3 × 4	Liver		X		Exploratory laparotomy	Cyproheptadine, Streptomycin 5-FU Dacarbazine	Well after 10 months
[29]	—	—	X	X		X		Head	6 × 5 × 5	Liver	X	X		Whipple		
[30]	M	66						Body	9,5 × 3						Distal pancreatectomy	
[31]	M	60	X	X		X	X		2,5	LN	X	X			Exploratory laparotomy	5-FU Streptozotocin
[32]	M	55				X		Head	4 × 4					Whipple		
[33]	M	28						Head			X			Exploratory laparotomy		
Unpublished	F	54		X	X	X	X	Head	7 × 9 × 10			X		Whipple		Well after 7 months	

LN, distant lymph nodes; NL, normal levels; F, flush, D, diarrhoea; N, nausea; P, pain; W, weight-loss; C, cardiac symptoms.

(34%) (Table 1), and all of these patients had distant metastases [12,14,17–19,21,23,26]. 10 other patients with distant metastases did not show flushing, despite elevated levels of urine 5-HIAA in 7 cases. Only 13/29 patients (45%) experienced weight loss, in contrast with 75% of patients with pancreatic carcinoma [34–36]. Jaundice is not a typical symptom of pancreatic carcinoid (3/29, 10%). Pancreatitis as a consequence of tumour obstruction was seen in 4 patients. The association of pancreatic carcinoid with other endocrine disease was found only in 1 patient who suffered from MEN-I syndrome [24]. Symptoms lasted 12 months (median, range 3–60 months) until diagnosis. The mean age of 26 patients with pancreatic carcinoid was 49.3 years (range 22–78 years), comparable to the carcinoids of the ampulla of Vater [40] and is lower than in pancreatic carcinoma (mean 65 years) [33, 38, 39]. Of the 29 patients, 15 were women (52%), 9 were men (31%) and in 5 cases (17%) gender was not reported. The sex ratio was 1.5:1 (F:M), in contrast to 1:1.5 (F:M) in pancreatic cancer [40, 41].

Work-up–Diagnosis

CT scan was useful in diagnosis of carcinoid tumour. In all 11 patients undergoing CT-scan, a pancreatic tumour could be demonstrated [21, 22, 25, 26, 28–32](Figure 1a). Endoscopic retrograde cholangiopancreatography (ERCP) was done only in two patients, raising the suspicion of a pancreatic tumour. The long-distance stenosis of the distal parts of the pancreatic and common bile duct, in the absence of calcifications and enlargement of ductal branches in the pancreatic head and body, reflected the usually slow and displacing growth of endocrine tumours (Figure 1b). Angiography of the coeliac trunk (and the superior mesenteric artery) confirmed the suspected diagnosis of an endocrine tumour by its marked vascularisation and helped to distinguish invasion from displacement of adjacent large vessels (Figure 1c). Investigations of the gut hormones were important for diagnosis. In 20/29 (69%) patients, serum serotonin and/or urine 5-HIAA showed pathologically elevated values (Table 1). Of the 21 patients with available data regarding serotonin metabolism, 20 had elevated levels of serum serotonin and/or urine 5-HIAA. When fine needle aspiration or biopsy was carried out (5/29, 17%) [17,19,25,29], cell morphology was found to be typical for neuroendocrine tumour in all cases. The ^{111}Indium-Octreoscan served as a screening method for distant metastases (see Discussion).

Staging and histopathology

Thirty per cent of carcinoid tumours of the pancreas were found in the head and 70% in the body and tail. Tumours ranged in diameter from 2 to 12 cm (mean 4 cm), a mean of 3 cm in the presence of distant metastases, and a mean of 6 cm if distant metastases were absent (Table 1). Infiltration of adjacent organs by the tumour was noted in 10/29 (34%) patients. Metastatic disease was found in 21/29 (72%) patients, 9 (31%) and 20 (69%) of them with regional lymph node metastases and distant metastases, respectively. Distant metastases involved the liver in 17/20 (85%) patients, the supraclavicular lymph nodes in 4 (20%), bones in 3 (15%), the lung twice and the spleen, breast and axillary lymph nodes once each.

The typical histological picture of carcinoids is sheets or trabecules of medium sized cells with fine granular cytoplasm and monomorphic round nuclei. Often they form glandular

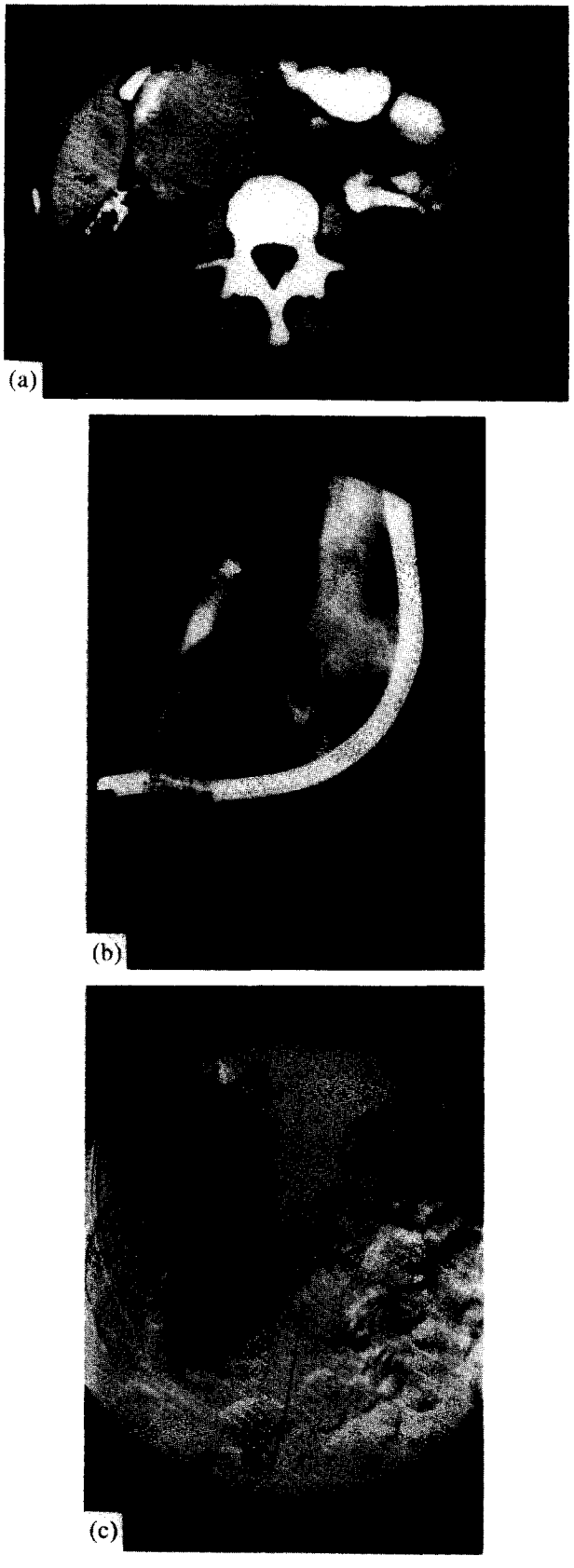

Figure 1. (a) Abdominal CT scan showing a homogeneous, solid tumour in the pancreatic head with distension of the duodenal C-loop. (b) Endoscopic retrograde cholangiopancreatogram showing an extended stenosis of both the pancreatic duct and the common bile duct with prestenotic dilatation of ducts. (c) Angiography of the cocliac trunk showing a markedly vascularised tumour in the region of the pancreatic head.

structures. Mitosis is rare, and nuclear atypism is not obvious (Figure 2a). Typically the cells show argentaffin cytoplasmic granules (Figure 2b) and a positive immunohistochemical reaction for serotonin (Figure 2c). Other findings, e.g. argyrophilic granules and positivity of neuroendocrine "markers" as well as somatostatin receptors (Figure 3a–c) are common but not specific features.

The tumour cells of 10 patients were argentaffin-positive, but 6 others were negative. Argyrophilia was shown in 8/12 studied cases. Two authors simply described enterochromaffin cells (Table 2). As is known for foregut carcinoids in general, the argentaffin reaction of Fontana–Masson and the argyrophil reaction of Grimelius are therefore not reliable methods for showing a classical carcinoid.

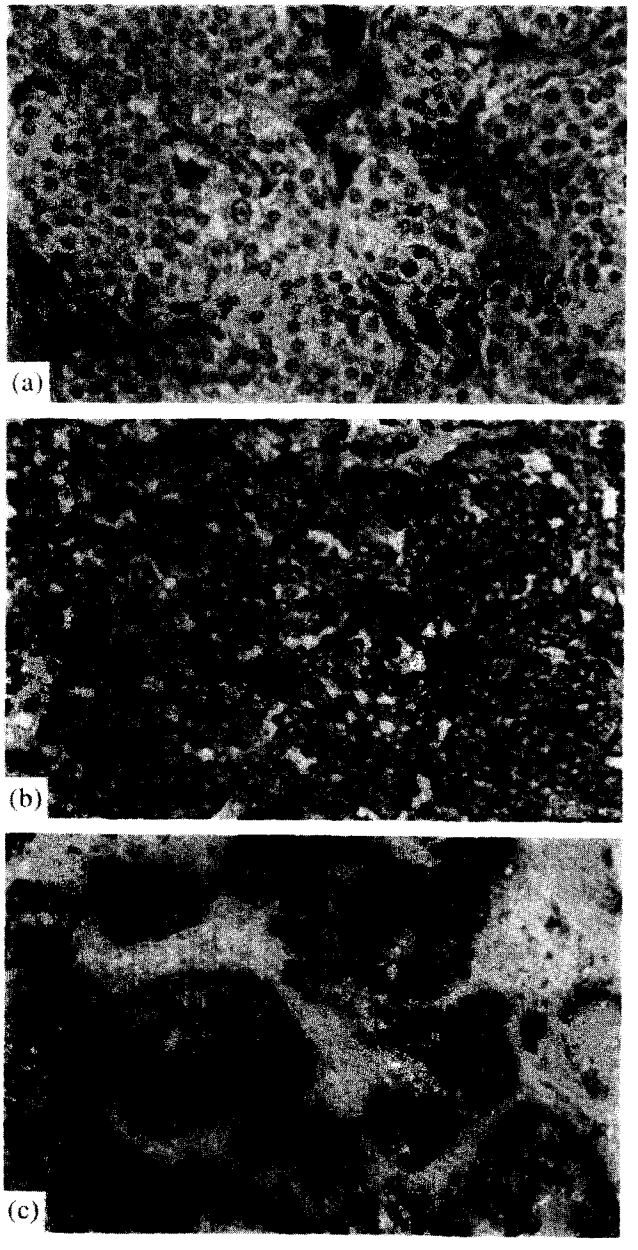

Figure 2. (a) Sheets of monomorphous tumour cells with fine granular eosinophilic cytoplasm and slightly polymorphous nuclei with inconspicuous nucleoli (haematoxylin–eosin, original magnification × 100). (b) Strong argentaffinity of tumour cells demonstrated by the method of Fontana–Masson (original magnification × 100). (c) Intense serotonin-immunostaining in most cells (original magnification × 100).

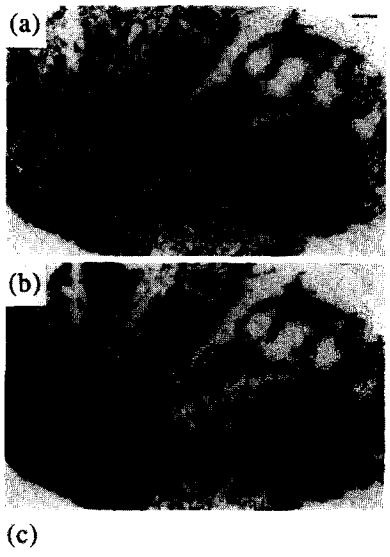

Figure 3. Somatostatin receptors in the carcinoid tumour detected with *in vitro* receptor autoradiography. (a) Haematoxylin–eosin stained section, bar = 1 mm. (b) Autoradiogram showing total binding of ^{125}I-Tyr^3-octreotide. Note that the whole tumour tissue is strongly labelled (black areas). (c) Non-specific binding.

Where data were available for hormonal immunohistocytochemistry, 11 patients studied for serotonin were positive. Neuron-specific enolase (NSE) was demonstrated immunohistochemically in all four specimens tested. No failure of serotonin staining was reported, suggesting a high sensitivity of serotonin as an immunohistochemical marker (Table 2).

Treatment

Laparotomy was performed in 20/29 (69%) patients. Partial or total pancreatectomy followed in 12/29 (41%) cases, while in the remaining 8 cases laparotomy remained explorative or resulted in a palliative bypass-procedure. Four tumours were found to be non-resectable because of locally advanced tumour growth. Laparotomy was combined with pre-operative or postoperative hormone therapy in 3 patients, with chemotherapy in 2 and with hormone therapy and chemotherapy in 2 patients. Chemotherapy as the only treatment modality was given in 2 patients. Hormone therapy alone, chemo-embolisation alone or combined radiochemotherapy alone were administered each to one patient. No information about therapy was available from four reports (Table 1).

Prognosis

21 out of 29 patients developed metastases, 20 of them at distant sites. At the time of diagnosis, 19/29 (66%) already had metastases. 11 follow-ups were reported in this series. The follow-up period ranged from 2 to 34 months. No local recurrence after resection of the primary tumour occurred.

Table 2. Histochemical and immunohistochemical results in 29 patients with carcinoid of the pancreas

[Ref.]	Histochemistry		Immunocytochemistry			
	Arg.	Argy.	Ser.	Chr.	NSE	Others
[10]	pos.	N/A	N/A	N/A	N/A	N/A
[11]	neg.	neg.	N/A	N/A	N/A	N/A
[12]	pos.	pos.	pos.	N/A	N/A	N/A
[13]	N/A	pos.	N/A	N/A	N/A	N/A
[14]	neg.	N/A	N/A	N/A	N/A	N/A
[15]	neg.	N/A	pos.	N/A	N/A	N/A
[16]	pos.	N/A	N/A	N/A	N/A	N/A
[17]	neg.	neg.	N/A	N/A	N/A	N/A
[17,18]	pos.	pos.	N/A	N/A	N/A	N/A
[17]	neg.	neg.	N/A	N/A	N/A	N/A
[19]	neg.	pos.	N/A	N/A	N/A	N/A
[20]	pos.	pos.	N/A	N/A	N/A	Somatostatin
[21]	N/A	N/A	pos.	N/A	N/A	β-HCG
[22]	pos.	N/A	pos.	N/A	N/A	N/A
[23]	N/A	N/A	N/A	N/A	N/A	N/A
[23]	N/A	N/A	N/A	N/A	N/A	N/A
[24]	N/A	N/A	N/A	N/A	N/A	N/A
[25]	pos.	neg.	pos.	N/A	pos.	β-HCG/VIP
[26]	N/A	N/A	N/A	N/A	N/A	Somatostatin
[27]	N/A	N/A	N/A	N/A	N/A	ACTH
[27]	N/A	N/A	N/A	N/A	N/A	VIP/Sub. P.
[28]	pos.	pos.	pos.	N/A	pos.	N/A
[29]	N/A	N/A	pos.	N/A	N/A	Gastrin
[29]	N/A	N/A	pos.	N/A	N/A	N/A
[30]	N/A	N/A	pos.	pos.	pos.	N/A
[31]	N/A	pos.	N/A	N/A	N/A	N/A
[32]	pos.	pos.	N/A	N/A	N/A	N/A
[33]	N/A	N/A	pos.	pos.	N/A	N/A
Unpubl	pos.	N/A	pos.	pos.	pos.	N/A

Arg., argentaffin (Fontana-Masson); Argy., argyrophil (Grimelius); Ser., serotonin; Chr., chromogranin; NSE, neuron-specific enolase; VIP, vasoactive intestinal polypeptide; Sub P, substance P; N/A, data not available; pos., positive; neg., negative.

6 patients died because of progressive tumour disease and its complications.

DISCUSSION AND CONCLUSION

The diagnosis of carcinoid tumours of the pancreas may puzzle physicians and pathologists. The reasons, therefore, are as follows: it is impossible to be familiar with this exceedingly rare disease. The literature is quite confusing because of different definitions and different nomenclature. Years ago, when the first cases were described [10–13], the possibilities for histological and serological studies of these tumours were still limited. Thus, in the past, the diagnosis was based on the clinical features and histological picture of a neuroendocrine tumour of the pancreas. However, nowadays 19 different gastroenteropancreatic neuroendocrine cells and 40 different secretory products are known and can be distinguished [42]. Carcinoids are often multihormone producers, but as a rule one hormonal substance predominates [43, 44]. Carcinoids, originating from foregut especially, may show normal levels of serotonin and its metabolites in plasma and urine [48, 49]. In contrast, there are pancreatic carcinomas with neuroendocrine characteristics and carcinoid-like symptoms [14, 50]. All these facts make the diagnosis of pancreatic carcinoid difficult.

We propose the following criteria for the diagnosis of a primary pancreatic carcinoid tumour: (a) histological features of an endocrine tumour (e.g. argyrophilic granula, positivity for chromogranin A, synaptophysin and/or NSE), with the characteristics of a "classical" carcinoid, i.e. serotonin immunoreactivity and—less sensitive—argentaffinity within the majority of the tumour cells. (b) Obviously increased serotonin metabolism with elevated 5-HT/5-HTP plasma levels and/or pronounced urinary 5-HIAA output and partial or complete carcinoid syndrome. In our opinion, neuroendocrine pancreatic tumour with significant multihormone production, carcinoma with serotonin secretion and carcinoid tumour in ectopic pancreatic tissue should be considered separately.

In this report we analysed 29 enterochromaffin cell carcinoid tumours of the pancreas which fulfilled our inclusion criteria defined above. Jaundice is an exceptional finding in pancreatic carcinoids (10%), which is explained by tumour localisation in the pancreatic body and tail in 14/20 (70%) patients and the slow and late infiltrative (34%) growth. Additionally, in the reported series, no complete typical carcinoid syndrome occurred, despite the evidence of distant metastases in 69%. This is remarkable because midgut carcinoids which metastasise to the liver frequently produce carcinoid syndrome. Foregut carcinoids like pancreatic carcinoids tend to produce an atypical carcinoid syndrome with increases in plasma 5-HTP levels, but usually not serotonin levels because they lack the appropriate decarboxylase [48, 51–53]. Thus,

only 6 patients showed elevated plasma 5-HT levels. Nevertheless, urinary 5-HIAA levels were markedly increased in 17/20 (85%) cases, suggesting a 5-HTP decarboxylation in the intestine and other tissues [49, 54].

A peculiarity of our case is the history of recurring pancreatitis more than 10 years before the onset of the first tumour symptoms. The aetiology remained unknown. The question might, therefore, arise as to whether pancreatitis is a predisposing factor for pancreatic carcinoid or even an early sign of tumour growth. In the reports from Patchefsky [17,18], Nagai [30] and Taidi [32] pancreatitis seemed to be the consequence of tumour obstruction.

Pre-operative diagnosis of carcinoid tumour of the pancreas relies on CT-scan, fine needle aspiration and measurements of plasma 5-HTP levels and/or urinary 5-HIAA, the latter having a sensitivity of 85% in this report. Plasma serotonin, as mentioned above, is of lesser diagnostic value.

Tumour diameters did not correspond with the presence or absence of metastases. Small tumours metastasised even more often in this series. Although these tumours grow slowly and show late infiltration of adjacent structures, pancreatic resection was performed only in 41% of the reported cases because 62% revealed synchronous distant metastases, most of them in the liver. The high incidence of metastases may be due to the late onset of clinical symptoms and hence late diagnosis, giving the tumour enough time to metastasise. In the situation of a carcinoid tumour which metastasises to the liver with an unknown primary site, one should remember to check the pancreas.

The generally poor prognosis of pancreatic carcinoids is explained by the high incidence of metastases. As far as data are available, patients with metastatic carcinoid tumour of the pancreas showed a median survival of 7 months. However, in the absence of metastatic disease, normal overall survival may be expected after tumour resection; no local recurrence should be encountered.

In the future, the Octreoscan might be of clinical relevance. Reubi and coworkers found 54/62 (87%) carcinoid tumour specimens to be somatostatin receptor-positive, using receptor autoradiography techniques with two different iodinated somatostatin analogues as radioligands [55]. The clinical implications of the presence of somatostatin receptors in carcinoid tumours are as follows: as a diagnostic tool in the pre-operative examination of patients; as a marker for pathobiochemical classification of tumours using *in vitro* detection methods; as a predictive marker for effective therapy with surgery or octreotide; as a marker in the follow-up of patients and as a potential target for radiotherapy.

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