August 1987
Volume 206, Number 2

Annals of Surgery

Malignant Carcinoid Tumors

An Analysis of 103 Patients with Regard to Tumor Localization, Hormone Production, and Survival

INGRID NORHEIM, M.D.,* KJELL ÖBERG, M.D.,* ELVAR THEODORSSON-NORHEIM, M.D.,†
PER GUNNAR LINDGREN, M.D.,‡ GUDMAR LUNDQVIST, M.D.,§ ANDERS MAGNUSSON, M.D.,‡ LEIF WIDE, M.D.,§
and ERIK WILANDER, M.D.||

From the Department of Internal Medicine, University Hospital, Uppsala, the Department of Clinical Chemistry, Karolinska Hospital, Stockholm,† the Department of Diagnostic Radiology,‡ the Department of Clinical Chemistry,§ and the Department of Pathology,|| University Hospital, Uppsala, Sweden*

In a prospective study of 103 patients with carcinoid tumors consecutively referred for medical treatment, the most common sites of the primary tumors were the ileum (73%), bronchi (7%), and jejunum (4%). All patients had local metastases, and 96 (93%) also had liver metastases. The most common initial symptoms were diarrhea (32%), ileus (25%), and flush (23%). The overall frequency of diarrhea was 84% and of flush was 75%. Heart insufficiency caused by cardiac valve disease was seen in 33% of the patients. The carcinoid syndrome, including flush, diarrhea, and elevated urinary 5-hydroxyindole acetic acid (5-HIAA) concentrations, was manifested by 69 patients (67%), 64 of whom (93%) had carcinoid tumors of mid-gut origin. Elevated urinary 5-HIAA was found in 91 patients (88%), of which 89 displayed liver metastases. The plasma concentration of the tachykinin neuropeptide K (NPK) was elevated in 67 patients (66%), 63 of whom had tumors of the mid-gut region. Serum pancreatic polypeptide (PP) and human chorionic gonadotrophin α levels were elevated in 43% and 28% of the patients, respectively, and the highest levels were found in patients with metastatic bronchial carcinoid tumors. Thirty-nine of the 103 patients are now dead; 18 died of tumor progression, whereas 14 patients died of heart failure secondary to a carcinoid tricuspidal valve insufficiency. The estimated median survival from the time of histologic diagnosis was 14 years, and from the time of carcinoid syndrome was 8 years.

Supported by the Swedish Cancer Research Fund (1925-B84-10x and 1665-B84-03x), Pharmacia Research Fund, Swedish Medical Research Council (03x-07464), Nordisk Insulinfond, Swedish Society for Medical Sciences, Smith, Kline & French, Åke Wibergs Fund, Konung Gustav V:s Jubileumsfond (85:464), and funds of the University of Uppsala.

Reprint requests and correspondence: Ingrid Norheim, M.D., Department of Internal Medicine, University Hospital, S-751 85 Uppsala, Sweden.

Submitted for publication: October 13, 1986.

THE CARCINOID TUMOR is a neuroendocrine neoplasm with malignant potential and the most frequent of all endocrine gut tumors. When liver metastases have appeared, the hormone secretion from the tumor cells may induce characteristic symptoms of flush, diarrhea, bronchial obstruction, and failure of the right side of the heart. The mechanisms behind the symptoms are not fully known, but serotonin might be a factor involved in diarrhea[1] and the flush might be induced by kallikrein-bradykinin,[2] or by ta-

chykinin[3,4] secretion from the tumor cells. Secretion of prostaglandins[5] and histamine[6] also have been associated with carcinoid tumors. Acromegaly and Cushing's syndrome have been reported in patients with carcinoid tumors,[7-9] possibly caused by ectopic secretion of releasing factors from the tumor.[10]

The current study reports data from 103 patients with carcinoid tumors who were consecutively referred to our unit for evaluation. All patients were thus seen at one clinic, by the same physicians, and evaluated according to the same protocols. Special attention was paid to the localization of the primary tumor, metastases, and circulating tumor markers.

Patients

The study includes 103 patients (57 women and 46 men) with carcinoid tumors, seen at the Endocrine Unit of the Department of Internal Medicine, University Hospital, Uppsala, Sweden, during an 8-year period (January 1978–1986). The criterion for inclusion into the study was histologically and clinically verified metastatic carcinoid tumor. The Endocrine Unit serves as a referral unit for central Sweden, which has around 1 million inhabitants. Fifty-four of the patients (52%) in this series came from this region, and the annual incidence rate of individuals with metastatic carcinoid tumors was thus 0.7 patients/100,000 population. The incidence of the carcinoid syndrome was 0.5 patients/100,000 population/year. The remaining 49 patients were referred from other parts of Sweden, either because of an unusually complicated clinical picture or for evaluation for inclusion in clinical trials of specific medical treatments such as interferon.[11]

Altogether 69 patients had been subjected to operation before referral, and an exploratory laparatomy was done at our hospital in an additional 17 patients. These operations were performed to resect the primary tumor, which was possible in 54 patients with intraabdominal tumors and in five patients with pulmonary carcinoid tumors. If a recent tumor specimen from an operation was not available for histopathologic examination, a needle biopsy was executed from liver metastases. Thus, in all patients, the diagnosis of carcinoid tumor was based on a histopathologic examination. The diagnosis of a carcinoid tumor was established before operation in 40 of the 86 patients who had operation (47%), based on histopathology and/or elevated urinary 5-hydroxyindole acetic acid (5-HIAA) concentrations.

Methods

Routine investigations of blood and urine, including hemoglobin content, leucocyte and platelet counts, liver enzymes, serum creatinine, albumin, electrolytes, and fasting blood glucose were performed. The thyroid function was investigated by serum thyroid-stimulating hormone (TSH), thyroxine, and thyroid binding protein. An intravenous glucose tolerance test[12] was performed in 81 patients. Serum pancreatic polypeptide (PP) was determined in 96 patients, human chorionic gonadotrophin α and β subunits (HCG α and β) was determined in 102 patients.[13,14] Serum calcitonin concentrations were measured in 102 patients and gastrin levels were measured in 96 patients.[15,16] The plasma neuropeptide K (NPK) concentration was determined in 101 patients by a newly established radioimmunoassay.[17] Reference values are given in Table 7. The blood samples were drawn in the morning after an overnight fast, and the concentrations at the first visit to our clinic are reported. However, as the technique for NPK analysis is recent, it was impossible to determine its concentration in plasma from the first visit in 30 patients. In these cases the first evaluated plasma sample is used instead.

The urinary 5-HIAA excretion was determined[18] as an average of two 24-hour samples in all patients. Urinary cortisol was analyzed using a commercial radioimmunoassay (Farmos Group, Stockholm, Sweden) in a 24-hour sample of urine.

Computerized tomography (CT scan) and/or ultrasonography techniques were used in 101 patients for evaluation of metastatic disease to the liver. Two patients were not evaluated by these techniques; however, liver metastases were seen at operation in both patients. Ultrasonically guided needle (diameter 2.1 mm) biopsy from the liver metastases was obtained in 90 patients using a previously described technique.[19] In 42 patients with unknown primary tumor location, an angiography of the celiac and mesenteric arteries was performed. All patients were evaluated by roentgenography of the lungs. When the patients had local symptoms from the skeleton, scintigraphy and roentgenography were carried out. Bone marrow aspiration for evaluation of metastases was performed in only a small number of patients. Echocardiography of the heart to detect valvular involvement was performed in 70 patients.

Tumor tissue specimens (N = 103) were stained with hematoxylin and eosin, and investigated morphologically for homogeneous cell structures and characteristic growth patterns of endocrine tumors. For further identification of the tumor as a neuroendocrine neoplasm, the Grimelius (N = 101),[20] Masson (N = 96),[21] and Sevier–Munger (N = 42)[22] silver staining techniques were used. In addition, a technique with monoclonal antibodies for serotonin was used in specimens from 47 patients.[23]

Statistical Analysis

Nonparametric statistical methods as described by Conover[24] were used throughout the study. The median

and interquartile ranges were used as indicators of central tendency and variation, respectively. The Mann-Whitney test was used to test for differences between two independent groups. The estimated median survival was calculated as described by Colton.[25]

Results

The Primary Tumor and Metastases

The median age at diagnosis for all patients was 59 years (interquartile range: 51–66 years). The patients with appendical and bronchial carcinoid tumors (Table 1) were younger at the time of diagnosis than the remainder (median age: 38 and 52 years, respectively). A slight predominance of women was seen in the total group (females/males: 57/46).

In 75 patients (73%) the primary tumor was localized to the ileum (Table 2), whereas four patients had jejunal carcinoid tumors, three had cecal tumors, and two had appendical carcinoid tumors. In nine patients the location of the primary tumor was unknown, but six of them probably had tumors of mid-gut origin because of typical histopathologic examination and a positive silver staining with the Masson technique. Thus, 90 of 103 patients (87%) presumably had a mid-gut carcinoid tumor. Intrathoracal carcinoid tumors were found in eight patients; seven had bronchial tumors and one had a mediastinal (thymic?) tumor. The surgeons believed the excision to be radical in only six of the 86 patients who had operation. Five of these patients had a primary tumor of less than 2 cm in diameter. However, liver metastases developed later in all these patients who were considered surgically cured. In 16 patients (17%) multiple primary tumors in the small intestines were found. Local metastases were verified in all patients, and 96 (93%) also had metastases to the liver (Table 3).

Peripheral metastases to sites other than the liver were seen in 31 patients (30%). Of the eight patients with intrathoracal tumors and liver metastases, five revealed metastases to the skeleton and one had metastases to the pituitary gland.

TABLE 1. *The Median Age at the Time of Diagnosis and the Sex of 103 Patients with Metastatic Carcinoid Tumors Related to the Localization of the Primary Tumor*

Location	Median Age (range)* (years)	Males/ Females
Mid-gut (-appendix)	61.0 (52–68)	40/48
Appendix	38.0 (26–50)	0/2
Thoracal	52.5 (29–60)	5/3
Unknown	60.0 (53–61)	1/2
Duodenum	57.0	0/1
Rectum	51.0	0/1
Total	59.0 (51–66)	46/57

* Variation given as the interquartile range.

Symptoms and Delay in Diagnosis

Diarrhea was most frequently the first symptom, prompting 33 patients (32%) to consult a physician (Table 4). The second most common initial symptoms were ileus/subileus (25%) and flush (23%). The median duration of any symptoms before diagnosis was 1 year (interquartile range: 0.5–3 years). The patients with subileus/ileus as the first symptom had the shortest delay before diagnosis, *i.e.*, median 0.6 years (interquartile range: 0–3 years). The median time from the onset of diarrhea until diagnosis was 1.5 years (interquartile range: 1–4 years). The patients with flush had a median delay of 2 years (interquartile range: 1–4 years).

Table 5 illustrates the total number of patients with symptoms of diarrhea, flush, intestinal obstruction, tricuspidal heart failure, and asthma. Altogether 69 patients (67%) had a complete carcinoid syndrome with flush, diarrhea, and elevated urinary 5-HIAA concen-

TABLE 2. *Location of the Primary Tumor Related to Symptoms of Flush and Diarrhea, and Elevated Levels of Urinary 5-HIAA and Plasma NPK.*

Origin	Total (%)	Flush	Diarrhea	5-HIAA	NPK	Carcinoid Syndrome (%)*
Ileum	75 (73.0)	61	68	67	51	54 (72)
Jejunum	4 (3.9)	2	2	4	2	2 (50)
Cecum	3 (2.9)	3	3	3	3	3 (100)
Appendix	2 (1.9)	1	1	2	1	1 (50)
Bronchial	7 (6.8)	3	4	5	2	3 (43)
Mediastinum	1 (0.9)	0	0	1	0	0
Duodenum	1 (0.9)	1	1	1	0	1 (100)
Rectum	1 (0.9)	0	0	0	0	0
Unknown peripheral	3 (2.9)	1	2	2	2	1 (33)
Unlocalized mid-gut	6 (5.9)	5	5	6	6	4 (66)
Mid-gut tumor	90 (87.4)	72	79	82	63	64 (71)
Total	103 (100.0)	77	86	91	67	69 (67)

* Number and percentage of patients with complete carcinoid syndrome.

TABLE 3. *The Localization of Metastases in 103 Patients with Carcinoid Tumors*

Metastases	No. of Patients	%
Local	103	100.0
Liver	96	93.0
Skeleton	14	13.6
Peripheral lymph gland	7	6.7
Ovarian	4	3.6
Lung	2	1.9
Skin	1	0.9
Pancreas	1	0.9
Pleural	1	0.9
Pituitary gland	1	0.9

TABLE 5. *Clinical Symptoms at Referral in 103 Patients with Carcinoid Tumors*

Symptoms	No. of Patients	%
Diarrhea	86	84
Flush	77	75
Ileus/subileus	45	44
Cardiac insufficiency	34	33
Asthma	15	15
Carcinoid syndrome*	69	67

* Includes flush, diarrhea, and elevated levels of urinary 5-HIAA.

trations (Table 2 and Table 5). In the patients with mid-gut carcinoid tumors, the syndrome was seen in 64 patients (62%). A total of 70 patients (68%) had symptoms of both flush and diarrhea, and 12 of them also had asthmatic attacks. One of these patients with flush and diarrhea had no liver metastases and normal urinary 5-HIAA excretion. The remainder had both liver metastases and elevated urinary 5-HIAA excretion. Four patients (4%) had only flushing and 14 (14%) had only diarrhea. Asthma, which occurred in 15 patients (15%), was not seen as a sole symptom in any patient. Four patients (4%) with intrathoracic tumors had symptoms of invasive growing neoplasm, but no carcinoid symptoms such as flush or diarrhea, and they also had normal urinary 5-HIAA levels. Four patients (4%) with mid-gut tumors did not have any apparent symptoms, and in these patients the primary tumor was detected during operation for ileus.

Thirty-four patients (33%) with cardiac insufficiency had systolic murmur and signs of abnormal tricuspidal valve function at echocardiography. All these patients, except one patient with unknown tumor localization, had carcinoid tumors of mid-gut origin. Only one patient had valve replacement. Thirty patients had a complete carcinoid syndrome and four had diarrhea but no flush. The median age of these patients at the time of diagnosis was 60 years and the median duration of flush and/or diarrhea was 2 years.

TABLE 4. *Initial Symptoms in 103 Patients with Carcinoid Tumors*

First symptom	No. of Patients	%	Delay of Diagnosis (Years)	
			Median	Interquartile Range
Diarrhea	33	32	1.5	(1–4)
Ileus/subileus	26	25	0.6	(0–3)
Flush	23	23	2.0	(1–4)
Pain	10	10		
Cough	2	2		
Asthma	2	2		
Loss of weight	2	2		
Melena	1	1		
No symptoms	3	3		
Unknown	1	1		
Total	103		1	(0.5–3)

CT Scan and Ultrasound Investigations

Abdominal CT scans were performed in 96 patients (93%) and the ultrasound technique was used in 96 patients (93%). One or both techniques were used in evaluating 101 patients, and metastases to the liver were found in 93 patients (92%). At operation, an additional three patients had small miliary metastases in the liver. Multiple liver metastases were found in 73 patients. The size of the liver metastases varied from miliary lesions undetectable by CT scan to large metastases, with a diameter of 10–12 cm, often with central necrosis. On CT scan the metastases had a low attenuation, whereas by ultrasound the echodensity varied considerably.

Histopathology

All tumors had the characteristic growth patterns of endocrine tumors at histopathologic examination. The mid-gut tumors, except one appendical carcinoid tumor, contained homogeneous cells with insular-like growth patterns. A positive staining using the Grimelius silver staining technique was noted in 101 evaluated specimens (Table 6). A positive reaction was found in 83 (88%) of the 96 tumor specimens evaluated with the Masson staining technique. Six of nine tumors of unknown origin had the characteristic growth pattern of mid-gut carcinoid tumors and positive staining using the Grimelius and the Masson techniques. These tumors were therefore presumably of mid-gut type. Negative staining with the Masson technique was found in all bronchial tumors, the mediastinal, the rectal, and three tumors of unknown localization outside the mid-gut. One appendical carcinoid tumor with uncharacteristic growth pattern stained neither with the Masson silver staining technique nor with the specific monoclonal antibodies against serotonin. The rest of the tested mid-gut

TABLE 6. *Histopathologic Investigations of Tumor Specimens Using Different Silver Staining Techniques and Serotonin Immunohistochemical Staining, Related to the Localization of the Primary Tumor*

Primary Tumor Localization	Total No.	Grimelius	Masson		Sevier-M		Serotonin	
		+	+	−	+	−	+	−
Mid-gut	88	88	82	1	30	0	42	1
Bronchial	7	7	0	7	4	2	(1)	2
Mediastinal	1	1		1		1		
Unknown	3	3	0	3	3	0		1
Rectum	1	1		1		1		
Duodenum	1	1	1		1			
Total	101	101	83	13	38	4	43	4

tumors had a positive staining with both these techniques.

Tumor Markers

Elevated levels of urinary 5-HIAA were present in 91 patients (88%) (Tables 2 and 7). The median 5-HIAA level was 360 μmol/24 hours (range: 30–3370). Patients with carcinoid tumors located in the mid-gut had a median value similar to that of the whole group, and individuals with bronchial tumors generally had a higher value (median: 480 μmol/24 hours [range: 29–1436]) (Fig. 1). Plasma NPK was elevated in 67 patients (66%) with a median plasma level of 25 pmol/L (range: 7.8–2023). Sixty-three of them (94%) had tumors of the mid-gut type, whereas patients with carcinoid tumors of thoracal origin or of other unusual localizations (Table 2) had plasma NPK median levels close to the normal range (Fig. 2).

The serum PP level was elevated in 43% of the patients, median 0.4 ng/mL (range: 0.03–155). HCG α was above the reference range in 28%; median for men and premenopausal women was 1.5 μg/L (range: 0.34–390), and median for postmenopausal women was 6.15 μg/L (range: 0.41–1500). The highest levels of PP and HCG α were found in patients with bronchial carcinoid tumors (Figs. 3 and 4). A slightly elevated serum gastrin level was observed in 14 patients (15%), and HCG β and calcitonin levels were elevated in 12 and four patients, respectively (Table 7).

In eight patients (8%) elevated levels of all four principal markers, 5-HIAA, NPK, PP, and HCG α were

TABLE 7. *Tumor Secretory Products ("Markers") in Patients with Carcinoid Tumors*

"Tumor marker"	N	%	Median Value (mean)	Normal Range
5-HIAA	91/103	88	360 (560)	<80 μmol/24 h
NPK	67/101	66	25 (99)	<12 pmol/L
PP	41/95	43	0.4 (2.4)	<0.4 ng/mL
HCG α	29/102	28	6.2* (33.7)	<8.5 μg/L
			1.5‡ (14.9)	<3.0 μg/L
Gastrin	14/96	15	25 (51.6)	<55 pmol/L
HCG β	12/102	12	1.0 (1.43)	<2.5 μg/L
Calcitonin	4/82	4		<290 pmol/L

* Postmenopausal women.
† Mean and premenopausal women.

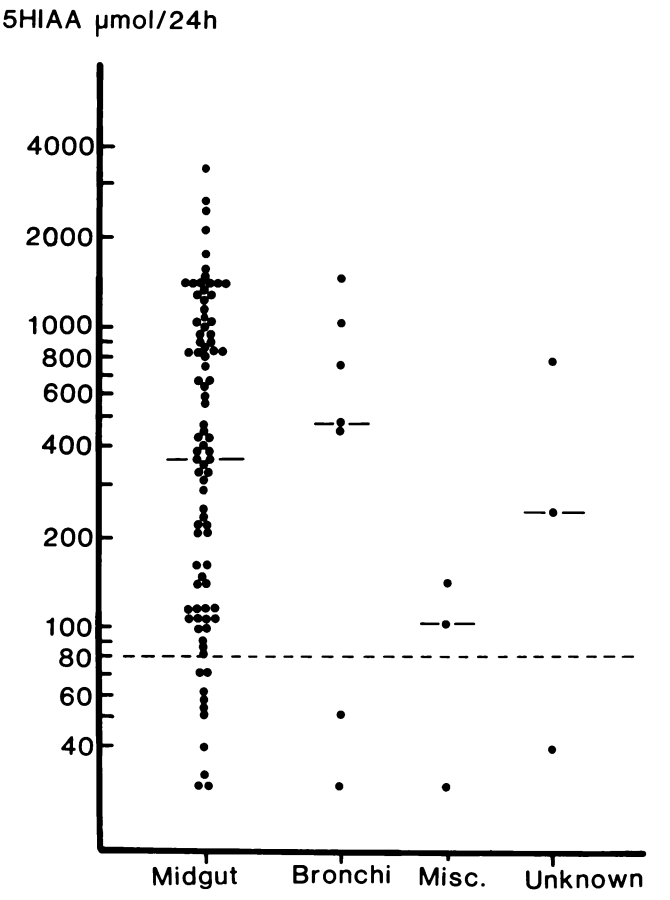

FIG. 1. The urinary 5-HIAA excretion in patients with carcinoid tumors originating in the mid-gut (N = 90), bronchi (N = 7), unknown site outside mid-gut (N = 3) and miscellaneous: mediastinum (N = 1), rectum (N = 1), and duodenum (N = 1). Reference value for 5-HIAA < 80 μmol/24 h.

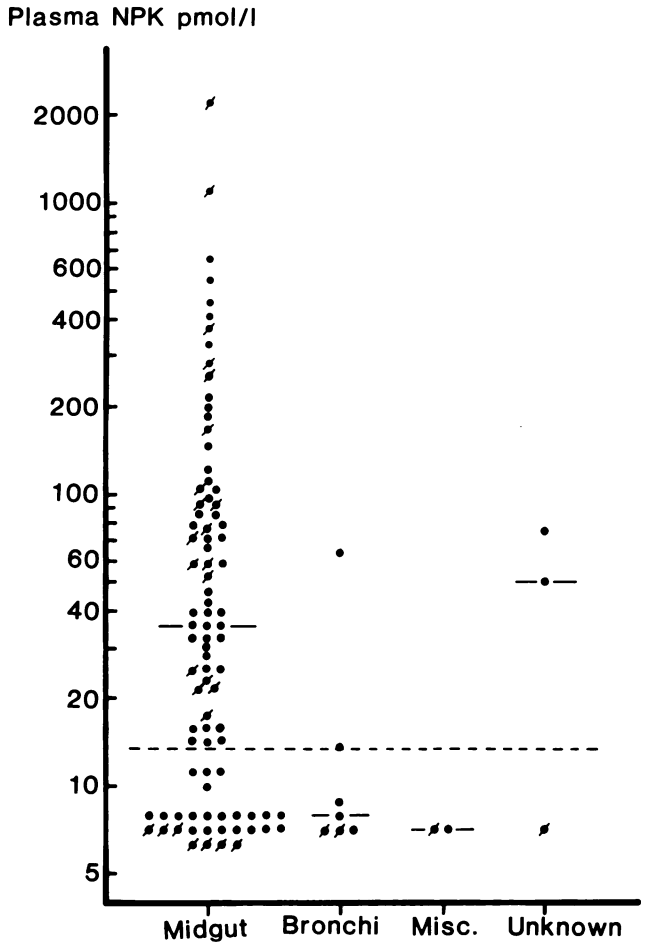

FIG. 2. The concentrations of NPK in plasma from carcinoid patients related to the localization of the primary tumor. Reference level for NPK < 12 pmol/L. NPK concentrations not taken at first visit are marked.

found (Table 8). Only three of 103 patients (3%) had no measurable tumor marker in blood or urine, and no patients had metastases to the liver.

The patients with diarrhea had somewhat higher median values for 5-HIAA and NPK than the whole group of carcinoid patients (Table 8, Figs. 5 and 6). The patients with flush had significantly ($p < 0.05$) higher levels of 5-HIAA excretion and plasma concentration of NPK than the whole group. The highest levels of 5-HIAA and NPK were seen in the group of patients who had failure of the right side of the heart and tricuspidal valve insufficiency. The median value for 5-HIAA was 885 μmol/24 hours and for NPK was 75 pmol/L. These levels were significantly higher ($p < 0.01$) than in the whole group of patients.

Clinical and Laboratory Screening

At the first referral to the hospital, 28 patients (27%) had advanced disease with a median weight loss of 10 kg (interquartile range: 7–17 kg) together with a palpable liver-edge more than 5 cm below the right costal margin. Of these patients, 17 are now dead. Nineteen patients (18%) had anemia (B-hemoglobin < 110 g/L). Thirty-six patients (35%) had a sedimentation rate above 20 mm/h, and 15 (14.5%) had leukopenia ($<4.0 \times 10^9$/L). Platelet counts of less than 150×10^9/L were found in 10 patients (9%) (Table 9). Elevated serum levels of the enzymes, ASAT, ALAT, lactate dehydrogenase, as well as serum alkaline phosphates and bilirubin were present in 22 patients. Thirteen patients (12%) showed abnormality in three of the four liver function tests, and all these patients had a liver enlarged by more than 5 cm below the right costal margin. Eleven of these patients are now dead. Twenty-seven of 45 patients with palpable liver had one or more abnormal liver function tests. Serum albumin level below 34 g/L was found in 38 patients (37%). All patients had normal serum levels of sodium, potassium, and chloride.

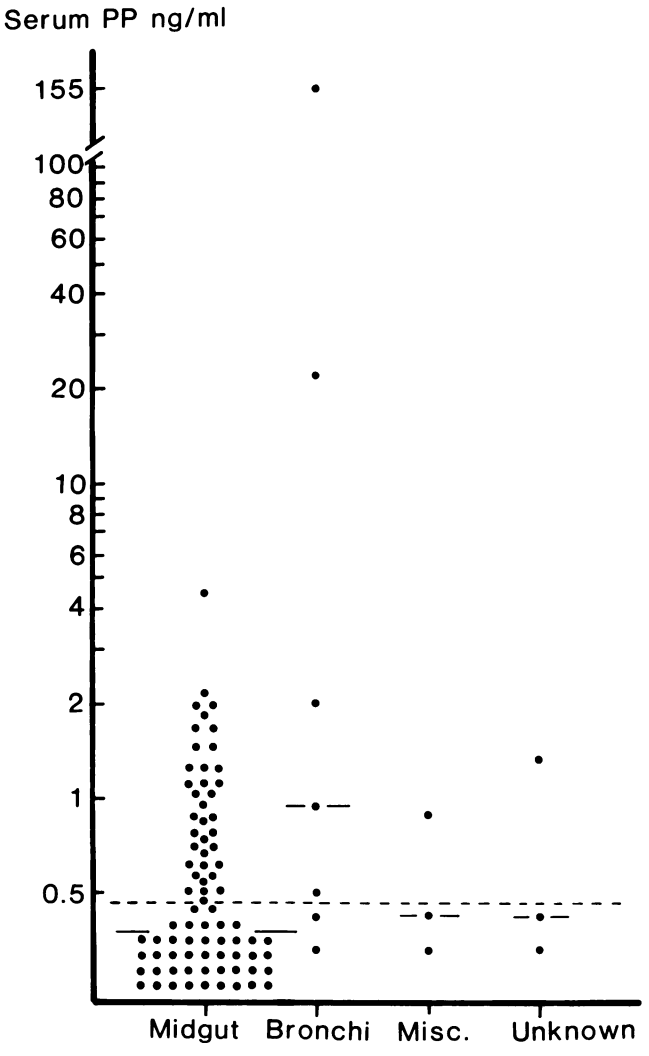

FIG. 3. The concentrations of pancreatic polypeptide (PP) in serum from patients with carcinoid tumors, related to the localization of the primary tumor. Reference level for PP < 0.4 ng/mL.

Additional Endocrine Diseases

Five patients had been treated earlier for hyperthyroidism, and a nodular goiter was found in four patients. Four patients had insulin-dependent diabetes mellitus. Endocrine screening revealed three patients with hypothyroidism and one with a primary hyperparathyroidism, verified by surgery. One patient with a bronchial carcinoid tumor had Cushing's syndrome developed probably as a result of ectopic corticotropin releasing factor (CRF) production in the tumor.

Accessory Tumor Diseases

An accessory malignant tumor was seen in five patients (5%). Two patients had mammary carcinoma. Chronic myelogenic leukemia, rectal, and prostatic carcinoma were seen in three patients. The accessory tumor disease was diagnosed after the carcinoid tumor in three of the patients.

TABLE 8. *The Median Concentrations of 5-HIAA and NPK in Relation to the Clinical Symptoms in the Patients*

Signs	N	5-HIAA (μmol/24 hours)*	NPK (pmol/L)*
Diarrhea	86	425 (178–1038)	35 (11–91)
Flush	77	539 (210–1050)	41 (17–101)
Cardiac	34	885 (683–1395)	76 (25–219)

* Numbers in parentheses are variations given as interquartile ranges.

Survival

The median time from histologically diagnosed carcinoid tumor until referral to our unit for evaluation, the doctor's delay, was 0.5 years (interquartile range: 0.2–3.2 years).

Altogether 39 of 103 patients (38%) died during the observation period. Tumor progression was the cause of death in 18 patients (46%), whereas in 14 patients (36%) cardiac insufficiency was the main reason (Table 10). All

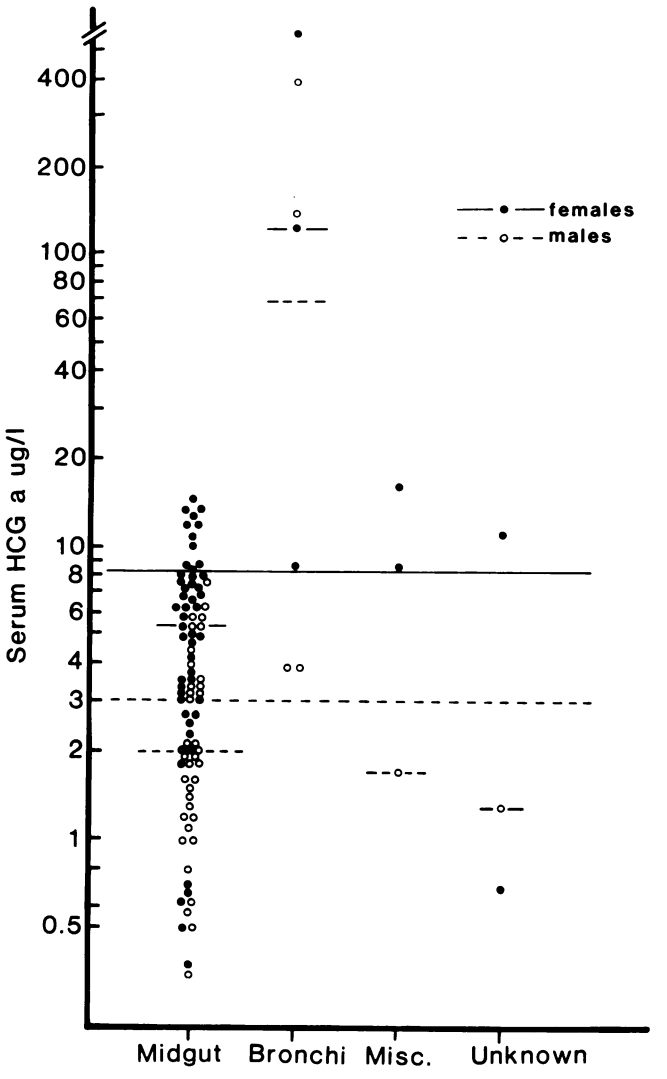

FIG. 4. The concentrations of HCG α in serum from patients with carcinoid tumors, related to localization of the primary tumor localization. Reference level for HCG α men and premenopausal women < 3.0 μg/L; postmenopausal women < 8.5 μg/l.

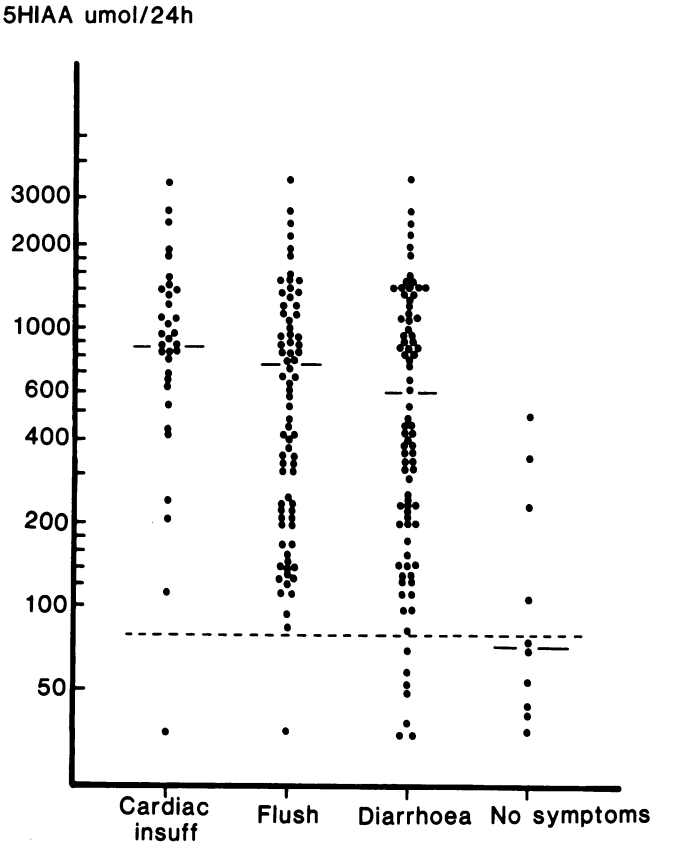

FIG. 5. The concentrations of urinary 5-HIAA excretion related to the symptoms in patients with carcinoid tumors.

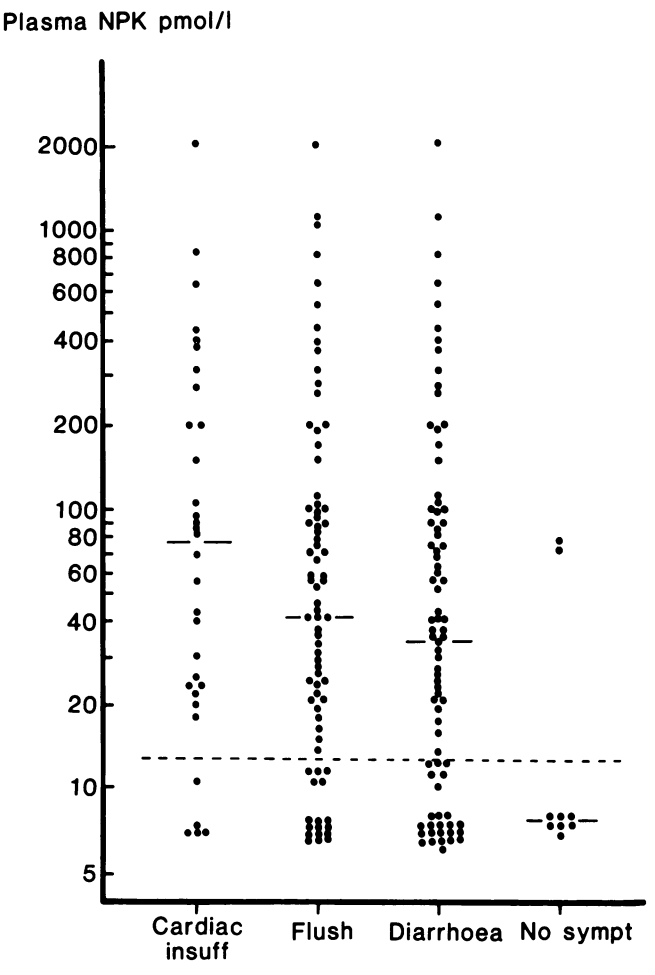

FIG. 6. The concentrations of NPK related to the patient's symptoms.

these patients also had an advanced tumor disease. The median time from carcinoid symptoms until death in these 39 deceased patients was 3.5 years, and the median time from histologic diagnosis was 2 years. For the whole patient group, the estimated 5-year survival rate

TABLE 9. *The Number of Patients with Abnormal Routine Laboratory Parameters*

Test	Reference Level	No. of Patients	%
Hemoglobin	<110 g/L	19	18
Sedimentation rate	>20 mm	36	35
ASAT	>0.6 μkat/L	15	14
ALAT	>0.6 μkat/L	18	17
Alkaline phosphatase	>4.8 μkat/L	22	21
Lactat dehydrogenase	>6.7 μkat/L	16	15
Bilirubin	>20 μmol/L	6	6
Leukocyte particle concentration	$<4 \times 10^9$/L	15	14
Leukocyte particle concentration	$>9 \times 10^9$/L	6	6
Thrombocyte particle concentration	$<150 \times 10^9$/L	10	9
Thrombocyte particle concentration	$>400 \times 10^9$/L	8	7
Creatinine	>106 μmol/L	5	4
S-albumin	<34 g/L	38	37
S-calcium	>2.6 mmol/L	5	4

TABLE 10. *Causes of Deaths in 39 Deceased Patients (Of 103 Patients) with Carcinoid Tumors*

Causes of Death	N	%
Tumor progression	18	45.2
Cardiac insufficiency	14	36.0
Myocardial infarction	1	2.5
Intestinal necrosis	1	2.5
Cushing's syndrome	1	2.5
Pulmonary emboli	1	2.5
Sepsis	1	2.5
Unknown	2	5.3
Total	39	

from the time of histologic diagnosis was 65% and from the time of definitive symptoms of a carcinoid syndrome, flush, or diarrhea was 67% (Figs. 7 and 8). Estimated median survival from the time of histologic diagnosis was 14 years, and from the time of carcinoid syndrome was 8 years. The survival curves are not adjusted for the age of the patients.

Discussion

Carcinoid tumors, originally described by Oberndorfer[26] in 1907, have proved to be a heterogeneous group of tumors. However, Williams and Sandler,[27] in 1963, proposed that carcinoids arising in three areas: the fore-gut (bronchi, stomach, duodenum), mid-gut (jejunum, ileum, appendix, and proximal colon) and hind-gut (distal colon and rectum), form three distinct groups based on histologic, biochemical, and clinical evidence. The relevance of this subdivision in the clinical situation, however, has to be further evaluated. The expression of clinical symptoms as well as the hormone production may vary among patients with different categories of carcinoid tumors. Furthermore, there are considerable differences in clinical symptoms, hormone production, and tendency to become malignant even in tumors within the same group, *e.g.*, the appendical carcinoid tumor, which is the most frequent carcinoid tumor, rarely becomes malignant or induces clinical symptoms caused by hormone production, whereas ileal carcinoid tumors often give rise to metastases and the carcinoid syndrome.[28] Thus, carcinoid tumors, which are the most frequent neuroendocrine tumors, deserve careful assessment and discerning management.

In the current prospective study of a large number of patients with carcinoid tumors, we have concentrated on hormone production related to localization of the carcinoid tumors and metastases. All patients, who were consecutively referred to our unit during an 8-year period, were investigated according to the same procedure.

In agreement with other studies that were done retrospectively, the majority of our patients with metastatic carcinoid tumors had mid-gut tumors.[28,29] As the patients were referred for treatment of clinical symptoms,

e.g., carcinoid syndrome, it is not surprising that most of the tumors were of mid-gut origin, since mid-gut carcinoid tumors most often display hormone-related clinical symptoms.

The annual incidence rate of metastatic carcinoid tumors in our study was 0.7 patients/100,000 population, and the annual incidence of the carcinoid syndrome was 0.5/100,000. This is less than found in the necropsy study by Berge and Linell[30] who demonstrated an annual incidence of malignant carcinoid tumors of 2.1 patients/100,000 population. The true annual incidence of clinically significant tumors is likely to be somewhere between the results of these two studies. Our clinical study may underestimate the true frequency because patients with only local metastases are treated surgically and thus not referred and very old individuals with metastatic tumors are rarely referred to our clinic. The average age of 59 years at the time of diagnosis is in agreement with other studies.[28,31] The lower onset ages of appendical and pulmonary carcinoid tumors is also in accordance with earlier studies.[31]

Our data emphasize the difficulty in determining the surgical curability at the time of the primary operation. Even in patients with small primary tumors (diameter < 2 cm) that are considered to be radically removed, metastatic carcinoid disease may later develop. However, appendical carcinoid tumors, which are often small (less than 2 cm) and frequently incidentally found at operation for appendicitis, seldom develop metastases. Only two of our patients with metastatic carcinoid disease had the primary tumor located to the appendix. This may support the suggestion that appendical carcinoid tumors originate from neuronal cells instead of the enterochromaffin cells,[32,33] which are the source of other mid-gut carcinoid tumors. The majority (93%) of our patients had liver metastases, but unusual localizations of metastases, such as the skeleton, the ovary, and the pituitary, were also found. These unusual localizations frequently occurred in patients with tumors of fore-gut origin.

The most frequent initial symptom was diarrhea (32%), followed by symptoms of intestinal obstruction (25%) and flushing (23%). The relative predominance of diarrhea and flushing in our material may be due to the high frequency of patients with the carcinoid syndrome (67%). The delay between initial symptom and diagnosis was shortest in patients with symptoms of intestinal obstruction (0.6 years), but considerably prolonged when the disease presented with flush and/or diarrhea (1.5–2 years).

The frequency of cardiac involvement was in the same range as found by Graham-Smith, who found cardiac involvement in 41% of patients with carcinoid syndrome.[34] All but one of our patients with tricuspidal valve disease had a primary tumor of mid-gut origin.

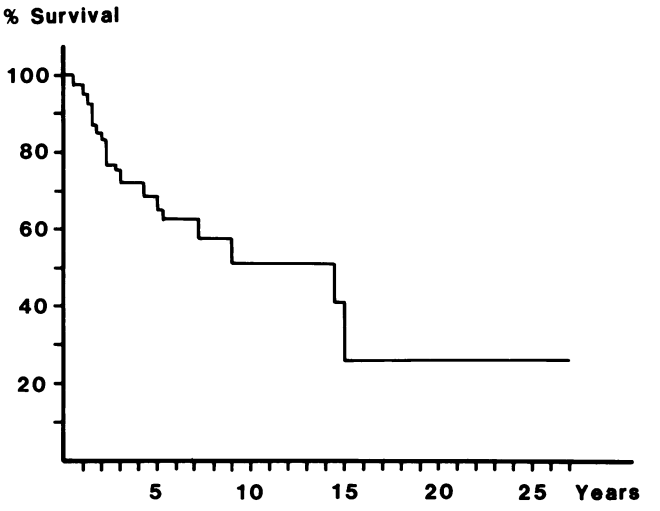

FIG. 7. Survival from the time of histologic diagnosis in patients with carcinoid tumors. The estimated 5-year survival rate was 65%.

The mean age at diagnosis of a carcinoid tumor and cardiac failure did not diverge from that of the rest of the patients, but the median duration of symptoms before referral and start of treatment was 2 years, which is somewhat longer than for other patients. The patients in whom carcinoid cardiac involvement developed presumably have hormonally active tumors, secreting a spectrum of biologically active substances, and the levels of urinary 5-HIAA and plasma NPK were significantly higher in this group than in all patients (Figs. 5 and 6). None of our patients with bronchial carcinoid tumors displayed cardiac valve disease, although these patients had high excretion of 5-HIAA in the urine. However, plasma NPK was not significantly increased in patients with bronchial carcinoid tumors and liver metastases (Fig. 2). Serotonin has been proposed earlier to be an etiologic factor for the development of carcinoid heart disease, including fibrosis of the cardiac valves. How-

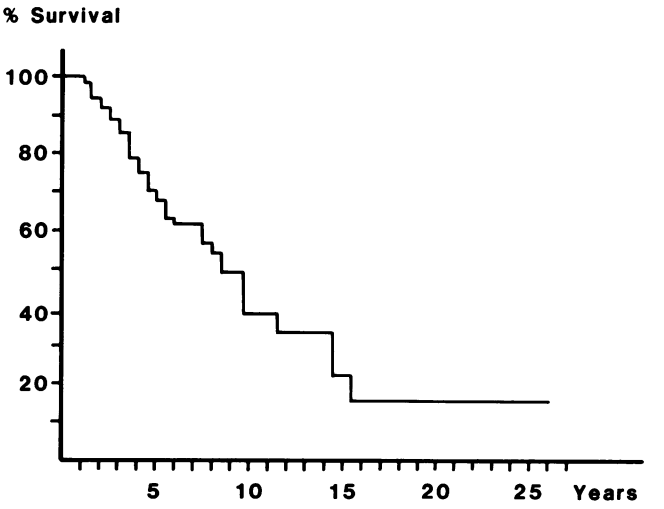

FIG. 8. Survival from the time of definite symptoms in patients with carcinoid syndrome. The estimated 5-year survival rate was 67%.

ever, tachykinins, such as neurokinin A and substance P, have recently been demonstrated to stimulate fibroblast growth,[35] and the same tachykinins are known to be secreted in a majority of our patients with mid-gut tumors. Thus, tachykinin-like substances might be etiologic agents for the fibrosis seen in the carcinoid heart disease.

There was a difference in tumor-secreted products between patients with mid-gut and fore-gut carcinoid tumors as stated previously. High levels of urinary 5-HIAA were seen in both groups, but NPK was predominantly recorded in patients with mid-gut tumors. HCG α and PP were found in high levels in patients with bronchial carcinoid tumors, whereas these peptides were only slightly elevated in the mid-gut group. This is in accordance with the theory of Williams and Sandler,[27] which proposed different origin and biochemistry of bronchial and ileal carcinoid tumors.

Flushing was seen in 77 patients; all but one patient had elevated urinary 5-HIAA, whereas 60 patients had elevated plasma NPK. Both serotonin and tachykinins are vasoactive substances that may be responsible for the carcinoid flush. However, the serotonin receptor antagonist (Ketanserin®) can eradicate the diarrhea but not the flush,[36] which indicates that serotonin cannot be the only mediator of flush. Furthermore, the somatostatin analogue SMS 201-995 (Sandoz Pharmaceuticals Corporation, Stockholm, Sweden) can block the carcinoid flush, and in parallel, reduce the plasma NPK levels, indicating a role of tachykinins in the etiology of flush (unpublished data). Similarly, plasma NPK is known to increase during spontaneous and pentagastrin stimulated flush.[4] In patients with malignant carcinoid tumor, urinary 5-HIAA and plasma NPK were the best "markers," especially in tumors of mid-gut origin.

Plasma concentrations of PP and HCG α have been reported earlier to be frequently elevated in patients with malignant carcinoid tumors.[37,38] However, in this more extended study, the frequency is somewhat lower, which might be explained by the fact that in the current study we have only reported the concentrations at the time of referral to the unit. However, the concentrations frequently increased with time. Another explanation might be that initially only advanced cases were referred, whereas more recently, many patients with less advanced disease have been sent to us.

Eighty-six patients had diarrhea, and of these patients, 79 had elevated urinary 5-HIAA and 61 had elevated plasma NPK. The diarrhea may possibly depend on the intestinal effects of serotonin secreted from the tumor,[36] but some patients may also display short-bowel syndrome after resection of intestinal carcinoid tumors. Local mechanical effects on the gut by the tumor itself cannot be ruled out as some patients had normal circulating serotonin levels and normal urinary 5-HIAA excretion.

Seven patients had no detectable metastases in the liver. However, two patients had elevated 5-HIAA excretion in the urine and symptoms of both flush and diarrhea, and one patient had elevated 5-HIAA excretion and no symptoms. In addition, one patient had elevated serum HCG α and diarrhea. Only three patients revealed no tumor markers to be followed and none of them had liver metastases. The lack of relation between symptoms, urinary 5-HIAA excretion, and liver metastases might depend on the detection limits of the CT scan and ultrasound techniques, which are unable to perceive lesions less than 0.5 cm in diameter. However, occasionally patients with carcinoid tumors of mid-gut origin may have the carcinoid syndrome in the absence of hepatic metastases.[39]

Most patients had normal results of routine laboratory tests. Elevated levels of liver enzymes, particularly alkaline phosphatases, occurred, especially in patients with large metastases in the liver, and among our patients, 11 of 13 with elevated levels of liver enzymes and enlarged liver are now dead. Thus, these findings together with loss of weight seem to be a poor prognostic factor.

An accessory malignant neoplasm was found in only five patients, which is a lower frequency than published in other reports: Barclay and Shapira reported a frequency of 17%[40] and Dawes et al. reported a frequency of 15%.[41] The Mayo Clinic study[28] had a second malignancy in 5% of patients, which is comparable with our findings. The differential diagnosis between carcinoid tumor, mammary cancer, and small cell lung cancer may be difficult in some instances, and the exact diagnosis frequently depends on the experience of the pathologist.

The prognosis of the patients with carcinoid tumors varies depending on the localization of the primary tumor and the stage of disease. In patients with only local metastases, Dawes et al.[41] found that 80% of the patients lived for 5 years. When liver metastases were present, the 5-year survival rate was 19–38%.[28,42,43] Our findings of an estimated 5-year survival rate of 65% in our patients with malignant carcinoid tumors seems interesting. Although different patient materials might not be compared, our data might indicate that new therapeutic alternatives such as interferon, which was used in 92 of the patients,[11] and new somatostatin analogues (SMS 201-995), which were used in about 15 patients, might add years to life and not only improve the quality of life. Besides earlier awareness and diagnosis of the disease, this might contribute to the better survival data.

In conclusion, the current prospective study of malignant carcinoid tumors demonstrates that mid-gut tumors, except appendical tumors, often become malignant, and that diarrhea and flushing are the most frequent clinical symptoms when liver metastases have appeared. Furthermore, cardiac insufficiency is often seen,

especially in patients with mid-gut carcinoid tumors and carcinoid syndrome. Nearly all patients have one or more tumor-secreted products, which can be used as markers for both diagnosis and follow-up. Urinary 5-HIAA excretion is elevated in carcinoid tumors irrespective of the origin of the primary tumor, whereas levels of NPK is elevated mainly in patients with mid-gut carcinoid tumors. Fore-gut tumors, on the other hand, more often present high levels of HCG α and PP. The most frequent causes of death were tumor progression followed by carcinoid heart failure. Our survival data are somewhat more favorable than those earlier reported, which may indicate development of more effective therapeutic alternatives such as interferon and somatostatin analogues.

References

1. Williams RH. *In* Textbook of Endocrinology. W. B. Saunders, 1982; Chapter 10; 564–576.
2. Oates JA, Pettinger WA, Doctor RB. Evidence of the release of bradykinin in carcinoid syndrome. J Clin Invest 1966; 45:173–178.
3. Norheim I, Theodorsson-Norheim E, Brodin E, et al. Antisera raised against eledoisin and kassinin detect elevated levels of immunoreactive material in plasma and tumor tissue from patients with carcinoid tumors. Regulatory Peptides 1984; 9:245–257.
4. Norheim I, Theodorsson-Norheim E, Brodin E, Öberg K. Tachykinins in carcinoid tumors: their use as a tumor marker and possible role in carcinoid flush. J Clin Endocrinol Metab 1986; 63:605–611.
5. Sandler M. Prostaglandins in amine-secreting tumors. Lancet 1968; 2:1053–1054.
6. Waldenström J, Pernow B, Silwer H. Case of a metastatizing carcinoma (argentaffinoma?) of unknown origin showing peculiar red flushing and increased amounts of histamine and 5 hydroxytryptamine in blood and urine. Acta Med Scand 1956; 156:73–83.
7. Dabek JT. Bronchial carcinoid tumor with acromegaly in two patients. J Clin Endocrinol Metab 1974; 38:329–333.
8. Öberg K, Norheim I, Lundqvist G, Wide L. Serum growth hormone in patients with carcinoid tumors, basal levels and response to glucose and thyrotrophin releasing hormone. Acta Endocrinol 1985; 109:13–18.
9. Steel K, Baerg RD, Adams DO. Cushing's syndrome in association with a carcinoid tumor of the lung. J Clin Endocrinol Metab 1967; 27:1285–1289.
10. Scheithauer BW, Carpenter PC, Bloch B, Brazeau P. Ectopic secretion of a growth hormone-releasing factor. Report of a case of acromegaly with bronchial carcinoid tumor. Am J Med 1984; 76:605–616.
11. Öberg K, Funa K, Alm G. Effects of leucocyte interferon on clinical symptoms and hormone levels in patients with midgut carcinoid tumors and carcinoid syndrome. N Engl J Med 1983; 30:129–133.
12. WHO Expert Committee on Diabetes Mellitus, Second Report. Techn Rep. Ser. 646. Geneva: WHO, 1980.
13. Hällgren R, Lundqvist G, Chance RE. Serum levels of human pancreatic polypeptide in renal disease. Scand J Gastroenterol 1977; 12:923–927.
14. Öberg K, Wide L. HCG subunits as tumor markers in patients with endocrine pancreatic tumours and carcinoids. Acta Endocrinol 1981; 8:256–260.
15. Almqvist S, Telenius-Berg M, Wästhed B. Serum calcitonin in medullary thyroid cancer. Acta Med Scand 1974; 196:177–180.
16. Lundqvist G, Wide L. Serum gastrin determination with a radioimmunosorbent technique. Clin Chem Acta 1977; 79:357–362.
17. Theodorsson-Norheim E, Norheim I, Öberg K, et al. Neuropeptide K: a major tachykinin in plasma and tumor tissues from patients with carcinoid tumors. Biochem Biophys Res Comm 1985; 131:77–85.
18. Wahlund KG, Edlen B. Simple and rapid determination of 5-hydroxyindole-3-acetic acid in urine by direct injection on a liquid chromatographic column. Clin Chem Acta 1981; 110:71–76.
19. Lindgren P-G. Percutaneous needle biopsy: a new technique. Acta Radiol (Diagn) 1982; 23:653–656.
20. Grimelius L. A silver nitrate stain for A2 cells in human pancreatic isles. Acta Soc Med Uppsala 1968; 73:243–278.
21. Singh I. A modification of the Masson Hamperl method for staining argentaffin cells. Anat Anz 1964; 115:81–82.
22. Sevier AC, Munger BL. A silver method for paraffin sections of neural tissue. J Neuropathol Exp Neurol 1965; 24:130–135.
23. Consolazione A, Milstein C, Wright B, Cuello A. Immunocytochemical detection of serotonin monoclonal antibodies. J Histochem Cytochem 1981; 29:1425–1430.
24. Conover WJ. Practical Nonparametric Statistics. New York: John Wiley & Sons, 1980.
25. Colton T. Statistics in Medicine. Boston: Little, Brown and Co, 1974.
26. Oberndorfer S. Karcinoide Tumoren des Dunndarms. Frankfurt Z Pathol 1907; 1:426–429.
27. Williams ED, Sandler H. The classification of carcinoid tumors. Lancet 1963; 1:238–239.
28. Davis Z, Moertel CG, McIlrath DC. The malignant carcinoid syndrome. Surg Gynecol Obstet 1973; 137:637–644.
29. Mengel CE, Shaffer RD. The carcinoid syndrome. *In* Holland JF, Frei E III, eds. Cancer Medicine. Philadelphia: Lea & Febiger, 1973; 1584–1594.
30. Berge T, Linell F. Carcinoid tumors. Acta Pathol Microbiol Scand Sect A 1976; 84:322–330.
31. Mårtensson H, Nobin A, Sundler F. Carcinoid tumors in the gastrointestinal tract: an analysis of 156 cases. Acta Chir Scand 1983; 149:607–616.
32. Wilander E, Lundqvist M, Movin T. S-100 protein in carcinoid tumours of appendix. Acta Neuropathol 1985; 66:306–310.
33. Lundqvist M, Wilander M. Subepithelial neuroendocrine cells and carcinoid tumours of the human small intestine and appendix. A comparative immunohistochemical study with regard to serotonin, neuron-specific enolase and S-100 protein reactivity. J Pathol 1986; 148:141–147.
34. Graham-Smith DF. The carcinoid syndrome. Am J Cardiol 1968; 21:376–387.
35. Nilsson J, Von Euler AM, Dalsgaard CJ. Stimulation of connective tissue cell growth by substance P and substance K. Nature 1985; 315:61–63.
36. Ahlman H, Dahlström A, Grönstad K, et al. The pentagastrin test in the diagnosis of the carcinoid syndrome: blockade of gastrointestinal symptoms by Ketanserin. Ann Surg 1985; 201:81–86.
37. Öberg K, Grimelius L, Lundqvist G, Lörelius LE. Update on pancreatic polypeptide as a specific marker for endocrine tumours of pancreas and gut. Acta Med Scand 1981; 210:145–152.
38. Öberg K, Wide L. HCG α and HCG-subunits as tumor markers in patients with endocrine pancreatic tumours and carcinoids. Acta Endocrinol 1981; 98:256–260.
39. Feldman, Jones. Carcinoid syndrome from gastrointestinal carcinoids without liver metastases. Ann Surg 1982; 196:33–37.
40. Barclay THC, Shapira DV. Malignant tumors of the small intestines. Cancer 1983; 51:878–881.
41. Dawes L, Schulte WJ, Condon RE. Carcinoid tumors. Arch Surg 1984; 119:375–378.
42. Godwin JD. II Carcinoid tumors: An analysis of 2837 cases. Cancer 1980; 45:104–107.
43. Zeitels J, Naunheim K, Kaplan EL, Strauss F II. Carcinoid tumors. A 37-year experience. Arch Surg 1982; 117:732–737.