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Original article

Recent aspects in diagnosis, treatment and follow-up in a series of 116 carcinoid tumors of the gastrointestinal tract

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SUMMARY

Aim of the study: We present in this study our diagnostic and therapeutical approach in a series of 116 patients (pts) with carcinoid tumors originating from the Gastrointestinal (GI) tract and pancreas, in parallel with a brief review of the literature.

Methodology: One hundred and sixteen (75 females and 41 males, aged from 16 to 85 years) pts were included.The diagnosis was confirmed histologically. Pts were evaluated several times per year with clinical, biochemical and imaging assesments, including neuroendocrine markers [Chromogranin-A(CgA),5-HIAA] and OCTREOSCAN. The follow-up period ranged between 1.5 to 12.5 years (mean time: 5 years and 3 months) and it is still in progress.

Results: Pts' symptoms depended mainly on the location of the primary tumors and the existence or not of metastases. CgA and 5-HIAA levels were increased especially in metastatic tumors. OCTREOSCAN was positive in 94% pts with metastatic disease. The majority of pts underwent a surgical resection of the primary tumor, while in 18%, an endoscopic polypectomy was performed. Somatostatin analogues when used, resulted in control of symptoms (71%), stabilization of tumor growth (66%) or tumor shrinkage (8.5%).

Conclusions: a) Tumor size and dispersion of disease highly predict the evolution of pts b) serum Chromogranin-A seems to be a very useful tumor marker c) OCTREOSCAN contributes to the better localization of the primary tumors and their metastases d) surgery is the treatment of choice in non-metastatic tumors and, is recommended when possible, in already metastatic ones and e) in metastatic disease, Somatostatin analogues improve the pts' quality of life and result in stabilization of disease in most cases. The results of most studies are in agreement with our experience.

Key words: Carcinoid tumors,Chromograninn -A, Somatostatin Receptor Scintigraphy, carcinoid syndrome, surgical excision, Somatostatin analogues, neuroendocrine tumors.

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INTRODUCTION

Carcinoids of gastrointestinal (GI) tract have been proved to be slowly growing malignancies, which are thought to arise from neuroendocrine cells and characterized histologically by positive reactions to silver stains and to markers of neuroendocrine tissue, including neuronal-specific enolase (NSE), synaptophysin and chromogranin. These tumors have commonly been found to secrete serotonin or histamine and also a variety of other hormones and bioactive peptides, such as neuropeptide K, substance P etc. The release of these substances into the systemic circulation is thought to cause the symptoms of "carcinoid syndrome", including cutaneous flushing, wheezing, diarrhea and less frequently right-sided valvular heart disease, myopathy and skin pigmentation.[1]

The first classification of carcinoid tumors was based on their origin from the embryonic foregut, midgut, and hindgut. Carcinoid tumors arising from these sites were distinguished based on histochemical reaction with silver salts, production of serotonin and its principal metabolite, 5-hydroxyindoleacetic acid (5-HIAA), and the presence of the carcinoid syndrome. Inconsistencies within this

classification have become readily apparent with the advances in understanding of the complex biology of the dispersed endocrine cells. The GI tract contains at least 14 different endocrine cell types, including the enterochromaffin cell, which classically has been associated with carcinoid tumors. Modern classification of GI endocrine tumors is based on: (1) the organ of origin such as the stomach. (2) clinical associations such as coincidence of type 1 gastric carcinoids with chronic atrophic gastritis. (3) histological features relating to the degree of differentiation, and (4) histochemical criteria intended to discover the endocrine cell of origin of the tumor, for example, a gastrinoma. In recent years, the term "carcinoid" tumor has been criticized as outdated and non-specific. At present, we are in a transition phase from the classical histological description of a tumor as "carcinoid" to alternative terminology based on additional modern criteria. The new World Health Organization (WHO) classification of GI endocrine tumors acknowledges the classical nomenclature by recommending use of "carcinoid" as synonymous with well-differentiated endocrine tumor and "malignant carcinoid" as an alternative to well-differentiated endocrine carcinoma. This alternative terminology should not present a problem when used for a tumor, which is not associated with a recognized syndrome of excessive hormone secretion, such as a rectal carcinoid, or in other words, a well-differentiated endocrine tumor of the rectum. In the case where a GI endocrine tumor is known to produce a hormone associated with a clinical syndrome, the new WHO classification advises restricting the term "carcinoid" for tumors associated with the carcinoid syndrome, a well-established and distinct clinical entity. This would avoid confusion arising from describing a somatostatinoma or gastrinoma as a carcinoid tumor.

The overall incidence of GI carcinoids in the United States has been estimated to be 1 to 2 cases per 100,000 people.[2-4] However, their true incidence is higher, as it has been proved in large autopsy series. In many cases, these tumors are discovered incidentally at the time of surgery for other abdominal disorders and their presence may be undetectable for many years.

The age distribution of GI carcinoids ranges from the second to the ninth decade, with the peak incidence occurring between the ages of 50 and 70.[5]

Currently, the estimation of serum Chromogranin-A, as well as, the use of Somatostatin Receptor Scintigraphy (SRS) and Somatostatin analogues have made a major breakthrough in the diagnosis and treatment of carcinoid tumors.

Among a total number of 214 patients (pts) with neuroendocrine tumors, (Table 1) we present in this study 116 pts with carcinoids tumors originated from the GI tract, who have been diagnosed and treated in our Section of Gastrointestinal Neuroendocrinology, during the last 15 years. Also, we analyse the clinical and pathological characteristics of this category of neoplasms and describe our diagnostic and therapeutical approach, focusing in the contribution of serum Chromogranin-A, SRS and Somatostatin analogues.

MATERIALS AND METHODS

One hundred and sixteen (116) pts were included in our study. Seventyfive of them (64.6%) were female (aged from 16 to 85 years, median age 50.5 years) and fourty-one (35.4%) were male (aged from 26 to 79 years, median age 52.5 years). Tumor location is shown in *Table 2*. The clinical suspicion was confirmed in all cases by histopathological features and immunohistochemical markers, after surgical excision of the primary tumor, or after biopsies taken during endoscopy of the GI tract. As immunohistochemical markers were used: NSE (Dako M0873 dilution 1:50), Chromogranin A (Dako A 0430 dilution 1:100), Synaptophysin (Dako M0776, dilution 1:10). Following confirmation of diagnosis, all patients

Table 1. Patients with neuroendocrine tumors treated in the section of gasrointestinal neuroendocrinology, "Laikon Ge-neral Hospital, Athens, Greece

TUMOR	No OF PATIENTS	%
CARCINOIDS OF GI TRACT	116	54.3
CARCINOIDS OF THE THUMUS	4	1.9
PULMONARY CARCINOIDS	18	8.5
GASTRINOMAS	33	15.5
INSOULINOMAS	14	6.5
VIPOMAS	11	5.1
SOMATOSTATINOMAS	2	0.9
GLUCAGONOMAS	1	0.4
PANCREATIC POLYPEPTIDIOMAS	1	0.4
NON-FUNCTIONAL	14	6.5
TOTAL	**214**	**100**

Table 2. Tumor location

TUMOR LOCATION	No of Patients	%
Stomach	19	16
Duodenum	6 *	5
Pancreas	4	3.5
Jejunum and ileus	31	27
Appendix	38	33
Colon	7	6
Rectum	11	9.5
Sum	116	100

*1 located in the ampulla of Vater

were evaluated several times per year with clinical, biochemical and radiographic assesments. The follow-up data included: 1) measurement of 24-hour secretion of urinary 5- hydroxyindole-acetic acid (a metabolite of serotonin, 5-HIAA) and estimation of serum Chromogranin-A (CgA) every three or six months, depending on the presence or not of metastases, 2) measurement of serum neurohormonal peptides such as gastrin and pancreatic polypeptide (PP), when necessary, 3) liver biochemistry tests every three months, 4) an abdominal ultrasound (US) every four months, 5) an abdominal Computed Tomography (CT) scan every six months, 6) a Somatostatin-Receptor-Scintigraphy (OCTREOSCAN, Mallinckrodt Medical BV, Petten, Holland) once a year. This test is supplied as a two vial kit. The first contain ^{111}In as $^{111}In\ Cl_3$ diluted in 1.1ml hydrochlorid acid and the other lyophilised pentetreotide. The radiolabelled ^{111}In – DTPA-octreotide was administered as an intravenus bolus. Whole body scanning and plannar images were obtained with a large field of view gamma camera. Images were obtained 24 and sometimes 48 hours after tracer administration and 7) an Echocardiography, once a year in patients with metastatic disease.

The follow-up period ranged between 1.5 to 12.5 years (mean time 5 years and 3 months) and it is still in progress.

The patients were classified finally as alive with no evidence of disease (ANED), alive with disease (AWD) and dead with disease (DWD)

RESULTS

Clinical features

Some pts were asymptomatic, while in some others symptoms were not specific. In all cases of appendiceal carcinoids, diagnosis was made after operation for acute appendicitis. In the rest of the symptomatic pts, symptoms and clinical features correlated mainly with the location of tumors, or depended on the presence of hepatic metastases. It should be pointed out that all pts who presented with symptoms of "carcinoid syndrome" had already liver metastases.

The symptoms of our pts at the time of diagnosis and the endoscopic or surgical findings are summarized in Tables 3, 4 respectively.

Rindi et al[6] and Stamm et al[7] have proposed two classification systems for gastric and duodenal carcinoids respectively, which are shown in Table 5, 6.

According to these, 13/19 (69%) pts with gastric carcinoids are classified as type I, 3/19 (15.5%) as type II and 3/19 (15.5%) as type III. On the other hand, 5/6 (83%) pts had type I duodenal carcinoids, while the patient with the tumor located at the ampulla of Vater had type II duodenal carcinoid, without, however, any evidence of neurofibromatosis.

Metastases

Most pts with gastric, duodenal and colorectal carci-

Table 3. Presenting symptoms of patients

Symptoms / Tumor location	Dyspepsia Patients %	GI Bleeding Patients %	Iron Defficiency anemia Patients %	Pernicious Anemia Patients %	Acute Intestinal Obstruction Patients %	"Carcinoid Syndrome" Patients %	Disturbed defecation Patients %
Stomach	37.5	25	-	37.5	-	-	-
Duodenum	66.6	16.7	16.7	-	-	-	-
Pancreas	75	-	-	-	-	25	-
Small intestine	-	-	-	-	55	45	-
Colon	-	57	-	-	-	-	43
Rectum	-	33.4	-	-	-	-	66.6

Table 4. Endoscopic - Surgical findings

Endoscopic / Surgical findings / Tumor location	Atrophic Gastritis + multiple polyps Patients %	Polyps > 2cm Patients %	Polyps < 2cm Patients %	Ulcers Patients %	Tumor masses < 1cm Patients %	Tumor masses 1 – 2 cm Patients %
Stomach	69	21	-	10.5	-	-
Duodenum	-	33.4 *	66.6	-	-	-
Small intestine	-	-	-	-	-	90
Appendix	-	-	-	-	85	15
Colon	-	43	57	-	-	-
Rectum	-	36	64	-	-	-

* (the polyp located in the ampulla was larger than 3cm)

Table 5. Classification and characteristics of gastric carcinoids

TYPE	Main characteristic	Frequency	Serum Gastrin	Histology	Metastases
I	Associated With chronic Atrophic gastritis	65%	Increased	Tumor consists of mainly ECL cells	Rare
II	Associated With Zollinger Ellison Syndrome And MEN-I	14%	Increased	Tumor consists of mainly ECL cells	More frequent than type I Less Frequent than type II
III	Sporadic	21%	Normal	Tumor consists of ECL , enterochromafin and X cells	Frequent

Table 6. Classification of duodenal carcinoids

Type	Tumor usual location	Characteristics
I	Proximal duodenum	Gastrin-producing Associated with ZES and MEN I
II	Ampulla of Vater	Somatostatin-producing Often a component of neurofibromatosis
III	Ampullary-periampulary region	Gangliocytic paragangliomas
IV	Outside of the ampulla	Serotonin ,Calcitonin and Pancreatic Polypeptide producing
V	Ampulla of Vater	Highly-malignant neoplasms

noids, appearing as large polypoid (>2cm) lessions (13/43, 30.2%), already had distal metastases at the time of diagnosis (4/13, 31%) or developed them two years later (7/13, 54%).

Furthermore and despite the smaller size of the primary tumor, many pts with carcinoids of jejunum and ileus already had metastases to the regional lumph nodes and to the liver at the time of diagnosis (14/31, 45%), while 9/31 (29%) developed them, within five years after resection of the primary tumor.

Finally, ¾ (75%) pts with pancreatic carcinoids also had hepatic metastases: two at the time of diagnosis and one two years later.

None of the pts with appendiceal carcinoids was found to have metastases, during the operation or during the follow-up period.

Laboratory findings

A) Biochemical

At the time of diagnosis, urinary 5-HIAA was significantly (up to ten times the upper normal limit) or moderately elevated (up to two or three times the upper normal limit) in all patients with metastatic tumors of the small intestine and slightly elevated in the pts with metastatic tumor of the proximal colon and pancreas. However, it was within normal limits in patients with metastatic tumors of stomach, duodenum and distal colon, as well as, in all patients with no evidence of metastases. Furthermore, urinary 5-HIAA was increased in the patients with carcinoids of small intestine and pancreas, who developed metastases during the follow-up period, even though symptoms of "carcinoid syndrome" were absent at the same time.

Serum chromogranin-A levels were significantly elevated in all patients with metastases, independently of

the location of primary lession, although they were higher in those with tumors of the small intestine *(Table 7)*. On the contrary, in patients with non-metastatic tumors, CgA was within normal limits, except for two patients with gastric carcinoids, in whom it was slightly elevated (less than twice the upper normal limit). A strong correlation between the symptom severity and CgA levels was noticed in most of the patients with metastatic tumors of the small intestine, while in all the patients who responded to treatment a marked reduction of CgA levels was also observed. Finally, serum CgA was increased in all patients who developed metastases during the follow-up period, as with urinary 5-HIAA.

Serum gastrin was increased in most patients with gastric and duodenal carcinoids: slightly raised (<200 pmol/l) in 2/19 and in 4/6 of them, respectively, moderately raised (300-500 pmol/l) in 10/19 with gastric ones, while in two patients , one with duodenal and one with gastric carcinoid, serum gastrin levels were greater than 1000 pmol/l. The latter patient also had hypercalcemia at the time of diagnosis and further investigation revealed a pituitary adenoma and two adenomas of the parathyroid glands. Thus, this patient with type II gastric carcinoid also fulfilled the criteria for MEN I syndrome.

B) Imaging studies – Localisation procedures

Previously imaging studies and localisation procedures had included Barium enema (Figure 1), angiographies and pulmonary X-rays. Nowadays, the basic program includes CT-scan, MRI, Ultrasound investigations, upper GI endoscopy (Figure 2) and colonoscopy. Furthermore, endoscopic ultra-sound (EUS) provides useful information on local tumor invasion and regional lymph node involvement, in order to choose between endoscopic or surgical treatment in polypoid carcinoids of the GI tract. This procedure (Figure 3) was applied in all of our patients, before the endoscopic polypectomy, to rule out invasion of the intestinal muscularis propria and regional lymph nodes.

However, the localisation of these tumors and the detection of metastases have been significantly improved, by the introduction of Somatostatin Receptor Scintigra-

Table 7. Mean values of chromogranin-A in patient with metastatic carcinoid tumors (Normal values: 14-98 ng/ml)

TUMOR LOCATION	CHROMOGRANIN-A (Mean values , ng/ml)
Stomach	848
Duodenum	352
Pancreas	953
Small intestine	1018
Colon	741

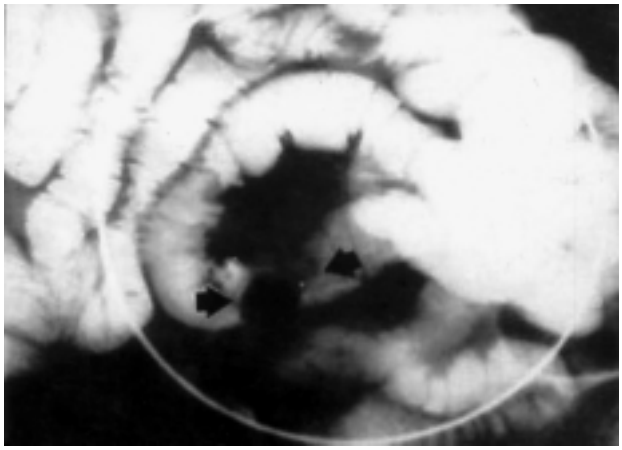

Figure 1. Enteroclysis in a patient with carcinoid tumor of the small intestine

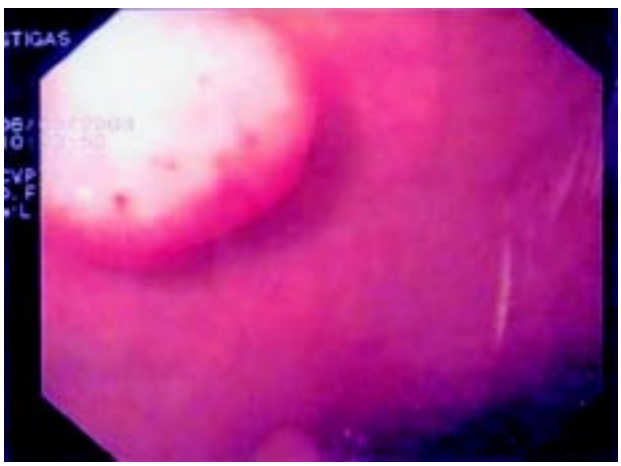

Figure 2. Upper GI endoscopy of a patient with a carcinoid of 2cm diameter located at the bulb of the duodenum.

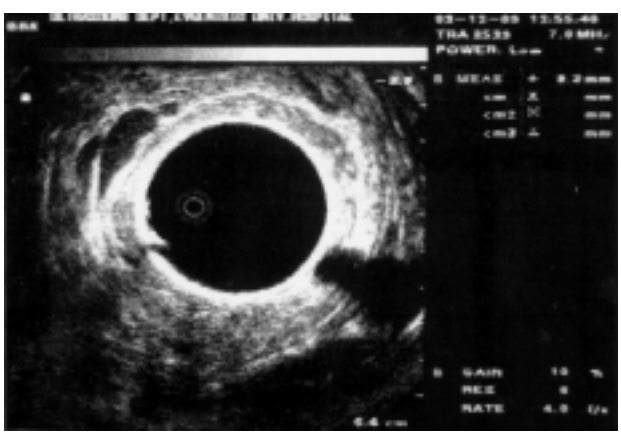

Figure 3. EUS of a patient with a rectal carcinoid, showing invasion of the muscularis propria. This patient underwent a surgical excision of the tumor

phy. Thus, all of our patients underwent ^{111}In – DTPA-D-Phe – Octreotide scintigraphy (OCTREO-SCAN) at the time of diagnosis and during the follow-up period. This specific scintigraphy revealed metastases to the liver, lymph nodes and bones in the vast majority (94%) of patients with metastatic tumors, while the sensitivity of conventional imaging methods U/S, C/T, MRI at the same time was 54%, 66 %, 79%, (mean senisitivity 66%), respectively. (Figure 4). Furthermore, the detection of a previously unknown primary site in 5/31 (16%) pts with a tumor of the small intestine was provided only by OCTREOSCAN. It should be also pointed out that, in a patient with carcinoids of the sigmoid colon (surgically treated), who complained of pain in pelvis, the OCTREOSCAN revealed a local reccurence in the sigmoid colon, as well as a metastasis in the iliac bone, not detected by a 99-MTC-MDP bone scanning, which was performed 20 days before. (Figure 5) However, OCTREOSCAN was false negative in 2/37 (5.5%) patients with metastatic tumors. In these patients , detection of metastases was achieved only by MRI. Finally, a SPECT (Single Photon Emission Computed Tomography) technique which was used in 8 patients during OCTREOSCAN, when the specific origin of the metastatic lession was not distinguishable, helped us to make the right decision about the treatment of those patients. It showed that, in 2 cases the lessions were not in the liver but in the peripancreatic region. (Figure 6A, 6B)

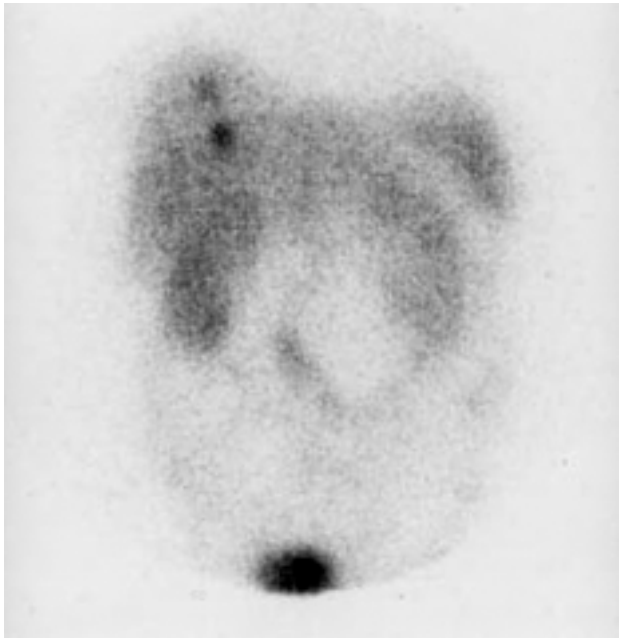

Figure 4. OCTREOSCAN of a patient with carcinoid tumor of the small intestine, revealing two hepatic metastatic lessions. The C/T scan and the MRI, were normal at the same time

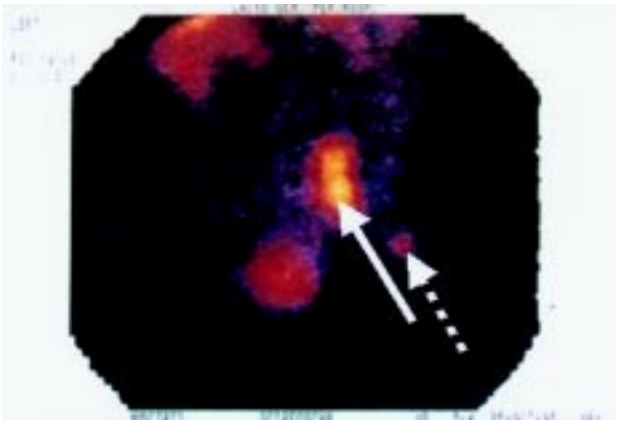

Figure 5. OCTREOSCAN of a patient with carcinoid tumor of the sigmoid colon. *Continuous arrow*: local reccurence after endoscopic polypectomy. *Intermittent arrow*: metastasis in the ileac bone.

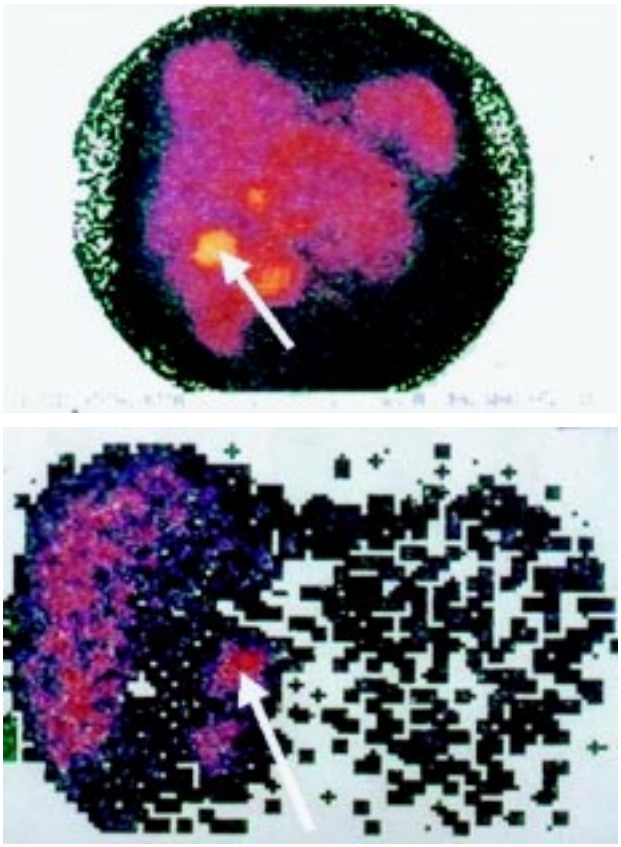

Figure 6. Histology of a patient with appendiceal carcinoid tumor, **A.** OCTREOSCAN, **B.** SPECT OCTREOSCAN

Pathology

Recently, a new histopathological classification system has been proposed for these tumors, taking into account not only their embryologically based divisions, but also the variations in their histologic characteristics.[8] According to this, they are classified as well-differentiated neuroendocrine tumors and well-differentiated or poorly differentiated neuroendocrine carcinomas. The histopathological characteristics of tumors (Figure 7) in our study are summarized in *Table* 8

Treatment

Surgery or endoscopic excision of the primary lession was the initial treatment in many of our patients and is summarized in *Table 9.* The precise surgical management of the tumors of the stomach, duodenum, small intestine, appendix or colon depended on the localization and the size of the lession. Even in patients with metastatic disease at the time of diagnosis, an aggressive surgical approach was performed, as far as possible. Finally, the patients, in whom a local recurrence developed underwent a second operation.

The patient with the type II gastric carcinoid (with Zollinger – Ellison syndrome + MEN I syndrome) underwent only a resection of the parathyroid adenomas and also received Proton Pump Inhibitors (PPIs), 60mg / day, resulting in permanent relief of his symptoms.

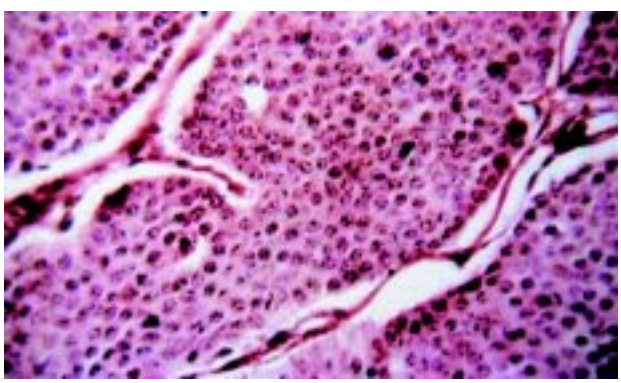

Figure 7.

In pts with advanced disease (presence of metastases, inoperable tumors) an additional biotherapy or chemo-therapy was necessary in all cases. Biotherapy was based mainly on Somatostatin analogues and less on Interferons. Thus, Somatostatin analogue, Octreotide, and, in a small number of cases Lanreotide, had a central role in ameliorating symptoms and particularly malignant "carcinoid syndrome". Moreover, in some cases, Octreotide treatment resulted in tumor arrest or tumor shrinkage. More particularly, in 19 out of 20 patients (95%) with advanced disease at the time of diagnosis and in 16 out of 17 patients (94%) who developed metastases during the follow-up period, the metastatic lessions contained a large number of somatostatin receptors, as they were visualized by a stronger uptake of ^{111}In-labelled Octreotide, during OCTREOSCAN. Thus, Octreotide was initiated subcutaneously (Sc) in a dosage ranging between 50-600μg tid, in the former patients of our series, while in the remaining patients a new form of the medicine, Octreotide LAR (Long Acting Release) [Sandostatin LAR ^{R}, Novartis] was given intramuscularly (IM) in a dosage of 20mg, every 28 days. Finally, the patients who received initially Sc Octreotide, were switched to the new form, when it was commercially available. Also, Lanreotide (Ipsen) switched from sc (5-15 mg tid) to Autogel IM-regimen (90-120 mg) every month.

Twentyfive out of thirtyfive patients (71%) demonstrated full and ten of them (29%) partial, clinical (control of diarrhea and flusing) and biochemical (normalisation of 5-HIAA values, decrease of serum CgA) response. In the patients who did not respond sufficiently (10/35, 29%) and in 6 patients who relapsed a few months after the initiation of therapy, octreotide dosage was increased to 30 or 40mg IM every 28 days. Eight of them

Table 8. Pathologic classification of carcinoids of our study

Tumor location	Well-differentiated Endocrine tumor Patients %	Well-differentiated Endocrine carcinoma Patients %
Stomach	76 %	24%
Duodenum	83%	17%
Small intestine	53%	47%
Pancreas	-	100 %
Appendix	96%	4%
Colon and rectum	-	100%

Table 9. Endoscopic / Surgical treatment in patients with carcinoid tumors of the GI tract

Tumor location	Endoscopic treatment Patients %	Surgical treatment Patients %	Local reccurence Patients %
Stomach	Polypectomy in 69%	Antrectomy in 19% Subtotal gastrectomy in 6%	-
Duodenum	Polypectomy in 66.6%	Local excision in 16.7% Pancreaticoduodenectomy in 16.7% *	-
Pancreas	-	Pancreatectomy in 75%	-
Small intestine	-	Excision in 90%	14%
Appendix	-	Appendicectomy only in 83% Right hemicolectomy in 17%	-
Colon	Polypectomy in 57%	Right hemicolectomy in 28.5% Sigmoidectomy in 14%	14%
Rectum	Polypectomy in 64%	Low anterior resection in 36%	-

* This surgical procedure referred to the tumor located at the ampulla of Vater

were relieved of symptoms permanently, and eight of them temporarily (for about 2-3 months). However, the decrease of administration intervals (from 28 to 20 days) resulted in sustained response in these sixteen patients (10 with octreotide LAR 30mg and 6 with 40mg every 20 days) for about 28-36 months. The increase of Octreotide dosage to 30 mg IM was finally necessary in the remaining 19/35 (54%) patients who had responded for a long time with the initial dosage of 20mg, (about two years after the initiation of treatment), while in seven of them (7/19, 36%) we were obliged to decrease the administration intervals, also. Stabilization of metastases was finally apparent by all imaging methods, in 23/35 (66%) patients, while tumor shrinkage was achieved in 3/35 (8.5%) of them. The response rates of our patients with Octreotide therapy is summarized in *Table 10*.

A combination therapy with Octreotide LAR, IM, plus Interferon-α ($3x10^6$ units tiw, Sc) was administered finally in 9 patients (9/35,26%) who had clinical and biochemical relapse, despite the increase of Octreotide dosage and decrease of its administration intervals. This combination resulted in symptom control in all these patients for about 14-20 months. However, in five of them (5/35, 14%), the size of liver metastatic lesions had been increased, so cytotoxic chemotherapy with streptozocin plus fluorouracil was administered.

Cytotoxic chemotherapy was also given in the 2/37 (5.5%) patients who did not have Somatostatin receptors in the metastatic lesions. The chemotherapy with streptozocin plus fluorouracil resulted in stabilization of these lessions for about 10 months.

No serious adverse effects were reported during the treatment with Somatostatin analogues, except asymptomatic cholelithiasis, detected by US in 4 (11%) patients. On the contrary, all patients who were treated with Interferon-α complained of "flu-like" symptoms, while these who received chemotherapeutic agents had more serious adverse effects (vomiting, bone marrow suppression etc)

Two out of seven pts who had received systematic chemotherapy, also underwent a hepatic artery chemoembolization using doxorubicin, which resulted in effective paliation of their symptoms and a slight regression of the tumor mass, although these results were temporary. A cryosurgery ablation was also performed in one of the remaining patients who had a large solitary metastatic lesion in the right hepatic lobe, unfortunately with poor results. At present a new therapeutic procedure, targeted treatment with radioactive somatostatin analogues, is being performed on two more of these patients. The treatment consists of intravenous injections of 177Lu-DOTA(0), Tyr3, a β-emitting radionuclide based on Octreotide. This treatment is programmed to be administered at intervals of 6 weeks and it is still in progress.

The current status of our pts is summarized in *Table 11.*

DISCUSSION

Carcinoid tumors may occur in any part of the GI tract, but more commonly they are located in the appendix and the small intestine, followed by the large intestine and the stomach, while the pancreas is a rare location of these tumors. In our study, appendix was the most common location (33%), followed by jejunum and ileum (27%), stomach (16%), while in only 3.5 % of our patients the tumor was located in the pancreas.

According to a large study,[9] the overall incidence rates were 2.0 per 100.000 for men and 2.5 per 100.000 for women. In our study, the female / male (F/M) ratio was 1.8, while the female predominance was more significant in the appendiceal carcinoids (F/M:7.7/1), which may be due to the large percentage of appendicectomies, performed in young females. The same, but less significant

predominance was apparent in carcinoids of the small and large intestine, while a male predominance was found in patients with tumors of stomach and pancreas.

In large series, the peak incidence of carcinoid tumors occurs between the ages of 50 and 70, while in our series the average age of the patients at the time of diagnosis was 51.3 years.

The initial symptoms of the patients are not specific and are due either to local tumor effects or to the bioactive products of the neoplasm. In our study, dyspepsia, GI bleeding or disturbed defecation were the most common symptoms of the patients with carcinoids of the stomach, duodenum, colon and rectum, while about one-half of the patients with tumors of the small intestine, presented with symptoms indicating bowel obstruction. On the contrary, all patients with appendiceal carcinoids were asymptomatic and the tumor was found incidentally, during appendicetomy for acute appendicitis. A typical "carcinoid syndrome" (including diarrhea and cutaneous flushing) was apparent in 16/19 (84%) patients who had already liver metastases at the time of diagnosis. In most of them 14/16 (87.5%) the primary lession was located at the small intestine.

The tricuspid valve was also affected in two of our patients with metastatic tumors at the time of presentation. However, their valvular heart disease was improved when urinary 5-HIAA, the serotonin metabolite, was decreased, as a result of medical treatment. According to a recent study,[11] high serum serotonin levels are related to the progression of carcinoid heart disease, while the risk of progressive heart disease is higher in patients who receive chemotherapy than in those who do not. The improvement of heart disease following 5-HIAA decrease after medical treatment is a very interesting point, which was also observed in our patients .

The biochemical diagnosis of carcinoid tumors is very important in the clinical workup and, usually, relies on the secretion of specific peptides and amines by these tumors, which may serve as tumor markers not only for diagnosis, but also for the follow-up of treatment of the patients. The urinary 5 – hydroxyindole-acetic acid is usually increased in metastatic carcinoid tumors of the small intestine, appendix or proximal colon (formerly classified as "midgut" carcinoids),[12] while in carcinoid tumors of other origins its sensitivity as a tumor marker is rather low. In our study, it was significantly elevated in all patients with metastatic tumors of the small intestine, as well as, in 33.3% and 50% of patients with metastatic tumors of pancreas and proximal colon, at the time of diagnosis, respectively. Moreover, it was increased in the patients with tumors of the pancreas and the small intes-

Table 10. Response rates to octreotide in patients with metastic carcinoid

Dosage of Octreotide	Full response No Patients , %	Partial response No Patients , %	Relapse No Patients , %
Initial dose 20mg / 28 days	25 / 35 , 71 %	10 / 35 , 29%	6 / 25 , 24%
30 or 40 mg / 28 days	8 / 16 , 50 %	8 / 16 , 50%	
30 or 40 mg / 20 days	16 / 16 , 100 %		

Final dose and administration intervals of Octreotide LAR in our patients
- Octreotide LAR 30 mg / 28 days : 19 / 35 , 54 %
- Octreotide LAR 30 mg / 20 days : 10 / 35 , 28.5 %
- Octreotide LAR 40 mg / 20 days : 6 / 35 , 17 %

Table 11. Current status of the patients

TUMOR LOCATION	ANED	AWD	DWD	M.dur.follow-up (y)	Range
Stomach					
- Type I	100%			4.8	1.5 – 9
- Type II	100%			4.2	
- Type III (Metastatic)		33%	66%	3.9	3.4 – 4.5
Duodenum					
- Non – metastatic	100%			4.4	0.5 – 5.2
- Metastatic		100%		2.2	
Small intestine					
- Non – metastatic	100%			4.2	1.2 – 5.5
- Metastatic		64%	36%	5.8	3.5 – 11.4
Pancreas					
- Non – metastatic	100%			2.4	
- Metastatic		66%	33%	2.2	1.3 – 3.1
Appendix	100%			8.3	2.1 - 12.5
Colon and rectum					
- Non – metastatic	100%			6.5	2.1 – 7.2
- Metastatic		25%	75%	2.9	2.5 – 3.5

ANED : Alive with no evidence of disease , **AWD :** Alive with disease , **DWD :** Died with disease
M.dur : Median duration

tine who developed hepatic metastases during the follow-up period even though symptoms of "carcinoid syndrome" were absent in some of them, at the same time. However, during the follow-up of treatment, the levels of urinary 5-HIAA did not correlate with patients' symptoms in most cases, as many of them who relapsed despite treatment, had urinary 5 – HIAA values within normal limits at the same time.

The chromogranins A, B, and C make up a family of proteins produced by neuroendocrine tumors. The first member of this family, is chromogranin-A (CgA) which is expressed in many endocrine cells. It is also present in the wide spread neuroendocrine system of the bronchial and gastrointestinal tract. Immunohistochemical techiques to detect the presence of CgA in tumor tissues are widely used in clinical practice. Since CgA is stored in a majority of different neuroendocrine tumors, the release to the circulation can be used as a "general marker" for various neuroendocrine tumors.[13,14] A study by Janson et al. [15] has shown the relationship between tumor burden and plasma CgA levels, as patients with midgut carcinoids and extensive liver metastases had significantly higher levels than those with a few liver metastases or lumph node metastases only. In another study by Bajetta et al,[16] CgA measurements seemed to be superior to urinary 5-HIAA and neuron-specific enolase as tumor markers. In our study, plasma CgA levels were significantly elevated in all patients with metastatic carcinoid tumors, especially in those with tumors of the small intestine. Moreover, there was a correlation between patient' symptoms and plasma CgA levels during the follow-up of treatment, as patients who did not respond or patients who relapsed, had increased CgA values, altough in many of them urinary 5-HIAA was normal at the same time. On the contrary, CgA levels were decreased in patients who respond to treatment, although they never returned to normal limits. However, it should be pointed out that elevated plasma CgA levels are not entirely specific for neuroendocrine tumors, as slightly elevated levels have been intentified in patients with non-endocrine tumors (for example, prostatic adenocarcinoma), while "false-positive" slight elevation of CgA can be also seen in patients with renal impairment, liver failure, atrophic gastritis and inflammatory bowel disease.

Serum gastrin is elevated in all pts with type I and type II gastric carcinoids,[17] and also in type I duodenal carcinoids, while it is within normal limits in patients with type III gastric carcinoids as well as in patients with carcinoid tumors of other locations in the GI tract. In our study, gastrin was extremely raised in the patient with type II gastric carcinoid and in one patient with type I duodenal carcinoid (that with tumor mass >2cm). Also it was slightly or moderately raised in all patients with type I gastric carcinoids and in 66% of patients with type I duodenal carcinoids, while it was normal in all three patients with type III gastric carcinoids.

The localization of carcinoid tumors has been improved by the introduction of new imaging methods like triple-phase helical computerized tomography, magnetic resonance imaging, selective mesenteric angiography and endoscopic ultrasound. However, the precise localization of the primary lession and its metastases should be undertaken, using Somatostatin Receptor Scintigraphy. (SRS)[18].

Somatostatin and its analogues like octreotide, exert diverse biological effects through interaction with specific somatostatin receptors (ssts) in the target tissues. At present, five different human sst subtypes-sst_1, sst_2, sst_3, sst_4 and sst_5- have been cloned and characterized.[19] A large variety of primary carcinoid tumors and their metastases can express a high density of ssts, particularly of the subtypes 2 and 5 for which octreotide has a high affinity. Thus, these lesions, can be visualized in vivo using gamma camera pictures obtained after injection of ^{111}In labelled Octreotide [(^{111}In-DTPA^0-D-Phe^1)octreotide-^{111}In-pentetreotide, OCTREOSCAN ^{R}]. The efficacy of SRS, not only to detect, but also to predict a therapeutic effect of somatostatin analogues on hormonal hypersecretion by these tumors, has been established by several studies.[20-23] The sensitivity of the method can be further enhanced by the simultaneous use of the single photon emission computed tomography (SPECT) with a triple head camera. SPECT technique adds the abilility to localize upper abdominal tumors, that may be obscured on plannar imaging, secondary to the physiologic uptake of the radiolabelled octreotide by the liver, kidneys, spleen and bowel. Moreover, SRS can also be useful in the follow-up of patients who had undergone curative surgery to detect tumor regrowth or new metastases at a very early stage. In our study, SRS detected metastatic lesions in the vast majority of our patients, which furthermore in many cases (33%) were unexpected, as other conventional imaging studies (C/T, MRI) showed no abnormalities at the same time. False-negative SRS can be produced by tumors with low sst_2 and sst_5 density or tumors with high endogenous somatostatin production. In our study, it failed to detect metastases, in only 5.5% of pts with metastatic tumors.

The initial management of carcinoid tumors has to be surgical in order to prevent not only local effects of

the tumor, but also the symptoms caused by the secretory agents. The precise surgical management depends on the localization and size of the lesion. Carcinoid tumors of the appendix and rectum seem to have the best prognosis and therefore a local excision is the most effective treatment for lessions smaller than 1cm[24,25]. A wide surgical resection is also necessary in carcinoid tumors of the small intestine and colon. In the stomach, surgical treatment depends mainly on the type of the lession. Type III gastric carcinoids (sporadic) require a more aggressive surgery, as they display a moderate aggressive behaviour with invasive growth and a high incidence of metastases. By contrast, gastric carcinoids of the other two types (I and II) may be managed by endoscopic or local excision[26]. In our patients, an endoscopic resection was performed in 21 patients with polypoid lessions, smaller than 1 cm. Most of these patients underwent an EUS examination, before the polypectomy to eliminate invasion of the muscularis propria and regional lymph nodes. A surgical approach was reserved for all the other patients with tumors in the stomach, small intestine, pancreas, appendix and colon and, when possible, in patients who had already hepatic metastases at the time of diagnosis, in order to reduce the severity of patients' symptoms and to improve survival. A local recurrence was developed in 14% of patients with tumors of the small intestine, as well as in one patient with primary lession in the sigmoid colon, so they all underwent a second operation.

Altough surgery, either by moving the primary lesion or by debulking the hepatic metastatic lesions is quite common nowadays.[27] The somatostatin analogues have been recently the treatment of choice in patients with carcinoid tumors and positive OCTREOSCAN. Somatostatin and its analogues, as we have mentioned before, acts by binding to the specific somatostatin receptors, which are expressed on more than 80% of carcinoid tumors. Somatostatin inhibits the secretion of a broad range of hormones, including growth hormone, insulin, glucagon, and gastrin, but also it may exert antiproliferative effects on endocrine tumors, by inhibition of angiogenesis and cancer cell growth or by inducing apoptosis. Because of Somatostatin's short half-life (three minutes), a new analogue Octreotide, an eight amino-acid peptide with longer half-life (two hours) has been developed. This analogue binds with a high affinity to receptor subtypes 2 and 5, and with a moderate affinity to subtype 3, while its clinical efficacy appears to be related to its ability to bind to receptor subtype 2. Recently, long-acting forms of somatostatin analogues have been developed with formulation by microcapsules (Figure 8). Thus, Octreotide LAR (Long Acting Release) or another analogue, Lanreotide SR (Slow Release), which can be injected intramuscularly every four or two weeks respectively, have made treatment much easier.

Several reports[28-30] agree that, subcutaneous Octreotide or Lanreotide treatment in patients with metastatic carcinoid tumors resulted in symptomatic improvement, biochemical response, temporary stabilization of tumor growth, or in objective tumor regression, in 90%, 70%, 80%, 10% of them, respectively. Similar results have been obtained with the slow-release depot intramuscular formulations.[31-34] A symptomatic and biochemical response (decrease of urinary 5-HIAA and serum CgA)was achieved with the initial dose of octreotide in 71% of our patients, while in 29% that response was partial. However, in the latter patients as well as in patients who relapsed, an increase in the Octreotide dose and a decrease of administration intervals between the two doses from four to three weeks, seemed to be crucial, in order to control their symptoms and stabilize the tumor growth. The latter was achieved in 66% of our patients, while a temporary tumor shrinkage was obtained in 8.5% of them. No serious adverse effects were reported to us at the same time, except for an asymptomatic cholelithiasis which was revealed in 11 % of our patients by U/S.

Interferon-alpha has also been reported to be effective in these patients either as a monotherapy[35] or in combination with Somatostatin analogues in patients, who stopped to respond to treatment with these analogues alone.[36] This combination therapy was finally necessary in 26% of our patients. However, in these reported series as well as in our patients, there was a high incidence of adverse effects. ("flu-like" symptoms, bone marrow suppression etc.)

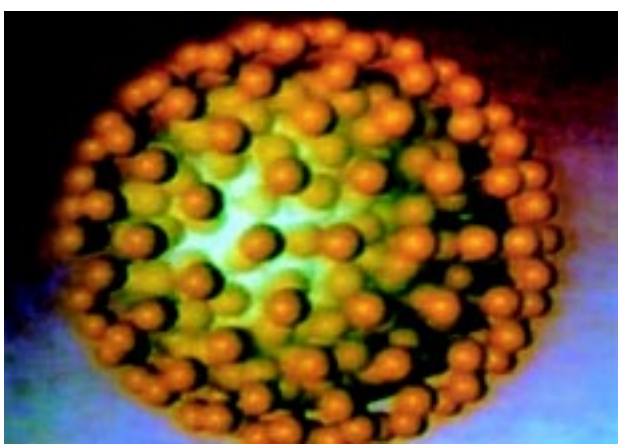

Figure 8. Octreotide LAR molecule, consisted of microcapsules

Cytotoxic chemotherapy has had only limited success in the treatment of metastatic carcinoid tumors.[37] In 7 of our patients (with disease resistant to combination therapy or with negative OCTREOSCAN), a chemotherapy with streptozocin plus fluorouracil was administered. A temporary (for 10 months) stabilization of the metastases was achieved in 3/7 patients.

Management of hepatic metastases in patients with carcinoid tumors also include: 1) Hepatic artery embolization combined with sequential chemotherapy, which has been slightly more encouraging, resulted in temporary reduction of tumor size in 78% of patients.[38] In two of our patients, a similar procedure using doxorubicin, resulted in effective paliation of their symptoms and a slight regression of the tumor mass. However, these results were temporary and patients relapsed ten months later. 2) Cryosurgical ablation is another procedure which has been used for the treatment of liver metastases in patients with colorectal cancer. The greatest experience with this technique on neuroendocrine tumors was reported by Seifert et al.[39] One of our patients with a large solitary metastatic lession in the right hepatic lobe underwent a cryosurgery ablation, unfortunately with poor results. 3) Radiofrequency ablation (RFA) is an alternative method for treating primary and secondary liver tumors. Siperstein et al[40] reported preliminary results of laparoscopic RFA of hepatic neuroendocrine tumor metastases in six patients with 13 tumors, with encouraging results. However, the efficacy of this method remains to be rigorously evaluated. We have no experience of this method in any of our patients . 4) Currently, a tumor-targeted treatment with radioactive somatostatin analogues has been developed. In a recent study,[41] 41 patients with neuroendocrine tumors underwent treatment with ^{90}Ytrium-DOTA-TOC, a β-emitting radionuclide based on Octreotide, with overall response rate of 24%. Another study,[42] showed similar results by using another readionuclide (lutetium-177, 177Lu-DOTA-OTyr3). This new therapeutic technique seems promising and it is still in progress in two of our patients, non-responders to other treatment.

According to other large series and to our data, non-metastatic carcinoids of the appendix with less than 2cm of diameter, as well as, type I gastric carcinoids seemed to have the best prognosis. On the contrary, metastatic carcinoids of the small bowel, pancreas and colon, as well as type III gastric carcinoids, exhibit the worst prognosis of all carcinoids of the GI tract. Negative prognostic factors, associated with metastases and poor survival in all types of GI carcinoids, include tumor size greater than 2 cm, involvement of the muscularis propria and the presence of high-mitotic rate. It has been estimated that the 5-year survival of the tumors of stomach, duodenum, small intestine, pancreas, appendix, colon and rectum is 49%, 55%, 55%, 35%, 86%, 42% and 72% respectively.

The findings of our series in conjunction with the review of the literature suggest that: a) tumor size (especially in appendiceal and gastric carcinoids) and the dispersion of the disease, highly predict the patient's survival b) serum Chromogranin-A seems to be a very useful tumor marker for diagnosis and follow-up of these tumors, c) the introduction of new imaging techniques and especially, the Somatostatin Receptor Scintigraphy have contributed to the better localization of the primary tumors and their metastases, as well as to the choice of the appropriate medical treatment, d) surgery is the treatment of choice in non-metastatic tumors, and also is recommended, when possible, in already metastatic tumors and e) in patients with metastatic disease, the administration of Somatostatin analogues improves their quality of life and results in stabilization of the disease in most cases.

REFERENCES

1. Kulke MH, Mayer RJ. Carcinoid tumors. N Engl J Med 1999; 340:858-868
2. Lauffer JM, Zhang T, Modlin IM: Review article: current status of gastrointestinal carcinoids. Aliment Pharmacol Ther 1999 ; 13: 271-287
3. Godwin J. Carcinoid tumors: an analysis of 2837 cases. Cancer 1975; 36: 560-569
4. Modlin IM, Sandor A. An analysis of 8305 cases of carcinoid tumors. Cancer 1997; 79: 813-829
5. Perry RR, Vinik AI. Endocrine tumors of the gastrointestinal tract.Annu Rev Med 1996; 47: 57-68
6. Rindi G, Lunetti O, Cornaggia M, Capella C, Solcia E. Three subtypes of argyrophilic carcinoid and the gastric neuroendocrine carcinoma. A clinicopathological study. G astroenterology 1993; 104: 994-1006
7. Stamm B, Hedinger CE, Saremaslani P. Duodenal and ampullary carcinoid tumors. report of 12 cases with pathological characteristics, polypeptide content and relation to MEN I syndrome and von Recklinghausen's disease (neurofibromatosis) Virhows Arh A 1986; 408: 475-89
8. Capella C, Heitz PU, Hofler H,Solcia E, Kloppel G. Revised classification of neuroendocrine tumors of the lung, pancreas and gut. Virchows Arch 1995; 425: 547-560
9. Hemminki K, Li X. Incidence trends and risk factors of carcinoid tumors. Cancer 2001; 92: 2204
10. Tomasseti P. Clinical aspects of carcinoid tumors Ital J Gastroenterol Hepatol 1999; 31: S143-6
11. Moller J E, Connolly HM, Rubin J, Seward JB et al: Factors associated with progression of carcinoid heart disease. N Engl J med 2003; 348: 1005-15

12. Williams ED, Sandler M. The classification of carcinoid tumors. Lancet 1963; 1: 238-239
13. Deftos LJ. Chromogranin A, its role in endocrine function and as an endocrine and neuroendocrine tumor marker. Endocr Rev 1991; 12: 181-187
14. Tomasseti P, Migliori M, Simoni P, Casadei R et al. Diagnostic value of plasma chromogranin-A in neuroendocrine tumors. Eur J Gastroenterol & Hepatol 2001, 13: 55-58
15. Janson ET, Holmberg L, Stridsberg M, Erikson B, Theodorsson E, Wilander E. Oberg K. Carcinoid tumors. Analysis of prognostic factors and survival in 301 patients from a referral center. Ann Oncol 1997; 8: 685-690
16. Bajetta E, Ferrari L, Merlonetti A, Celio L et al: Chromogranin A, neuron-specific enolase, carcinoembryonic antigen and hydroxyindole acetic axid evaluation in patients with neuroendocrine tumors. Cancer 1999; 86: 858-865
17. Granberg D, Wilander E, Stridsberg M, Granerus G et al: Clinical symptoms, hormone profiles, treatment and prognosis in patients with gastric carcinoids. Gut 1998; 43: 223-228
18. Oberg K: Carcinoid tumors: molecular genetics, tumor biology, and update of diagnosis and treatment. Curr Opin Oncol 2002; 14: 38-45
19. Schonbrunn A: Somatostatin receptors. Present knowledge and future directions. Ann Oncol 1999; 10(Suppl 2): S17-S21.
20. Nikou GC, Kyriaki D, Kitsou E et al. Somatostain-receptor imaging in the diagnosis and management of gut endocrine tumors. Hell J Gastroenterol 1995; 8: 312-318
21. Krenning EP, de Jong M, Kooij PPM, Breeman WAP et al: Radiolabelled somatostatin analogues for peptide receptor scintigraphy and radionuclide therapy. Ann Oncol 1999; 10(Suppl 2): S23-S29
22. Nikou GC. Octreotide in the treatment of gastroenteropancreatic endocrine tumors.In: Therapeutic advances in the management of neuroendocrine gastrointestinal tumors. Published by Excepta Medica. Limited, Hong Kong, 1998:4-6.
23. De Herder WW, Lamberts SWJ. Somatostatin and somatostatin analogues: diagnostic and therapeutic uses. Curr Opin Oncol 2002; 14: 53-57
24. Sandor A, Modlin I. A retrospective analysis of 1570 Appendiceal Carcinoids. Am J Gastroenterol 1998; 93: 422-428.
25. Nikou GC, Kikilas A, Nikolopoulos A et al: Carcinoid tumors of the appendix. Characteristics and treatment. Hell J Gastroenterol 1995; 8: 141-144.
26. Schindl M, Kaserer K, Niederle B. Treatment of gastric neuroendocrine tumors. Arch Surg 2001; 136: 49-54.
27. Soreide O, Berstad T, Bakka A et al: Surgical treatment as a principle in patients with advanced abdominal carcinoid tumors. Surgery 1992; 111:48.
28. Kvols LK, Moertel CG, O'Connell MJ, Schutt AJ et al. Treatment of the malignant carcinoid syndrome: Evaluation of a long-acting somatostatin analogue. N Engl J Med 1986; 315: 663-666.
29. Nikou GC, Dossios T, Samolada O. et al. Treatment of metastatic carcinoids. Ten year experience with Octreotide. Hell J Gastroenterol 1996, 9:317-321.
30. Ruszniewski P,Ducreaux M, Chayvialle JA et al. Treatment of the carcinoid syndrome with the long-acting somatostatin analogue lanreotide: A prospective study in 39 patients. Gut 1996; 39:279-283.
31. Tiensuu Janson E, Oberg K: Long – term management of the carcinoid syndrome. Acta Oncologica, Vol 32, No 2, pp 225-229, 1993.
32. Rubin J, Ajani J, Schirmer W, Venook A et al: Octreotide Acetate Long-Acting- Formulation versus Open-Label Subcutaneous Octreotide Acetate in Malignant Carcinoid Syndrome. Journal of Clinical Oncology, Vol 17, No 2, 1999: pp 600-606
33. Tomasseti P, Migliori R, Corinaldesi R, Gullo L. Treatment of gastroenteropancreatic neuroendocrine tumors with octreotide LAR. Aliment Pharm Ther 2000; 14: 557-560
34. Garland J, Buscombe JR, Bouvier C, Bouloux P et al. Sandostatin LAR (long-acting-octreotide acetate) for malignant carcinoid syndrome: a 3-year experience. Aliment Pharmacol Ther 2003; 17: 437-44
35. Oberg K, Eriksson B: The role of interferons in the management of carcinoid tumors. Acta Oncol 1991; 30: 519-522
36. Tiensuu Janson E, Ahlstrom H, Andersson T: Octreotide and interferon alfa: A new combination for the treatment of malignant carcinoid tumors. Eur J Cancer 1992; 28A: 1647-1650.
37. Moertel CG, Hanley JA. Combination chemotherapy trials in metastatic carcinoid tumor and the malignant carcinoid syndrome. Cancer Clin Trials 1979; 2:327-334.
38. Clouse ME, Perry L, Stuart K, Stokes KR. Hepatic artery chemoembolization for metastatic neuroendocrine tumors. Digestion 1994; 55(Suppl 3): 92-97
39. Seifert JK, Cozzi PJ, Morris DL. Cryotherapy for neuroendocrine liver metastases. Semin Surg Oncol 1998; 14: 175.
40. Siperstein AE, Rogers SJ, Hansen PD, Gitomirsky A.: Laparoscopic thermal ablation of hepatic neuroendocrine tumor metastases. Surgery 1997; 122: 1147.
41. Waldherr C, Pless M, Maecke HR et al. The clinical value of [^{90}Y-DOTA]-D-Phe^{1}-Tyr^{3}-octreotide [^{90}Y-DOTA-TOC] in the treatment of neuroendocrine tumors: a clinical phase II study. Ann Oncol 2001, 12: 941-945.
42. Kwekkeboom DJ, Bakker WH, Kooij PP, Konijnenberg MW et al. [177Lu-DOTAOTyr3]octreotate: comparisoon with [^{111}In – DTPAo]octreotide in patients, Eur J Nucl Med 2001; 28: 1319-25.