Carcinoid Tumors: Current Concepts in Diagnosis and Treatment

KJELL ÖBERG

Endocrine Oncology Unit, Department of Medicine, University Hospital, Uppsala, Sweden

ABSTRACT

Neuroendocrine tumors of the gut, carcinoids have been a diagnostic and therapeutic challenge over the years. The primary diagnostic work-up includes biochemical testing, particularly analysis of chromogranin A and urinary 5-HIAA. The most sensitive localization procedure is somatostatin receptor scintigraphy, which will be supplemented by ultrasonography for liver metastases and concomitant biopsy for histopathological verification. The treatment needs a multimodal approach, including surgery, embolization, tumor-targeted radiotherapy, and biotherapy. Chemotherapy plays a small role in the treatment of classical midgut carcinoids. Two decades ago, the median survival of patients with malignant carcinoid tumors and the carcinoid syndrome was only two years, but today, using this multimodal approach including biotherapy, it is more than eight years for the same category of patients. This may not only reflect the most effective treatment, but also a more active attitude to therapy among physicians. Future therapy will be tumor-biology-based and "tailor-made" for each patient. *The Oncologist 1998;3:339-345*

INTRODUCTION

Carcinoid tumors belong to the family of neuroendocrine tumors which derive from the neuroendocrine cell system, widely distributed in the body. These tumors are rather rare, with age-adjusted incidence rates for all types of carcinoids of 1.2-2.1/100,000 population/year [1]. The incidence of the carcinoid syndrome (see below) is about 0.5/100,000 [2]. The term "carcinoid" is at the moment under debate among specialists working in this field. The term was originally introduced by *Oberndorfer* in 1907, who described a type of tumor in the gut with less malignant behavior [3]. Today, people are using the term "carcinoid" for many different kinds of neuroendocrine tumors, which will cause a lot of confusion. The term "carcinoid" might only be used for classical midgut carcinoids, as other types of carcinoids will be termed "neuroendocrine tumor" followed by their primary location, e.g., neuroendocrine lung, gastric, duodenal, pancreatic, colonic, or rectal tumor. The dominant hormone production may be included, e.g., gastrin-producing neuroendocrine duodenal tumor, etc. Such classification would certainly be helpful in communicating information about these tumors and also in evaluating therapy studies.

The traditional classification of carcinoid tumors (Table 1) is foregut tumors with primaries located in the lung, stomach, or proximal duodenum, as well as the thymus. Midgut tumors arise from the jejunum, ileum and proximal colon (appendix), and hindgut carcinoids originate in the distal part of the colon

Table 1. Classification of carcinoid tumors

	Localization	Hormone production
Foregut carcinoids	Thymus	ACTH, CRF, CgA
	Lung	ACTH, CRF, ADH, GHRH, gastrin, PP, HCG-α/β, 5-HT, CgA
	Stomach	Gastrin, histamine, 5-HT, CgA
	Duodenum	Gastrin, somatostatin, CgA
Midgut carcinoids	Ileum Prox. colon	5-HT, CgA, NKA, substance-P, bradykinin, prostaglandins
	Appendix	No hormone production
Hindgut carcinoids	Colon Rectum	CgA, PYY HCG-α/β

and rectum [4]. This classification will be used during this review to prevent misunderstandings.

Foregut carcinoids comprise 20% of all carcinoid tumors and include thymic and lung carcinoids in addition to gastric and duodenal carcinoids. The thymic carcinoids are mostly of the nonfunctioning type, but a subset of tumors produces CRF and ACTH, thus resulting in Cushing's syndrome. These tumors are rather malignant compared with other carcinoid tumors and rather resistant to different kinds of medical treatment. Lung carcinoids are most often diagnosed incidentally during a routine x-ray of the lung. Surgical cure can be obtained by resection, but a fraction of these tumors give rise to widespread metastatic disease within two to four years after the primary operation. These tumors may produce and secrete a number of different hormones, such as CRF, ACTH, GH-releasing hormone, ADH, gastrin, PP, HCG-α and -β subunits [5, 6]. Most gastrointestinal foregut carcinoids are confined to the gastric and duodenal mucosa. Duodenal carcinoids sometimes secrete gastrin and produce the Zollinger-Ellison syndrome. There are three separate groups of gastric carcinoids, one of which is related to chronic atrophic gastritis (CAG) with aclorhydria and increased serum gastrin from antral G-cells. Gastrin stimulates the ECL-cells to proliferation with the formation of multiple polyps in the corpus/fundic region of the stomach, so-called "ECL-omas." These tumors are essentially benign and may secrete histamine and chromogranin A. The second type of gastric carcinoid is related to multiple endocrine neoplasia type 1 (MEN-1) and exhibits a malignant phenotype. The third type (type 3) is the so-called "mixed type," including neuroendocrine carcinomas, which reveals a severe malignant potential and is not related to CAG [7].

Foregut carcinoids, such as thymus, lung, gastric, and duodenal tumors may be related to endocrine MEN-1. This is a familial disorder, inherited as an autosomal dominant trait with variable penetrance. In MEN-1, the pituitary, parathyroids, and endocrine pancreas are most commonly affected but sometimes also the adrenal cortex and the thyroid. A specific genetic deletion has been located to chromosome 11 [8], and the MEN-1 gene was cloned last year [9]. Different mutations have been reported within this gene; however, the physiology of the native protein is not yet known. A pattern of organ involvement related to a specific mutation is not found.

Midgut carcinoids constitute about 40% of all carcinoids. These tumors present clinically with the carcinoid syndrome, including flushes, diarrhea, bronchial constriction, and right heart failure and are mostly located in the ileum with lymph node and liver metastases [1, 2, 4, 5]. They secrete serotonin, tachykinins, bradykinins, and prostaglandins. Hot flushes and bronchial constriction are related to overproduction of tachykinins and bradykinins, whereas the diarrheas are supposed to be related to serotonin and prostaglandins [2, 10].

Carcinoid heart disease is located on the right side of the heart, presenting with fibrosis of the endocardium and heart valves. It is related to circulating levels of serotonin and tachykinins. Locally, there is a deposition of TGF-β1 within the lesions [11]. The carcinoid syndrome might sometimes also be present in foregut carcinoids, predominantly lung carcinoids and gastric carcinoids, which might then also produce histamine besides serotonin. These patients present another type of flushing with a more long-lasting bluish-red flushing for several hours, whereas the typical midgut flush is bright red and short-lasting, from a couple of minutes up to half an hour.

Appendix carcinoids are considered to be benign if they are less than 2 cm in diameter and located in the tip or mid-portion of the appendix [1]. They are often found incidentally during appendectomy. However, appendix carcinoids located at the base of the appendix should be regarded as regular midgut carcinoid with malignant potential. A wider resection should be done including right hemicolectomy [12].

Hindgut carcinoids constitute about 15% of the carcinoids and belong to the group of nonfunctioning neuroendocrine tumors. Despite their production of hormones such as chromogranin A, PYY, HCG-α and -β subunits, they do not present any hormone-related clinical symptoms. They present clinically with bleeding, intestinal obstruction, and/or abdominal mass which cannot be distinguished from symptoms of a colorectal cancer [5, 13]. They run a more benign course than midgut carcinoids [1].

DIAGNOSIS (FIG. 1)

Tumor Biology

Carcinoid tumors are derived from so-called APUD-cells (amine precursor uptake and decarboxylation). These specialized cells accumulate amine precursors (DOPA, 5-hydroxytryptophan) and decarboxylate them to produce biogenic amines (catecholamines or serotonin). They also produce peptides stored with the amines in secretory granules [5, 14]. The APUD-concept is currently abandoned, but it continues to provide a convenient framework for explaining the multipotential capacity of these cells to produce various hormones and amines. Classical midgut carcinoids develop from the so-called enterochromaffin cells (EC-cells) in the mucosa of the small intestine, whereas hindgut and foregut carcinoids can develop from either pluripotent stem cells or already differentiated neuroendocrine cells in the various regions of the gastrointestinal tract. The gastric carcinoids derive either from the ECL-cells (ECL-omas) or antral G-cells (gastrinoma). The genetic background for tumor formation is not elucidated. Mutations in different tumor suppressor genes have been suggested. Such candidate genes are the MEN-1 gene [9], p16 [15] and PLCβ3

*Figure 1. Suggested algorithm for diagnostic workup of patients with midgut and carcinoids.*

(to be published). Carcinoid tumors express a number of different growth factors such as IGF-1, PDGF-α, bFGF, TGF-α and the TGF-β family. Receptors for the different growth factors are also upregulated both in the tumor cells and in the tumor matrix, indicating paracrine and autocrine loops. DNA analysis of tumors has been of limited value since most of them show diploid characteristics. However, the nuclear antigens Ki-67 and PCNA have been useful for delineating the proliferative capacity of carcinoid tumors. Usually, classical midgut carcinoids show a low proliferation index, whereas foregut tumors present heterogeneous patterns. High Ki-67

Diagnostic workup

index is related to a significantly shorter survival in patients with carcinoid tumors [16-19].

Histopathology

The histopathological diagnosis of carcinoids is based on silverstainings, argyrophil stainings by Grimelius, which is a general marker for neuroendocrine differentiation, and the argentaffin staining by Masson to demonstrate content of serotonin. However, these two methods have recently been mostly replaced by immunohistochemistry using antibodies against chromogranin A and synaptophysin. In order to show the content of serotonin, specific antibodies are used. All well-differentiated neuroendocrine gastrointestinal tumors show positive staining for chromogranin A, except some insulin-producing tumors which might be stained by chromogranin B antibodies instead. Synaptophysin shows similar sensitivity, but these antibodies have to be used on frozen sections rather than formalin-fixed material, which limits their clinical use. Neuron-specific enolase has been used routinely in many laboratories for staining of neuroendocrine tumors, but it is not quite specific and should therefore be combined with chromogranin A immunocytochemistry [5, 14]. A correct histopathological diagnosis is the prerequisite for therapeutic considerations.

Biochemical Diagnosis

The biochemical diagnosis developed with the introduction of radioimmunoassays for various peptide hormones in the mid-1960s.
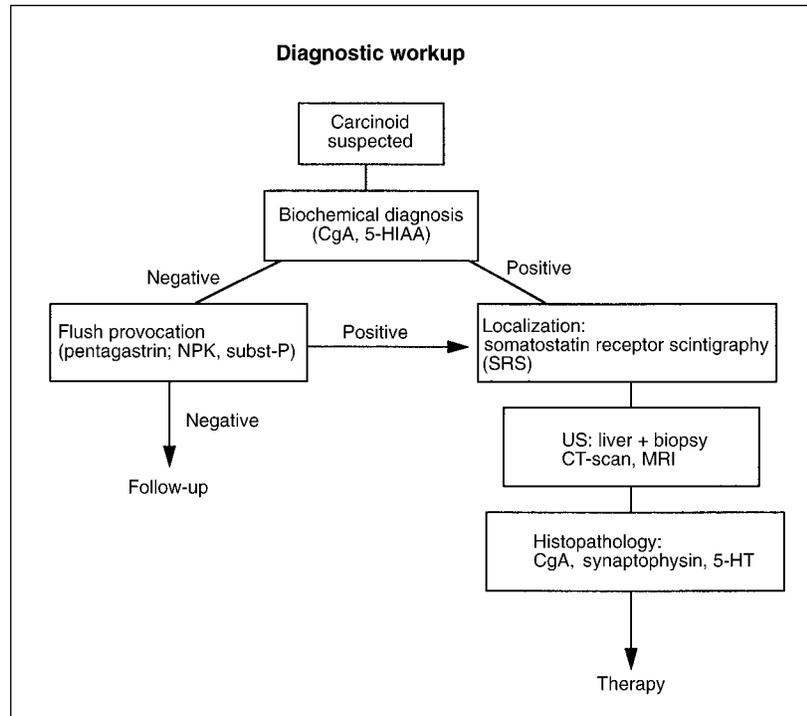
During the succeeding decades, more- or less-specific radioimmunoassays were developed for various hormones. Every laboratory made panels of different radioimmunoassays. The past decade has seen the emergence of more stringent indications for the use of hormone analysis, partly due to cost constraints. The most important biochemical marker for screening of carcinoid tumors is the analysis of chromogranin A in plasma or serum. The sensitivity is between 80% and 100% of patients with differentiated tumors, and the circulating level also reflects the tumor load [6, 20]. Chromogranin A belongs to a family of glycoproteins, which also includes chromogranin B and secretogranin II. Pancreastatin and vasostatins are spliced products of chromogranin A. Chromogranin B has been useful in diagnosing foregut carcinoids and insulin-producing endocrine pancreatic tumors [20]. Many laboratories are running assays for pancreastatin instead of chromogranin A, but plasma pancreastatin is a less sensitive marker for carcinoid tumors than is chromogranin A [20]. This may reflect the inability of certain tumor cells to produce pancreastatin because of lack of essential cleavage enzymes due to low differentiation of the tumor cells.

Urinary 5-HIAA, the breakdown product of serotonin, is still an important marker for midgut carcinoid tumors, and the combination of urinary 5-HIAA and plasma chromogranin A is sufficient to diagnose all clinically significant midgut carcinoid tumors. Tachykinins, such as neuropeptide-K and substance-P, are also elevated in patients with midgut carcinoids but to a lesser extent (30%-40%) [6]. Pancreatic polypeptide has been considered an important

general tumor marker and might be increased in 40%-60% of patients with carcinoids [6]. Unfortunately, it is a very unspecific marker, and its elevation may be caused by diarrhea, diabetes mellitus and other causes. HCG-α and -β subunits are increased in 20%-30% of the patients and might be a predictor of bad prognosis [2, 6]. In some patients, basal hormone measurements may fail to clear the diagnosis. Therefore, various stimulatory tests have been developed. Flush stimulation test measuring neuropeptide-K and substance-P after pentagastrin injection is useful for early diagnosis of midgut carcinoids [2].

Localization Procedures

In patients with suspected carcinoid tumors, somatostatin receptor scintigraphy is the most important and primary investigation. Since more than 80% of carcinoid tumors express somatostatin receptor type 2, [111]Indium-DTPA-octreotide can be used as a tracer. When combined with SPECT, it will be the most reliable staging procedure [21-23]. It also gives information about the somatostatin receptor content in the tumor and thereby predicts the results of forthcoming somatostatin analog therapy. The most sensitive method for demonstrating liver metastases is ultrasonography, which can be combined with biopsy for histopathology. CT scan and MRI can be used for demonstrating lymph node metastases in the abdomen and also for localization of mediastinal and lung tumors [24]. A rectal or gastroduodenal tumor can be demonstrated by colono- or gastroscopy, respectively. Angiography and barium enema are rarely used now but can be used in certain cases.

Positron emission tomography using ^{11}C-labeled 5-HTP has been developed at our institution and has proven quite effective in localizing carcinoids as small as 0.5 cm [25]. It also provides information about the metabolism of the tumor, since 5-HTP is a precursor serotonin synthesis. The method is quite unique, and in the future a number of different substances can be labeled with short-lived isotopes to obtain information about the tumor biology directly in the patient.

TREATMENT (FIG. 2)

Successful treatment of malignant carcinoid tumors requires a multimodal approach, including various means of tumor reduction. Since a majority of these tumors are malignant already at clinical presentation, surgical cure is seldom obtained. Resection of local disease or of regional nodular metastatic disease can cure some patients, but even if radical surgery cannot be performed, debulking procedures and bypassing should always be considered and can be performed at any time during the course of treatment [12]. In recent years, a more active attitude among surgeons has emerged, and, in general, more wide resections and debulking procedures are performed today than 10 years ago. Liver transplantation in suitable cases has also been considered, but

these procedures need further evaluation before being incorporated into the general management of carcinoid tumors [26, 27]. A prerequisite for surgery is always optimal diagnostic and localization procedures.

Another means of tumor reduction is hepatic artery ligation for liver metastases, and that can be done either by surgical ligation or by embolization with starch powder (Spongostan®, Ivalon®). The latter procedure is currently the most common. In general, biochemical responses are occurring in about 50% of the patients with or without regression of hepatic metastases. The duration of responses is usually about 6-12 months, and the procedure has to be repeated in most patients [28, 29]. Chemoembolization has been performed in some studies, whereby embolization or hepatic artery ligation is combined with chemotherapy using agents such as dacarbazin, doxorubicin, 5-fluorouracil (5-FU), methotrexate, and streptozotocin. Such procedures have led to long-lasting responses in some patients, but the precise role remains to be defined, particularly since the side effects are considerable [29, 30].

In general, external irradiation therapy has not been successful in the treatment of metastatic neuroendocrine tumors of the GI tract [31]. It has mainly been applied for amelioration of pain due to bone, skin, and brain metastases. Carcinoid tumors have been treated with local irradiation using ^{125}I-MIBG with some success, particularly in patients with high uptake rates [32, 33]. Most recently, high-dose treatment with [111]Indium-DTPA-Phe-Octreotide has been attempted, giving some significant tumor responses. The patients receive 6 Gbq of [111]Indium-DTPA-Phe-Octreotide every four weeks for a total dose of 45-60 Gbq. The most severe adverse reaction so far has been thrombocytopenia (to be published). Results on the first patients treated with 90Y-DOTA-Lanreotide have been published [34] with promising results, and several trials have just started worldwide. The local "tumor-targeted" irradiation therapy is still to be considered investigational.
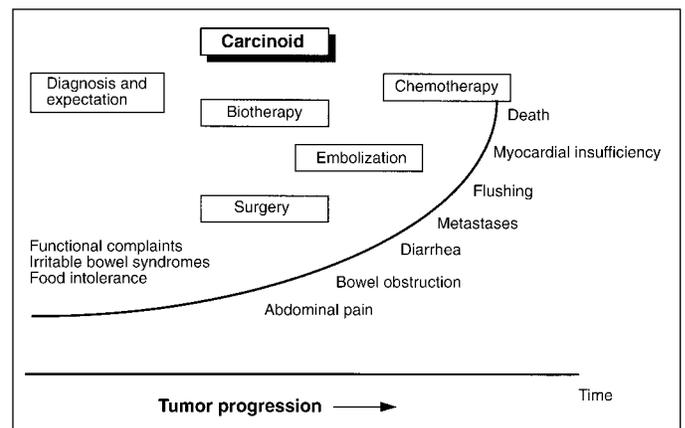

Figure 2. Clinical progression of a midgut carcinoid and suggested therapeutic options.

Medical Treatment

The medical treatment must be based on the growth properties of the tumor. Medical treatment includes chemotherapy, somatostatin analogs, and α-IFNs. Because of the rarity of these tumors, clinical studies have frequently been reported in a very tenuous fashion. Furthermore, many of the studies do not take into account the difference in biological behavior between classical midgut carcinoids and foregut and hindgut tumors. In addition, many clinicians are still reluctant to treat patients with classical carcinoid tumors, since they have been assigned a good prognosis. However, a critical look at survival data in patients with malignant carcinoid tumors shows a five-year survival rate of about 20%, and a median survival of two years when liver metastases are present [35, 36].

Chemotherapy

Single-agent chemotherapy of carcinoid tumors has given very low response rates, less than 10%. Clinical trials including streptozotocin plus doxorubicin or 5-FU have not generated significantly better response rates, between 0% and 30% [37-39]. This is in contrast to closely related endocrine pancreatic tumors, which show response rates of 50%-60%. Therefore, today, chemotherapy is not considered as first-line treatment for patients with classical midgut carcinoid tumors. However, anaplastic neuroendocrine tumors might benefit from treatment with a combination of cisplatinum and etoposide. Response rates up to 65% have been reported in this combination, which seems promising for more aggressive tumors but needs further evaluation [40]. Malignant foregut and hindgut carcinoids with higher proliferation indices might benefit from chemotherapy.

Biotherapy

Somatostatin Analogs

The observation that somatostatin inhibits the release of various peptide hormones has stimulated the interest in its use as an antiproliferative agent for endocrine tumors [41]. Natural somatostatin 14 has a short half-life of about two min and is not suitable for clinical use. Analogs of somatostatin with a longer half-life, two to three hours, were developed in the past decade (octreotide, lanreotide, RC160). They are all octapeptides binding to somatostatin receptor subtypes 2 and 5. The antitumor effect is suggested to be mediated through induction of tyrosine phosphatases by receptor type 2 and the inhibition of calcium flux through receptor type 5 [42, 43]. Octreotide (Sandostatin®) has been clinically the most commonly applied somatostatin analog, yielding biochemical response rates in the range of 30%-70%, but objective tumor shrinkage in less than 10% of the patients [41, 42, 44, 45-47]. The dosing has been 50-150 µg s.c. two to three times/day.

High-dose somatostatin analog treatment (>3.000 µg/day) might induce apoptosis in neuroendocrine tumors, a possibility which should be explored in forthcoming clinical trials. Apoptosis is reported to be induced through receptor subtype 3, and the current available analogs bind to receptor 3 with rather low affinity [48]. Somatostatin analog treatment produces subjective improvement in more than 70% of the patients at regular doses of 150-300 µg s.c./day. It is well tolerated, with only a few side effects such as gallbladder dysfunction, gallstones, and, in isolated cases, hyperglycemia and hypocalcemia. Recently, a long-acting formulation of Sandostatin®, Sandostatin-LAR®, has come into clinical use at doses at 10-30 mg given i.m. every four weeks. Preliminary data indicate an objective and biochemical response rate similar to that of regular Sandostatin®. Also, a long-acting formulation of lanreotide, Somatuline-PR®, is ready for clinical use. A dose of 30 mg is applied every two weeks i.m.

In summary, somatostatin analog treatment has been the real breakthrough in the treatment of patients with carcinoid tumors. Clinical symptoms can easily be controlled over long periods, even though tachyphylaxis may develop with time. The drug is generally well tolerated. High-dose treatment or receptor type-3-specific analogs might generate more tumor responses in the future. Long-acting formulations of somatostatin analogs give a significantly improved quality of life.

Interferons

Interferon-α (IFN-α) was introduced by our group in the treatment of carcinoid tumors in 1982 [49], because of its ability to stimulate natural killer cell function and to control hormone secretion, clinical symptoms, and tumor growth. Since then, more than 400 patients with carcinoid tumors have been treated with IFN-α in our institution, and as many have been reported in the literature [50-53]. Natural human leukocyte interferon contains more than 15 subtypes of IFN-α, whereas the recombinant IFN-α 2b (Intron-A®) and 2a (Roferon®) contain one subtype of interferon. The applied doses of IFN-α have been 3-9 MU, three to seven times/week s.c. The dose has to be individually titrated in the patients, and as a guideline, the leukocyte count should be reduced to 3.0×10^9/l. By using such titration, the biochemical response rate in carcinoid tumors has been reported to be 50%, and significant tumor reduction is 15% [54]. The median duration of response has been 32 months. Thirty-five percent of the patients showed stabilization of their disease with no further tumor growth, and only 15% of the patients continued to progress. Survival data from our own center, and also from others, show improved survival after treatment with IFN-α in malignant classical midgut tumors with the carcinoid syndrome [54, 55]. The median survival for patients with malignant carcinoids and

liver metastases at our own institution is today more than eight years during biotherapy. The side effects of IFN-α include chronic fatigue syndrome, flu-like symptoms for the first three to five days, slight anemia, and increased liver enzymes in 15%-20% of the patients. Most of the side effects are dose-dependent and were reduced by dose adjustments. It is noticeable that recombinant IFN-α might generate neutralizing interferon antibodies, particularly IFN-α 2b (Roferon®), which generates high titers of neutralizing antibodies in 35%-40% of the patients. Such antibodies might abrogate the antitumor response [56].

Recently, several centers have started combination trials in carcinoid patients whereby IFN-α is combined with a somatostatin analog. In a recent study from our own institution, 77% of patients resistant to octreotide or IFN-α alone show biochemical remission when IFN-α at a dose of nine million units was added to regular doses of octreotide (100 µg 3 times/day). However, no significant tumor shrinkage was noticed in this trial [57].

To summarize, IFN-α has demonstrated significant anti-tumor responses in carcinoid tumor patients. It has a stronger antiproliferative effect than somatostatin analogs at current doses. By combining IFN-α and a somatostatin analog, the response rates might be further improved. IFN-α is better tolerated by the patients when combined with somatostatin analogs.

The future therapy of patients with carcinoid tumors will be tumor-biology-based and will include surgery, biotherapy, and tumor-targeted irradiation. Every patient will get a "tailor-made" therapy based on his or her particular tumor biology profile.

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