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## Diagnostic modalities in carcinoid tumors

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## Summary

This thesis is divided in two parts. The first part addresses studies of the primary diagnosis of carcinoid tumors and the second part of this thesis deals with the diagnosis of complications of carcinoid tumors.

### *First Part*

In **chapter 1** an overview is given of diagnostic strategies based on features that are typical for carcinoid tumors. Attention is focused on biochemical markers and radionuclide imaging procedures.

Circulating chromogranin A can be used as a tumor marker, and has a high sensitivity and specificity for neuroendocrine tumors. However, chromogranin A can not discriminate within the group of neuroendocrine tumors. Because serotonin is the characteristic tumor product of carcinoid tumors, biochemical markers of serotonin metabolism are essential for the diagnosis. Increased synthesis of serotonin is detected by measuring the serotonin metabolite 5-hydroxyindole acetic acid (5-HIAA) in urine, or the more sensitive marker serotonin content of platelets. The determination of other tumor products such as catecholamines and histamine, can explain unusual symptoms in carcinoid patients.

Ocrototide receptor scintigraphy (ocrototide scintigraphy) visualizes specific receptors at the cell membrane and is recommended as a first step in the localization of carcinoid tumors.

The diagnostic value of various positron emission tomography (PET) tracers remains to be determined. The  $^{18}\text{F}$ -labeled deoxyglucose (FDG), which reflects increased glucose metabolism in cancerous tissue, was studied to visualize these tumors. This tracer was however not sufficiently taken up by the carcinoid tumors. Other PET tracers involved in serotonin metabolism do however seem to be interesting.

Better knowledge about both the metabolic behavior and accurate localization of tumor deposits will be helpful to optimize patient management.

**Chapter 2** describes the analysis of the discriminating capacity of the indole markers urinary 5-HIAA, urinary serotonin, and platelet serotonin in the diagnosis of carcinoid tumors. Indole markers were measured in 688 patients with suspected carcinoid disease. The initial values of indole markers from patients, in whom a carcinoid tumor was proven during follow-up ( $n=98$ ), were used for Receiver Operator Characteristic (ROC) analysis. ROC curve analysis showed platelet serotonin to have the highest discriminating capacity, especially in foregut carcinoids. We also used ROC analysis to determine optimal cut-off values. For platelet serotonin a cut-off value of  $5.4 \text{ nmol}/10^9$  platelets resulted in a sensitivity 74%, specificity 91%, positive predictive value 63%, and negative predictive value 95%. Slight increases of markers were associated with non-carcinoid neuroendocrine tumors, non-neuroendocrine tumors, and disturbed bowel motility. It was concluded that ROC curve analysis showed that platelet serotonin is the most discriminating indole marker for the diagnosis of

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carcinoid tumors. Platelet serotonin especially improved the diagnosis of carcinoids producing small amounts of serotonin.

In **chapter 3** the profiling of tryptophan related plasma indoles in carcinoid patients using automated on line solid phase extraction with high performance liquid chromatography and fluorescence detection is described. This method can be used to determine the amount of serotonin, together with its precursors and metabolites in one procedure. Deficiencies of tryptophan as well as excessive production of serotonin and 5-HIAA can be determined. This information can be helpful to explain symptoms, and customize treatment to the individual patient.

Serotonin is the principal product of carcinoid tumors. In addition, these tumors give rise to increased excretion of urinary catecholamine metabolites. Not clear is if carcinoid tumors contain specific enzymes for catecholamine synthesis. Therefore it was studied whether catecholamine-synthesizing enzymes (tyrosine hydroxylase, dopamine- $\beta$ -hydroxylase, phenylethanolamine-N-methyltransferase) are present in midgut carcinoid tumors, and whether expression of these enzymes correlates with the actual production of catecholamines. This study is described in **chapter 4**. We used a three-step biotin-avidin-peroxidase method on paraffin-embedded tumor specimens of 21 midgut carcinoid tumors. The amount of catecholamines produced by each tumor was estimated by measuring the urinary excretion of catecholamines and metabolites. The results in carcinoid patients were compared to 20 patients with pheochromocytoma (ten sporadic and ten MEN type IIa related tumors). Tyrosine hydroxylase, dopamine- $\beta$ -hydroxylase and phenylethanolamine-N-methyltransferase were demonstrated both in carcinoids and in pheochromocytomas. The percentage of patients with positive immunohistochemistry was higher among the pheochromocytoma patients. Among the carcinoid patients, immunoreactivity for phenylethanolamine-N-methyltransferase was associated with increased urinary excretion of catecholamines or metabolites. It was concluded that catecholamine-synthesizing enzymes are present in carcinoid tumors. Therefore it is considered that catecholamines can be synthesized by carcinoid tumors, using the same metabolic pathway as pheochromocytomas.

The clinical presentation of carcinoids depends on the site of origin of the tumor, the site of metastases and the secretory activity of the tumor. These factors possibly also determine the sensitivity of octreotide scintigraphy. In **chapter 5** the role of these factors on the imaging of carcinoid tumors with octreotide scintigraphy was evaluated. In a retrospective, single center study we evaluated the initial octreotide scintigraphy of 52 carcinoid patients, with primary tumors in the foregut- (n=6), midgut region (n=38), or with unknown primary site (n=8). Octreotide scintigraphy was compared with all available alternative imaging procedures (conventional imaging). Tumor sites detected with either octreotide scintigraphy or conventional imaging were used as a standard. Sensitivity was evaluated separately for four anatomical domains: liver-, abdominal- (extra-hepatic), thoracic- or the peripheral domain. Serotonin secreting activity was measured by 5-HIAA and platelet serotonin content. The sensitivity of

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octreotide scintigraphy was not related to either the primary site of the tumor or its serotonin secreting activity. Octreotide scintigraphy and conventional imaging are complementary for the detection of liver metastases. Octreotide scintigraphy is more sensitive than conventional imaging for abdominal sites, enabling the detection of a previously unknown primary tumor. Because octreotide scintigraphy provides whole-body imaging we recommend octreotide scintigraphy (with upper abdominal SPECT) as a first step in the staging of carcinoid tumors. The absence of pathological lesions in the liver region on octreotide scintigraphy should be confirmed with upper abdominal ultrasound or CT.

As carcinoid tumors can produce serotonin and catecholamines from their precursors tryptophan and tyrosine we studied in **chapter 6** the tyrosine analogue L-3-[<sup>123</sup>I]iodo-alpha-methyl-tyrosine (IMT) in the detection and in the determination of biochemical activity of these tumors in comparison with <sup>111</sup>In-octreotide scintigraphy. SPECT and planar whole-body imaging was performed 15 minutes after administration of 300 MBq IMT in 22 patients with metastatic carcinoid tumors. The number of lesions detected was compared with <sup>111</sup>In-octreotide scintigraphy. Size and intensity of uptake of all lesions were graded using a simple scoring system, yielding a total body uptake score for both tracers. These scores were compared with biochemical markers of serotonin and catecholamine metabolism. IMT SPECT detected 43% of the lesions detected by <sup>111</sup>In-octreotide imaging. IMT SPECT performance was relatively best in the liver. Both IMT uptake and <sup>111</sup>In-octreotide uptake scores correlated with markers of serotonin metabolism. No correlation with adrenaline or noradrenaline metabolites was found. However, IMT uptake but not <sup>111</sup>In-octreotide uptake correlated with dopamine metabolites excretion, as IMT uptake was higher in patients with increased dopamine metabolite excretion. It was concluded that IMT uptake can be demonstrated in carcinoid lesions, but is not as sensitive as <sup>111</sup>In-octreotide. Uptake of <sup>111</sup>In-octreotide but also of IMT is related to serotonin secretory activity. IMT but not <sup>111</sup>In-octreotide uptake, was related to tumor dopamine metabolism. These findings may be of interest in metabolic targeting of carcinoids.

#### *Second Part*

**Chapter 7** reviews the developments in the diagnostic and therapeutic management of carcinoid heart disease. Carcinoid patients often suffer from carcinoid heart disease. This article reviews the histopathology, etiology, incidence, clinical presentation, diagnosis, medical and surgical therapy of carcinoid heart disease. Emphasis is put on developments in diagnostic procedures that evaluate not only cardiac morphology but also cardiovascular function. These procedures comprise Doppler imaging, analysis of heart rate variability, plasma levels of atrial natriuretic peptide and urinary excretion of catecholamines. The use of these techniques can lead to a better understanding of the pathophysiology of carcinoid heart disease. A potential application of these techniques is the monitoring of drug treatment, and the optimization of the timing of valve replacement.

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Carcinoid heart disease can lead to clinical signs of heart failure. Catecholamines have a role in the pathophysiology of heart failure and are products of carcinoid tumors. Both catecholamines and heart failure contribute to a derangement of autonomic function. Therefore, we evaluated cardiovascular manifestations of autonomic dysfunction in patients with a carcinoid syndrome as described in **chapter 8**. Twenty patients with a midgut carcinoid, who had a carcinoid syndrome with a median duration of 72 months and markedly elevated urinary 5-HIAA excretion were studied. Ten patients had no symptoms of heart failure (New York Heart Association [NYHA] functional class I), 6 had class II, and 4 class III heart failure. Transthoracic echocardiography showed right-sided valvular abnormalities in 13 of 19 evaluable patients. Fourteen of the 20 patients had an elevated concentration of plasma N-terminal atrial natriuretic peptide, which correlated with NYHA class, transthoracic echocardiography abnormalities, and increased urinary metanephrine excretion. Heart rate variability parameters, in particular those associated with increased sympathetic activity were impaired. Parameters of heart rate variability were markedly abnormal in patients with increased urinary metanephrine excretion, but were independent of NYHA class and transthoracic echocardiography. In these 20 carcinoid patients with substantial secreting activity of the tumor, morphologic changes of the cardiac valves were relatively mild. However, plasma N-terminal atrial natriuretic peptide values and heart rate variability profile were markedly abnormal, and related to enhanced urinary excretion of catecholamine and metabolites, suggesting autonomic derangement. These abnormalities possibly herald the development of more severe cardiac dysfunction and may be indicative of the need for preventive drug treatment.

In **chapter 9** troponin I, troponin T, and CKMB-mass were analyzed to detect myocardial damage in patients with a carcinoid syndrome, who are exposed to elevated levels of circulating serotonin. The outcomes of the troponin I, troponin T and CKMB-mass measurements were compared between the carcinoid patients with and without heart failure, and between patients with and without carcinoid heart disease as determined by echocardiography. No elevated levels of troponin I, troponin T, or CKMB-mass were found. Furthermore, no differences were observed between the respective subgroups. From these findings it was concluded that patients with a carcinoid syndrome have no detectable signs of myocardial damage if the new and sensitive markers are used. Even patients with prolonged exposure to high serotonin levels, clinically observable heart failure and echocardiographic evidence of carcinoid heart disease, show no detectable troponin I and troponin T concentrations.

In **chapter 10** the role of biochemical markers of bone metabolism in the diagnosis and monitoring of bone metastases in solid tumors is reviewed. In metastatic bone disease, bone formation and resorption become uncoupled processes, leading to abnormalities on plain radiography with a predominantly osteoblastic or osteolytic appearance. In osteolytic metastases, bone resorption is enhanced without appropriate acceleration of bone formation. In osteolytic metastases the resorption markers are useful for the detection of bone metastases. Urinary pyridinium cross-

links and serum collagen telopeptides are sensitive and specific markers of bone resorption. These markers can often identify bone metastases before visualization by imaging techniques. When osteolytic lesions are responding to treatment, the physiologic coupling between bone resorption and formation is partly restored. An increase in formation markers, bone specific isoenzyme of alkaline phosphatase, osteocalcin and carboxyterminal propeptide of collagen type I, will then closely reflect restoration of coupling.

In osteoblastic metastases, bone formation markers can accurately indicate early and advanced bone involvement. Bone resorption markers are less sensitive for the detection of osteoblastic lesions. The collagen telopeptides however, are resorption markers with the ability to detect early bone metastases. Osteoblastic lesions responding to therapy are indicated by declining values of formation as well as resorption markers. The precise role of the recently developed markers of bone metabolism in early diagnosis and monitoring of bone metastases needs further evaluation in longitudinal studies. Since the delicate derangements in bone metabolism may be obscured in mixed patient groups, these studies should address uniform patient groups with respect to the primary tumor type.

Treatment with somatostatin analogues and interferon  $\alpha$  has improved control of the carcinoid syndrome. As a result, the growth of the tumor and the development of metastases become more important determinants for the clinical manifestations of carcinoid tumors. At present, the optimal diagnostic approach for bone metastases in carcinoid tumors is not known. In **chapter 11** the clinical presentation of bone metastases in patients with carcinoid tumors is described with the aim to determine the diagnostic value of imaging techniques and markers of bone metabolism. In a single-center, retrospective study, 11 (8%) out of 131 patients with a carcinoid tumor had symptomatic bone metastases. All bone metastases occurred in 74 patients with midgut carcinoids. In contrast, in 36 patients with foregut carcinoids no bone metastases were detected. Ten of 11 patients had painful bone metastases. Plain radiography had a sensitivity of 44%, magnetic resonance imaging 100%, bone scintigraphy 90%, and octreotide scintigraphy 60%. Octreotide scintigraphy and bone scintigraphy provided complementary results in seven of nine patients. Markers of bone metabolism could not discriminate between carcinoid patients with and those without bone metastases. It can be concluded that pain is the principal symptom of bone metastases. Magnetic resonance imaging shows the highest sensitivity for bone metastases. Both bone scintigraphy and octreotide scintigraphy have acceptable sensitivity, and can provide complementary results.

### **Future perspectives**

Carcinoids are malignant tumors that differ from non-neuroendocrine tumors. Diagnostic and therapeutic approaches, specific for carcinoids are based on differences in metabolic properties. Such differences are the synthesis of biogenic

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amines, the presence of somatostatin receptors, and a usually slow rate of proliferation. Further elaboration of these specific approaches is needed for future improvements in the management of carcinoid tumors.

### *Synthesis of biogenic amines*

Profiling of the biogenic amines secreted by the tumor can be helpful to understand the symptoms in an individual patient. Recently, several specific antagonists have become available, such as antagonists for serotonin receptor subtypes, histamine receptor subtypes, *catecholamine receptor subtypes*, and *prostaglandin inhibitors*. In the future the benefits of therapy targeting on these receptor subtypes need evaluation. Of interest is the possibility to inhibit the endocrine activity via the  $\beta$ -receptor that is present on carcinoid cells.

At present, radiolabeled or "cold" meta-iodo benzylguanidine (MIBG), is an example of metabolic targeted treatment. Scintigraphic techniques, in particular PET, can elucidate the metabolic pathways present in carcinoid cells. This knowledge can be extended towards treatment modalities aiming on new metabolic targets.

### *Presence of somatostatin receptors*

Somatostatin receptor scintigraphy and somatostatin analogue treatment have markedly improved the diagnostic and therapeutic management of carcinoid tumors. The recognition of distinct subtypes of somatostatin receptors and subsequently, the development of subtype-specific analogues holds promise for a further refinement of somatostatin therapy. Radionuclide treatment, utilizing the specific binding to somatostatin receptors, is a fascinating new development. At present, the efficacy and safety of this treatment modality deserves further exploration.

### *Proliferation rate*

Carcinoids usually have a slow proliferation rate. Therefore, surgical interventions should always be considered, also when cure is no longer possible. In the future, the merits of extensive debulking, partial liver resections and liver transplantation, as palliative or curative procedures must be determined in a collaborative effort of referral centers in sufficiently large studies. Carcinoid tumors are usually well vascularized. Embolization techniques exploit this characteristic. The development of antiangiogenic drugs may therefore also be of particular interest for the treatment of metastatic carcinoids in the future.