Diagnostic and treatment modalities in carcinoid tumours

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Summary and future perspectives
Carcinoid tumours are rare neuroendocrine tumours (NET), arising from cells of the diffuse neuroendocrine system which is made up of amine precursor and decarboxylation (APUD) cells. The annual incidence rate of carcinoid is 2 of 100,000 and the main primary tumour sites are appendix (27%) and lung (22%). In 62% the primary tumour is located in the gastro-intestinal tract and the primary remains unknown in about 10%. Presentation with distant metastases is found in 20%. Half of them with unknown primaries. As a result of the neuroendocrine origin, carcinoid tumours are capable of secreting vaso-active substances, mainly serotonin. In patients with liver metastases this can induce the characteristic symptoms of the carcinoid syndrome, such as attacks of flushing, diarrhoea and wheezing. Serotonin also plays a key role in the development of carcinoid related heart disease (CHD), but the exact pathogenesis has yet not been elucidated.

The aim of this thesis is to evaluate different diagnostic and treatment modalities in carcinoid patients in an effort to refine the therapy and follow-up in these patient group.

**First part: Diagnostic modalities**

**Chapter 1** describes the evaluation of various nuclear modalities in the detection and clinical management of bone metastases in patients with metastatic carcinoid tumours. In addition, the occurrence of bone metastases in these patients was calculated. Nine out of 86 consecutive carcinoid patients developed bone metastases (10%). $^{111}$In-pentetreotide scintigraphy and the $^{131}$I-meta-iodobenzylguanidine (MIBG) scintigraphy are positive in 70-80% in carcinoid tumours, but in the detection of bone metastases these scans were positive in only 50% and 20% respectively. However, bone scintigraphy using $^{99m}$Tc-MDP showed multiple metastases in all these nine patients. The axial skeleton and the pelvis were affected in all and the extremities were involved in more than half of the patients. In the nine cases with symptoms and a positive standard bone scintigraphy medical treatment with MIBG (either non-radioactive or radioactive), octreotide analogues or interferon induced a symptomatic improvement of carcinoid syndrome in most of these patients. However, no pain relief of bone metastases was obtained. Palliation of the pain by means of radiation therapy was successful in 5/6 patients. In one additional patient this was achieved by application of Rhenium-186-hydroxyethylidene diphosphonate. In conclusion, bone scintigraphy is a sensitive imaging technique for detection of bone metastases in carcinoid patients, while the $^{111}$In-pentetreotide and the $^{131}$I-MIBG scintigraphy are often negative in those cases. Radiotherapy and nuclear medicine modalities can be applied for palliation of pain in carcinoid patients with bone metastases.
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The incidence of the characteristic right-sided carcinoid heart disease (CHD) in patients with metastatic carcinoid tumours is 20-70%, pending on the definition used. In many patients the cause of death is attributed directly to cardiac disease. Although serotonin seems to play a key role in the development of CHD, the exact mechanism has yet not been elucidated. Chapter 2 discusses the relationship between hormonal activity and the development of CHD. In chapter 2.1 we compared 24-hours urinary 5-hydroxyindoleacetic acid (5-HIAA) excretion levels and the plasma levels of atrial natriuretic peptide (ANP), transforming growth factor-β (TGF-β) and fibroblast growth factor (FGF) in patients with and without CHD to investigate the relationship between the development of valvular fibrosis and hormonal activity and markers of fibrosis. By applying the criteria: thickened tricuspid valve with additional III/IV or IV/IV tricuspid valve regurgitation, we found CHD in 9 of 37 patients (24%). All CHD patients had symptoms of the carcinoid syndrome compared with 71% of the non-CHD group. Median 5-HIAA excretion was significantly higher in the CHD group compared with the non-CHD group (576 μmol/24h and 233 μmol/24h respectively, p=0.02). The calculated area under the curve (AUC) as a measure of serotonin load over time of the 5-HIAA excretion during the complete disease period underscored the difference between both groups (p<0.001). ANP levels were significantly higher in the group with CHD compared with those without (p=0.026). No significant difference in TGF-β and FGF plasma levels was observed between both groups. Survival was significantly longer (23 months) for patients without CHD compared with those with CHD (13 months, p=0.026). We concluded that high levels of 5-HIAA excretion and ANP were associated with CHD. In addition to the level of 5-HIAA excretion, the duration of exposition is also important in the development of CHD. No significant relation with TGF-β and FGF was found.

Chapter 2.2 is a comment on a article of Moller et al. (NEJM 2003) who evaluated 71 carcinoid patients for the development of CHD. They concluded that a higher peak urinary 5-HIAA excretion was a predictor for a deterioration of cardiac performance. In our reply we underlined that duration of exposure to elevated serotonin levels (calculated as the AUC) might be an even more important factor in the formation of valvular fibrosis as reported in chapter 2.1.

The study, described in chapter 3, was performed to investigate the relationship between carcinoid heart disease (CHD) and blood levels of natriuretic peptides ANP (atrial natriuretic peptide) and NT-proBNP (N-terminal fragment of brain natriuretic peptide). In addition, we examined the prognostic values of these hormones. Blood samples of 32 carcinoid patients were compared with the findings of the cardiac ultrasound performed at follow-up. CHD was found in 9/32 patients (28%). Median levels of NT-proBNP were significantly higher in patients with CHD (894 ng/L) compared with those without (89 ng/L, p<0.001). No significant differences were detected in ANP levels (p=0.11). Degree
of dilatation of right atrium and ventricle and degree of regurgitation and thickening of the tricuspid valve were statistically significant correlated with NT-proBNP levels. The accuracy of NT-proBNP in the diagnosis of CHD was higher than the accuracy of ANP. At a cut-off value of 220 ng/l the positive predictive value of NT-proBNP was 69% with a negative predictive value of 100%. Survival was significantly better in patients with normal NT-proBNP levels (p=0.02). We concluded that NT-proBNP is helpful as a simple marker in the diagnosis of CHD and can be used to adjust therapy in these patients.

Twenty-four-hour urinary 5-HIAA concentrations, the degradation product of serotonin, is the cornerstone in diagnosis, follow-up and monitoring treatment in patients with carcinoid tumours. Although metabolism of serotonin into 5-HIAA is regulated by rapid clearance mechanisms, former studies determined urinary 5-HIAA levels in 24-hours collection intervals instead of a simple urine sample as a measure of serotonin production. Collection of 24-hours urine is troublesome for the patient and can be unreliable due to inaccurate collection for instance in case of severe diarrhoea. It would yield considerable profit if an urine sample collected during a shorter interval would already reflect disease activity. Our clinical impression is that symptoms of the carcinoid syndrome seem to deteriorate by physical efforts, food intake or starting the day. Information about influences of these factors on hormonal excretion is scarce and clear-cut correlation between markers of hormonal excretion and the severity of symptoms of the carcinoid syndrome are not convincing. In chapter 4 we investigated the relationship between symptoms of the carcinoid syndrome and daily activity on the 5-HIAA excretion sampled in 4- and 8-hour intervals. We also evaluated possible cyclic changes and assessed the possibilities of replacing 24-hours urine collection by a shorter collection interval. No clear correlation between hormonal excretion and degree of activity could be found (p=0.766). Watery diarrhoea was only reported by patients with strong variations in hormonal excretion. In relation to the 24-hours 5-HIAA excretion, the interval in the morning showed significantly higher hormonal levels and a significant lower excretion was found in the evening. The overnight collected interval produced the best estimate value compared with the 24-hours excretion. Thus, cyclic changes were found in patients with a high variability in 5-HIAA excretion. An overnight collected portion can replace 24-hours urine collection.

Second part: Treatment modalities

In chapter 5.1 an overview is given of the use of various applications of meta-iodobenzylguanidine (MIBG) in the palliation of symptoms of the carcinoid syndrome. In this paper we describe three patients in whom pharmacological MIBG, $^{131}$I-labelled MIBG
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and the combination was applied. Pharmacological (unlabelled) MIBG can give symptomatic relief in a simple and safe way for 3-4 months, while long-term palliation (8 months) can be obtained by application of radioactive labelled MIBG in case of a positive scan. Predosing with unlabelled MIBG immediately before start of radioactive MIBG can improve tumour targeting in some patients with a negative or weakly positive scan and can lead to an impressive clinical response. Chapter 5.2 is a reply on an article of Pathirana et al. (EJSO 2001) who described that application of $^{131}$I-MIBG therapy is a safe and cost-effective treatment to control the symptoms of the carcinoid syndrome. Although these findings are in line with our experience, we draw attention to the effect of predosing with unlabelled MIBG followed by the radioactive treatment with MIBG. By improving uptake of MIBG in the tumour by this approach, the number of patients eligible for radioactive treatment can be increased and the clinical results more pronounced.

Interferon-α and MIBG are both active in metastatic carcinoid. Improved uptake of $^{123}$I-MIBG was seen after interferon-γ in neuroblastoma cell lines. In chapter 6 a phase II study is described in which we evaluated the effect of interferon-α upon diagnostic $^{131}$I-MIBG uptake in the tumour and the clinical response of the combination. The tumour over non-tumour (T/NT) ratios were quantitatively determined by comparing counts in the centre of the tumour (liver metastases) with those in an adjacent area of normal liver uptake (T/NT1) and with abdominal background area (T/NT2). An increase of $>10\%$ in MIBG uptake was considered significant. After 8 weeks treatment with interferon-α T/NT1 ratios showed an increase in 19% of the patients. After application of unlabelled MIBG 50% of the patients showed an increase in T/NT1 ratio. The absolute uptake in tumour deposits was also increased if compared with the abdominal background, leading to a significant T/NT2 increase in respectively 23% and 83%. Overall, changes after interferon-α were not statistically significant ($p=0.178$), in contrast to those after application of MIBG ($p=0.016$). No significant improvement in quality of life was observed after interferon or MIBG. Patients with systemic symptoms other than carcinoid syndrome responded significantly better on treatment with MIBG compared with those with complaints of the carcinoid syndrome who showed a better response on IFN.

Local treatment of hepatic metastases of carcinoid tumours is attractive because of the slow and localised growth pattern. However, the metastatic pattern in the liver is often diffuse and with multiple localisations. Therefore, resection is usually not feasible. In chapter 7 local treatment modalities for liver metastases other than resection are described. Hepatic artery embolisation showed a median overall decrease in 5-HIAA excretion of 32%. In 3/13 (23%) treated patients a long-lasting symptomatic improvement was achieved. Three patients were treated with radiofrequency ablation (RFA). This resulted in a reduction of hormonal excretion in all of them, with a long-lasting
symptomatic improvement in two patients. Although the number of patients treated with RFA was limited, the first experiences with this treatment modality are encouraging.

In chapter 8 we compared histology of (sub)cutaneous metastases in four patients with metastatic carcinoid tumours. Two of them suffered from severely painful skin lesions and the other two had no complains of pain. On the pathological slides we could not determine differences in neuroinvasion, angioinvasion or mitosis between painful and non-painful metastases. However, the painful lesion rapidly multiplied, while the others remained indolent in nature. Pain was very difficult to manage and did not respond to analgesics, irradiation or systemic treatment. Local excision was the only successful treatment option.

Future perspectives

Prognosis of carcinoid tumours has improved during the last decade. The treatment of these patients remains a challenge for the physician and a multidisciplinary approach is advocated.

In a substantial number of patients the primary tumour remains unknown despite extensive diagnostic investigations. However, primary tumours in the small bowel can cause complications as bowel obstruction and fibrosis with abdominal complaints during follow-up of patients. Application of the video capsule endoscopy as a non-invasive imaging technique of the complete small bowel can probably reduce the number of unknown primary tumours. Chromogranin A (CgA) seems a promising marker for detection and follow-up of carcinoid patients. Advantages of CgA compared with urinary 5-HIAA levels are a higher sensitivity in detection of metastatic disease and a stronger correlation with tumour volume and survival. In addition, CgA is more stable than serotonin and the urinary metabolite 5-HIAA. However, serial measurements during follow-up to determine progression is only reported in small series of patients. Thus, there is a great need for a large study to define the role of CgA to monitor disease activity during follow-up.

Local treatment of liver metastases with radiofrequency ablation (RFA) seems promising and extending the experience with the application of this therapy is recommended. A systemic new treatment modality is radioactive labelled somatostatin analogues ($^{111}$-indium, $^{90}$-yttrium, and $^{177}$-lutetium) which can be used in patients with a positive $^{111}$In-pentetreotide scintigraphy. First results are encouraging and can be used to expand therapeutic options in patients with metastatic disease failing on other systemic therapies. Although the annual incidence rate of carcinoid is growing, the overall survival of metastatic carcinoid patients has improved over the last decades. Due to this improved survival complications such as carcinoid heart disease and new metastatic patterns like skin and bone metastases will become a more important aspect in carcinoid disease.
Therapy focused on these complications must be part of the approach. Replacement of heart valves must be considered in patients with metastatic disease and a good clinical condition. Therapy focused on tumour reduction (surgical approach alone or in combination with hepatic artery embolisation of RFA) early in the treatment of patients with metastatic midgut carcinoid seems to be related with improvement in survival, a reduction in hormonal excretion and fewer complications such as bowel obstruction or mesenterial fibrosis during follow-up.

Combining new diagnostic and treatment modalities in metastatic carcinoid patients may result in a better quality of life and a longer survival.