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Persistent low urinary excretion of 5-HIAA is a marker for favourable survival during follow-up in patients with disseminated midgut carcinoid tumours

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ABSTRACT

Survival of patients with disseminated midgut carcinoid tumours varies. We investigated which factors predict survival at referral and during follow-up, with emphasis on urinary 5-hydroxyindolacetic acid (5-HIAA) levels.

Between 1992 and 2003, 76 patients were studied; urine was prospectively collected over a 24 h period every 3 months in order to measure 5-HIAA levels. Uni- and multivariate analyses were performed.

Median follow-up was 55 months with a median survival of 54 months. Prognostic factors for poor survival were high age, high gamma-glutamyltransferase levels and greatly increased 5-HIAA levels (>20 mmol/mol creatinine) The Hazard Ratio (HR) of a greatly increased 5-HIAA level was 3.33 (95% confidence interval (CI) 1.66–6.66, $p = 0.001$).

In a multivariate survival analysis with the 5-HIAA level as time dependent covariable, the HR for the 5-HIAA level was 1.007 (95% CI 1.004–1.010, $p = 0.000$).

In conclusion, patients with persistent moderately increased urinary 5-HIAA levels ($\leqslant$ 20 mmol/mol creatinine) have favourable outcome.

1. Introduction

Midgut carcinoid tumours are rare, slowly growing neuroendocrine tumours (NET) originating in the small intestine and proximal colon. They are derived from enterochromaffin cells and capable of secreting serotonin.[1] The World Health Organisation nowadays classifies these tumours as well differentiated neuroendocrine carcinomas of the small bowel.[2] However, the term midgut carcinoid tumour is still being used for those tumours originating from the enterochromaffine

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cells, with serotonin secretion and associated with the carcinoid syndrome. In patients with disseminated midgut carcinoid tumours, an increased urinary 5-hydroxyindolacetic acid (5-HIAA) level, the metabolite of serotonin, is found.[3] The urinary 5-HIAA level is used as a diagnostic test and is used in the evaluation of disease progression and treatment.[4,5] Treatment of patients with disseminated midgut carcinoid tumours is primarily palliative and aimed at ameliorating symptoms, improving quality of life and prolonging survival. This can be achieved by somatostatin analogues,[6] interferon,[7] targeted radionuclide therapy[8] and in selective patients by surgery.[9] Treatment leads, in the majority of patients, to a reduction of the urinary 5-HIAA levels but rarely in objective tumour responses. Recently, however, several targeted drugs such as sunitinib, bevacizumab and mTOR inhibitors showed signs of antitumour activity in these tumours.[10–14] This raised the interest in the course of the disease in order to decide, in the future, when during this protracted disease to start which drug.

Survival varies greatly between these patients and it is difficult to predict the course of an individual patient. In a large population based study, 5 year survival rate was 44.1% for patients with disseminated midgut carcinoid tumours.[15] In several studies prognostic factors were studied (Table 1).[9,15–37] Unfavourable factors for survival are high urinary 5-HIAA levels at first visit in referral centres, high plasma Chromogranin A (CgA) levels, the presence of liver or lymph node metastases, carcinoid heart disease, tumour size, histological grade of differentiation and old age (Table 1). With the exception of the study of Turner and colleagues no studies are available that focussed on biochemical parameters during follow-up to predict survival.[34] Given the numerous drugs that seem to become available for these tumours it would be extremely helpful, in addition to radiological tumour measurements, to have a marker available that indicates prognosis during follow-up. This could guide selection of patients that potentially might benefit from intervention with newer agents. Therefore, the aim of the present study was to determine factors that predict survival of patients with disseminated midgut carcinoid tumours at referral and during follow-up with the emphasis on the urinary 5-HIAA level.

2. Material and methods

2.1. Patients

Between January 1992 and December 2003 all patients with a disseminated midgut carcinoid tumour who were referred for treatment at the Department of Medical Oncology, University Medical Centre Groningen, University of Groningen, were studied. The diagnosis of a disseminated midgut carcinoid tumour was based on the review of operation reports, the pathology specimens, thoracoabdominal computed tomography, somatostatin scintigraphy and increased levels of 5-HIAA in a 24 h urine collection (upper reference limit 3.8 mmol/mol creatinine) and/or an increased level of serotonin in platelets (upper reference limit 5.4 nmol /10^9 platelets). Data on gender, age at diagnosis, race, metastases at presentation, resection of the primary tumour, the presence of flushes and diarrhoea, the use of somatostatin analogues and/or interferon and survival were derived from the carcinoid database of the Department of Medical Oncology. This database contains medical information from the first appointment at the outpatient clinic and during follow-up of all patients with a midgut carcinoid tumour referred since 1987. Patients are regularly seen during follow-up every 3 to 6 months by the medical oncologist. An echocardiography is performed at referral and thereafter when patients are suspected of having carcinoid heart disease, i.e. complaints of dyspnoea and/or oedema, new findings on cardiac auscultation or physical signs of heart failure. In this database the patient is anonymous using a unique patient code, only known to one dedicated data manager. The database can only be checked through this data manager. Last moment of follow-up was February 2007.

2.2. Laboratory and biochemical markers

Serotonin in platelet-rich plasma was determined by high performance liquid chromatography (HPLC) with fluorometric detection, expressed in nmol/10^9 platelets.[38] The upper reference limits of alkaline phosphatase (ALP) and gamma-glutamyltransferase (GT) were 120 U/l and 50 U/l respectively. Urinary 5-HIAA was determined by HPLC with fluorometric detection, in a 24 h urine collection and expressed as mmol/mol creatinine.[39] These data were prospectively collected every 3 to 6 months and put in the carcinoid database.

2.3. Statistical analysis

2.3.1. Univariate testing

Differences in survival between groups were analysed using Kaplan–Meier survival curves and tested with the log rank test. We used the following parameters: gender, the presence of liver metastases at referral, resection of the primary tumour prior to referral, plasma ALP and plasma GT levels (above or beneath the reference limit) and the urinary 5-HIAA levels at referral. Patients were grouped according to their urinary 5-HIAA levels with a cut-off level of 20 mmol/mol creatinine according to previous reported prognostic levels.[9,19] Hazard ratios (HR) were calculated using a univariate Cox regression analysis with plasma ALP, plasma GT, age and urinary 5-HIAA levels as a continuous variable. Since laboratory investigations were determined at presentation, 'survival since referral' instead of 'survival since diagnosis' was used in the survival analyses.

All tests were performed two-sided and a p value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 14.0.

2.3.2. Multivariate testing

To study the effect of several prognostic factors at presentation we performed a multivariate Cox regression analysis including factors related to outcome in the univariate analysis ($p < 0.1$). All variables were included in this analysis as continuous variables; the urinary 5-HIAA level was also included as a grouping variable.

Table 1 – Previous studies identifying prognostic factor for survival for patients with midgut carcinoid tumours

Author	No.	Tumour	5-year survival rate	5-year survival rate subgroups	Prognostic factors univariate	Prognostic factors, multivariate
Gatta et al.[17]	7693	GEP-NET^{P}	47%			age, time period, histological grade of differentiation
Janson et al.[19]	256	midgut^{R}	63%		liver metastases, 5-HIAA (> 300 μmol/24 h), high Cg A, NPK, age	age
Wangberg et al.[35]	64	midgut^{R}	69%			
Hellman et al.[9]	314	midgut^{R}	57%	liver metastases median 4.9 years	resection primary and/or lymph nodes, liver metastases, 5-HIAA (> 250 μmol/24 h), biotherapy	
Maggard et al.[23]	2778	small bowel^{P}	55%	distant metastases 32%		tumour size
Makridiset al.[24]	121	midgut^{R}			age	
Modlin et al.[15]	3458	small bowel^{P}	61% ('92–'9)	midgut, distant metastases 44%		
Pape et al.[26]	254	GEP-NET^{R}	57%	ileojejunum 67%	tumour size (> 2 cm), grade of differentiation	
Agranovich et al.[16]	87	GEP-NET^{R}			grade of differentiation, 5-HIAA	
Shebani et al. [30]	150	GI carcinoid^{R}		ileojejunum 68%	tumour site, male gender, age	age, liver/lymph node metastases, male sex
Turner et al.[34]	139	midgut^{R}	53%		age, 5-HIAA, NKA, liver metastases, resection primary tumour	age
Zar et al.[37]	2526	small bowel^{P}		duodenal 60% ileojejunum 56%	age, period of diagnosis	age, period of diagnosis
Söreide et al.[33]	154	GI carcinoid^{R}	69%		age, tumour site, tumour size, depth of invasion, liver/lymph node metastases	age, liver metastases
Soga et al.[32]	748	CS^{P}	76%	digestive 67% extra digestive 89%		
Westberg et al.[36]	64	CS^{R}	CHD + 30% CHD – 75%		age, tricuspid abnormalities	
Quaedvlieg et al.[28]	2391	carcinoid^{P}	72%	GI tumour, distant metastases 21%		age, stage, gender, tumour site, year of diagnosis
Kirshbom et al.[20]	434	carcinoid^{R}	midgut 10 year survival 50%	Midgut, distant metastases 10 year survival 28%		
McDermott et al.[25]	188	GEP-NET^{R}		small bowel 66%	male sex, T4 tumour, tumour size, liver/lymph node metastases	male sex, metastases
Greenberg et al.[18]	270	carcinoid^{P}		small bowel 66%	tumour site, stage	age, tumour site, stage
Lepage et al.[21]	229	GEP-NET^{P}	43%	small bowel 48%	age, male sex, stage, curative resection	age, tumour site, stage
Lepage et al.[21]	3233	GEP-NET^{P}	57%	small bowel 59%	age, male sex, tumour site	
Sjoblom et al.[31]	48	small bowel^{R}		liver metastases 54%		
Saha et al.[29]	112	GEP-NET^{R}		ileojejunum 30%		
Pellika et al.[27]	132	CS^{R}	CHD + 20% CHD – 50%		CHD	

GEP-NET = gastroenteropancreatic neuroendocrine tumour, GI = gastrointestinal, CS = carcinoid syndrome, CHD = carcinoid heart disease, 5-HIAA = 5 hydroxyindolacetic acid, NKA = neurokinin A, NPK = neuropeptide K, R = referral based, P = population based, CgA = Chromogranin A.

2.3.3. *Urinary 5-HIAA level as a time dependent variable*

Next to survival after referral we also studied the prognostic value of the urinary 5-HIAA levels across time using a Cox Regression model with the urinary 5-HIAA level as a time-dependent covariate, also including factors mentioned above. The urinary 5-HIAA level was evaluated as a 3 monthly measurement. If data on the urinary 5-HIAA level was missing (203 (23%) out of 666 measurements), we interpolated using the level 3 months prior to and 3 months after this date. We used the urinary 5-HIAA level 6 months prior to the visit to predict survival. If the difference between the actual follow-up since referral and the last moment of urine collection was < 6 months, then the last urinary 5-HIAA level was extrapolated. For patients with missing data on urinary 5-HIAA levels > 12 months before the last moment of follow-up, the last follow-up date was determined as 6 months after the last urine collection. These patients were alive at this moment of follow-up. To determine the effect of the cumulative exposure to serotonin we also used the cumulative 5-HIAA level at every moment of follow-up as a time-dependent variable. The cumulative 5-HIAA level was calculated as the sum of the separate urinary 5-HIAA levels measured every 3 months.

3. Results

3.1. *Patients*

A total of 76 patients, 33 male and 43 female patients, all Caucasian, were included. Table 2 shows the characteristics of patients at referral. Nine patients (11.8%) developed carcinoid heart disease during follow-up. Patients with carcinoid heart disease had higher urinary 5-HIAA levels at referral, 52.8 mmol/mol creatinine (range 8.5–252.0 mmol/mol creatinine) compared to patients without carcinoid heart disease, 18.6 mmol/mol creatinine (range 1.3–418.4 mmol/mol creatinine) ($p = 0.085$). Patients were referred after a median duration of disease of 2 months (range 0–184 months). The median duration of complaints for patients with an urinary 5-HIAA level of $\leqslant 20$ mmol/mol creatinine was 13 months (range 1–577 months) compared to 26 months (range 1–247 months) for patients with an urinary 5-HIAA level >20 mmol/mol creatinine ($p = 0.229$). Patients with liver metastases ($n = 61$) had higher levels of ALP and GT at referral, median 99 U/l versus 74 U/l ($p = 0.316$) and 42 U/l versus 32 U/l ($p = 0.072$) respectively.

Median follow-up was 55 months (range 0.5–143). Fig. 1 shows the median urinary 5-HIAA levels during follow-up with interquartile ranges.

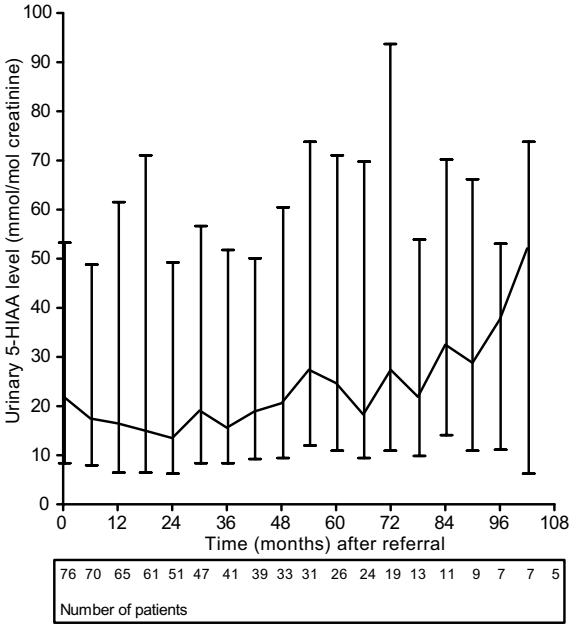

Fig. 1 – Median urinary 5-hydroxyindolacetic acid (5-HIAA) levels during follow-up with interquartile ranges.

Table 2 – Characteristics of patients at referral

Mean age at diagnosis – years (±SD)	59.4 (9.6)
Mean age at referral – years (±SD)	60.7 (9.3)
Median duration of complaints before referral-months (±SD)	20 (1–577)
Primary tumour site – *n* (%)	
Ileum	43 (56.6)
Small bowel	4 (5.3%)
Colon	7 (9.2%)
Unknown	22 (28.9)
Presence of liver metastases	61 (80.3%)
Complaints – *n* (%)	
Diarrhoea	49 (64.5)
Flushes	51 (69.9)
Treatment – *n* (%)	
Somatostatin analogues	11 (14.5%)
Interferon	1 (1.3%)
Laboratory values	
Median alkaline phosphatase - U/l (range)	93 (35–401)
Median gamma-glutamyltransferase - U/l (range)	41 (12–505)
Mean serotonin in platelets – nmol/10^9platelets (SD)	26.2 (10.5)
Median urinary 5-HIAA level – mmol/mol creatinine (range)	21.0 (1.3–418.4)

5-HIAA = 5-hydroxyindolacetic acid.

3.1.1. *Survival, univariate testing*

Overall median survival from diagnosis and since referral was 75 months (95% confidence interval (CI) 61–88 months) and 54 months (95% CI 42–67 months) respectively, with a 5 year survival rate of respectively 56.8% and 48.5% (Fig. 2). Age as a continuous variable was a prognostic factor with a HR of 1.043 (95% CI 1.014–1.073, $p = 0.003$) Table 3 shows the univariate analysis of different characteristics at referral. Lowering or raising the cut-off level of the urinary 5-HIAA level did not increase the difference in survival between the groups when compared to the difference of 57 months for patients with a urinary level of $\leqslant$20 mmol/mol creatinine and >20 mmol/mol creatinine (Fig. 3).

3.1.2. *Survival, multivariate testing*

In the multivariate model, age, a greatly increased urinary 5-HIAA level (>20 mmol/mol creatinine) and a raised GT level at referral were independent prognostic factors for survival

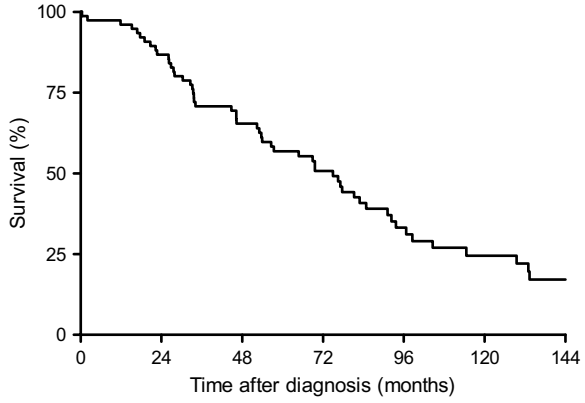

Fig. 2 – Survival after diagnosis (months).

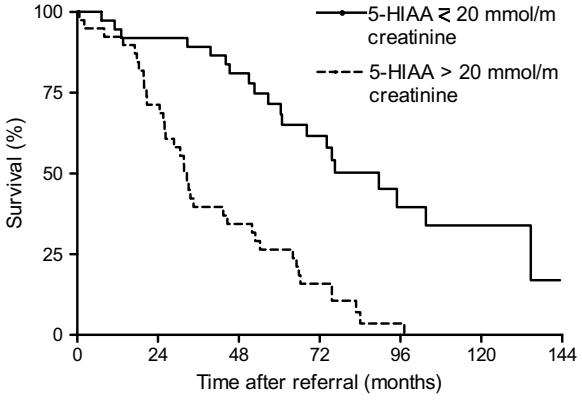

Fig. 3 – Survival after referral, difference between patients with urinary 5-hydroxyindolacetic acid (5-HIAA) ⩽20 mmol/m creatinine and >20 mmol/m creatinine.

(Table 4). Patients with an urinary 5-HIAA level of >20 mmol/mol creatinine at referral had a worse survival compared to patients with a urinary 5-HIAA level of ⩽ 20 mmol/mol creatinine with a HR of 3.33 (95% CI 1.66–6.66) ($p = 0.001$).

3.1.3. Urinary 5-HIAA level as a time dependent variable

Eleven patients (14%) did not collect urine for measurement of 5-HIAA levels for >12 months prior to the last follow-up date. Median difference between the actual follow-up and the follow-up until the last urine collection in these patients was 38 months (range 14–80 months). Five out of 11 patients had a change in vital status; deceased at the last follow-up moment of February 2007, but still alive 6 months after the last moment of urine collection. In the extended multivariate Cox regression analysis, the HR of the urinary 5-HIAA level as a time dependent variable was 1.007 (95% CI 1.004–1.010 $p = 0.000$). The cumulative urinary 5-HIAA level as a time dependent variable had an HR of 1.001 (95% CI 1.000–1.001, $p = 0.000$).

4. Discussion

To our knowledge, this is the first study to demonstrate that the urinary 5-HIAA level is an independent prognostic factor both at referral and during follow-up for patients with a disseminated midgut carcinoid tumour. Patients with a greatly increased urinary 5-HIAA level at referral (>20 mmol/mol creatinine) had a median survival of 33 months compared to 90 months for patients with a moderately increased level (⩽20 mmol/mol creatinine). Next to the urinary 5-HIAA level we found that high age and a high GT level at referral were independent prognostic factors for a worse survival. An extended multivariate analysis identified the urinary 5-HIAA level as an independent predictor for worse survival with an HR of 1.007 for each increment of the urinary 5-HIAA level (mmol/mol creatinine).

The data obtained with a 5 year survival rate of 56.8% is comparable to the survival found in previous studies (Table

Table 3 – Univariate analysis with respect to survival

Factor	No.	HR	95% CI	Survival (months)	95%CI	5 year survival (%)	p
Age (years)	76	1.043	1.014–1.073				0.003
Gender		0.786	0.462–1.336				0.372
Male	33			65	54–77	60	0.670
Female	43			51	41–61	40	
Liver metastases		1.790	0.845–3.789				0.104
Present	61			52	37–69	45	0.123
Not present	15			64	31–97	64	
Resection primary tumour		0.606	0.341–1.076				0.087
Yes	27			75	44–107	57	0.084
No	49			52	37–68	44	
Gamma-glutamyltransferase (U/l)		1.009	1.004–1.013				0.000
Normal	47			66	53–79	60	0.026
Raised	29			43	23–64	28	
Alkaline phosphatase (U/l)		1.006	1.003–1.010				0.001
Normal	59			64	51–77	55	0.063
Raised	17			29	23–35	25	
Urinary 5-HIAA level (mmol/mol creatinine)		1.004	1.001–1.006				0.003
⩽20	37			90	69–111	72	0.000
>20	39			33	29–36	26	

HR = hazard ratio, CI = confidence interval, 5-HIAA = 5 hydroxyindolacetic acid.

Table 4 – Multivariate analysis with respect to survival

Factor	HR	95%CI	*p*
Age	1.052	1.02–1.084	0.001
Resection primary tumour	0.581	0.306–1.104	0.097
Gamma-glutamyltransferase	1.009	1.003–1.015	0.002
Alkaline phosphatase	1.002	0.997–1.008	0.4
Urinary 5-HIAA level (mmol/mol creatinine)	1.003	1.000–1.006	0.033

HR = Hazard ratio, CI = confidence interval, 5-HIAA = 5 hydroxyindolacetic acid.

1) and therefore allows generalisation of our findings. Several studies did observe urinary 5-HIAA levels at presentation to be related with outcome in univariate analysis but after correction for other factors such as age, it did not stand out.[9,19,34] Our study with a relatively high number of measurements per patient, validates the use of the urinary 5-HIAA level during follow-up not only for monitoring the effect of therapy but also for predicting survival in an individual patient at any moment during follow-up.[3,5] The HR of the cumulative 5-HIAA level, as a time dependent variable, was 1.001. This suggests that the absolute urinary 5-HIAA level, and thus the absolute serotonin production, is important, as previously described by Denney and colleagues for the development of carcinoid heart disease.[40] A cumulative 5-HIAA level does not seem to give additive information in predicting survival. At presentation there seems to be a threshold for the urinary 5-HIAA level at 20 mmol/mol creatinine for predicting survival, since raising the cut-off level (to the level of 40 mmol/mol creatinine) did not influence the difference in survival of 57 months between the groups (data not shown).[9,19] Serotonin has its harmful effects through five different serotonin receptors, and saturation of these receptors could potentially well explain this threshold.

We observed that GT levels predicted survival, probably as a reflection of the presence, or the extent of liver metastases, since GT and ALP rise in the presence of liver metastases.[41,42] Clancy and colleagues also observed that ALP predicted survival in patients with disseminated neuroendocrine tumours.[43] Their analysis did not include GT levels. A recent study of Formica and colleagues also showed that raised liver enzymes were associated with a worse prognosis, including GT but not ALP.[44] The HR of the presence of liver metastases did not reach statistical significance in our analysis; however, we did not collect information on the extent of the liver metastases.

Our findings might have a number of potential implications for the clinic. First, since urinary 5-HIAA levels are prognostic at every moment during follow-up it seems justified to initiate treatment not only for symptoms but also because of greatly increased urinary 5-HIAA levels.[6,7] In two previous studies it was already suggested that somatostatin analogues, by lowering serotonin secretion, prolong survival in patients with midgut carcinoid tumour.[28,34] Secondly, when a patient first presents, it is often difficult to predict prognosis and justify starting antitumour treatment with e.g. the newer tumour agents. Currently, in clinical trials, clear radiological tumour progression is often required. However, based on our findings, patients with a high urinary HIAA level might be eligible without proof of recent anatomical tumour progression.[45]

A limitation has to be mentioned, although this is also true for other prognostic studies. Patients with midgut carcinoid tumours and also disseminated disease often present following a long patient and doctors delay.[5] As a consequence these analyses are based on values after the first visit and not after disease onset.

In summary, our study shows that next to high age and a high GT level at referral, the urinary 5-HIAA level is an independent prognostic factor both at referral and during follow-up.

Conflict of interest statement

None declared.

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REFERENCES

1. Williams ED, Sandler M. The classification of carcinoid tumours. *Lancet* 1963;**1**:238–9.
2. Solcia E, Kloppel G, Sobin LH. *Histological typing of endocrine tumours*. New York: Springer Verlag; 2000.
3. Meijer WG, Kema IP, Volmer M, Willemse PH, De Vries EG. Discriminating capacity of indole markers in the diagnosis of carcinoid tumors. *Clin Chem* 2000;**46**:1588–96.
4. Clark OH, Ajani J, Benson AJ. Neuroendocrine tumor panel. NCCN clinical practice guidelines in oncology. *Neuroendocrine tumors* 2007:V.1.
5. Van der Horst-Schrivers AN, Wymenga AN, De Vries EG. Carcinoid heart disease. *N Engl J Med* 2003;**348**:2359–2361.
6. Kvols LK, Moertel CG, O'Connell MJ, Schutt AJ, Rubin J, Hahn RG. Treatment of the malignant carcinoid syndrome. Evaluation of a long-acting somatostatin analogue. *N Engl J Med* 1986;**315**:663–6.
7. Oberg K, Funa K, Alm G. Effects of leukocyte interferon on clinical symptoms and hormone levels in patients with midgut carcinoid tumors and carcinoid syndrome. *N Engl J Med* 1983;**309**:129–33.
8. Kwekkeboom DJ, Teunissen JJ, Bakker WH, et al. Radiolabeled somatostatin analog [177Lu-DOTA0,Tyr3]octreotate in patients with endocrine gastroenteropancreatic tumors. *J Clin Oncol* 2005;**23**:2754–62.

9. Hellman P, Lundstrom T, Ohrvall U, et al. Effect of surgery on the outcome of midgut carcinoid disease with lymph node and liver metastases. *World J Surg* 2002;**26**:991–7.
10. Bello CL, Deprimo SE, Friece C, et al. Analysis of circulating biomarkers of sunitinib malate in patients with unresectable neuroendocrine tumors (NET): VEGF, IL-8, and soluble VEGF receptors 2 and 3. *J Clin Oncol* 2006;**24**(18S):4045.
11. Duran I, Kortmansky J, Singh D, et al. A phase II clinical and pharmacodynamic study of temsirolimus in advanced neuroendocrine carcinomas. *Br J Cancer* 2006;**95**: 1148–54.
12. Yao JC, Ng C, Hoff PM, et al. Improved progressio ee survival (PFS), and rapid, sustained decrease in tumor perfusion among patients with advanced carcinoid treated with bevacizumab. *J Clin Oncol* 2005;**23**:309s.
13. Yao JC, Zhang JX, Rashid A, et al. Clinical and in vitro studies of imatinib in advanced carcinoid tumors. *Clin Cancer Res* 2007;**13**:234–40.
14. Zhang J, Jia Z, Li Q, et al. Elevated expression of vascular endothelial growth factor correlates with increased angiogenesis and decreased progression-free survival among patients with low-grade neuroendocrine tumors. *Cancer* 2007;**109**:1478–86.
15. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. *Cancer* 2003;**97**:934–59.
16. Agranovich AL, Anderson GH, Manji M, Acker BD, Macdonald WJ, Threlfall WJ. Carcinoid tumour of the gastrointestinal tract: prognostic factors and disease outcome. *J Surg Oncol* 1991;**47**:45–52.
17. Gatta G, Ciccolallo L, Kunkler I, et al. Survival from rare cancer in adults: a population-based study. *Lancet Oncol* 2006;**7**:132–40.
18. Greenberg RS, Baumgarten DA, Clark WS, Isacson P, McKeen K. Prognostic factors for gastrointestinal and bronchopulmonary carcinoid tumors. *Cancer* 1987;**60**:2476–83.
19. Janson ET, Holmberg L, Stridsberg M, et al. Carcinoid tumors: analysis of prognostic factors and survival in 301 patients from a referral center. *Ann Oncol* 1997;**8**:685–90.
20. Kirshbom PM, Kherani AR, Onaitis MW, Feldman JM, Tyler DS. Carcinoids of unknown origin: comparative analysis with foregut, midgut, and hindgut carcinoids. *Surgery* 1998;**124**:1063–70.
21. Lepage C, Bouvier AM, Phelip JM, Hatem C, Vernet C, Faivre J. Incidence and management of malignant digestive endocrine tumours in a well defined French population. *Gut* 2004;**53**:549–53.
22. Lepage C, Rachet B, Coleman MP. Survival from malignant digestive endocrine tumors in England and Wales: a population-based study. *Gastroenterology* 2007;**132**:899–904.
23. Maggard MA, O'Connell JB, Ko CY. Updated population-based review of carcinoid tumors. *Ann Surg* 2004;**240**:117–22.
24. Makridis C, Ekbom A, Bring J, et al. Survival and daily physical activity in patients treated for advanced midgut carcinoid tumors. *Surgery* 1997;**122**:1075–82.
25. McDermott EW, Guduric B, Brennan MF. Prognostic variables in patients with gastrointestinal carcinoid tumours. *Br J Surg* 1994;**81**:1007–9.
26. Pape UF, Bohmig M, Berndt U, Tiling N, Wiedenmann B, Plockinger U. Survival and clinical outcome of patients with neuroendocrine tumors of the gastroenteropancreatic tract in a german referral center. *Ann N Y Acad Sci* 2004;**1014**: 222–33.
27. Pellikka PA, Tajik AJ, Khandheria BK, et al. Carcinoid heart disease. Clinical and echocardiographic spectrum in 74 patients. *Circulation* 1993;**87**:1188–96.
28. Quaedvlieg PF, Visser O, Lamers CB, Janssen-Heijen ML, Taal BG. Epidemiology and survival in patients with carcinoid disease in The Netherlands. An epidemiological study with 2391 patients. *Ann Oncol* 2001;**12**:1295–300.
29. Saha S, Hoda S, Godfrey R, Sutherland C, Raybon K. Carcinoid tumors of the gastrointestinal tract: a 44-year experience. *South Med J* 1989;**82**:1501–5.
30. Shebani KO, Souba WW, Finkelstein DM, et al. Prognosis and survival in patients with gastrointestinal tract carcinoid tumors. *Ann Surg* 1999;**229**:815–21.
31. Sjoblom SM. Clinical presentation and prognosis of gastrointestinal carcinoid tumours. *Scand J Gastroenterol* 1988;**23**:779–87.
32. Soga J, Yakuwa Y, Osaka M. Carcinoid syndrome: a statistical evaluation of 748 reported cases. *J Exp Clin Cancer Res* 1999;**18**:133–41.
33. Soreide JA, van Heerden JA, Thompson GB, Schleck C, Ilstrup M, Churchward M. Gastrointestinal carcinoid tumors: long-term prognosis for surgically treated patients. *World J Surg* 2000;**24**:1431–6.
34. Turner GB, Johnston BT, McCance DR, et al. Circulating markers of prognosis and response to treatment in patients with midgut carcinoid tumours. *Gut* 2006;**55**:1586–91.
35. Wangberg B, Westberg G, Tylen U, et al. Survival of patients with disseminated midgut carcinoid tumors after aggressive tumor reduction. *World J Surg* 1996;**20**:892–9.
36. Westberg G, Wangberg B, Ahlman H, Bergh CH, Beckman-Suurkula M, Caidahl K. Prediction of prognosis by echocardiography in patients with midgut carcinoid syndrome. *Br J Surg* 2001;**88**:865–72.
37. Zar N, Garmo H, Holmberg L, Rastad J, Hellman P. Long-term survival of patients with small intestinal carcinoid tumors. *World J Surg* 2004;**28**:1163–8.
38. Kema IP, Meijer WG, Meiborg G, Ooms B, Willemse PH, De Vries EG. Profiling of tryptophan-related plasma indoles in patients with carcinoid tumors by automated, on-line, solid-phase extraction and HPLC with fluorescence detection. *Clin Chem* 2001;**47**:1811–20.
39. Mulder EJ, Oosterloo-Duinkerken A, Anderson GM, De Vries RB, Minderaa RB, Kema IP. Automated on-line solid-phase extraction coupled with HPLC for measurement of 5-hydroxyindole-3-acetic acid in urine. *Clin Chem* 2005;**51**:1698–703.
40. Denney WD, Kemp Jr WE, Anthony LB, Oates JA, Byrd III BF. Echocardiographic and biochemical evaluation of the development and progression of carcinoid heart disease. *J Am Coll Cardiol* 1998;**32**:1017–22.
41. Li X, Mortensen B, Rushfeldt C, Huseby N-E. Serum gamma-glutamyltransferase and alkaline phosphatase during experimental livermetastases. Detection of tumour-specific isoforms and factors affecting their serum levels. *Eur J Cancer* 1998;**12**:1935–40.
42. Missotten GS, Korse CM, van Dehn C, et al. S-100B protein and melanoma inhibitory activity protein in uveal melanoma screening. A comparison with liver function tests. *Tumour Biol* 2007;**28**:63–9.
43. Clancy TE, Sengupta TP, Paulus J, Ahmed F, Duh MS, Kulke MH. Alkaline phosphatase predicts survival in patients with metastatic neuroendocrine tumors. *Dig Dis Sci* 2006;**51**:877–84.
44. Formica V, Wotherspoon A, Cunningham D, et al. The prognostic role of WHO classification, urinary 5-hydroxyindoleacetic acid and liver function tests in metastatic neuroendocrine carcinomas of the gastroenteropancreatic. *Br J Cancer* 2006;**96**: 1178–82.
45. O'Donell PH, Ratain MJ. Evaluating the activity of temsirolimus in neuroendocrine cancer. *Br J Cancer* 2007;**96**:177.