

Total ^{18}F -dopa PET tumour uptake reflects metabolic endocrine tumour activity in patients with a carcinoid tumour

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Abstract

Purpose Positron emission tomography (PET) using 6- ^{18}F fluoro-L-dihydroxyphenylalanine (^{18}F -dopa) has an excellent sensitivity to detect carcinoid tumour lesions. ^{18}F -dopa tumour uptake and the levels of biochemical tumour markers are mediated by tumour endocrine metabolic activity. We evaluated whether total ^{18}F -dopa tumour uptake on PET, defined as whole-body metabolic tumour burden (WBMTB), reflects tumour load per patient, as measured with tumour markers.

Methods Seventy-seven consecutive carcinoid patients who underwent an ^{18}F -dopa PET scan in two previously published studies were analysed. For all tumour lesions mean standardised uptake values (SUVs) at 40% of the maximal SUV and tumour volume on ^{18}F -dopa PET were determined and multiplied to calculate a metabolic burden

per lesion. WBMTB was the sum of the metabolic burden of all individual lesions per patient. The 24-h urinary serotonin, urine and plasma 5-hydroxyindoleacetic acid (5-HIAA), catecholamines (nor)epinephrine, dopamine and their metabolites, measured in urine and plasma, and serum chromogranin A served as tumour markers.

Results All but 1 were evaluable for WBMTB; 74 patients had metastatic disease. ^{18}F -dopa PET detected 979 lesions. SUV_{max} on ^{18}F -dopa PET varied up to 29-fold between individual lesions within the same patients. WBMTB correlated with urinary serotonin ($r=0.51$) and urinary and plasma 5-HIAA ($r=0.78$ and 0.66). WBMTB also correlated with urinary norepinephrine, epinephrine, dopamine and plasma dopamine, but not with serum chromogranin A. **Conclusion** Tumour load per patient measured with ^{18}F -dopa PET correlates with tumour markers of the serotonin and catecholamine pathway in urine and plasma in carcinoid patients, reflecting metabolic tumour activity.

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Introduction

Carcinoids are rare tumours arising from neuroendocrine cells, which can produce and secrete a variety of biochemical markers, including serotonin. Carcinoid tumours can produce several other markers including catecholamines in 48% of patients [1–3]. Measuring urinary 5-hydroxyindoleacetic acid (5-HIAA), the main metabolite of serotonin, is currently the cornerstone in the diagnosis and response evaluation of metastatic carcinoid tumours, in combination with data provided by computed

tomography (CT) and magnetic resonance imaging (MRI) [4]. Recently, it has been suggested that serum chromogranin A is a better marker than urinary 5-HIAA excretion for follow-up of carcinoid patients [5, 6]. The disadvantage of urinary 5-HIAA is that the collection of 24-h urine samples can be unreliable and is inconvenient for the patient [7]. Therefore a more convenient and accurate marker is of interest. But in contrast to 5-HIAA, serum chromogranin A does not reflect the metabolic status of these tumours [6, 8].

The intrinsic property of neuroendocrine tumour cells to take up and decarboxylate amine precursors, which is reflected in the secretory activity of these tumours, is also used for positron emission tomography (PET) imaging of these tumours. PET using the catecholamine precursor 6- ^{18}F fluoro-L-dihydroxyphenylalanine (^{18}F -dopa) has an excellent sensitivity to detect carcinoid tumour lesions [9–11]. In the intracellular accumulation of ^{18}F -dopa by neuroendocrine tumours several essential steps play a role. ^{18}F -dopa is transported into the cell by the L-type amino acid transporter (LAT), which transports large neutral amino acids, and then decarboxylated by aromatic L-amino acid decarboxylase (AADC), resulting in the formation of ^{18}F -dopamine. This is subsequently transported into specific storage vesicles by vesicular monoamine transporter and protected from enzymatic degradation. Unstored ^{18}F -dopamine is subject to degradation in the cytosol and the metabolites formed leave the cell via diffusion [12]. The increased demand for precursors by the overactive secretory pathways in carcinoid tumours induces high ^{18}F -dopa uptake in tumour cells [2, 13].

Currently, functional information of PET is increasingly being incorporated into staging and follow-up. This information complements the anatomical information, such as exact size and location of lesions, provided by CT and MRI [14–17]. Whether ^{18}F -dopa PET can also complement biochemical tumour markers or become a surrogate marker is as yet unknown.

Attempts to quantitate metabolic disease activity are usually based on the maximum standardised uptake value (SUV_{max}) and the mean standardised uptake value (SUV_{mean}) within a certain volume of interest (VOI). PET imaging additionally opens ways to analyse whole-body metabolic tumour burden (WBM TB) as a quantitative measure of the overall tumour load. This approach was used with ^{18}F -fluorodeoxyglucose (FDG) PET in non-Hodgkin's lymphoma to measure the treatment response after chemotherapy with glucose uptake in the tumour. With PET WBM TB was the best measure of overall response when compared with SUV_{max} and SUV_{mean} [18].

With the increasing use of ^{18}F -dopa PET it is desirable to know whether the metabolic endocrine tumour activity measured by biochemical markers in plasma and urine

Table 1 Patient characteristics

Number of evaluable patients	76
Sex (<i>n</i> : male/female)	42/34
Age median (range)	58 (17–79)
New patients vs patients with known disease (<i>n</i>)	30/46
Metastatic disease (<i>n</i>)	74
Location of primary tumour	
Bronchus (<i>n</i>)	5
Duodenum (<i>n</i>)	4
Small intestine: jejunum-ileum (<i>n</i>)	62
Colon (<i>n</i>)	5
Treatment	
Somatostatin analogue treatment (<i>n</i>)	28
Interferon treatment (<i>n</i>)	2

correlates with metabolic activity, as measured on ^{18}F -dopa PET. Therefore, the aim of the present study was to evaluate

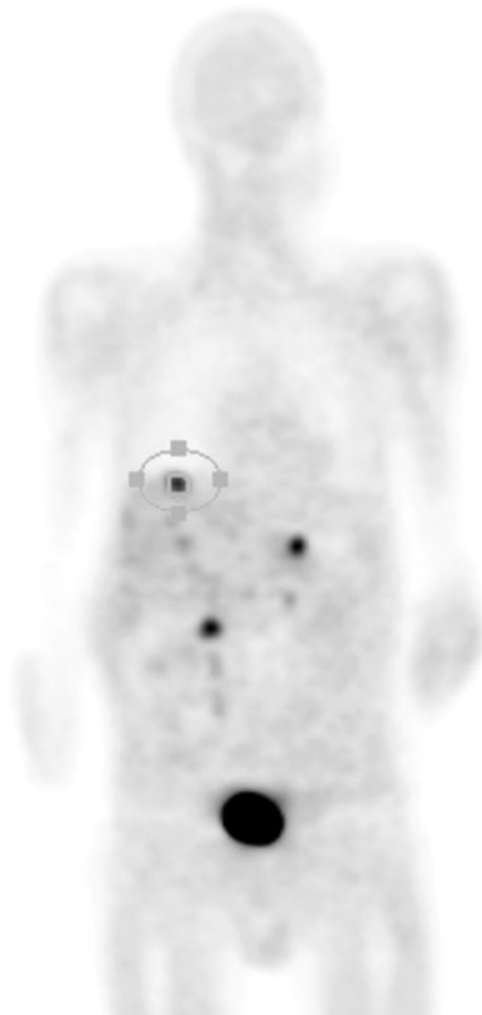


Fig. 1 Example of an ^{18}F -dopa PET scan of a patient with a semiautomatically generated VOI of a carcinoid lesion

Table 2 Lesion characteristics

Number of ^{18}F -dopa PET-positive lesions	979
Median number per patient (range)	12 (0–85)
SUV _{max} , median (range)	3.9 (0.8–33.4)
SUV _{mean} , median (range)	2.6 (0.5–22.7)
Volume in cm ³ , median (range)	7.6 (0.55–2,308)
WBMTB in cm ³ , range	712 (0–19,000)

in a group of patients who underwent ^{18}F -dopa PET as well as a careful collection of relevant biochemical tumour markers whether the total ^{18}F -dopa tumour uptake on PET reflects the tumour load per patient, as measured with the tumour markers.

Materials and methods

Patients

For this study we selected all consecutive patients with a carcinoid tumour ($n=77$) who underwent ^{18}F -dopa PET as well as a careful collection of relevant biochemical tumour markers in two previously published ^{18}F -dopa PET studies of our institute (between October 2003 and February 2007) (patients with other neuroendocrine tumours from the aforementioned studies were not considered for this analysis) [9, 10]. The inclusion criteria for these studies were patients with a strong suspicion of a carcinoid tumour, based on clinical and biochemical findings, and patients with histopathologically proven carcinoid tumour, with a clinical indication for (re)staging. All patients had to have at least one abnormal lesion on conventional imaging. These previous studies were designed to evaluate the diagnostic sensitivity of ^{18}F -dopa PET and ^{11}C -5-hydroxytryptophan PET in patients with carcinoid tumours. Ex-

tended biochemical analyses were performed and charts were checked for the presence of somatostatin analogue treatment. The studies were approved by the Medical Ethics Committee, and all patients gave informed consent.

^{18}F -dopa PET

^{18}F -dopa was locally produced and performed as described earlier [9, 10, 19]. In short, whole-body 2-D PET images were acquired 60 min after the intravenous administration of ^{18}F -dopa (180 ± 50 MBq). The patients fasted for 6 h before the examination and were allowed to continue all medication. For the reduction of tracer decarboxylation and subsequent renal clearance and to increase tracer uptake in tumour cells all patients received 2 mg/kg carbidopa orally as pretreatment 1 h prior to the ^{18}F -dopa injection [20–22].

Image analysis

The ^{18}F -dopa PET scans were reviewed. For each patient, a WBMTB was determined as the sum of the metabolic burden (MB) of each tumour lesion in the PET image [18]. In order to make the MB independent of body weight and injected dose the SUV was used, which is defined as: $\text{SUV} = \text{activity concentration (MBq/ml)} / \text{injected dose per gram (MBq/g)}$.

In turn, the MB was calculated as: $\text{MB} = \text{SUV}_{\text{mean}} \times \text{volume of tumour lesion}$. Using this calculation, WBMTB is expressed as one value (no max or mean as for example SUV itself). Both SUV_{mean} and tumour volume were obtained from the PET image using a VOI that was defined as the tumour volume enclosed by a 40% isodensity surface [23, 24]. This VOI was semiautomatically drawn. First, the tumour was fully enclosed by a hand-drawn ellipsoid. In this preselected volume the SUV_{max} was established. Finally, the VOI contained all voxels with values over 40% of the maximum.

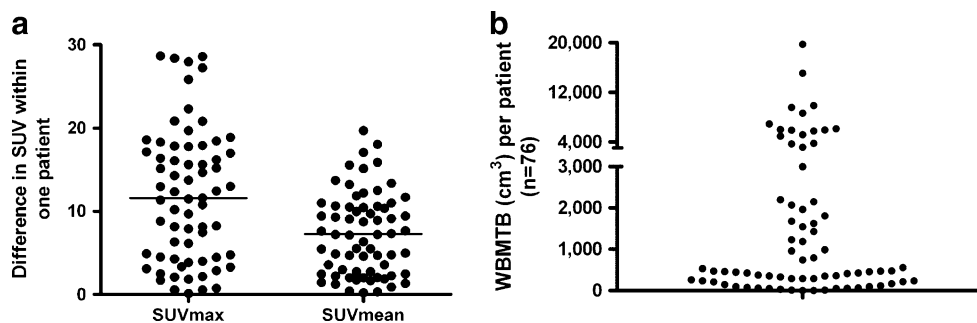


Fig. 2 a Illustration of the large difference in metabolic activity between different lesions within individual patients. On the y-axis for each individual patient the difference between the highest and lowest SUV is plotted, each dot representing one patient. This is performed

for both SUV_{max} and SUV_{mean} , respectively. Horizontal bars represent the median values. **b** Distribution of whole-body metabolic burden for all individual patients ($n=76$), each dot representing one patient

Biochemical analysis

Tumour markers measured for serotonin metabolism were serotonin concentration in a 24-h urine collection, urinary and plasma 5-HIAA concentrations [25]. As markers for catecholamine metabolism we determined urinary and plasma concentrations of adrenalin, noradrenalin and dopamine, and urinary concentrations of the major catecholamine metabolites homovanillic acid (HVA), 3,4-dihydroxyphenylacetic acid (DOPAC), vanillylmandelic acid (VMA), vanillic acid (VA), 3-methoxy-4-hydroxyphenylethylglycol (MHPG) metanephrine, normetanephrine and 3-methoxytyramine (3-MT) in a 24-h urine collection [26, 27]. Serum chromogranin A was determined using a radioimmunoassay (Cga-React, CIS Bio International, Gif-sur-Yvette Cedex, France, bioassays@cisbio.com) as a marker for general neuroendocrine tumour activity (reference interval 20–100 µg/l) [28].

All laboratory analyses were performed within 3 months of the ^{18}F -dopa PET scan in the original studies [9, 10].

Statistical analysis

For correlations between WBMTB and biochemical data, Spearman's r test was calculated. The significance level was 0.05, two-sided. The statistical tests were carried out using the SPSS package version 14.0.

Results

The characteristics of the patients included are shown in Table 1. Seventy-four patients had metastatic disease. In 76 of 77 carcinoid patients the tumour volume with ^{18}F -dopa PET generated by the computer using the SUV_{mean} correlated well with the visual tumour volume (Fig. 1). In one patient visual inspection of the computer-generated

tumour volume showed a gross underestimation of the visually identified tumour volume due to enormously heterogeneous uptake in the metastases. This patient had an extremely large tumour load in the liver and upper abdomen, consisting of confluent lesions with varying uptake intensities in different parts of the tumour. As a result, the less avid lesions, which had uptake values below the 40% threshold of the SUV_{max} of the hottest lesion, were not included in the lesion volume by the computer algorithm. Therefore, this patient was excluded from further analysis.

A total of 979 lesions were detected by ^{18}F -dopa PET (Table 2). ^{18}F -dopa PET tumour uptake was shown to vary greatly between carcinoid lesions within individual patients. Within patients SUVs of different lesions showed a large variance; this range was wider for SUV_{max} than for SUV_{mean} , as the former is more sensitive to outliers. The median difference between the SUV_{max} of different lesions within one patient was 11.6 (range 0.1–28.7) and the SUV_{mean} 7.2 (0.2–19.7), reflecting the large difference in metabolic activity between different lesions (Fig. 2a). This resulted in up to 29-fold differences for SUV_{max} and 25-fold for SUV_{mean} within individual patients. This wide range was caused by difference in size and probable difference in metabolic activity of the lesions. In addition, there was a wide range of measured SUVs between different patients; this range was also wider for SUV_{max} (0.8–33.4) than for SUV_{mean} (0.5–22.7). The large variability was also reflected in widely differing WBMTB between patients (Fig. 2b). The latter was caused by varying numbers of lesions between patients as well as by varying uptake intensities.

Urinary serotonin and/or 5-HIAA levels were elevated in 64 patients (84%). WBMTB showed significant correlations with both urinary serotonin and its metabolite 5-HIAA in urine and plasma (Table 3, Fig. 3). The strongest correlation was found between WBMTB and 24-h urinary 5-HIAA. There was no difference in strength of correlations between newly diagnosed patients and patients during follow-up.

Elevated levels of catecholamines and/or their metabolites were found in 35 patients (46%). The single most frequently elevated marker was 3-MT, which was elevated in 17 patients (22%). We found significant correlations between WBMTB and the urinary levels of the three main catecholamines norepinephrine, epinephrine and dopamine (Table 2). There was no difference between newly diagnosed patients and patients with known carcinoid tumour.

Chromogranin A was available for 64 patients; it was elevated in 35 patients and normal in 29. In the patients for which chromogranin A was available the serum levels of chromogranin A did not correlate with WBMTB ($p=0.14$) (Fig. 4).

Table 3 Significant correlations between biochemical markers and ^{18}F -dopa PET in total group

	Correlation coefficient	Variance explained by correlation
Urinary serotonin	0.51	0.26
Urinary 5-HIAA	0.78	0.61
Plasma 5-HIAA	0.66	0.44
Urinary norepinephrine	0.53	0.28
Urinary epinephrine	0.38	0.14
Urinary dopamine	0.41	0.17
Urinary 3-MT	0.44	0.19
Plasma dopamine	0.39	0.15

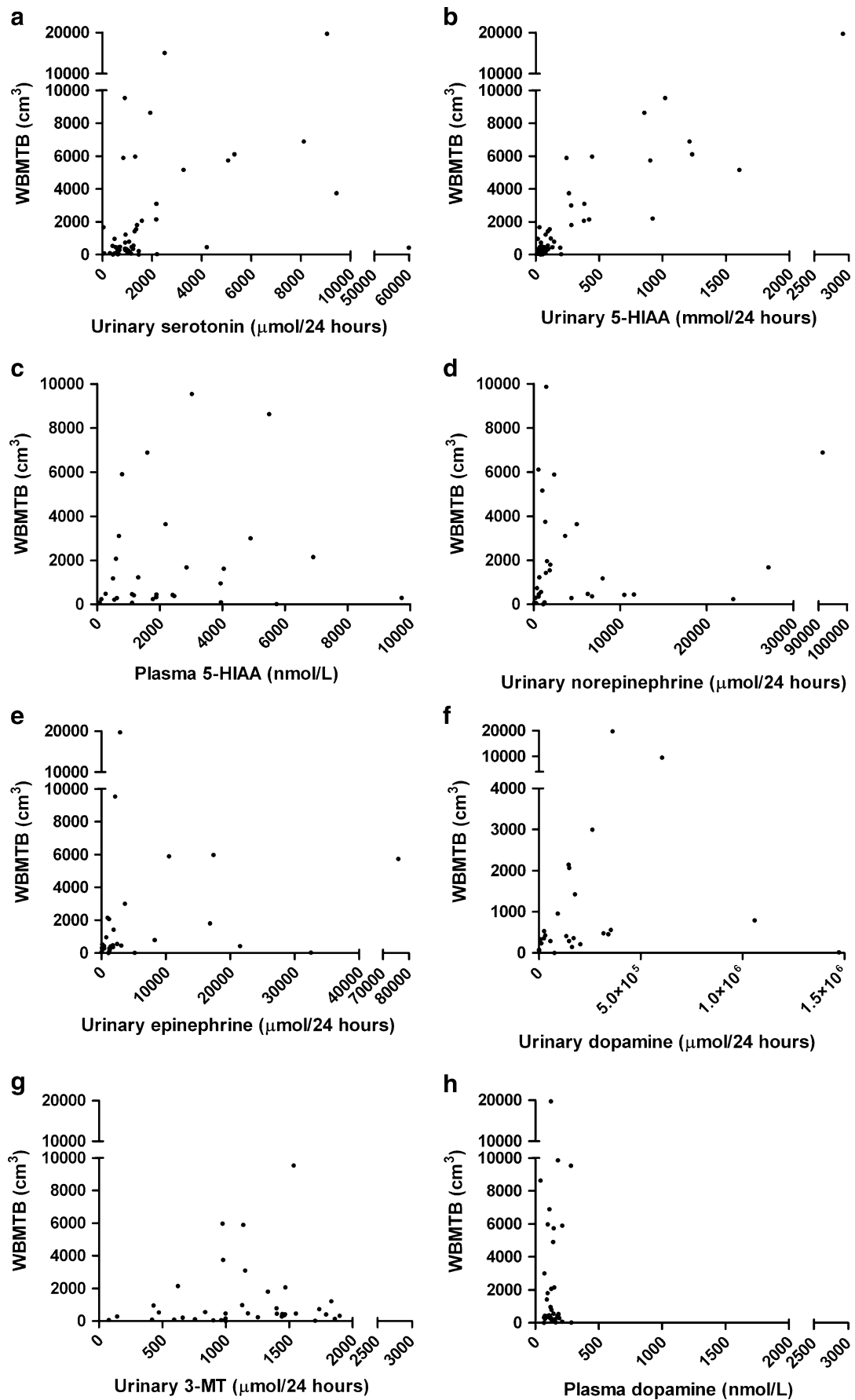


Fig. 3 Scatter plots of the correlation between whole-body metabolic tumour burden (*WBMTB*) and **a** 24-h urinary serotonin, **b** 24-h urinary 5-hydroxyindoleacetic acid (*5-HIAA*), **c** plasma 5-HIAA, **d** 24-h urinary norepinephrine, **e** 24-h urinary epinephrine, **f** 24-h urinary dopamine, **g** 24-h urinary 3-methoxytyramine (*3-MT*) and **h** 24-h plasma dopamine

Urinary 5-HIAA and serotonin levels were significantly correlated with levels of the three major catecholamines norepinephrine, epinephrine and dopamine in 24-h urine, but not with serum chromogranin A levels (data not shown).

Discussion

We demonstrated that *WBMTB*, as measured with ^{18}F -dopa tumour uptake on PET, correlates with biochemical tumour markers in patients with a carcinoid tumour, thus reflecting metabolic endocrine tumour activity. Tracer uptake correlated with urinary and plasma markers of both the serotonin and the catecholamine pathway, and presented a whole-body image of the specific sites where endocrine production is occurring. ^{18}F -dopa PET tumour uptake was shown to vary greatly between carcinoid lesions within individual patients; up to 29-fold differences between individual lesions were observed. In addition, there was also great inter-patient variance.

The strongest correlation was found between *WBMTB* and urinary 5-HIAA levels. This is interesting considering the fact that urinary 5-HIAA is the most widely used marker for follow-up and response assessment of carcinoid tumours.

Currently, there is some debate about the optimal tumour marker for follow-up and management of patients with a carcinoid tumour. Serum chromogranin A has been suggested to replace urinary 5-HIAA [5, 6]. Chromogranin A plays an important role in the regulation of storage and secretion of hormones and peptides. It is localised in the secretory granules of most neuroendocrine cells [29]. Chromogranin A was shown to correlate with tumour load

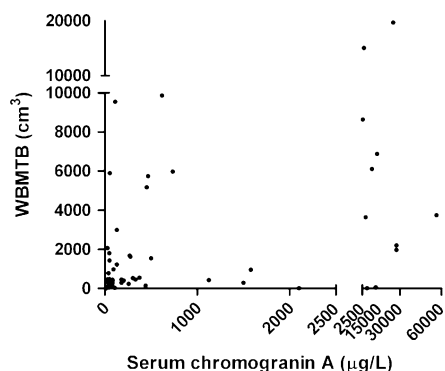


Fig. 4 Scatter plot of the correlation between *WBMTB* and chromogranin A (not significant)

in patients with carcinoid tumours [30, 31]. In this study we clearly show that chromogranin A does not reflect the metabolic activity of these tumours, since the whole-body metabolic tumour activity on ^{18}F -dopa PET did correlate with carefully collected urinary 5-HIAA but not with serum chromogranin A. As *WBMTB* is the product of tumour volume \times metabolic tumour activity, and chromogranin A is known to correlate with tumour burden, it follows that it does not correlate with metabolic tumour activity. This is underlined by the fact that in the current study serum chromogranin A does not correlate with urinary 5-HIAA levels. 5-HIAA levels are however accepted as markers for the metabolic activity of the tumour. Little is known about the correlation between metabolic tumour activity and serum chromogranin A levels. Although chromogranin A has been correlated to overall quality of life, it seems not to reflect the clinically relevant metabolic activity of carcinoid tumours [6, 8]. An automatically generated *WBMTB* may prove to be an interesting marker, since it has demonstrated a good correlation with the metabolic activity of the carcinoid tumour.

Currently, the clinical trials with novel promising targeting agents in these patients to determine progression are based on RECIST criteria [32], which include only anatomical tumour size measurements. 5-HIAAs are a relevant reflection of tumour burden. Regrettably this does not tell about the biochemical activity of individual lesions or provide information on for example clinically relevant well-known mixed responses. This is of major importance specifically in this disease, which in general is a very slowly growing tumour, with tumour lesions that are difficult to interpret with CT and MRI [33, 34]. The fact that *WBMTB* measurement provides information about both size and metabolic activity represents a clear additional advantage. This unique combination might well be used to guide (invasive) treatment decisions since excellent tumour localisation and information about the metabolic tumour activity are both obtained with one scan. Thereby, lesion activity can be taken into account when contemplating further treatment. *WBMTB* on ^{18}F -FDG PET is an excellent measure of treatment response in non-Hodgkin's lymphoma patients [19]. Although not yet investigated in neuroendocrine tumour patients, *WBMTB* on ^{18}F -dopa PET might be an interesting measure of treatment response in patients with a carcinoid tumour. Prospective studies are needed to study the usefulness of *WBMTB* on ^{18}F -dopa PET as a marker for (early) assessment of response.

In our patients we found a correlation between *WBMTB* and catecholamine markers, but these correlations were weaker than those found between *WBMTB* and serotonin markers. This demonstrates that *WBMTB* correlates not only with markers of the predominantly active serotonin pathway, but also with others, such as the catecholamine

pathway. About half of our patients had elevated catecholamine concentrations, which conforms with the numbers found in the literature [1–3]. This is less than the 84% of patients who had elevated serotonin or 5-HIAA. Intrinsic tumour catecholamine production explains at least partly the elevated catecholamine levels in these patients. In about two thirds of carcinoid tumours at least one of the enzymes necessary for catecholamine synthesis is present [2]. These enzymes are focally distributed within the tumour, indicating that a small subpopulation of carcinoid cells could be responsible for the catecholamine synthesis in these patients [2]. Catecholamine levels can also be influenced by sympathoadrenal activation and medication, which could provide an alternative explanation for elevated catecholamine levels in these patients. These influences affect catecholamines proportionally much stronger than their metabolites [35].

Several factors can influence SUVs, thereby influencing the strength of the correlation between tumour uptake and biochemical markers. Firstly, the time after injection is an important variable that can influence SUVs. A previous study on ^{18}F -dopa PET in carcinoid tumours found that SUVs did not differ when measured after either 30 or 90 min, indicating that a plateau phase is already reached at 30 min [36]. This was confirmed in other ^{18}F -dopa PET studies, which showed that most tumour uptake occurred in the first 30 min and that uptake then remained constant for at least 100 min [37, 38]. Thus, SUVs measured after 60 min, as was done in our study, render adequate and reliable measures of tumour tracer uptake. A second factor is the amount of available tracer. Pretreatment with carbidopa, a peripheral inhibitor of AADC, is known to improve image quality for ^{18}F -dopa PET due to higher tumour to background ratios. Carbidopa further improves lesion detection through increased SUV values of lesions [21–23, 37]. The fact that ^{18}F -dopa uptake is visible in other structures in our scans serves as a visual control for sufficient tracer availability; otherwise most ^{18}F -dopa would go to the tumour, as this is the most active tissue.

Primary carcinoid tumours that arise in different parts of the body show a different likelihood of serotonin and 5-HIAA production and excretion. The cells of foregut and hindgut carcinoids express low decarboxylase and therefore there is a low serotonin and 5-HIAA urinary excretion when carcinoid tumours originate from these locations [22]. In our study, the majority of patients had a ‘midgut’ carcinoid tumour (82%). However, it cannot be excluded that the inclusion of patients with foregut and hindgut tumours could have influenced the strength of the correlations that we found in the current study.

In conclusion, total tumour load per patient defined as WBMTB measured with ^{18}F -dopa PET correlates with biochemical markers, reflecting metabolic tumour activity

in carcinoid patients. WBMTB did not correlate with serum chromogranin A levels, nor did the latter marker correlate with 5-HIAA levels. WBMTB provides both a measure of the metabolic tumour activity and a whole-body overview of the specific sites where endocrine production is occurring, which might be used to guide (invasive) treatment decisions. In future, WBMTB could serve as an alternative assessment parameter to evaluate disease extent and biochemical activity in carcinoid patients. Future studies should investigate the use of this new parameter for follow-up or for the assessment of treatment response.

Conflicts of interest None.

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