Medullary Thyroid Carcinoma

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Chapter 6

Clinical relevance of ^{18}F-FDG PET and ^{18}F-DOPA PET in recurrent medullary thyroid carcinoma

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J Nucl Med. 2012; 53: 1863-71

Abstract

Introduction The transition from stable to progressive disease is unpredictable in patients with biochemical evidence of medullary thyroid carcinoma (MTC). Calcitonin and carcinoembryonic antigen (CEA) doubling times are currently the most reliable markers for progression, but for accurate determination serial measurements are required which need time. We compared ^{18}F-fluoro-2-deoxy-D-glucose (^{18}F-FDG) positron emission tomography (PET) and ^{18}F-dihydroxyphenylanaline (^{18}F-DOPA) PET with biochemical parameters and survival to assess whether these imaging modalities could be of value in detecting progressive disease.

Methods We evaluated outcome of ^{18}F-FDG PET and/or ^{18}F-DOPA PET with calcitonin and CEA doubling times in 47 MTC patients. A subgroup of patients was included in whole metabolic burden (WBMTB) analysis, with determination of standardized uptake values (SUV) and number of lesions. WBMTB of ^{18}F-DOPA PET and ^{18}F-FDG PET was compared with biochemical parameters. Furthermore survival was compared with ^{18}F-DOPA PET and/or ^{18}F-FDG PET positivity.

Results In 38 out of 40 patients with ^{18}F-FDG PET doubling times were available. There was a significant correlation with ^{18}F-FDG PET positivity. Doubling times were <24 months in 77% (n=10/13) of ^{18}F-FDG PET positive patients, while 88% (n=22/25) of ^{18}F-FDG PET negative patients had doubling times >24 months ($p<0.001$). Between doubling times and ^{18}F-DOPA PET positivity no significant correlation existed. ^{18}F-DOPA PET detected significantly more lesions (75%, 56 of 75) compared to ^{18}F-FDG PET (47%, 35 of 75) in the 21 patients included in WBMTB analysis ($p=0.009$). Calcitonin and CEA levels correlated significantly with WBMTB on ^{18}F-DOPA PET but doubling times did not. ^{18}F-FDG PET positivity was a more important indicator for poor survival in patients with both scans performed.

Conclusion ^{18}F-FDG PET is superior in detecting patients with biochemical progressive disease and identifying patients with a poor survival. Although ^{18}F-DOPA PET has less prognostic value it can more accurately assess the extent of the disease in patients with residual MTC. Hence, both scans are informative regarding tumour localization and behaviour. Based on these results we designed a clinical flow diagram for the general practice in detecting recurrent MTC.

Introduction

Medullary thyroid carcinoma (MTC) accounts for about 4% of all thyroid cancers. The overall 10 year survival ranges between 40% and 80% and has not increased substantially in the past few decades.[1-3] Unfortunately, even in MTC that is clinically confined to the neck, many patients already have metastatic disease and are beyond cure even by surgery. Furthermore, though the overall survival in patients with only biochemical evidence of residual MTC is good, a number of patients will develop progressive and symptomatic disease.[4] Early identification of these patients is clinically relevant because appropriate therapeutic interventions may delay symptomatic deterioration. However, the transition from a stable status to a progressive disease course is unpredictable and it is hard to identify patients who may benefit from early intervention.

Calcitonin is a specific tumour marker for MTC, carcinoembryonic antigen (CEA) is less specific, but can also be useful.[5] Currently, short calcitonin and CEA doubling times are considered the best available indicators to assess progressive disease, MTC recurrence and cancer mortality.[6,7] Calcitonin and CEA levels can fluctuate, however, and determination of the doubling times needs serial measurement for 12-24 months and is therefore time-consuming.

Most imaging techniques have a moderate sensitivity in detecting MTC.[8] Positron emission tomography (PET) using the radioactive tracers ^{18}F-fluoro-2-deoxy-D-glucose (^{18}F-FDG) and more recently ^{18}F-dihydroxyphenylanaline (^{18}F-DOPA) are available for the staging and follow-up of MTC.[9-15] Some studies have suggested that ^{18}F-FDG PET might be more sensitive in patients with a short calcitonin doubling time.[16,17] Furthermore, a higher metabolic activity, expressed as the maximum standardized uptake value (SUV), on ^{18}F-FDG PET compared with the maximum SUV on ^{18}F-DOPA PET, might be related to a more aggressive tumour type.[18] PET also enables determination of the total tumour load expressed as the whole-body metabolic burden (WBMTB), reflecting metabolic tumour activity, as was shown in a recent study of ^{18}F-DOPA PET in carcinoid patients.[19]

In this retrospective study of patients with biochemical evidence of MTC, our aim was to assess the ability of ^{18}F-FDG PET and ^{18}F-DOPA PET to discriminate between patients with progressive disease and patients with stable disease.

Materials and methods

Patients

We analysed all patients with histologically proven MTC seen at the Department of Endocrinology for follow-up and who had undergone ^{18}F-FDG PET and/or ^{18}F-DOPA PET for detection of residual or metastatic MTC between 2002 and 2010. We excluded patients with undetectable calcitonin levels, patients with concurrent systemic treatment at the time of ^{18}F-FDG PET or ^{18}F-DOPA PET, and patients with less than 2 calcitonin or CEA values at the time of ^{18}F-FDG PET or ^{18}F-DOPA PET imaging. For WBMTB analysis, we excluded patients with more than 6 months between ^{18}F-FDG PET and ^{18}F-DOPA PET imaging. Several patients (n=21) were also described in a previous study assessing the value of ^{18}F-DOPA PET in patients with MTC.[16] That study was approved by the local medical ethics committee, and the patients gave written informed consent to participate in it. After completion of that study PET was performed as part of standard patient care; therefore in concordance with national law no further Institutional Board Review approval was required.

We initially analysed 47 MTC patients (Figure 1). In group A, composed of 40 patients, ^{18}F-FDG PET was performed and we compared outcome with doubling times (n=38) and survival (n=37). For the 38 patients composing group B, ^{18}F-DOPA PET was performed, and we compared outcome with biochemical parameters (n=36) and survival (n=34).Thirty one patients had undergone both scans and in 24 patients these scans were performed within 6 months of each other. We performed WBMTB and survival analysis in respectively, 21 and 22 patients (group C), of which 14 and 15 patients respectively, were also included in the previous study.[16] The number of patients participating in each analysis and reasons for exclusion are shown in Figure 1. Patient characteristics of the different groups are shown in Table 1.

^{18}F-DOPA PET, ^{18}F-FDG PET and image analysis

^{18}F-FDG and ^{18}F-DOPA were locally produced as described previously.[20] All patients were studied after a 6-h fasting period, were allowed to continue all medication, and were encouraged to drink water. For ^{18}F-FDG PET, data acquisition started after 60 or 90 min after injection of ^{18}F-FDG intravenously(5 MBq/kg; range 250-824 MBq). For ^{18}F-DOPA PET, whole body 2-dimensional-PET images were acquired 60 min after the intravenous administration of a standard dose of ^{18}F-DOPA (range 70-220 MBq). To reduce tracer

decarboxylation and subsequent renal clearance and thereby increase tracer uptake in tumour cells, patients received carbidopa (2 mg/kg; maximum 150 mg) orally as pre-treatment 1 h before the ^{18}F-DOPA injection.

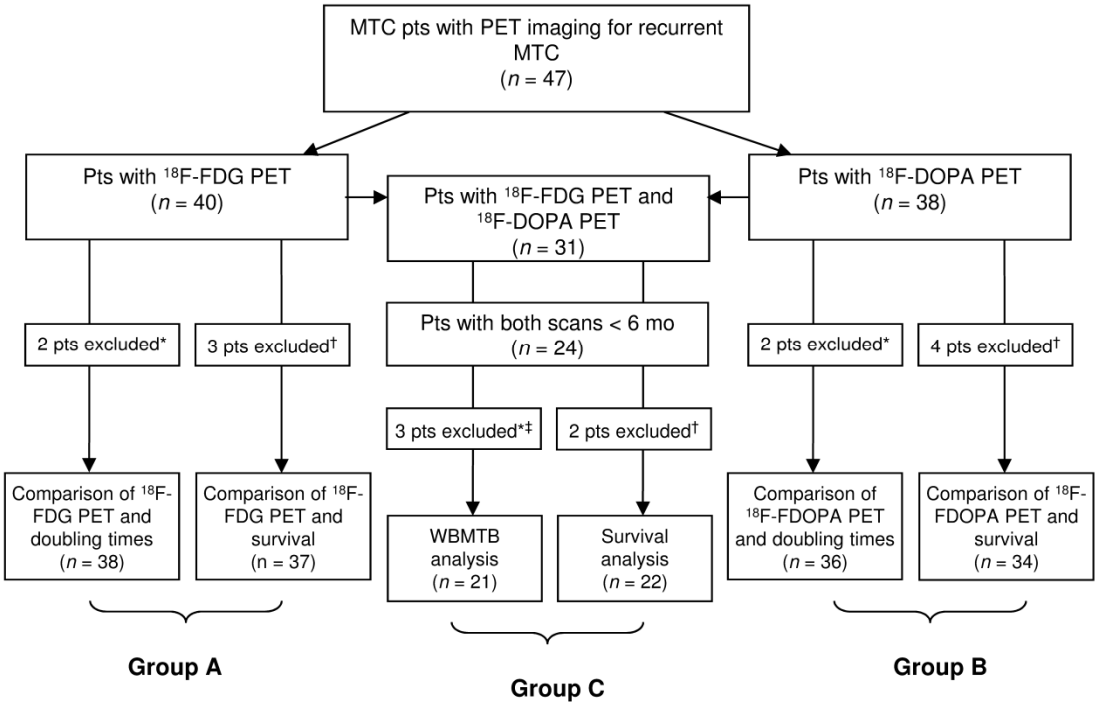

Figure 1 Flow diagram for inclusion and analysis of MTC patients.*Insufficient biochemical data for calculation of doubling times. †Insufficient follow-up data. ‡n = 1 without suitable scan for WBMTB analysis due to technical problems. pts = patients.

^{18}F-FDG PET and ^{18}F-DOPA PET images were interpreted by two dedicated nuclear medicine specialists as part of routine patient care and were subsequently independently reviewed. We calculated the WBMTB, defined as the sum of the metabolic burden of each tumour lesion in the PET image, for both PET methods. We defined metabolic burden as mean SUV × volume of tumour lesion obtained from the PET image using a volume of interest that was enclosed by a 40 % isodensity contour (Figure 2).[21,22] We categorized patients according to differences in WBMTB uptake on paired ^{18}F-FDG and ^{18}F-DOPA PET scans; more than 10% WBMTB on ^{18}F-FDG PET, more than 10% WBMTB on ^{18}F-DOPA PET, equal uptake (less than 10% difference) or no uptake on both scans.

Biochemical analysis

Calcitonin was determined using an enzyme-linked immunosorbent assay (Biomerica, Irvine, Califorina, USA) with a reference value of 0.3-12 ng/L. CEA levels were measured using a chemiluminescent microparticle immunoassay (Abbott Laboratories, North Chicago, Illinois, USA) with a reference value of 0.5-5.0 μg/L.

Table 1 Patient characteristics

	^{18}F-FDG PET analysis (group A; n = 38)	^{18}F-DOPA PET analysis (group B; n = 36)	WBMTB analysis (Group C; n = 21)
Sex			
Male	19	17	10
Female	19	19	11
Age (y)			
Mean	53.2	52.4	56.7
Range	19-79	19-79	19-79
Type			
Sporadic	18	18	12
Familial	20	18	9
Calcitonin (ng/L)			
Median	346.2	825	817
Range	1.8-161,275	17.8-240,325	17.8-161,275
CEA (μg/L)			
Median	10.2	12.3	9.7
Range	0.5-2620	0.5-2620	0.5-2620
Calcitonin doubling time			
<24 mo	13 *(34%)*	13 *(36%)*	9 *(43%)*
>24 mo	25 *(66%)*	23 *(64%)*	12 *(57%)*
CEA doubling time			
<24 mo	6 *(19%)*	5 *(14%)*	3 *(14%)*
>24 mo	32 *(81%)*	30* *(86%)*	18 *(86%)*
Calcitonin and CEA doubling time			
Calcitonin or CEA <24 mo	13 *(34%)*	14 *(39%)*	9 *(43%)*
Calcitonin and CEA >24 mo	25 *(66%)*	22 *(61%)*	12 *(57%)*
PET			
Positive	13 *(34%)*	16 *(44%)*	10 *(48%)*
Negative	25 *(66%)*	20 *(56%)*	11 *(52%)*

*Of one patient CEA doubling time could not be calculated. mo = months.

Calcitonin and CEA serum levels and doubling times

For calculating the calcitonin and CEA doubling time, we used in principle 4 values (with a minimum of 2), obtained within a median period of 11 months (range 2-47 months) around ^{18}F-FDG PET and ^{18}F-DOPA PET imaging. We used the average of these values for further analysis. We calculated exponential growth curves a^B, using standard linear regression of the serum levels on time and doubling times as ln(2)/B. To identify progressive patients we defined biochemical progressive disease as a calcitonin or CEA doubling time of less than 24 months in concordance with the study of Giraudet et al..[6]

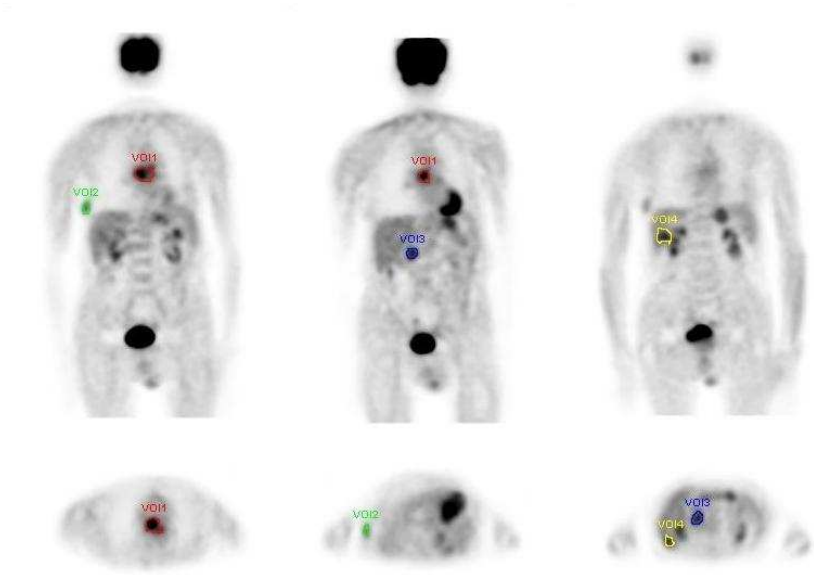

Figure 2 Determination of volume of interest (VOI) and standardized uptake value (SUV) for calculation of the whole metabolic burden. On this ^{18}F-FDG PET scan four lesions (respectively subcarinal, in the lateral hemithorax, and in the liver region) are enclosed by a 40% iso-contour, after manual designation, with automatic calculation of SUVmean, SUVmax and lesion volume.

Follow-up

Follow-up was performed according to current guidelines, consisting of regular determination of calcitonin and CEA.[23] If there was an elevation in one of these tumour markers, further evaluation was performed with morphological or functional imaging. Depending on the outcome of imaging, the therapeutic strategy was determined.

Statistical analysis

For statistical analysis we used PASW statistics 18 (SPSS Ltd.). We performed a χ^2 test for comparison of PET outcome and doubling times. Correlation between WBMTB of ^{18}F-FDG

PET and ^{18}F-DOPA PET and calcitonin or CEA levels and doubling times was calculated with Spearman's *r* test. To determine the optimal calcitonin cut-off level for ^{18}F-FDG PET and ^{18}F-DOPA PET, we calculated the maximum value of sensitivity multiplied by specificity, as derived from ROC curve analysis. We performed a χ^2 test for comparison of uptake and WBMTB category with doubling times or a Fisher exact test when the frequency of cells with an expected value of 5 was higher than 20%. For comparison of the number of detected lesions between ^{18}F-FDG PET and ^{18}F-DOPA PET, a McNemar test was used. For survival analysis we used the Kaplan Meier method, and the log-rank test for comparison. The significance level was 0.05, 2-sided.

Results

Patients

^{18}F-FDG PET and biochemical parameters (Group A)

We analysed 38 patients for outcome of ^{18}F-FDG PET and calcitonin or CEA levels and doubling times. ^{18}F-FDG PET was positive in 13 patients (34%) (Table 2). In ^{18}F-FDG PET-positive patients, levels of calcitonin and CEA were significantly higher and more patients had calcitonin and CEA doubling times less than 24 months. Positive and negative predictive values for biochemical progressive disease were 77% and 88% respectively in ^{18}F-FDG PET-positive and -negative patients. In ROC curve analysis, we found an optimal calcitonin cut-off of 874 ng/L for PET positivity, with a sensitivity of 69% and a specificity of 70% for the detection of tumour lesions.

^{18}F-DOPA PET and biochemical parameters (Group B)

Of the 36 patients analysed for the outcome of ^{18}F-DOPA PET and biochemical parameters, ^{18}F-DOPA PET was positive in 16 (44%) (Table 3). Calcitonin and CEA levels differed significantly between ^{18}F-DOPA PET positive and -negative patients, but there was no significant difference in doubling times. The positive and negative predictive values for progressive disease were 56% and 75%, respectively, in ^{18}F-DOPA PET-positive and -negative patients. In ROC curve analysis, we found a calcitonin cut-off of 825 ng/l to be optimal for PET positivity, with a sensitivity and specificity of 88% and 80%, respectively, for detection of tumour lesions.

Table 2 Biochemical parameters of patients with ^{18}FDG PET (Group A)

	^{18}F-FDG PET Positive (n = 13)	**^{18}F-FDG PET Negative (n = 25)**	**P**
Calcitonin (ng/L)			
Median	2320	246	**0.040**
Range	(60.4 – 161,275)	(1.8 – 18565)	
CEA (ug/L)			
Median	32.4	6.5	**0.006**
Range	(0.8 -2620)	(0.5-187)	
Calcitonin doubling time			
< 24 mo	10 *(77%)*	3 *(14%)*	
> 24 mo	3 *(23%)*	22 *(86%)*	**< 0.001**
CEA doubling time			
< 24 mo	6 *(46%)*	0	
> 24 mo	7 *(54%)*	25 *(100%)*	**0.001**
Calcitonin and CEA doubling time			
Calcitonin or CEA < 24 mo	10 *(77%)*	3 *(14%)*	
Calcitonin and CEA > 24 mo	3 *(23%)*	22 *(86%)*	**< 0.001**

Mo = months.

Table 3 Biochemical parameters of patients with ^{18}F-DOPA PET (Group B)

	^{18}F-DOPA PET Positive (n = 16)	**^{18}F-DOPA PET Negative (n =20)**	**P**
Calcitonin (ng/L)		287	
Median	3626	(17.8 – 2320)	**< 0.001**
Range	(88 – 240,325)		
CEA (ug/L)	36.6	6.6	
Median	(1.2 – 2620)	(0.5 – 72)	**<0.001**
Range			
Calcitonin doubling time			
< 24 mo	8 *(50%)*	5 *(25%)*	
> 24 mo	8 *(50%)*	15 *(75%)*	NS
CEA doubling time			
< 24 mo	4 *(27%)*	1 *(5%)*	
> 24 mo	11 *(73%)*	19 *(95%)*	NS
Calcitonin and CEA doubling time			
Calcitonin or CEA < 24 mo	9 *(56%)*	5 *(25%)*	
Calcitonin and CEA > 24 mo	7 *(44%)*	15 *(75%)*	NS

*Of 1 pt CEA level was not available. †Of 1 pt CEA dt could not be calculated. mo = months.

WMBTB results of ^{18}F-FDG PET and ^{18}F-DOPA PET (Group C)

For the 21 patients with both ^{18}F-FDG PET and ^{18}F-DOPA PET who were included in WBMTB analysis, the results for both scans were negative in 11 patients. Of the remaining 10 patients, 4 had higher WBMTB on ^{18}F-FDG PET, another 4 had higher WBMTB on ^{18}F-DOPA PET, and 2 had equal WBMTBs (Table 4). The total number of lesions found was 75, and ^{18}F-DOPA PET detected significantly more lesions than ^{18}F-FDG PET (56 vs. 35)

(p=0.009). In PET-positive patients, WBMTB on ^{18}F-DOPA PET was significantly correlated with calcitonin levels (r=0.82) (p=0.013) and CEA levels (r=0.88) (p=0.004) but not with doubling times. There was no significant correlation between WBMTB of ^{18}F-FDG PET and calcitonin and CEA levels or doubling times. Between the different WBMTB categories and calcitonin and CEA doubling times, no significant relation was found.

Table 4 Biochemical parameters and WBMTB in different WBMTB categories (Group C)

	WBMTB Category				
	^{18}F-DOPA > ^{18}F-FDG (n= 4)	**^{18}F-FDG > ^{18}F-DOPA (n = 4)**	**^{18}F-DOPA = ^{18}F-FDG (n = 2)**	**Negative**	**P**
Calcitonin (ng/L)					
Median	13052	650	14958	246	**0.015**
Range	832-161,275	89-1,066	6,679-22,236	18-1,030	
CEA (µg/L)					**0.002**
Median	727	14.2	1088	3.1	
Range	22-2620	0.8-29.3	32.4 -2144	0.5-28.1	
Calcitonin and CEA doubling time					
Calcitonin or CEA < 24 mo	1	3	2	3	
Calcitonin and CEA > 24 mo	3	1	0	8	NS
No. of lesions					
^{18}F-FDG					
Mean	1.3	5.3	4.5	-	
Total	5	21	9		
^{18}F-DOPA					
Mean	9.5	2.5	4	-	
Total	38	10	8		
WBMTB (cm^3)					
^{18}F-FDG					
Median	55.4	83.3	275		
Range	0 – 121	18.8 - 920	11.5 – 538	-	
^{18}F-DOPA					
Median	271.6	6.1	271		
Range	15.3 – 983	0 - 465	12.5 - 530	-	

Treatment based on PET

Eight patients underwent reoperation because of recurrent disease. In 5 patients, PET showed local disease and contributed to the decision for surgery. ^{18}F-FDG PET was performed in 4 and positive in 2. ^{18}F-DOPA PET was performed in 4 patients and positive in 3. All PET lesions were confirmed on histological examination. In the other 3 patients, PET was negative and surgery was performed because of positive conventional imaging or palpable abnormalities. All patients who underwent reoperation had no clinical progression during follow-up (range 6.6–106 months). Seven patients received targeted treatment with tyrosine kinase inhibitors. ^{18}F-FDG PET imaging was performed in 6 patients and all showed

metastatic disease, ^{18}F-DOPA PET was performed in 5 and showed metastatic disease in 4. Three patients developed stable disease. The other 27 patients did not receive surgical or systemic treatment during follow-up.

Survival and PET outcome

In the 42 patients of whom follow-up data were available, median follow-up was 63.8 months (range 2.3-114 months). During follow-up 11 patients died: 7 because of progressive MTC, 3 because of other causes (prostate cancer, oesophageal cancer and sepsis due to perforated appendicitis) and in 1 patient for whom the reason of death was unknown. In 37 patients with ^{18}F-FDG PET imaging and sufficient follow-up, survival was significantly lower in ^{18}F-FDG PET positive patients than in ^{18}F-FDG PET negative patients ($p<0.001$) (Figure 3A). The same was true for ^{18}F-DOPA PET positive compared with -negative patients (n=34) (p=0.019) (Figure 3B). However, in univariate analysis of patients who had undergone both ^{18}F-FDG PET and ^{18}F-DOPA PET (n=22), the survival in patients with a positive ^{18}F-FDG PET was lower and independent of ^{18}F-DOPA PET outcome, whereas survival in ^{18}F-DOPA PET positive patients was dependent of ^{18}F-FDG PET outcome (p=0.018) (Figure 3C). Figure 4 shows a patient with biochemical progressive disease and uptake on both scans.

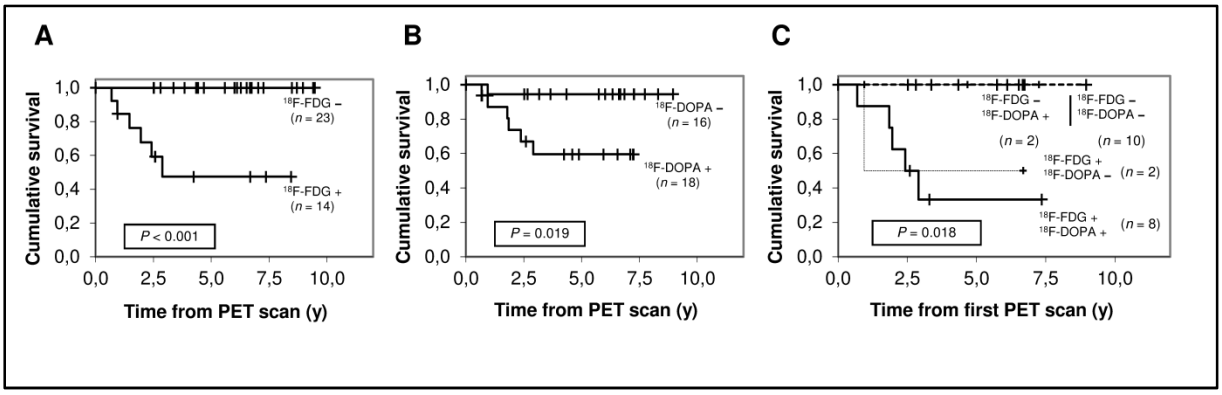

Figure 3 Kaplan Meier curve of survival (in years) after ^{18}F-FDG PET (A), ^{18}F-DOPA PET (B) and both ^{18}F-FDG PET and ^{18}F-DOPA PET(C).

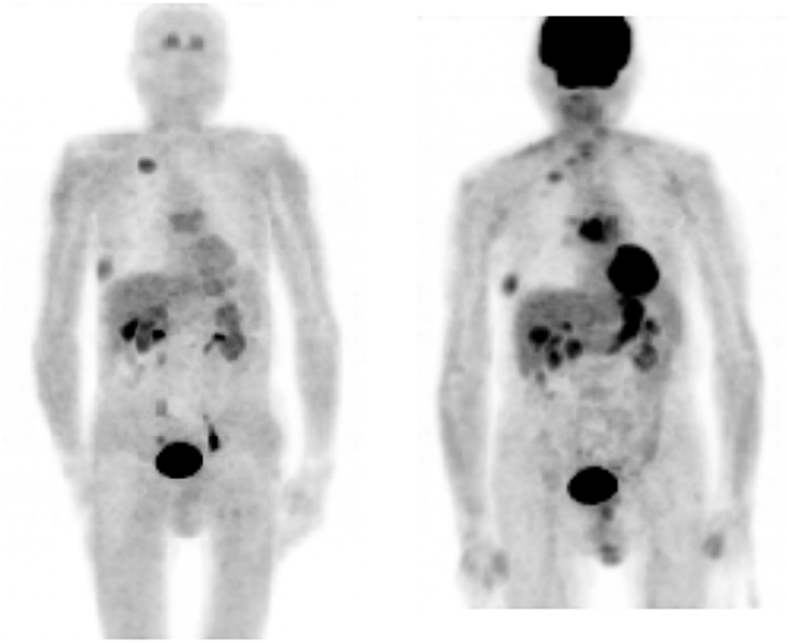

Figure 4 MTC patient with uptake on both ^{18}F-DOPA PET (left) and ^{18}F-FDG PET (right). On ^{18}F-DOPA-PET lesions are seen in the right supraclavicular region, the right hemithorax and there is slight uptake subcarinal. In the abdomen there are several lesions with faint uptake. Also on ^{18}F-FDG-PET uptake is seen in the right supraclavicular region, right hemithorax and intensive uptake subcarinal. Furthermore several lesions are seen in the liver region. Calcitonin and CEA levels were highly elevated (23236 ng/L (ref 0.3-12 ng/L) and 2144 ug/L (ref 0.5-5.0 µg/L)) and calcitonin and CEA doubling times were short; 13 months and 12 months respectively. The patient died 29 months after scans were performed due to progressive disease.

Discussion

In this study, ^{18}F-FDG PET was superior to ^{18}F-DOPA PET in identifying patients with progressive disease. Unlike ^{18}F-DOPA PET positivity, ^{18}F-FDG PET positivity correlated significantly with biochemical progressive disease. Furthermore, we showed that ^{18}F-FDG PET- and ^{18}F-DOPA PET positive patients, had a significantly decreased survival. However, univariate analysis in patients for whom both scans were performed showed that ^{18}F-FDG PET positivity had the most influence on survival. WBMTB analysis showed that metabolic activity on ^{18}F-DOPA PET correlated significantly with calcitonin and CEA levels. Differences (>10%) in WBMTB on ^{18}F-FDG PET and ^{18}F-DOPA PET could not distinguish stable from progressive disease.

In a previous study of our institute focusing on detecting residual disease with both ^{18}F-FDG PET and ^{18}F-DOPA PET, we already described the superiority of ^{18}F-FDG PET in 2

patients with progressive disease.[16] This outcome is probably based on the fact that aggressive (dedifferentiated) disease has a higher glucose metabolism and consequently higher ^{18}F-FDG uptake. This observation was also made by others but the described series are rather small.[14,15,17,18] Bogsrud et al. showed a higher mortality in ^{18}F-FDG PET positive patients than in ^{18}F-FDG PET negative patients.[24] However, survival data in patients with ^{18}F-DOPA PET have not been described before. This study shows that progressive patients can be identified with both PET techniques, taking into account biochemical parameters and survival.

For ^{18}F-FDG PET of patients with progressive MTC, not only have higher sensitivities been described but also increased tracer intensity. Marzola et al. included only patients with short doubling times (6-9 months) and showed significantly higher maximum SUV on ^{18}F-FDG PET versus ^{18}F-DOPA PET, although patient- and lesion-based sensitivity of ^{18}F-DOPA PET was higher.[18] In our WBMTB analysis, we did not find a significant difference in doubling times between patients with a higher uptake on ^{18}F-FDG PET and patients with a higher uptake on ^{18}F-DOPA PET. This lack of significance could have been caused by the small number of patients with positive scan results in WBMTB analysis (n=11) or the different doubling time cut-offs used for defining progressive disease.

Although the doubling times of calcitonin and CEA have thus far been the most reliable indicators of recurrence and progressive disease in MTC, cut-off values are still a matter of discussion. Meijer et al. showed a higher hazard ratio for recurrence for a calcitonin doubling time cut-off of 12 months (hazard ratio, 5.33) than 24 months (hazard ratio, 2.93), but warned about interpreting these cut-off values with caution.[7] Moreover that study focuses on disease recurrence and not progression in general. We based our 24 months cut-off for doubling times on the results of the study by Giraudet et al., who compared doubling times with progression according to the Response Evaluation Criteria in Solid Tumours (RECIST). They found progressive disease in 94% of patients with doubling times less than 25 months while 86% had stable disease when doubling times were more than 24 months.[6]

Our results show a significant correlation between WBMTB on ^{18}F-DOPA PET and calcitonin and CEA levels, demonstrating that ^{18}F-DOPA PET might be a good indicator of tumour load. Although ^{18}F-FDG PET is better in distinguishing progressive disease, ^{18}F-DOPA PET seems to be more important in assessing the extent of residual disease. In our WBMTB analysis, ^{18}F-DOPA PET also detected more tumour lesions than did ^{18}F-FDG PET. On the whole, ^{18}F-DOPA PET is superior to ^{18}F-FDG PET with a higher patient-based sensitivity (64% vs. 48%, respectively [range, 38%-83% vs. 17%-64%, respectively]) and lesion-based sensitivity (72% vs 52%, respectively [range 52%-94% vs. 28%-62%]) (Table

5).[12-15,17,18] However, in line with the study of Kauhanen et al. and a recent review by Wong et al., combining both modalities increases sensitivity and is complementary.[14,25]

Nevertheless, many patients with biochemical recurrent disease do not show lesions on currently available imaging modalities. Most of these patients have moderately elevated tumour markers and long doubling times, probably because of the nature of calcitonin-producing metastases (sclerotic, necrotic or calcified) and their small size.[26] A previous study of our centre showed that MTC lesions are best detected on ^{18}F -DOPA PET above >500 ng/L and ROC curve analysis in the current study found a cut-off value of 825 ng/l to be optimal in distinguishing ^{18}F -DOPA PET-positive from -negative patients.[16] This cut-off value is also dependent on the resolution of the PET camera system, which with new developments becomes increasingly sensitive. Also, the combination of PET with CT increases the yield of these scans and lowers the threshold for localization of tumour lesions.[27]

The negative predictive value for biochemical progressive disease in our study was 88% for ^{18}F-FDG PET and 75% for ^{18}F-DOPA PET. However, there are still patients - both in our study (n=3) and in other series – who have rapidly increasing tumour markers but do not have positive functional imaging results.[18] In these patients, there is still need for other modalities for the detection of occult MTC. Yet, the first results of new tracers like ^{68}Ga-somatostatin analogues or ^{11}C-Methionine are not convincing.[15,28,29]

Table 5 Patient and lesion based sensitivity of ^{18}F-FDG PET and ^{18}F-DOPA PET.

	PET patient based sensitivity % *(n)*				**PET lesion based sensitivity %** *(n)*		
	N	^{18}F-FDG	^{18}F-DOPA	Combined	Total no. of lesions	^{18}F-FDG	^{18}F-DOPA
Hoegerle et al. 2001	11	64% *(7)*	64% *(7)*	73% *(8)*	27	44% *(12)*	63% *(17)*
Beuthien-Baumann et al. 2007	15	47% *(7)*	47% *(7)*	60% *(9)*	NA	NA	NA
Beheshti et al. 2009	26	58% *(15)*	81% *(21)*	85% *(22)*	53	62% *(33)*	94% *(50)*
Marzola et al. 2010	18	61% *(11)*	83% *(15)*	89% *(16)*	111	58% *(64)*	76% *(84)*
Kauhanen et al. 2011	19	53% *(10)*	58% *(11)*	63% *(12)*	118	47% *(55)*	52% *(61)*
Treglia et al. 2012	18	17% *(3)*	72% *(13)*	72% *(13)*	72	28% *(20)*	85% *(61)*
This study	21‡	38% *(8)*	38% *(8)*	48% *(10)*	75	47% *(35)*	75% *(56)*
Total	128	48% *(61)*	64% *(82)*	70% *(90)*	456	48% *(219)*	72% *(329)*

*Average calcitonin, median not available. †Only 19 pts with data available. ‡Only patients included in WBMTB analysis.

On the basis of the results of this and previous studies, we recommend a combined approach for patients with recurrent MTC and increasing tumour markers (Figure 5). Conventional imaging of the neck (ultrasound, MRI or CT) to detect localized disease can be followed by ^{18}F-FDG PET or PET/CT to identify progressive disease. In the case of a negative ^{18}F-FDG PET result or the presence of only localized resectable disease (head and neck region), an ^{18}F-DOPA PET or PET/CT scan is recommended, to exclude distant metastasis and support the decision for local surgery.

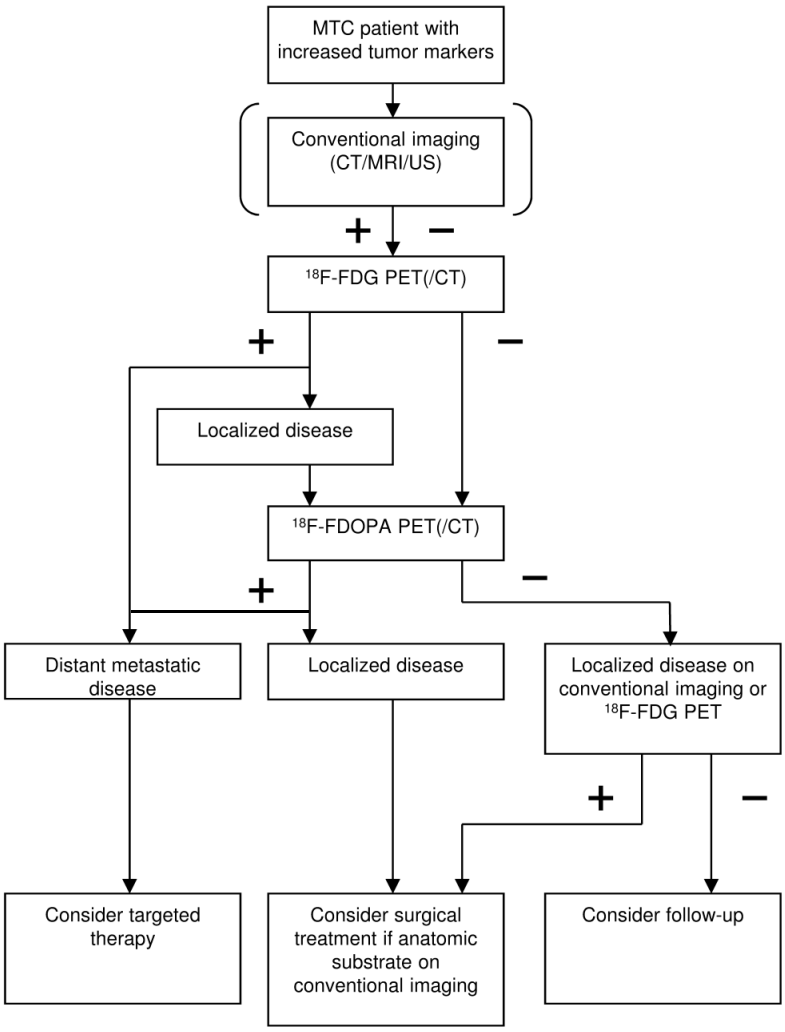

Figure 5 Flow-diagram for combined approach of ^{18}F-FDG PET and ^{18}F-DOPA PET in patients with recurrent MTC and increasing tumour markers. If ^{18}F-FDG PET or ^{18}F-DOPA PET shows distant metastatic disease, targeted therapy can be considered. If there is resectable localized disease on ^{18}F-FDG PET or ^{18}F-DOPA PET, with an anatomical substrate, surgery could be considered. If both ^{18}F-FDG PET and ^{18}F-DOPA PET are negative, follow-up would be appropriate.

This study is limited by its retrospective character and the differences in ^{18}F-FDG PET uptake time, which can result in differences in the mean SUV. Most of our patients who were included in the WBMTB analysis had an uptake time of 60 min (n=16). Because the WBMTB for determination of tumour load depends not only on the mean SUV but also on tumour volume and number of lesions we concluded that a slight difference in mean SUV does not significantly influence our results. Furthermore, there could be a selection bias in patients undergoing only 1 type of scan, or both scans. However, no significant difference existed in patient characteristics (including doubling times) between these 2 groups (data not shown). Other limitations are the small study size, which is often the case with rare tumours, and the fact that not all PET lesions were histologically confirmed.

Conclusion

In MTC patients, ^{18}F-FDG PET positivity seems to be associated with biochemical progressive disease and significantly affects survival. ^{18}F-DOPA PET has a higher sensitivity than ^{18}F-FDG PET, and WBMTB on ^{18}F-DOPA PET can be related to the tumour load. Therefore, ^{18}F-DOPA PET seems to be more important in assessing the extent of the disease in patients with residual disease whereas ^{18}F-FDG PET can more accurately identify patients with progressive disease. Both scans may be used to guide therapeutic strategies in patients with recurrent MTC.

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