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Predictive value of 18F-FDG PET in patients with advanced medullary thyroid carcinoma treated with vandetanib

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ABSTRACT

Introduction: Therapeutic options in advanced medullary thyroid carcinoma (MTC) have markedly improved since the introduction of tyrosine kinase inhibitors (TKI). We aimed to assess the role of metabolic imaging using 2-deoxy-2-(^{18}F)fluoro-D-glucose (18F-FDG) positron emission tomography/computed tomography (PET/CT) shortly before and 3 months after initiation of TKI treatment. Methods: Eighteen patients with advanced and progressive MTC scheduled for vandetanib treatment underwent baseline 18F-FDG PET/CT prior to and 3 months after TKI treatment initiation. During follow-up, CT scans were performed every 3 months and analyzed according to Response Evaluation Criteria In Solid Tumors (RECIST). The predictive value for estimating progression-free (PFS) and overall survival (OS) was examined by investigating 18F-FDG mean/maximum standardized uptake values ($SUV_{mean/max}$) of the metabolically most active lesion as well as by analyzing clinical parameters (tumor marker doubling times {calcitonin, carcinoembryonic antigen (CEA)}, prior therapies, RET (rearranged during transfection) mutational status, and disease type). **Results:** Within a median follow-up of 5.2 years, 9 patients experienced disease progression after a median time interval of 2.1y whereas the remainder had ongoing disease control (n=5 partial response and n=4 stable disease). Eight of the 9 patients with progressive disease died from MTC after a median of 3.5y after TKI initiation. Pre-therapeutic SUV_{mean} >4.0 predicted a significantly shorter PFS (PFS: 1.9y vs. 5.2y; p=0.04). Furthermore, sustained high 18F-FDG uptake at 3 months with a SUV_{mean}>2.8 tended to portend an unfavorable prognosis with a PFS of 1.9y (vs. 3.5y; p=0.3). Prolonged CEA doubling times were significantly correlated with longer PFS (r=0.7) and OS (r=0.76, p<0.01, respectively). None of the other clinical parameters had prognostic significance. **Conclusions:** Pre-therapeutic 18F-FDG PET/CT holds prognostic information in patients with advanced MTC scheduled for treatment with the TKI vandetanib. Low tumor metabolism of SUV_{mean} < 4.0 prior to treatment predicts longer progression-free survival.

KEYWORDS: medullary thyroid carcinoma, tyrosine kinase inhibitor, vandetanib, 2-deoxy-2-(^{18}F)fluoro-D-glucose, 18F-FDG, positron emission tomography

INTRODUCTION

Medullary thyroid carcinoma (MTC) which originates from parafollicular, calcitonin secreting cells, accounts for approximately 5% of all thyroid cancers (*1*). Since MTC cells do not accumulate radioiodine (*1*), surgery represents the only curative strategy in early disease stages. Until recently, in patients with advanced stages, cytotoxic chemotherapy was the only treatment option which is associated with low response rates (*2,3*). In the last decade, tyrosine kinase inhibitors (TKI) have led to a paradigm shift: after successful phase 3 trials, vandetanib and cabozantinib were approved for the treatment of advanced MTC (*4-6*). For instance, vandetanib demonstrated favorable antitumor activity with disease control rates in 73% and confirmed objective partial responses in 20% of the cases, yet no prolongation of overall survival (*4*). However, adverse effects including diarrhea, cutaneous reactions, hypertension, and even life threatening cardiac arrhythmias have been described and demand close patient monitoring (*7*). Given the more widespread use of TKI, reliable predictors of TKI responders prior to treatment initiation are intensely sought after (*8*).

The prognostic value of baseline 2-deoxy-2-(^{18}F)fluoro-D-glucose (18F-FDG) positron emission tomography/computed tomography (PET/CT) assessment prior to TKI initiation has been shown in several types of cancers such as renal cell carcinoma or gastrointestinal stromal tumor (*9,10*). Additionally, in iodine-refractory differentiated thyroid cancer scheduled for sunitinib treatment, early reduction of metabolic activity was associated with morphologic response (*11,12*).

In this bi-centric study, we aimed to elucidate the prognostic role of 18F-FDG PET/CT in MTC patients at the start of vandetanib treatment.

MATERIALS AND METHODS

Patient Population

All patients underwent imaging for clinical purposes and gave written informed consent to the diagnostic and therapeutic procedures. The requirement for additional approval was waived by the local institutional review boards due to the retrospective character of this study. All patients gave written informed consent for the recording and anonymized analysis of their data. Parts of this cohort received vandetanib in a clinical trial (*5*).

Between April 2007 and July 2016, 18 patients (6 females; median age, 48y, range, 28-78y) with advanced, progressive MTC were started on vandetanib (300mg orally per day) at the University Hospital of Würzburg (n=14) and at the Hospital of Augsburg (n=4), Germany. All patients had undergone previous therapies including surgery (all patients), external beam radiation therapy (4/18, 22.2%), chemotherapy (3/18, 16.7%), transarterial chemoembolization (2/18, 11.1%), radioiodine therapy (1/18, 5.6%; patient #16, initially misclassified as differentiated thyroid cancer) or sorafenib (1/18, 5.6%). Detailed patient information is given in Table 1.

Imaging-based Response Assessment

Treatment response was assessed every 3 months according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 based on CT (*13*). RECIST measurements were confirmed by an attending radiologist (JSS). Detailed information can be found in (*14*). During follow-up, the best response achieved by CT criteria (Complete Response (CR), Partial Response (PR), Stable Disease (SD) and Progressive Disease) was evaluated. Progression-Free-Survival (PFS) was defined according to RECIST by serial radiological assessment starting from the time point of TKI initiation (*13*). For Overall Survival (OS), the time interval between start of treatment and the date of death was used. Data were censored on August, 1, 2016.

Imaging

In 4/18 (22.2%) patients, dedicated PET was performed on a stand-alone lutetium oxyorthosilicate full-ring PET scanner (ECAT Exact 47, Siemens Medical Solutions, Erlangen, Germany). In the remaining patients, integrated PET/CT was performed. 12/14 (85.7%) patients were scanned using a Biograph mCT PET/CT (Siemens Medical

Solutions, Erlangen, Germany); 2/14 (14.3%) patients underwent imaging on a Gemini TF 16 PET/CT system (Philips Medical Systems, Hamburg, Germany). Before image acquisition, patients fasted for at least 6 h and blood glucose levels were < 160 mg/dl. 18F-FDG was injected intravenously. After 60 minutes, transmission data were acquired using either ^{68}Ge-rod-sources (in case of the stand-alone PET) or spiral CT with (n=13/14 (92.9%), dose modulation with a quality reference of 210mAs, 120 kV, a 512 ~ 512 matrix, 5mm slice thickness) or without (n=1/14 (7.1%), 80mAs, 120 kV, a 512 ~ 512 matrix, 5mm slice thickness) intravenous contrast enhancement including the base of the skull to the proximal thighs. Consecutively, PET emission data were acquired. After decay and scatter correction, PET data were reconstructed iteratively with attenuation correction, using the algorithm implemented by the manufacturer.

After 3 months, 18F-FDG PET/CT was performed in 16/18 (88.9%) and CT in 1/18 (5.6%) patients. In the remaining patient, imaging-based follow-up was not available due to early therapy termination because of adverse events.

Imaging Interpretation

For both baseline as well as follow-up scan, mean/maximum standardized uptake values (SUV_{mean} and SUV_{max}) were evaluated by selecting the axial PET image slice displaying the maximum uptake and drawing a 3D volume of interest around the whole tumor area. A standardized 15-mm circular region was placed over the area with the peak activity. This region of interest was used to derive the respective SUV_{mean} and SUV_{max}. The radiotracer concentration in the ROIs was decay corrected and normalized to the injected dose per kilogram of patient's body weight.

Tumor Markers

Serum levels of carcinoembryonic antigen (CEA, mg/L) and calcitonin (CTN, pg/ml) were measured before baseline using dedicated radioimmunoassays (*14*). A total of 3 to 22 determinations (median 6 determinations) were available per patient. Tumor marker doubling times were calculated using the American Thyroid Association calculator (*3*).

Clinical Parameters

The following clinical parameters were obtained: sex, age, metastatic sites at time of

baseline PET, prior therapy, and tumoral RET mutation status (Table 1).

Analysis and Statistics

Statistical analyses were performed using PASW Statistics software (version 22.0; SPSS, Inc. Chicago, IL, USA). Quantitative values were expressed as mean ± standard deviation and range as appropriate. The two-tailed paired Student's t test was used to compare differences between two dependent groups, and the two-tailed independent Student's t test for differences between independent groups. Cox multi-parametric regression analysis was applied to determine independent prognostic parameters. Cut-off values for the prediction of imaging-based PFS and OS were determined by receiver operating characteristic (ROC) analysis using the Youden-Index for maximization of specificity and sensitivity (*15,16*). Pearson's correlation was used to determine the association between tumor marker levels and other PET parameters as well as PFS and OS. Kaplan–Meier analysis was performed using thresholds established by ROC analysis in cases in which ROC showed statistically significant results. Non-parametric log-rank tests were used to assess the differences in the Kaplan–Meier curves. A *p* value of *.05* or less was considered statistically significant. To adjust for multiple testing, Bonferroni correction was performed.

RESULTS

Baseline 18F-FDG PET was positive in all patients. 17/18 (94.4%) patients presented with lymph node metastases. 10/18 (55.6%) demonstrated lung metastases, half of the cohort suffered from liver (9/18, 50.0%) and/or bone lesions (9/18, 50.0%), respectively. 2/18 (11.1%) subjects had soft tissue metastases and one patient (5.6%) showed tumor infiltration of the pancreas.

One patient had hereditary medullary thyroid cancer (patient #6 with a multiple endocrine neoplasia 2A syndrome). In the nonhereditary cases, somatic RET mutations were detected in 3/8 (37.5%) patients, in whom somatic RET mutational status was determined (Table 1).

Best morphological response according to RECIST was classified as follows: SD in 8/18 (44.4%), PR in 8/18 (44.4%) and CR in 1/18 (5.6%). In the remaining patient, response could not be assessed due to early therapy termination. During follow-up (median, 5.2 years; range, 1.8 years – 9.3 years), 9 (50%) patients experienced disease progression after a median of 2.1 y (range, 3 months – 9.1 years), whereas the remainder exhibited ongoing disease control. Eight of the progressive disease patients died from their disease (median, 3.5 years; range, 11 months – 9.1 years) during follow-up.

Correlation of Serum Tumor Markers Doubling Times and Clinical Parameters with PFS and OS

The doubling times were highly variable among patients and ranged from 1.7 months to 2.4 years for CTN and 1.4 months to 5.1 years for CEA. The median CTN and CEA doubling times were 6.8 months and 8.3 months, respectively. Longer CEA doubling times were significantly related with longer PFS and OS (PFS, $r=0.7$; OS, $r=0.76$, $p<0.01$, respectively), whereas no correlation could be observed for CTN.

The investigated clinical parameters (sex, age, metastatic sites at time of baseline PET, prior therapy, and RET mutation status) as given in Table 1 were not significantly correlated with PFS or OS.

Imaging-based Findings of 18F-FDG Baseline and Follow-up PET

At baseline, 10 LN and 6 visceral metastases were identified as the metabolically most active lesions. Median $SUV_{mean/max}$ were 4.6 (range, 3.2 – 27.4) and 7.4 (range, 3.8 – 37.5), respectively.

As derived by ROC analysis, a SUV_{mean} >4.0 at baseline was correlated with a significantly shorter PFS of 1.9 years as compared to 5.2 years for patients with lower metabolic activity (p=0.04, area under the curve=0.76), whereas no significant correlation could be observed for SUV_{max} (p= 0.06). Both parameters failed to predict OS (SUV_{mean}, p=0.2, SUV_{max}, p=0.3).

At follow-up, the above mentioned LN and visceral metastases were re-analyzed. SUV_{mean} dropped to median 3.0 (range, 2.1 – 6.6) with a median reduction of 26.9%. For SUV_{max}, a reduction of 25.6% to a median of 3.8 (range, 2.2 – 16.3) could be observed (Table 2; Supplemental Table 1, Figure 1).

Whereas sustained high 18F-FDG uptake with an SUV_{mean}>2.8 tended to be correlated with a shorter PFS of 1.9 years (vs. 3.5 years for SUV_{mean}<2.8; p=0.3), differences did not reach statistical significance. In parallel to baseline, no significant correlation could be observed for SUV_{max} (p=0.2) and both SUV_{mean} and SUV_{max} failed to predict OS (p=0.3, p=0.2, respectively).

In addition, the extent of metabolic activity reduction between baseline and 3-months follow-up PET was not predictive, neither for PFS (p=0.2) nor OS (p=0.4).

The results of ROC analysis including the area under the curve, sensitivity, specificity and dedicated thresholds for each group (> vs. < cut-off) can be found in Table 3.

Kaplan-Meier Analysis

Kaplan-Meier analysis revealed a significant distinction between high- and low-risk patients for PFS using the threshold for SUV_{mean} of 4 at the baseline PET as derived by ROC analysis (p<0.05); respective Kaplan-Meier-plots are given in Figure 2.

DISCUSSION

In this largest, but still relatively small patient cohort published to date, we report on the prognostic value of 18F-FDG in patients with advanced MTC at the start of TKI treatment. Interestingly, even though MTC is known to have a variable (and often even negative) 18F-FDG uptake in tumor lesions (*17,18*), all patients of our cohort had at least one hypermetabolic metastatic lesion.

A high 18F-FDG uptake at baseline had prognostic implications in terms of a significantly shorter PFS. An SUV_{mean} of the metabolically most active lesion >4.0 was associated with an almost 2.5-fold shorter PFS (1.9 years vs 5.2 years). The percentage of tumor metabolism reduction after 3 months of TKI treatment did not offer prognostic value and 18F-FDG failed to predict overall survival. This finding may be explained by the limited number of patients enrolled in this study. Additionally, vandetanib leads to reduced tumor proliferation, angiogenesis, or metastasis by inhibition of various tyrosine kinases but does not necessarily induce cell death (*19,20*).

In line with this consideration, *Walter* and colleagues have demonstrated the early transcriptional downregulation of key genes in glycolysis pathways such as STAT3 and Grb7/10 as soon as three days after vandetanib treatment initiation (*20*). However, this decline did not seem to be related to cell death as no increase in apoptotic cells was detected *in vitro* (*20*). Since the main aim of vandetanib treatment is disease stabilization rather than cure, 18F-FDG PET/CT could be used as a non-invasive tool to identify high-risk patients with more aggressive disease that need to be monitored more closely as compared to those with low 18F-FDG uptake at baseline.

Interestingly, clinical parameters such as age, sex, sites of metastases, prior therapy, or RET mutation status failed to predict response. The usefulness of analysis of serum marker doubling times as indicators of disease aggressiveness has been shown by a number of studies (*21,22*), however in our study, only pre-therapeutic CEA doubling times were strongly correlated with both PFS and OS, whereas no relation to CTN could be observed, perhaps also due to the small sample size.

As for 18F-FDG in our cohort, serum marker follow-up of thyroid cancer patients undergoing TKI treatment has been reported to be complicated by the phenomenon of tumor marker fluctuations not necessarily denoting true tumor escape. In contrast, morphologically measureable disease progression could only be confirmed after a series

of subsequent rises in serum markers (*14,23,24*). Given the earlier time point of response prediction obtainable, 18F-FDG PET might serve treating physicians outside the scenario of controlled studies as a suitable tool for therapy monitoring and patient-tailored decisions.

Additionally, when comparing our cohort to the phase 3 trial of *Wells* and co-workers (*5*), our study population was more advanced and/or progressive, since our PFS is shorter than the one in the prior study (30.5 months). Moreover, fairly short median CTN and CEA doubling times of 6.8 and 8.3 months before initiation of treatment were found in our patient cohort. Hence, given the fact that compared to the phase 3 vandetanib trial more aggressive tumors have been treated (*5*), a response rate of up to 50% (8 PR and one CR) could be achieved in our cohort. This indicates that vandetanib leads to tumor control and that the included patients most likely had a clinical benefit from the treatment; however, this cannot be verified in the absence of a control arm. In addition to that, even in one patient with slightly increased SUV_{mean} at baseline (patient #18, Supplementary Table a), vandetanib initiation led to a complete disappearance of tumor burden. Per contra, due to the underlying tumor biology, this achieved response may just persist shortly.

This study has several limitations: Limiting its statistical power, only a limited number of patients could be enrolled. As this is a retrospective bicentric study, different PET scanners have been used and imaging protocols slightly differed between imaging centers. No additional partial volume correction to reduce noise including normalizing values to body surface area or for the plasma glucose level has been performed. A future larger, multi-centric prospective study is warranted to strengthen our preliminary results.

Additionally, the RET mutation status was not determined in the majority of the cases which may represent another suitable predictor of PFS.

Last, potential intraindivdiual intertumoral heterogeneity regarding 18F-FDG-negative, 68Ga-DOTATATE-positive disease and its response to TKI treatment could not be assessed in this study but might be an interesting approach for further research (*25*).

CONCLUSION

In conclusion, 18F-FDG PET/CT can serve as a prognostic tool in patients with advanced MTC scheduled to undergo vandetanib treatment. An elevated glucose consumption assessed by baseline PET was related to shorter PFS, therefore, these patients need to be monitored more closely as compared to those with low 18F-FDG uptake at baseline. Changes in 18F-FDG uptake after 3 months in this small group of patients failed to predict progression free and overall survival.

DISCLOSURE

All authors had full control of the data and information submitted for publication. All authors disclosed no potential conflicts of interest. This project has received funding from the European Union's Framework Programme for Research and Innovation Horizon 2020 (2014-2020) under the Marie Skłodowska-Curie Grant Agreement. This publication was funded by the German Research Foundation (DFG) and the University of Wuerzburg in the funding programme Open Access Publishing. Parts of this cohort received vandetanib while participating in the ZACTIMA trial.

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FIGURES

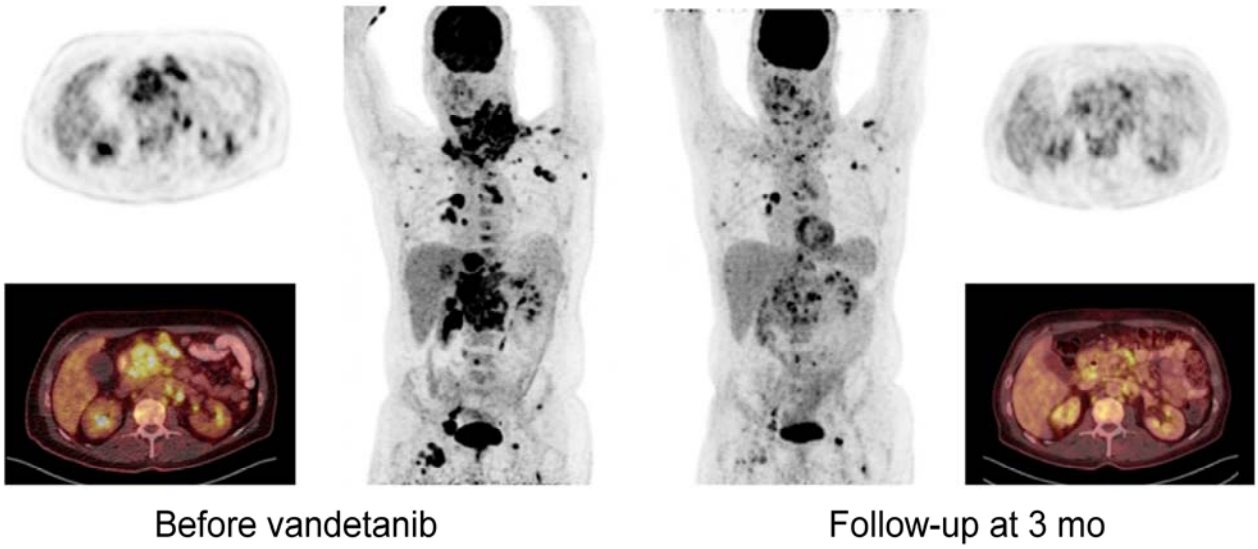

Figure 1. Example of a 47-year-old male with extensive tumor load (patient #12). Prior to tyrosine kinase inhibitor initiation the patient presented with highly aggressive disease with an mean standardized uptake value (SUV_{mean}) of the hottest lesion (right clavicular lymph node) of 13.4 After 3 months of vandetanib, a partial response could be detected with a decline of metabolic activity of 54.5% (SUV_{mean} = 6.1). However, due to disease aggressiveness, the patient died 11 months after start of treatment.

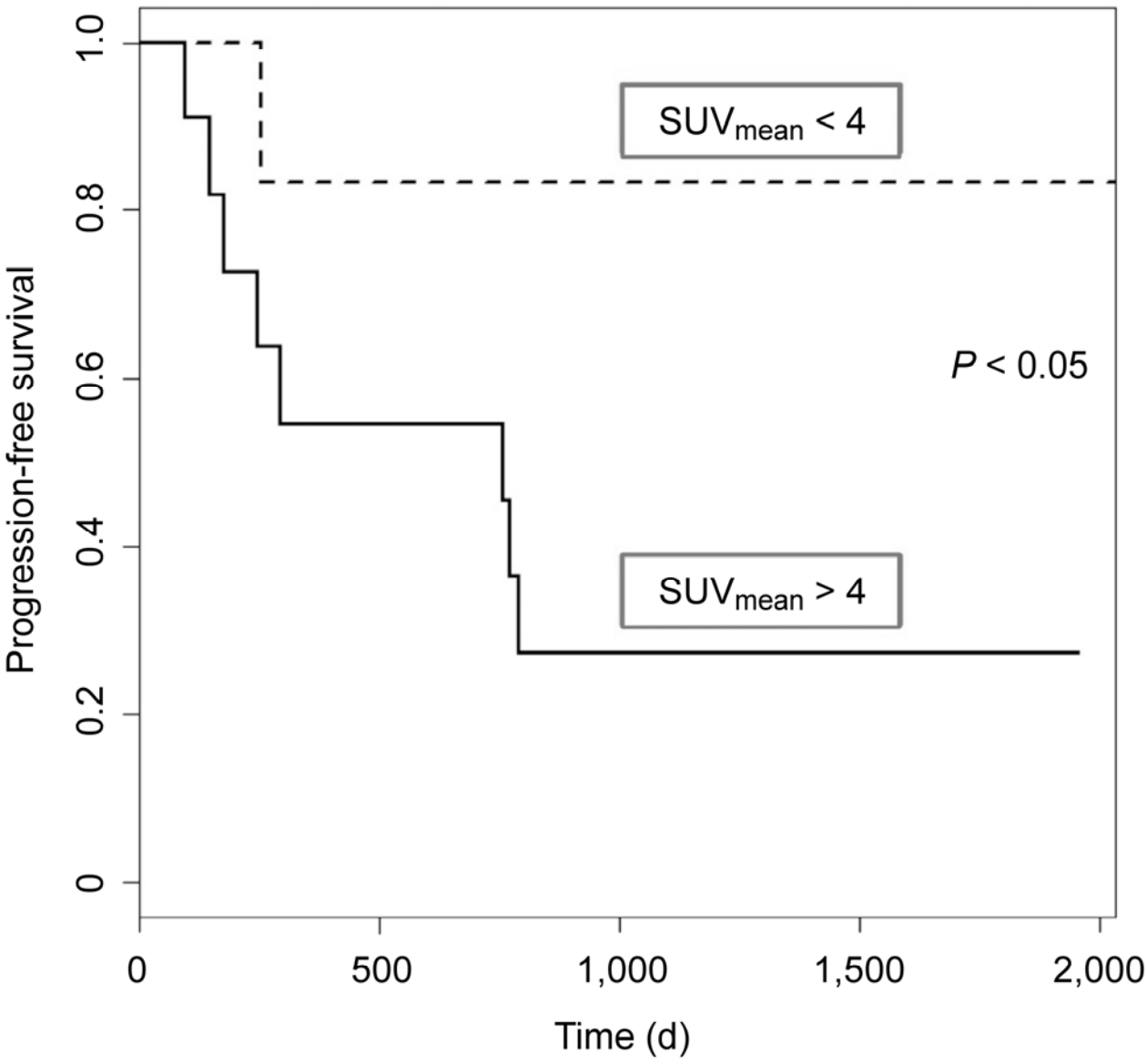

Figure 2. Kaplan–Meier plots for the probability of Progression-Free Survival using SUV_{mean} of baseline 18F-FDG PET. High-risk group is indicated by solid lines. A cut-off value of 4 derived by receiver operating characteristics analysis was used (Table 3).

TABLES

Case	Sex	Age (y)	Metastatic sites	Disease type	Prior therapy	Somatic RET mutation
#1	f	57	LN, lung, liver	sporadic	surgery	unknown
#2	f	59	LN, liver	sporadic	surgery, CTx, TACE	negative
#3	m	41	LN, bone	sporadic	surgery, CTx	unknown
#4	m	50	LN, lung	sporadic	surgery	unknown
#5	f	20	LN, lung, liver	sporadic	surgery	negative
#6	m	57	LN, lung, liver, bone	hereditary	surgery, TACE	-
#7	m	40	LN, lung	sporadic	surgery, CTx	unknown
#8	m	40	LN, liver, bone	sporadic	surgery	negative
#9	f	35	LN, lung	sporadic	surgery	negative
#10	m	59	LN, lung	sporadic	surgery	unknown
#11	m	30	LN	sporadic	surgery, RTx	negative
#12	m	47	LN, liver, bone, soft tissue, pancreatic infiltration	sporadic	surgery	unknown
#13	m	54	LN, lung, liver	sporadic	surgery	unknown
#14	m	78	LN, lung, bone	sporadic	surgery	unknown
#15	f	49	LN, liver, bone	sporadic	surgery, RTx	positive
#16	f	28	LN, bone	sporadic	surgery, radioiodine therapy*, RTx	positive
#17	m	46	liver, bone	sporadic	surgery, sorafenib	unknown
#18	m	55	LN, lung, bone, soft tissue	sporadic	surgery, RTx	positive

Table 1: Detailed patients` characteristics. CTx = chemotherapy, f = female, LN = lymph node, m = male, RET = rearranged during transfection, RTx = radiation therapy, TACE = transarterial chemoembolization, y = years. * initially classified as differentiated thyroid carcinoma.

	SUV_{mean}	SUV_{max}
Baseline PET	4.6 3.2 – 7.4	7.4 3.8 – 37.5
Investigated (Baseline)	LN: 10 (5 cervical, 2 mediastinal, 2 hilary, 1 clavicula) Visceral metastases: 6 (bone: 3, liver: 2, lung: 1)	
Follow-up PET	3 2.1 – 6.6	3.8 2.2 – 16.3
Investigated (Follow-up)	LN: 10 (5 cervical, 2 mediastinal, 2 paratracheal, 1 hilary) Visceal metastases: 6 (bone: 4, liver: 1, lung: 1)	
Reduction (in %)*	26.9 7.7 – 70	25.6 15.4 – 69.2

Table 2: Mean/maximum standardized uptake values ($SUV_{mean/max}$) of baseline and follow-up 18F-FDG positron emission tomography (PET) as well as the changes between both scans. Localization of investigated metastases is also given. Median and range is displayed for SUV, changes between both scans are given in %. Whole cohort. LN = lymph node. * in 12/16 cases, respectively.

^{18}F-FDG PET	p-value	Cut-off value	Sensitivity (%)	Specificity (%)	AUC	>cut-off	<cut-off
SUV_{mean} - PFS							
Baseline	*0.04**	4.0	88.9	62.5	0.76	1.9y (12/18)	5.2y (6/18)
Follow-up	0.28	2.8	71.4	62.5	0.6	1.9y (9/16) #	3.5y (7/16)#
SUV_{mean} - OS							
Baseline	0.2	6.9	37.5	100	0.63	2.0y (3/18)	3.8y (15/18)
Follow-up	0.28	2.8	62.5	71.4	0.6	2.8y (9/16)#	3.6y (7/16)#
SUV_{max} - PFS							
Baseline	0.06	7.25	77.8	75	0.74	2.0y (9/18)	3.5y (9/18)
Follow-up	0.19	2.7	85.7	50	0.64	1.8y (11/16)#	3.5y (5/16)#
SUV_{max} - OS							
Baseline	0.28	16.85	25	100	0.59	1.5y (2/18)	3.7y (16/18)
Follow-up	0.21	2.7	85.7	44.4	0.63	3.6y (11/16)#	3.6y (5/16)#

Table 3: Overview of results of Receiver Operating Curve analysis for mean/maximum standardized uptake value (SUV_{mean}/SUV_{max}) as obtained by 18F-FDG PET. Progression-Free Survival (PFS) and Overall Survival (OS) for the two groups above the cut-off (>cut-off) and below the cut-off (<cut-off) with the number of patients for each group. y = years. * = significant according to receiver operating characteristic analysis. # = 2 patients lost to PET-based follow-up.