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Prospective phase II trial of prognostication by ^{68}Ga-NOTA-AE105 uPAR PET in patients with neuroendocrine neoplasms: Implications for uPAR targeted therapy

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ABSTRACT (334 words)

The clinical course for patients with neuroendocrine neoplasms (NENs) ranges from indolent to highly aggressive. Non-invasive tools to improve prognostication and guide decisions on treatment are warranted. Expression of urokinase plasminogen activator receptor (uPAR) is present in many cancer types and associated with a poor outcome. Therefore, using an in-house developed uPAR PET tracer (^{68}Ga-NOTA-AE105) we aimed to assess uPAR expression in NENs. We hypothesized that uPAR expression was detectable in a significant proportion of patients and associated with a poorer outcome. In addition, as uPAR-targeted radionuclide therapy has previously proven effective in preclinical models, the study would also indicate the potential for uPAR-targeted radionuclide therapy in NEN patients.

METHODS

In a prospective clinical phase II trial, we included 120 patients with NENs of all grades of whom 96 subsequently had uPAR PET/CT performed with evaluable lesions. PET/CT was acquired 20 minutes after injection of approximately 200 MBq ^{68}Ga-NOTA-AE105. uPAR target-to-liver ratio (uPAR TLR) was used to define lesions as uPAR positive when lesion SUV_{max} /liver SUV_{mean} ≥ 2. Patients were followed for at least 1 year to assess progression-free survival (PFS) and overall survival (OS).

RESULTS

The majority of patients had small intestinal NEN (n=61) and metastatic disease (n=86). uPAR positive lesions were seen in 68% (n=65) of all patients and in 75% (n=18) of patients with high grade disease (NEN G3). During follow-up (median 28 months), 59 patients (62%) experienced progressive disease and 28 patients (30%) died. High uPAR expression, defined as uPAR TLR above median, had a hazard ratio (95% confidence interval) of 1.87 (1.11-3.17) and 2.64 (1.19-5.88) for PFS and OS, respectively ($p<0.05$ for both).

CONCLUSION

Using ^{68}Ga-NOTA-AE105 PET for imaging uPAR in patients with NEN, uPAR positive lesions were seen in the majority of patients and most notably in patients with both low and high grade NEN. Furthermore, uPAR expression was associated with a worse prognosis. We suggest that uPAR PET is relevant for risk stratification and uPAR may be a promising target for therapy in patients with NEN.

KEYWORDS

Urokinase plasminogen activator receptor (uPAR); neuroendocrine neoplasms, PET, prognosis, molecular imaging.

INTRODUCTION

Neuroendocrine neoplasms (NENs) originate from the neuroendocrine cells and are found primarily in the gastro-intestinal tract, pancreas and lungs. The clinical course for patients diagnosed with NEN ranges from indolent to highly aggressive. Origin of primary tumor, presence of metastases as well as tumor morphology and proliferation activity (i.e. Ki-67) are known prognostic factors. Patients are stratified by the World Health Organization (WHO) classification into neuroendocrine tumor (NET) G1 (Ki67 <3%), NET G2 (Ki67 3-20%), NET G3 (Ki67 > 20% and well differentiated) and neuroendocrine carcinoma (NEC) (Ki67 > 20% and poorly differentiated) (*1*). To further improve prognostication and guide decisions on treatment, non-invasive monitoring of tumor markers may be useful. PET is ideally suited for this task, as different specific radiotracers may be applied to visualize whole-body expression of tumor markers non-invasively. In NEN particularly, radiotracers for somatostatin receptor expression (e.g. ^{64}Cu-DOTATATE or ^{68}Ga-DOTATATE) and glucose metabolism (^{18}F-FDG) are useful for diagnosis, prognostication and therapy selection (*2,3*). In addition, peptide receptor radionuclide therapy (PRRT) with e.g. ^{177}Lu-DOTATATE targeting somatostatin receptors is approved for low grade NEN, whereas lower somatostatin receptor expression in high grade NEN can limit its application.

Urokinase plasminogen activator receptor (uPAR) is a promising diagnostic and prognostic biomarker as well as a target for therapy that has been extensively investigated in several cancer entities (*4*). uPAR is anchored to the cell membrane on the surface and localizes the proteolytic activity of its ligand, urokinase plasminogen activator (uPA). In normal tissues, uPAR expression is limited, however in cancer, uPAR expression is upregulated. Apart from uPA, uPAR also interacts with other proteins, among others the integrin family of membrane proteins. Collectively, uPAR is involved in promoting cell proliferation, motility, invasion, proteolysis and angiogenesis (*4-6*). Due to its integral role in cancer, our group has developed the PET radiotracer ^{68}Ga-NOTA-AE105 employing a high-affinity antagonist for uPAR (*7-9*). Safety and biodistribution were investigated in a phase I study, also showing accumulation of ^{68}Ga-NOTA-AE105 in primary tumors and metastases, as well as correlation with uPAR expression in excised tumor samples (*7*). Recently, we reported that ^{68}Ga-NOTA-AE105 uPAR PET is able to discriminate between low-risk and intermediate risk profiles in prostate cancer (*10*). Furthermore, we have previously shown a high efficacy of uPAR targeted PRRT in preclinical trials in

prostate and colorectal cancers (*11,12*). Thus, uPAR being a marker of aggressive disease may show upregulation in high grade NEN, and could provide a target for PRRT in these patients.

The aim of this phase II clinical trial of ^{68}Ga-NOTA-AE105 PET/CT in patients with NEN was to assess tumor uptake and clinical outcome. We hypothesized that uPAR-PET/CT with ^{68}Ga-NOTA-AE105 would show accumulation in NEN and that the uptake of the uPAR tracer would be associated with progression-free survival (PFS) and overall survival (OS).

METHODS

Patients

Patients with histologically confirmed NEN were included from the Dept. of Endocrinology (managing low grade NEN, Ki67 ≤20%) and Dept. of Oncology (managing high grade NEN, Ki67 >20%), Copenhagen University Hospital – Rigshospitalet, Denmark between November 17th 2017 – June 29th 2020. Rigshospitalet is a certified Neuroendocrine Tumor Center of Excellence by the European Neuroendocrine Tumor Society. The study was conducted in accordance with the Helsinki Declaration and Good Clinical Practice. The study was approved by the Danish Medicines Agency (EudraCT 2017-002312-13), Scientific Ethics Committee (H-17019400) and the Danish Data Protection Agency (2012-58-0004), and registered on clinicaltrials.gov (NCT03278275).

Eligible patients were aged above 18 years and should be able to read and understand the patient information in Danish and to give informed consent, diagnosed with gastro-entero-pancreatic NEN of all grades or broncho-pulmonary NEN, and have a WHO performance status of 0-2. Patients were excluded if pregnant/breast-feeding, had a body mass > 140 kg, a history of allergic reaction attributable to compounds of similar chemical or biologic composition to ^{68}Ga-NOTA-AE105 or in case of broncho-pulmonary NEN if the subtype was small cell lung cancer. After signature of written informed consent was obtained, the patients were referred for ^{68}Ga-NOTA-AE105 PET/CT at first given opportunity.

Image acquisition

Data acquisition was performed using a Biograph 128 mCT PET/CT (Siemens Medical Solutions) with an axial field of view of 216 mm. Based on the previous phase I trial (*7*), the scan was acquired 20 minutes after intravenous administration of approximately 200 MBq ^{68}Ga-NOTA-AE105.Tracer production was performed as previously described (*7*). Whole-body PET scans (mid of orbita to mid of thigh) were acquired with an acquisition time of 4 min per bed position. Attenuation- and scatter- corrected PET data were reconstructed iteratively using a 3D ordinary Poisson ordered-subset expectation-maximization algorithm including point-spread function and time-of-flight information using the TrueX algorithm (Siemens Medical Solutions); the settings were 2 iterations, 21 subsets, 2-mm Gaussian filter. A diagnostic CT scan was obtained before PET scan, with a 2-mm slice thickness, 120 kV, and a quality reference of 225 mAs modulated by the Care Dose 4D automatic exposure control system (Siemens Medical Solutions). An automatic injection system was used to administer 75 mL of an iodine containing contrast agent (Optiray 300; Covidien) for arterial and venous phase CT.

Image analysis

An experienced board certified nuclear medicine physician together with an experienced board certified radiologist analyzed side-by-side the PET/CT scans. The readers were blinded to patient data. Lesions were identified on CT and/or PET. SUV was calculated as decay-corrected measured radioactivity concentration/(injected activity/body weight). If more than one lesion was present in an organ, the lesion with the highest ^{68}Ga-NOTA-AE105 SUV_{max} was noted. If no uPAR positive lesions were identified, but lesions were visible on CT, the largest lesion (based on viable tumor) on CT was used as guide for delineation on the PET scan and SUV_{max} was determined. Physiological liver uptake was assessed in all patients' normal liver tissue, preferable in the right side of the liver avoiding major blood vessels. To standardize measurement of uPAR expression within and between patients, uPAR target-to-liver ratio (uPAR TLR) was used to define a lesion as uPAR positive when lesion SUV_{max} /normal liver $SUV_{mean} \geq 2$.

Follow-up

The patients were followed at the Rigshospitalet Neuroendocrine Tumor Center of Excellence with regularly visits including clinical examination, blood samples and imaging (CT, MR, ultrasound and/or PET/CT). The frequency was in accordance with ENETS guidelines (*13*). Follow-up for endpoints was performed on July 8th 2021. Routine CT and or magnetic resonance imaging were used for evaluation of PFS in accordance with Response Evaluation Criteria in Solid Tumors v. 1.1 (*14*). PFS was calculated as time from uPAR PET/CT to, if any, progression or death from any cause. If no progression or death from any cause occurred within the follow-up, the patient was censored at the time of last available diagnostic imaging. OS was calculated as time from uPAR PET/CT to death by any cause. As all death but two were directly related to NEN, we refrained from analyzing disease specific survival. Patients alive at follow-up were censored to the day of follow-up, i.e. July 8th 2021.

Statistics

Calculation of sample size was based on previous studies of prognostic markers in patients with NEN (*15,16*), where a 1-year follow-up of 100 patients was sufficient to detect significant differences in PFS and OS among groups (with a risk of Type I error of 0.05 and power of 0.8). To account for dropouts, 120 patients were included. Continuous variables are reported as mean ± standard deviation (SD) or median with range. Kaplan Meier analyses were used for estimation of time to outcome (PFS and OS) and using reverse Kaplan Meier analysis to estimate median follow-up time. We used the Cutoff Finder application to determine the optimal cutoff for uPAR TLR (*17*). Univariate and multivariate Cox regression analyses for OS and PFS with predictor variables being uPAR TLR and WHO grade were performed. A p-value<0.05 was considered statistically significant. R version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria) was used for the analyses.

RESULTS

Patients and image acquisition

We included 120 consecutive patients, whereof 21 patients did not undergo uPAR PET/CT (worsening of disease, n =5; withdrew consent, n=5; did not fulfill inclusion criteria, n= 2; died before uPAR PET/CT, n = 4; not possible to perform uPAR PET/CT due to COVID-19 restrictions, n= 5). Of 99 patients scanned with uPAR PET/CT, 96 patients had evaluable lesions (uPAR PET/CT failed due to technical issue, n = 1; no lesions visible on either CT or PET, n=2). Patients demographic data for study cohort (n=96) are given in Table 1. The majority of patients had small intestinal NEN (64%, 61/96) and 90% (86/96) had metastatic disease. Also, patients with high grade disease were well represented in the cohort with 9% NET G3 (9/96) and 16% NEC (15/96).

Patients were injected with a median (range) of 17.2 (8.7-39.8) µg NOTA-AE105 and the activity was 194 (104-236) MBq. Time from injection to PET scan was a median (range) of 22 (18-38) minutes. One patient experienced an adverse event (mild nausea), which was deemed unrelated to ^{68}Ga-NOTA-AE105 injection. No serious adverse events were recorded.

Image analysis

The tracer uptake in normal liver tissue was used as reference for tumor uptake. The mean ± SD normal liver SUV_{mean} was 1.50±0.39. uPAR positive lesions were seen in both patients with low grade (NET G1/G2) and high grade NEN (NET G3 and NEC) (Table 2). Representative examples of uPAR PET are shown in Fig. 1 and Fig. S1.

Follow-up

Median follow-up time after uPAR PET/CT was 28 months. During follow-up, 59 (62%) patients experienced progressive disease and median PFS was 17.3 months and 28 patients (30%) died. The patient's treatments after uPAR PET/CT are given in Table 3. Treatment with somatostatin analogue was the most frequent (77%, 74/96), and 28% (27/96) of all patients underwent peptide receptor radionuclide therapy during the follow-up period.

Progression-free survival and overall survival

uPAR TLR as a continuous variable was significantly associated with PFS with a HR (95% CI) of 1.27 (1.02-1.60), p=0.04. For OS, uPAR TLR as a continuous marker was borderline significant with a HR (95% CI) of 1.37 (0.98-1.92), p=0.06). TLR was then dichotomized at the median value (2.47) for Kaplan Meier analyses, see Fig. 2. Median OS was not reached in the group with low uPAR expression (TLR < median), and was 32.1 months (23.8; upper limit not reached) in the group with high uPAR expression (TLR ≥ median). Median PFS was 22.1 months (14.7; upper limit not reached) for patients with low uPAR expression and 14.1 months (11.4-22.4) patients with high uPAR expression. uPAR TLR dichotomized at median was significantly associated with PFS and OS where patients with a high uPAR expression had a significantly worse prognosis (Table 4 and 5). Other cut-offs were evaluated using Cutoff Finder, shown in Figure S2. By using a lower cutoff of TLR (1.32) a smaller group of patients (n=10) with no or a very low risk of death or progression could be identified (Figure 3). Patients with NET G3 and NEC had significantly worse PFS and OS as compared with NET G1, whereas no difference was seen between NET G2 and NET G1 (Table 4 and 5). In multivariate analyses including uPAR expression and WHO classification, both remained significantly associated with PFS, whereas uPAR expression was borderline significantly associated with OS (p=0.06) when controlling for WHO grade.

DISCUSSION

Our major finding in this prospective phase II study of ^{68}Ga-NOTA-AE105 uPAR PET was that uPAR expression was seen in the majority of patients with both low and high grade NEN. Furthermore, high uPAR expression was associated with a worse prognosis in regards to both PFS and OS. These findings implies that uPAR could be an attractive target for therapy both due to the availability of the target in patients with NEN and the possibility to specifically target the lesion(s) associated with a poorer prognosis for the patient.

The role of uPA and uPAR in cancer has been extensively investigated in the last decades and it is well established that higher uPAR expression is associated with tumor growth, invasiveness and metastatic spread, although this has not been thoroughly investigated in patients with NEN (*18*). Accordingly, several therapies targeting uPA and uPAR are undergoing investigation, e.g. an uPAR

antibody (huATN-658)(*19*) and a serine protease inhibitor targeting uPA (upamostat)(*20*). However, none of these therapies have yet been approved for clinical use.

Patients with NEN have highly varying aggressiveness of disease. The primary tumor site, presence of metastases and WHO classification are important prognostic markers and used for guiding selection of treatment (*21*). Our group and others have shown that in addition low somatostatin receptor density as determined by ^{64}Cu-DOTATATE PET and high glucose metabolism as determined by ^{18}F-FDG PET are prognostic factors (*2,3,16,22*). With the concept of tailored treatments, specific tumor markers are used to guide eligibility for targeted treatments. This concept has seen widespread implementation in the treatment of patients with NEN, where somatostatin receptor imaging as a companion is used for screening for eligibility to somatostatin receptor targeted therapy with ^{177}Lu-DOTATATE. In a randomized trial of ^{177}Lu-DOTATATE patients receiving ^{177}Lu-DOTATATE compared with high dose of cold somatostatin analogue treatment, the first group had significantly fewer deaths, longer PFS and the response rate was 18% (*23*). One drawback of targeting somatostatin receptor expressing tumors is the fact that lower expression of somatostatin receptors is seen with the less differentiated and more aggressive tumors (*24*). On the contrary, uPAR expression is particularly seen in lesions showing tumor growth, invasiveness, and metastatic capability. Previously, our group has investigated uPAR expression by immunohistochemical staining of primary tumor or metastasis from patients with NEN G3 (Ki67 >20%) showing uPAR expression in stromal and or tumor cells in 16/21 (76%) patients (*25*). However, to the best of our knowledge, expression of uPAR in patients with low grade NEN has never been studied in situ but only indirectly by measurement of soluble uPAR (suPAR) in serum (*26*). suPAR is the cleaved version of the membrane-bound uPAR and may thus be measured as a circulating uPAR biomarker. The study reported elevated levels of suPAR in patients with NEN compared with healthy controls, and elevated levels of suPAR in both patients with low and high grade disease. However, no association between suPAR levels and overall survival was seen. Contrary to that study, using PET to visualize uPAR expression at the tumor level is a more direct approach making it possible to identify the lesions with the greatest uPAR expression and the location of these lesions. Also, the expression pattern of uPAR has previously been shown to be heterogeneous with uPAR being highly expressed at the margin of the tumor and thus locally promoting tissue invasion and seeding of

metastases, a hallmark of cancer (*27*). In support of this, we found that high uPAR expression on PET was associated with a worse prognosis, both with regards to PFS and OS. In line with our previous observations in patients with NEC and the data on suPAR in NEN, we found uPAR expression to be present in both low and high grade NEN. Hence, uPAR targeted treatment may be relevant in patients with NEN of all grades. Our observations on uPAR expression should be viewed in the light that the patients included in this study mainly had small intestinal or pancreatic primary tumors with metastatic disease and were previously treated.

A potential innovative perspective is to combine uPAR PET imaging and uPAR-PRRT as a theranostics pair, hence using uPAR PET to assess eligibility to uPAR targeted therapy. We have previously shown a high efficacy of uPAR PRRT in preclinical models of human prostate and colorectal cancer (*11,12*), however further studies are warranted to assess the use of uPAR PRRT within NEN. However, the first step towards uPAR-PRRT for NENs was to provide evidence for a high and specific uptake of our uPAR-targeting radioligand and prognostic implications in NEN as done in the present study.

CONCLUSION

uPAR expression assessed by ^{68}Ga-NOTA-AE105 PET is seen in the majority of patients with both low and high grade NEN and high uPAR expression is associated with a worse prognosis with regards to both PFS and OS. Collectively, this points to uPAR as a relevant target to pursue for risk stratification and possibly also for targeted therapy in patients with NEN.

DISCLOSURE

This project received funding from the European Union's Horizon 2020 research and innovation programme under grant agreements no. 670261 (ERC Advanced Grant) and 668532 (Click-It), the Lundbeck Foundation, the Novo Nordisk Foundation, the Innovation Fund Denmark, the Danish Cancer Society, Arvid Nilsson Foundation, the Neye Foundation, Novartis Healthcare, the Research Foundation of Rigshospitalet, the Danish National Research Foundation (grant 126), the Research Council of the Capital Region of Denmark, the Danish Health Authority, the John and Birthe Meyer Foundation, the

Research Council for Independent Research and the Neuroendocrine Tumor Research Foundation. Andreas Kjaer is a Lundbeck Foundation Professor.

AK is inventor on a patent of the composition of matter of uPAR PET (WO 2014086364) and co-founder of Curasight, which has licensed the uPAR PET technology. No other authors declared any relevant conflicts of interest.

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KEY POINTS

Question

Is urokinase plasminogen activator receptor (uPAR) expression seen in patients with neuroendocrine neoplasms and associated with prognosis?

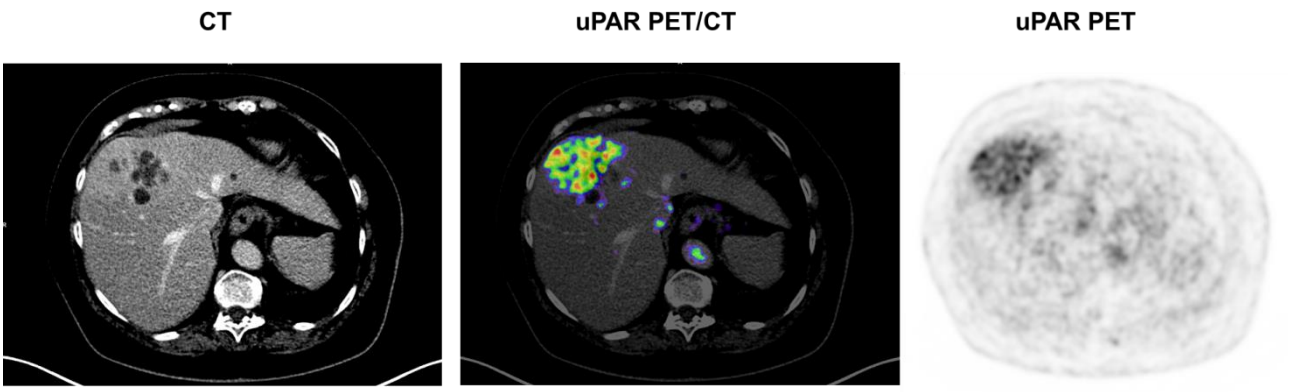
Pertinent Findings

Using ^{68}Ga-NOTA-AE105 for uPAR PET/CT imaging, we saw uPAR expression in the majority of NEN patients, including both high and low grade NENs. Furthermore, increased uPAR expression, both as a continuous variable and dichotomized at median was associated with increased hazard for progression of disease and death.

Implications for Patient Care

uPAR PET imaging may be useful for risk stratification in patients with NENs. Furthermore, uPAR may be a possible treatment target given the expression of uPAR across patients with both high and low grade NEN and uPAR expression being associated with a poor outcome.

GRAPHICAL ABSTRACT



uPAR positive liver metastasis from pancreatic NET G2 (Ki67: 5%)

TABLE 1: Baseline characteristics of patients with neuroendocrine neoplasms

Baseline characteristics		(N=96)
Median age (y)		66 (range, 34-82)
Gender		
	Female	39 (41%)
	Male	57 (59%)
Site of primary tumor		
	Small intestine	61 (64%)
	Pancreas	15 (16%)
	Colon	10 (10%)
	Lung	6 (6%)
	Esophagus	1 (1%)
	Stomach	2 (2%)
	Rectum	1 (1%)
Metastatic disease		86 (90%)
Liver metastases		73 (76%)
Median Ki67		7 (range, 1-100)
World Health Organization grade		
	NET G1	21 (22%)
	NET G2	51 (53%)
	NET G3	9 (9%)
	NEC	15 (16%)
Median time from diagnose to uPAR PET/CT (mo)		25 (range, 0.5-265)
Primary tumor resected		37 (39%)
Ongoing treatment at uPAR PET/CT scan time*		
	Somatostatin analogue	70 (73%)
	Interferon	8 (8%)
	Carboplatin or etoposide	19 (20%)
	Capecitabine/5FU	6 (6%)
	Streptozotocin	5 (5%)
	Temozolomide	2 (2%)
	Everolimus	2 (2%)
Completed treatment before uPAR PET/CT*		
	On 1. line of therapy	45 (47%)
	Peptide receptor radionuclide therapy	28 (29%)
	Temozolomide	6 (6%)
	Capecitabine/5FU	6 (6%)
	Streptozotocin	5 (5%)
	Carboplatin or etoposide	10 (10%)
	Everolimus or sunitinib	2 (2%)
	Interferon	6 (6%)
	Liver radiofrequency ablation or embolization	4 (4%)
	Resection of liver metastases	4 (4%)

*Some patients had received more than one treatment, therefore the number of treatments exceed the number of patients. Data are number followed by percentage in parentheses, unless otherwise indicated. Percentages were rounded and may not add up to 100%. NET: neuroendocrine tumor. NEC: neuroendocrine carcinoma.

TABLE 2: Proportion of patients with uPAR PET positive tumors by WHO grades

	G1 (n=21)	G2 (n=51)	G3 (n=24)	Overall (n=96)
uPAR PET positive	12 (57%)	35 (69%)	18 (75%)	65 (68%)

Data are number followed by percentage in parentheses. uPAR target-to-liver ratio was used to define lesions as uPAR positive when lesion SUV_{max} /normal liver $SUV_{mean} \geq 2$. Of patients with G3 were 8 of 9 NET G3 and 10 of 15 NEC uPAR PET positive.

TABLE 3: Treatment after uPAR PET/CT

Treatment after uPAR/PET (N=96)			
Somatostatin analog	74 (77%)	Telotristat	2 (2%)
Interferon	6 (6%)	Topotecan	2 (2%)
Peptide receptor radionuclide therapy	27 (28%)	Docetaxel	2 (2%)
Capecitabine/5FU	10 (10%)	Irinotecan	1 (1%)
Everolimus or sunitinib	11 (11%)	Surgery	9 (9%)
Temozolomide	8 (8%)	Liver embolization	7 (7%)
Carboplatin or etoposide	11 (11%)	Liver radiofrequency ablation	2 (2%)
Streptozotocin	3 (3%)	External radiation	11 (11%)

Some patients had received more than one treatment, therefore the number of treatments exceed the number of patients. Data are number followed by percentage in parentheses.

TABLE 4: Uni- and multivariate Cox regression analyses for progression-free survival

Progression-free survival		Univariate Cox		Multivariate Cox	
		HR (95% CI)	P-value	HR (95% CI)	P-value
uPAR TLR*					
	Low	*Reference*	-	*Reference*	-
	High	1.87 (1.11-3.17)	0.02	1.75 (1.02-2.99)	0.04
WHO grades					
	NET G1	*Reference*		*Reference*	
	NET G2	1.21 (0.57-2.55)	0.62	1.26 (0.59-2.66)	0.55
	NET G3	4.16 (1.52-11.36)	<0.01	3.56 (1.29-9.82)	0.01
	NEC	4.26 (1.82-9.95)	<0.001	4.43 (1.89-10.39)	<0.001

*uPAR TLR is dichotomized at median (2.47). TLR: target-to-liver ratio. NET: neuroendocrine tumor. NEC: neuroendocrine carcinoma. HR: hazard ratio. CI: confidence interval

TABLE 5: Uni- and multivariate Cox regression analyses for overall survival

Overall survival		Univariate Cox		Multivariate Cox	
		HR (95% CI)	P-value	HR (95% CI)	P-value
uPAR TLR*					
	Low	*Reference*	-	*Reference*	-
	High	2.64 (1.19-5.88)	0.02	2.23 (0.96-5.20)	0.06
WHO grades					
	NET G1	*Reference*	-	*Reference*	-
	NET G2	1.40 (0.29-6.76)	0.67	1.59 (0.33-7.70)	0.56
	NET G3	9.94 (2.00-49.52)	0.01	7.82 (1.55-39.44)	0.01
	NEC	15.55 (3.49-69.37)	<0.001	17.09 (3.80-76.81)	<0.001

*uPAR TLR is dichotomized at median (2.47). TLR: target-to-liver ratio. NET: neuroendocrine tumor. NEC: neuroendocrine carcinoma. HR: hazard ratio. CI: confidence interval

FIGURES

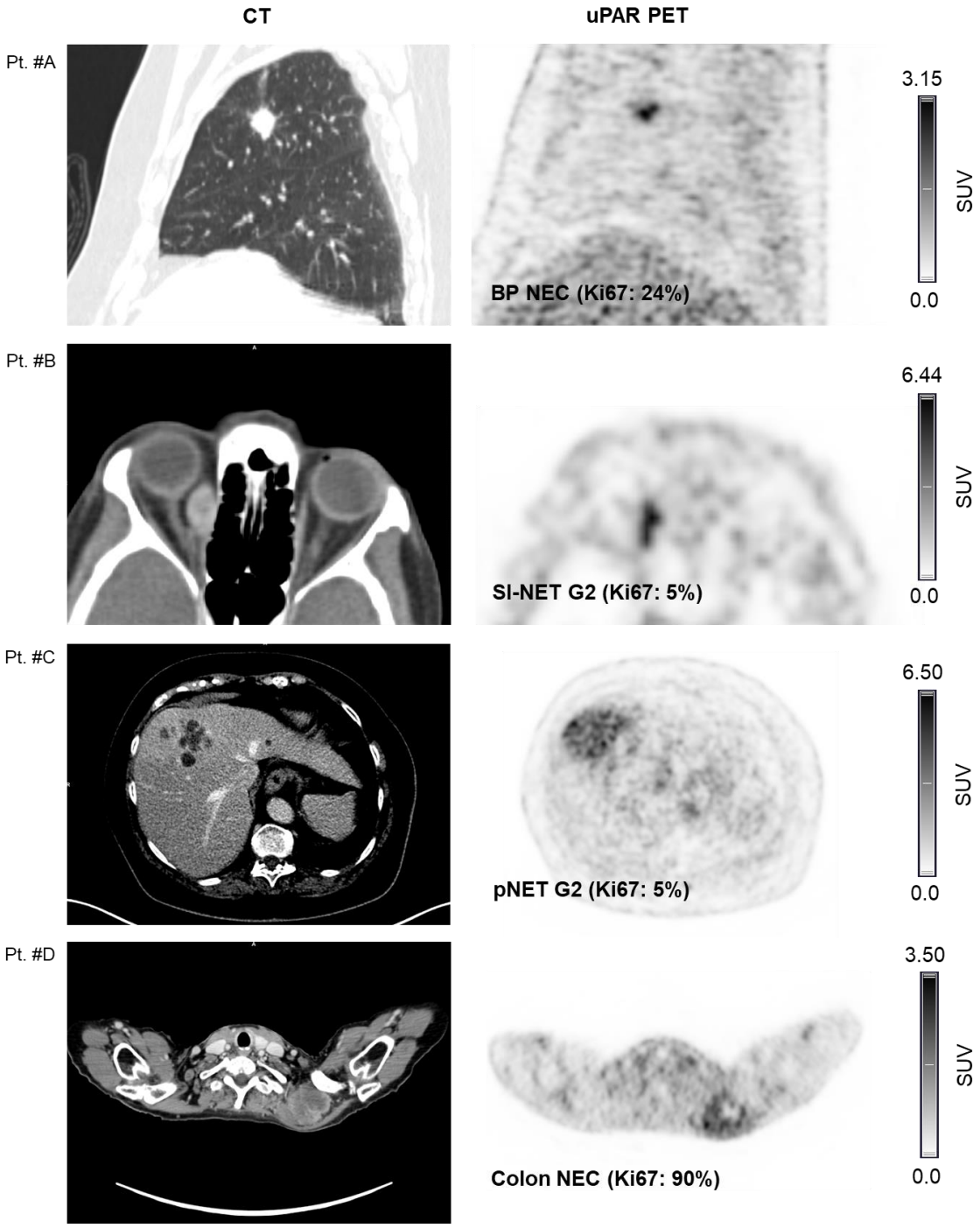


FIGURE 1: Representative examples of uPAR PET/CT imaging. CT (left column) and uPAR PET (right column) in 4 patients (#A-D) with high and low grade NEN. The top of the individual scale bar corresponds to the SUV_{max} value of the tumor. Pt. #A: Bronchopulmonary NEC (Ki67: 24%). Pt. #B: Orbital metastasis from small intestine NET G2 (Ki-67: 5%); Pt. #C: Large liver metastasis from

pancreatic NET G2 (Ki-67: 5%). Pt. #D: Large intramuscular metastasis from primary colon NEC (Ki-67: 90%).

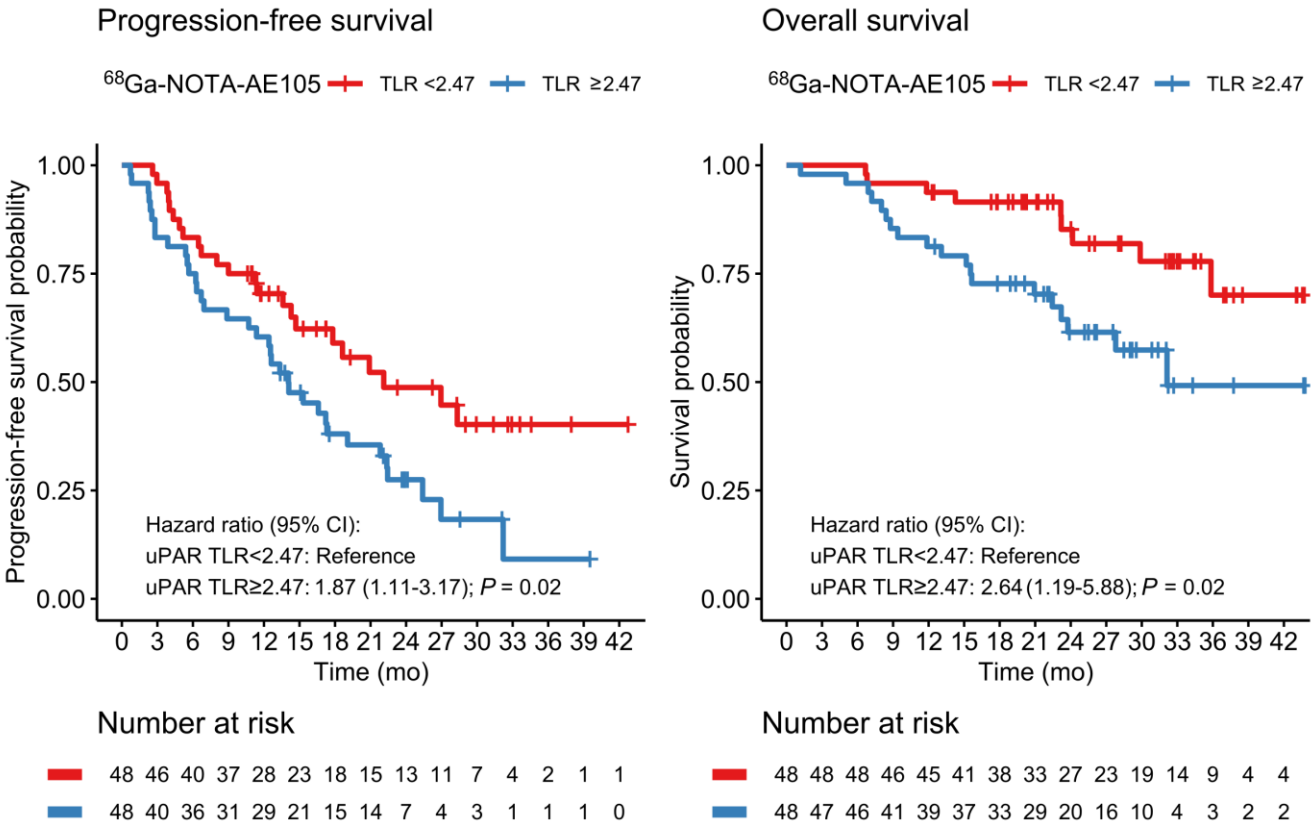


FIGURE 2: Kaplan-Meier plots of overall survival and progression-free survival using ^{68}Ga-NOTA-AE105 uPAR PET. uPAR target-to-liver-ratio dichotomized at median (TLR: 2.47).

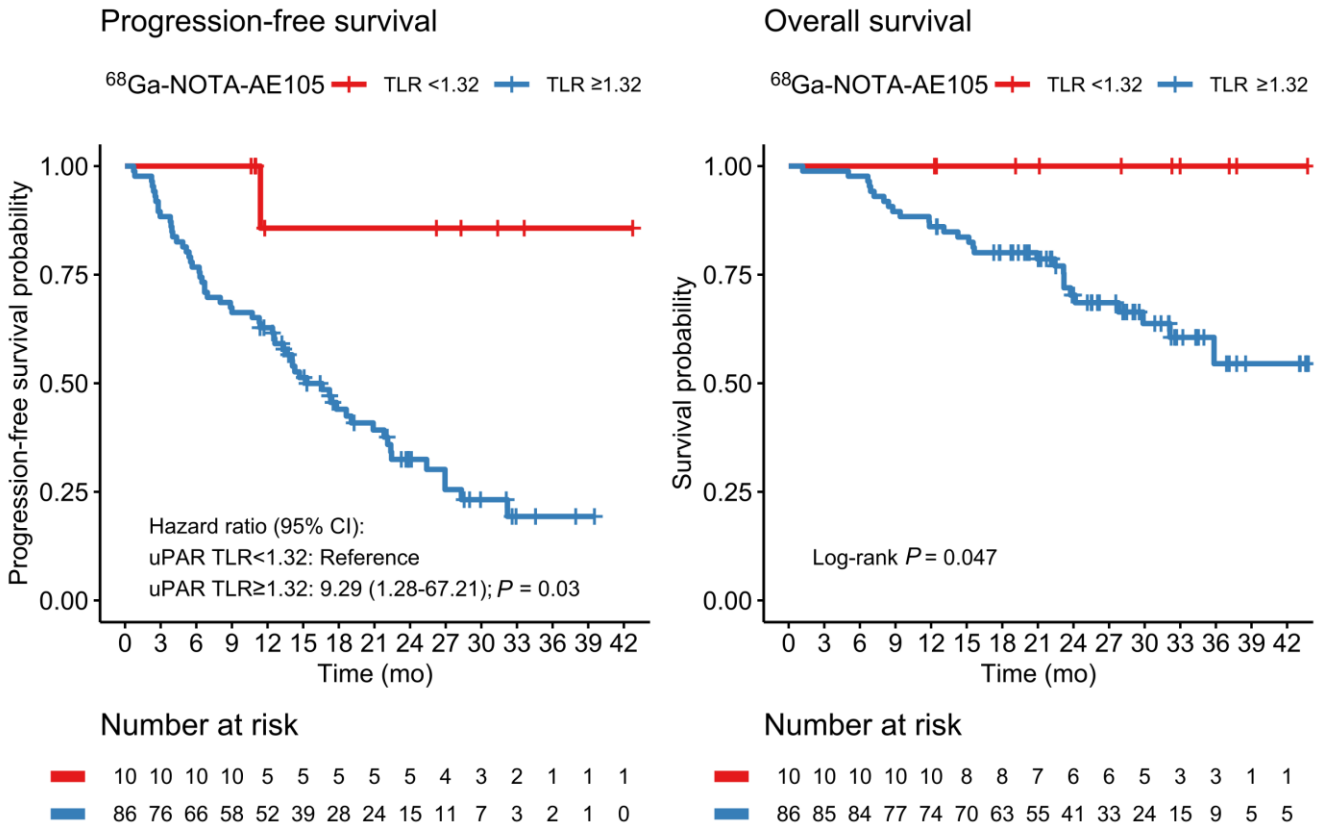
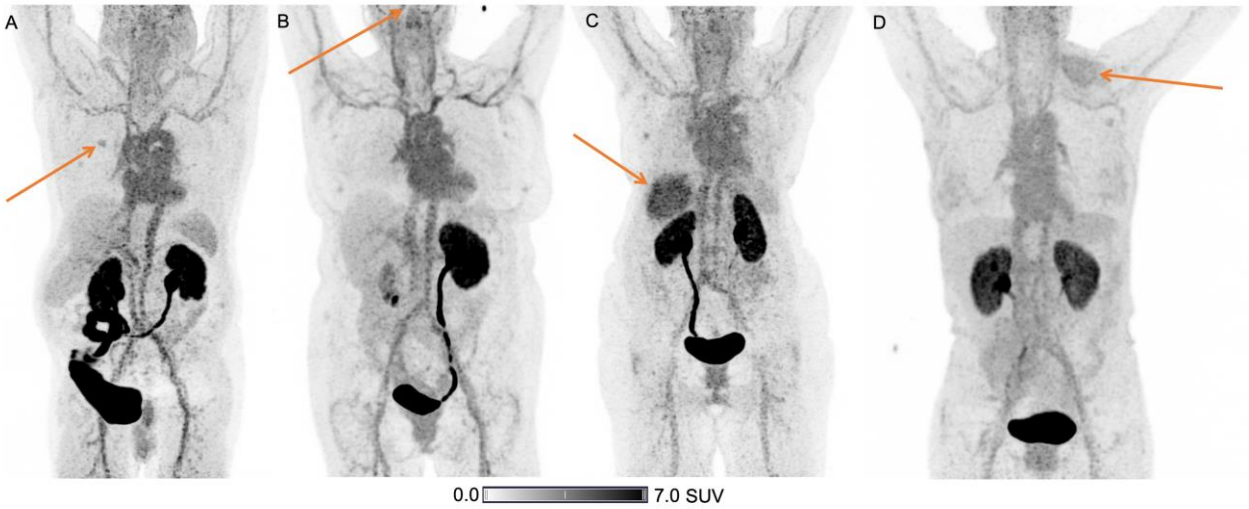


FIGURE 3: Kaplan-Meier plots of overall survival and progression-free survival using ^{68}Ga-NOTA-AE105 uPAR PET. uPAR TLR dichotomized at 1.32.

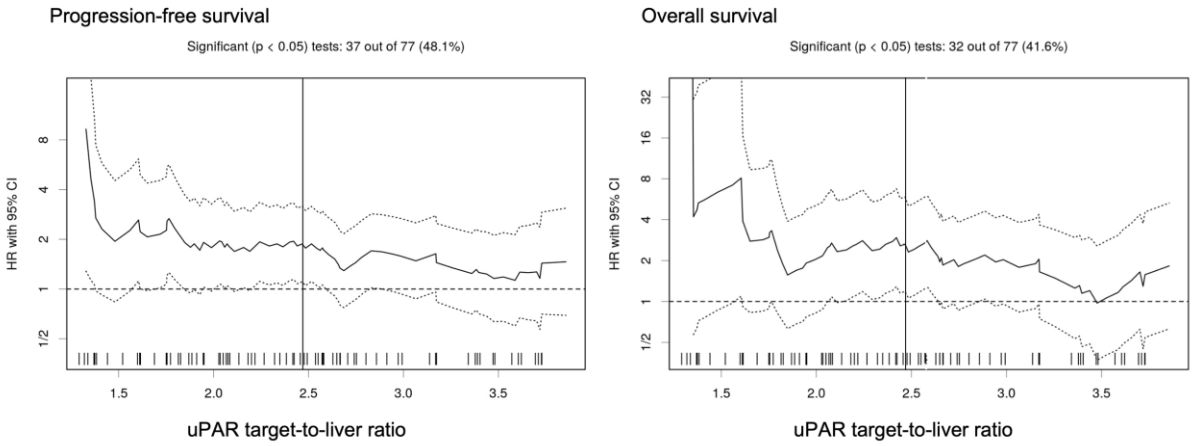
SUPPLEMENTARY FIGURE

Supplemental Figure 1



A: Arrow pointing to bronchopulmonary NET shown in Fig 1A. Tumor SUV_{max}: 3.2. Normal liver SUV_{mean}: 1.24. B: Arrow pointing to SI NET orbital metastasis shown in Fig 1B. Tumor SUV_{max}: 5.8. Normal liver SUV_{mean}: 1.42. C: Arrow pointing to pancreatic NET liver metastasis in Fig 1C. Tumor SUV_{max}: 6.8. Normal liver SUV_{mean}: 1.1. D: Arrow pointing to colon NEC intramuscular metastasis in Fig 1D. Tumor SUV_{max}: 3.5. Normal liver SUV_{mean}: 1.1

Supplemental Figure 2



Cutoff Finder output depicting hazard ratio and 95% confidence interval (HR with 95% CI) when uPAR TLR is dichotomized at any possible cutpoint (x-axis). Solid vertical line is placed at median uPAR TLR (2.47).

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