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Original Article

[^{68}Ga]Ga-DOTATATE-avid tumor volume, uptake and inflammation-based index correlate with survival in neuroendocrine tumor patients treated with [^{177}Lu]Lu-DOTATATE PRRT

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Abstract: To meet the increasing demand for PRRT in the treatment of patients with inoperable/disseminated well-differentiated neuroendocrine tumors (NETs) and to guide optimization strategies, adequate and accessible predictive tools that allow to stratify patients who will benefit from treatment from those who will not are becoming indispensable. Previously, we have investigated the role of baseline [^{68}Ga]Ga-DOTATOC PET tumor uptake and volumetric parameters and a blood-derived inflammatory biomarker, the inflammation-based index (IBI), for outcome prediction in NET patients treated with [^{90}Y]Y-DOTATOC. In this retrospective study in 83 NET patients treated with [^{177}Lu]Lu-DOTATATE in a routine clinical setting, we aimed to evaluate the generalizability of our previous findings to [^{177}Lu]Lu-DOTATATE treatment combined with a pre-therapeutic [^{68}Ga]Ga-DOTATATE PET. A semi-automatic customized SUV threshold-based approach was used for tumor delineation. The previously identified SUV_{mean} cut-off of 13.7 for better survival could not be applied to this patient cohort. Instead, a more optimal cut-off could be identified: an SUV_{mean} lower or equal than 11.2 was associated with worse overall survival (OS) (hazard ratio (HR) 2.28; P = 0.008). Also in line with our previous study, a [^{68}Ga]Ga-DOTATATE-avid tumor volume (TV) higher than 672 mL and an elevated baseline IBI were correlated with worse OS (HR 3.13 (P = 0.0001) and HR 2.00 (P = 0.034), respectively). Multivariate analysis confirmed independent associations between OS and baseline IBI (P = 0.032), SUV_{mean} (P = 0.027) and [^{68}Ga]Ga-DOTATATE-avid TV (P = 0.001). Taking baseline IBI, [^{68}Ga]Ga-DOTATATE-avid TV and [^{68}Ga]Ga-DOTATATE uptake into account may help guide PRRT treatment decisions.

Keywords: PRRT, [^{68}Ga]Ga-DOTATATE, [^{177}Lu]Lu-DOTATATE, neuroendocrine tumors, PET, survival, response

Introduction

Peptide receptor radionuclide therapy (PRRT) for neuroendocrine tumors (NETs) is a targeted treatment that involves the systemic administration of radiolabeled somatostatin analogues (SSAs), such as [^{177}Lu]Lu-DOTATATE and [^{90}Y]Y-DOTATOC [1]. Its position as a second-line treatment option in the management of inoperable or disseminated well-differentiated NETs has been further enforced by the excellent clinical results of the NETTER-1 trial [2]. Consequently, as PRRT is being more widely used, it is also likely to be applied in more heterogeneous clinical settings [3]. Disease control is typically achieved in around 80% (71%-92%) of patients [1]. To meet the increasing demand for PRRT, predictive tools that allow to identify those patients in whom therapy will fail, are thus becoming indispensable and represent an unmet clinical need. The most promising biomarker that has been proposed so far, is the PRRT predictive quotient (PPQ) which combines NET-specific gene expression in blood with histological grading [4]. The PPQ has been successfully validated in two independent patient cohorts and showed an overall accuracy of 94% for predicting PRRT responders and non-

responders [3]. However, the need for gene amplification could impose practical and economic restrictions to the widespread implementation of this biomarker in routine clinical practice. A more readily available parameter that has been proposed as a blood biomarker for PRRT response prediction is the inflammation-based index (IBI), derived from C-reactive protein (CRP) and albumin. In a retrospective study, baseline IBI and its changes throughout PRRT treatment were associated with progression-free survival (PFS) and overall survival (OS), but these findings need further validation [5].

As sufficient uptake on somatostatin receptor (SSTR) imaging is a prerequisite for PRRT [6], research has also focused on the role of SSTR uptake parameters for PRRT response prediction. High standardized uptake values (SUV_{max} and/or SUV_{mean}) on baseline [^{68}Ga]Ga-DOTA-SSA positron emission tomography (PET) have often been reported as predictive for PRRT response and varying cut-off values for patient stratification have been proposed [7-11]. However, these cut-offs lack validation in independent patient cohorts. Moreover, some studies observed no additional predictive value of tumor uptake on baseline PET [12, 13]. Uptake parameters alone are therefore insufficiently reliable to serve as an adequate PRRT response predictor.

Recently, we have performed post-hoc analyses on data of 43 NET patients treated with [^{90}Y]Y-DOTATOC in the setting of a prospective phase II trial, assessing the utility of pre-therapeutic [^{68}Ga]Ga-DOTATOC PET tumor uptake and volumetric parameters and IBI for prediction of response to [^{90}Y]Y-DOTATOC treatment [14]. We found that normal baseline IBI and an SUV_{mean} (of the whole tumor burden) higher than 13.7 were independently associated with better OS, whereas a [^{68}Ga]Ga-DOTATOC-avid tumor volume (TV) higher than 578 mL was associated with worse survival, although the latter was not corroborated by multivariate analysis. More importantly, a composite score based on this SUV_{mean} cut-off of 13.7 and IBI allowed to stratify patients in three categories with significantly different survival. Further validation is therefore required and the generalizability to [^{177}Lu]Lu-DOTATATE treatment needs to be confirmed, as [^{177}Lu]Lu-DOTATATE is currently the most commonly used PRRT radiopharmaceutical.

The primary objective of this retrospective study was to explore whether the composite score based on baseline SUV_{mean} and IBI, as previously identified in a [^{68}Ga]Ga-/[^{90}Y]Y-DOTATOC patient cohort, could be straightforwardly extrapolated to patients treated with [^{177}Lu]Lu-DOTATATE who had a pre-therapeutic [^{68}Ga]Ga-DOTATATE PET. Since [^{68}Ga]Ga-DOTATATE has a slightly different SSTR affinity profile compared with [^{68}Ga]Ga-DOTATOC [15], we also evaluated whether another SUV_{mean} cut-off value results in better patient stratification. Furthermore, we assessed whether [^{68}Ga]Ga-DOTATATE-avid TV, tumor grade and primary tumor were correlated with survival. Finally, we determined potential associations between baseline IBI and its changes throughout treatment with overall survival.

Materials and methods

Patient population

For this retrospective single-center study, all NET patients treated with [^{177}Lu]Lu-DOTATATE PRRT in a routine clinical setting between November 2013 and June 2019 (included) at our center (Nuclear Medicine, University Hospitals Leuven, Belgium) were eligible. PRRT treatment was given in patients fulfilling the eligibility criteria in standard clinical practice [6] after multidisciplinary review and after informed consent. In particular, patients had sufficient uptake (higher than normal liver parenchyma) on pre-therapeutic SSTR imaging. The main inclusion criteria for this retrospective study were patients diagnosed with a NET of all grades and origin who received at least one cycle of [^{177}Lu]Lu-DOTATATE, the availability of a pre-therapeutic [^{68}Ga]Ga-DOTATATE PET performed at our center within six months prior to the first treatment cycle and a minimum follow-up period for survival of 15 months. Patients for whom baseline IBI within five days prior to the first [^{177}Lu]Lu-DOTATATE administration was unavailable (n = 9), neural crest tumor patients (n = 4), patients who had previous [^{90}Y]Y-DOTATOC treatment (n = 2) or [^{177}Lu]Lu-DOTATATE treatment at another center (n = 1) and one patient in whom the [^{68}Ga]Ga-DOTATATE PET was acquired on a PET/MR system (n = 1) were excluded. As such, 83 patients were included for analysis. This retrospective study was approved by the Ethics Committee Research UZ/KU Leuven (S64247).

IBI and composite score

IBI was derived from serum albumin and CRP levels as previously described [5, 16]. If both values were normal (albumin > 35 g/L and CRP < 10 mg/L), patients received a score of 0. Further, one point was assigned for each abnormal parameter leading to a maximum score of 2 in patients with an elevated CRP and hypoalbuminemia. No correction for acute clinical changes, such as an acute, transient infection was made. Baseline IBI was determined within five days prior to the first PRRT cycle. To determine changes in IBI throughout treatment, a previously described approach was used [5]. Patients were divided in two groups. The first group of patients either showed an improvement in IBI score as compared with the baseline IBI value or retained a score of 0 and therefore had a "normalized" IBI score. The second group with a "persistently abnormal" IBI score, consisted of patients showing an increase in IBI value or persistently elevated IBI. IBI changes were evaluated at two time points: (1) after two PRRT cycles, within one week prior to administration of the third cycle, and (2) after four cycles, preferentially 3 to 12 weeks after end of treatment.

The composite score we previously derived from [^{68}Ga]Ga-/[^{90}Y]Y-DOTATOC data [14] was calculated as follows; patients with normal IBI and an SUV_{mean} higher than 13.7 received a score of 0. An elevated IBI or an SUV_{mean} equal or lower than 13.7 resulted in a score of 1. If both conditions were met, a score of 2 was assigned.

[^{68}Ga]Ga-DOTATATE PET/CT scans

[^{68}Ga]Ga-DOTATATE was synthesized using 30 µg of DOTATATE (ABX advanced biochemical compounds, Radeberg, Germany) per synthesis according to the previously described procedure for [^{68}Ga]Ga-DOTATOC [17]. A whole-body PET (PET/CT: with low or high dose CT (computed tomography) according to routine referrer's prescription) from head to mid-femur was obtained at 39 ± 8 minutes after IV administration of 157 ± 30 MBq [^{68}Ga]Ga-DOTATATE. Patients were asked to avoid long-acting SSA treatment four to six weeks before the scan. As patients were included from the routine clinical setting at our center, scans were performed on different PET systems. Twenty-five PET/CT scans were performed on a Siemens Biograph 16 HiRez LSO PET/CT system (Siemens Medical, Erlangen, Germany). Iterative reconstruction was done using an ordered subsets expectation maximization (OSEM) algorithm (5 iterations, 8 subsets) and a post-reconstruction Gaussian smoothing kernel of 6 mm full-width half-maximum (FWHM). In 52 patients, images were acquired on a Siemens Biograph 40 Truepoint TrueV PET/CT system (Siemens Medical, Erlangen, Germany) and iteratively reconstructed by means of a manufacturer-provided 3D OSEM algorithm with detector response modelling (3 iterations, 21 subsets) and a post-reconstruction Gaussian smoothing kernel of 4 mm FWHM. Finally, six patients underwent a PET/CT scan on a GE Discovery MI 4-ring PET/CT system (GE, Milwaukee, WI, USA). Emission data was iteratively reconstructed with the VPFXS algorithm, which makes use of Time-of-Flight information and includes detector response modelling (2 iterations, 34 subsets). A post-reconstruction Gaussian smoothing kernel of 5 mm FWHM was applied.

Quantitative measurements

[^{68}Ga]Ga-DOTATATE PET images were analyzed using the MIM software package, version 7.0.6 (MIM Software Inc., Cleveland, Ohio, USA). Tumor lesions were semi-automatically delineated as previously described [14]. Briefly, a series of segmentations of the whole-body PET image was automatically generated using different SUV thresholds. These segmentations were carefully compared to select the optimal SUV cut-off for each patient. From the remaining optimal segmentation, regions of physiologic or other non-disease related [^{68}Ga]Ga-DOTATATE uptake were manually removed. In patients with diffuse bone metastases with markedly lower uptake compared with extraosseous tumor lesions (n = 7), an additional customized SUV threshold was applied to segment the bone lesions. Finally, any small but definite tumor lesions missed by the initial segmentation due to low [^{68}Ga]Ga-DOTATATE uptake were manually delineated with the PET Edge® tool (MIM software v. 7.0.6) and added to the [^{68}Ga]Ga-DOTATATE-avid tumor volume-of-interest (VOI). From the resulting total tumor VOI, the parameters SUV_{max}, SUV_{mean} and TV were automatically derived.

Statistical analyses

The Python package *lifelines* (CamDavidson-Pilon/lifelines) version 0.24.11 was used for

Table 1. Clinical and tumor characteristics of the patient cohort (n = 83)

Characteristics	Number (%) or Median
Age at 1st PRRT cycle (years)	62 (range: 24-84)
Sex	
Male	46 (55.4%)
Female	37 (44.6%)
Primary tumor	
Intestine	39 (47.0%)
Pancreas	28 (33.7%)
Lung	6 (7.2%)
Unknown origin	10 (12.0%)
Grade	
G1	22 (26.5%)
G1/G2 (i.e. Ki-67 < 5%)	3 (3.6%)
G2	45 (54.2%)
G3	4 (4.8%)
Unknown	9 (10.8%)
Time between pre-therapeutic PET and first treatment cycle (months)	2.1 (range: 0-5.3)
PRRT cycles received	
1	2 (2.4%)
2	3 (3.6%)
3	5 (6.0%)
4	73 (88.0%)
Baseline IBI	
0	63 (75.9%)
1	16 (19.3%)
2	4 (4.8%)
OS (months)	53.5 (range: 0.1-86.3)

Ki67: Ki-67 proliferation index; PRRT: peptide receptor radionuclide therapy; IBI: inflammation-based-index; OS: overall survival.

statistical analysis. To compare OS between different groups, Kaplan-Meier curves with log-rank tests were applied. Subgroups for continuous PET-derived parameters were created using the 25th, 50th and 75th percentile values as cut-off, resulting in three comparisons between two subgroups for each parameter. Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated by means of uni- and multivariate Cox proportional-hazards models. Two-sides *P* values of less than 0.05 were considered statistically significant.

Results

Eighty-three patients (46 men, 37 women; 67 gastroenteropancreatic NETs, 6 lung NETs and 10 NETs of unknown primary) were included in this retrospective study. Patient and tumor characteristics are presented in **Table 1**. The intended treatment schedule was four cycles of 7.4 GBq [^{177}Lu]Lu-DOTATATE, every 8 weeks. Reasons to end the therapy prematurely were persistent or recurrent grade 3 or 4 hematotoxicity (n = 4), severe clinical deterioration (n = 3), disease progression (n = 1) and patient death (n = 2). Furthermore, in two patients, the administered activity of two treatment cycles was reduced due to hematotoxicity.

At the time of data lock (July 31 2021), 45 patients (54.2%) had died. The median follow-up time for patients who were still alive was 49.8 months. The median OS was 53.5 months. The median interval between baseline [^{68}Ga]Ga-DOTATATE PET and the first treatment cycle was 2.1 months (range: 0-5.3 months). Baseline PET tumor uptake and volumetric parameters are provided in **Table 2**.

Table 2. Baseline [^{68}Ga]Ga-DOTATATE PET tumor uptake and volumetric parameters

Parameter	Mean ± SD	Median (range)
SUV_{max}	43.7 ± 23.6	37.0 (11.3-131.3)
SUV_{mean}	14.9 ± 5.4	14.4 (5.2-32.0)
TV (mL)	523 ± 694	196 (10-3368)

SUV: standardized uptake value; TV: tumor volume.

First, we evaluated whether our previously identified composite score [14] was able to stratify patients from this cohort into three groups with significantly different survival. As can be seen in **Figure 1**, patients with composite score 2 (elevated IBI and SUV_{mean} equal or lower than 13.7; n = 12) showed a significantly worse survival than the 71 patients in the other two categories (HR 3.27; 95% CI 1.54-6.91; P = 0.001). However, no significant differences in survival were observed between patients with composite score 0 and score 1 (P = 0.67).

Looking at baseline [^{68}Ga]Ga-DOTATATE SUV_{mean} alone, patients with an SUV_{mean} lower or equal than 11.2 (25th percentile) showed a significantly worse OS (HR 2.28; P = 0.008) (**Table 3**; **Figure 2**). Note that a cut-off value of 13.7 was not associated with different OS (P = 0.13). For [^{68}Ga]Ga-DOTATATE-avid TV, all percentile value cut-offs resulted in subgroups with significantly different OS (**Table 3**). The highest HR was reached with the 75th percentile cut-off. A [^{68}Ga]Ga-DOTATATE-avid TV higher than 672 mL was correlated with worse survival (HR 3.13; P = 0.0001) (**Figure 2**). For multivariate analysis only this cut-off value for TV was used.

Tumor grade and primary tumor were not correlated with survival (P = 0.85, 0.93 and 0.86 for G1, G2 and G3, respectively and P = 0.92, 0.16, 0.75 and 0.056 for intestine, pancreas, unknown primary and lung, respectively).

Elevated baseline IBI was associated with worse OS (HR 2.00; P = 0.034) (**Table 3**; **Figure 2**). IBI values after two and four PRRT cycles could be determined for 75 (90.4%) and 52 (62.7%) patients, respectively. After two therapy cycles, 13 patients (17.3%) had a persistently abnormal IBI score, but survival in this group did not differ significantly from patients with normalized IBI (P = 0.089). After end of treatment, 10 patients (19.2%) showed a persistently abnormal IBI value. Survival in this group was lower than in the normalized IBI group (HR 2.52; P = 0.043) (**Table 3**; **Figure 2**).

Results of the multivariate analysis are shown in **Table 3**. Independent associations were observed between OS and all three included parameters: IBI (HR = 2.09; P = 0.032), SUV_{mean} (HR = 2.06; P = 0.027) and [^{68}Ga]Ga-DOTATATE-avid TV (HR = 2.81; P = 0.0001).

Since our previously defined composite score was no longer able to stratify patients from this cohort in three groups with significantly different survival, we evaluated whether adding [^{68}Ga]Ga-DOTATATE-avid TV could result in a better stratification, as this parameter was also found to be independently associated with OS in the present cohort. Patients with normal IBI, an SUV_{mean} value higher than 11.2 and a [^{68}Ga]Ga-DOTATATE-avid TV equal or lower than 672 mL, received score 0. If one condition was no longer met, a score of 1 was assigned, and if two or three conditions were unmet, a score of 2 was given. Similarly to the original composite score (**Figure 1**), the group with the highest score showed a significantly worse survival than patients from the other two groups (HR 3.86; 95% CI 1.96-7.62; P = $3*10^{-5}$), but an important improvement was that the patient category with score 0 had a significantly better survival compared with the other patients combined (HR 0.44; 95% CI 0.24-0.81; P = 0.007) (**Figure 3**). However, OS between patients with score 0 and 1, was still not significantly different (P = 0.14).

Figure 4 shows the survival analysis according to a four-point score combining baseline IBI, SUV_{mean} and [^{68}Ga]Ga-DOTATATE-avid TV. As the group with the highest score and thus worst survival contained only four patients, the Cox proportional-hazards model suffered from a convergence error and did not lead to a meaningful HR calculation.

Discussion

The increasing demand for PRRT in the treatment of patients with disseminated or inoperable well-differentiated NETs, underscores the need for accessible, predictive tools that allow to stratify patients who will benefit from treatment from those who will not. Previously, we have investigated the role of baseline [^{68}Ga]

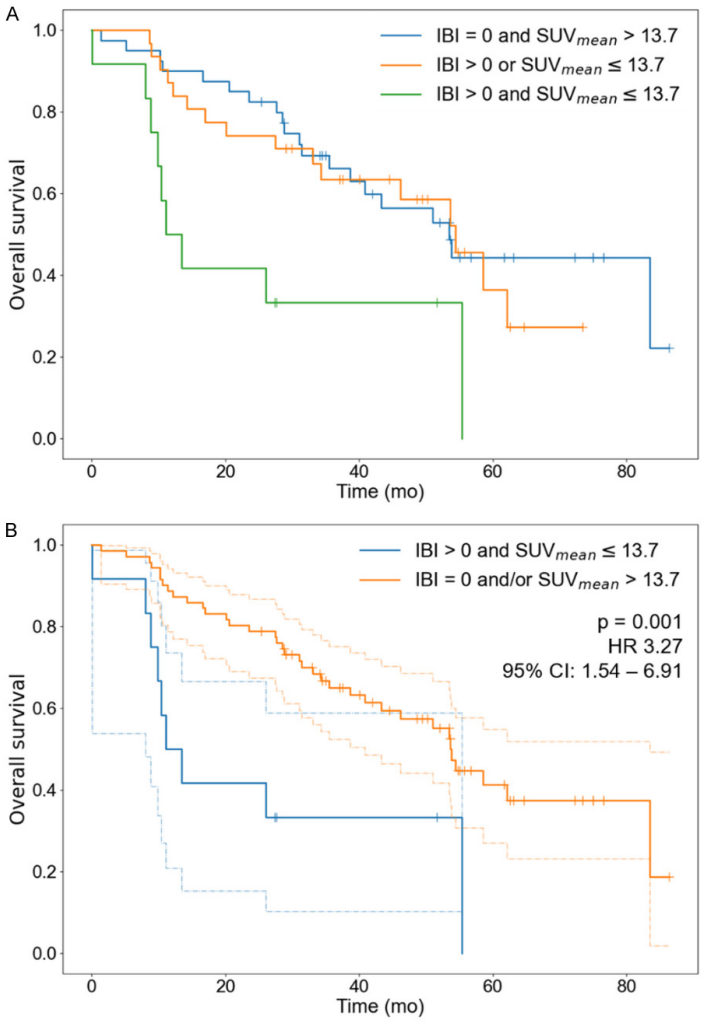

Figure 1. Survival analysis according to a previously identified [14] composite score based on mean standardized uptake value (SUV_{mean}) and inflammation-based index (IBI). Dashed lines represent the 95% confidence interval (CI). HR: hazard ratio.

Ga-DOTATOC PET tumor uptake and volumetric parameters alone, and combined with IBI for outcome prediction in NET patients treated with [^{90}Y]Y-DOTATOC [14]. The aim of this retrospective study was to evaluate whether these findings could be extrapolated to an independent patient cohort treated with [^{177}Lu]Lu-DOTATATE in combination with a pre-therapeutic [^{68}Ga]Ga-DOTATATE PET.

Although our previously defined composite score using baseline IBI and an SUV_{mean} cut-off of 13.7 was able to identify a group of patients with significantly worse survival, this score was no longer able to stratify patients in three different survival groups. This was to be expected, as the SUV_{mean} cut-off of 13.7 alone was not associated with different survival. Instead, a more optimal cut-off of 11.2 could be identified; patients with an SUV_{mean} lower or equal than 11.2 showed significantly worse OS. [^{68}Ga]Ga-DOTATATE has a slightly different SSTR affinity profile compared with [^{68}Ga]Ga-DOTATOC, with a more than tenfold higher affinity for SSTR2 [15], the most abundant SSTR subtype in the majority of NETs [18]. It is therefore not surprising that a [^{68}Ga]Ga-DOTATOC uptake cut-off cannot be straightforwardly extrapolated to [^{68}Ga]Ga-DOTATATE data. Mean SUV_{max} and SUV_{mean} in our previous study were 25.8 ± 10.1 and 11.3 ± 3.6, respectively [14], compared with 43.7 ± 23.6 and 14.9 ± 5.4, respectively, in the current patient cohort. Although a correct comparison across the two different datasets is not straightforward, these data are in line with the higher SSTR2 affinity of [^{68}Ga]Ga-DOTATATE. In the last decade, several authors have reported that high uptake on pre-therapeutic [^{68}Ga]Ga-DOTA-SSA PET was associated with better survival after PRRT, proposing varying cut-off values for SUV_{max} and/or SUV_{mean} [7-11]. However, often slightly different approaches to determine these parameters were used across the different studies and further validation is still lacking. Moreover, other authors observed no additional predictive value of tumor uptake on baseline PET [12, 13]. In light of these findings, PET uptake parameter cut-off values should not be used as the sole basis for PRRT treatment decisions.

In this patient population, [^{68}Ga]Ga-DOTATATE-avid TV was clearly associated with survival, with a volume higher than 672 mL being independently associated with worse OS. Also the other two percentile values resulted in subgroups with different survival, whereas in our previous study only one cut-off, 578 mL (75th percentile), was identified, above which OS was significantly worse, although not confirmed

Table 3. Uni- and multivariate analysis for overall survival according to baseline mean standardized uptake value (SUV_{mean}), tumor volume (TV), inflammation-based index (IBI) and changes in IBI score after 2 or 4 treatment cycles compared with the baseline value

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
$SUV_{mean} \leq 11.2$	2.28 (1.22-4.26)	0.017	2.06 (1.09-3.91)	0.027
TV > 672 mL (*75th percentile*)	3.13 (1.69-5.79)	0.0001	2.81 (1.50-5.25)	0.001
IBI > 0	2.00 (1.04-3.84)	0.034	2.09 (1.07-4.10)	0.032
TV > 98 mL (*25th percentile*)	2.62 (1.11-6.21)	0.023		
TV > 196 mL (*median*)	2.11 (1.15-3.87)	0.014		
Persistently abnormal IBI after 2 cycles	1.91 (0.90-4.07)	0.089		
Persistently abnormal IBI after 4 cycles	2.52 (1.00-6.36)	0.043		

HR: hazard; CI: confidence interval.

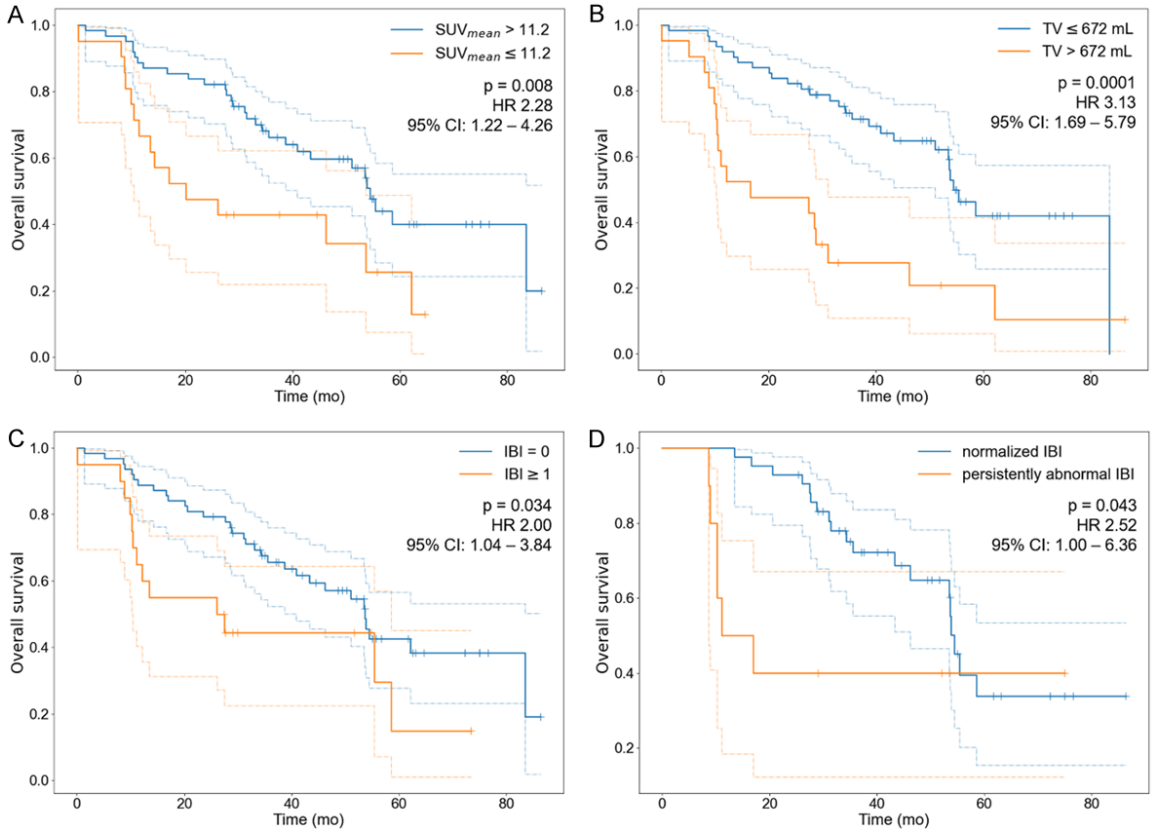

Figure 2. Survival analysis according to baseline (A) mean standardized uptake value (SUV_{mean}), (B) [^{68}Ga]Ga-DOTATATE-avid tumor volume (TV) and (C) inflammation-based index (IBI), and (D) changes in IBI score after 4 treatment cycles compared with the baseline value. Dashed lines represent the 95% confidence interval (CI). HR: hazard ratio.

by multivariate analysis [14]. Nevertheless, the [^{68}Ga]Ga-DOTA-SSA-avid TV values in both study populations were of the same order of magnitude. A prospective study by Tirosh et al. [19] in a general population of 184 patients with NETs, reported that a [^{68}Ga]Ga-DOTATATE-avid TV of 35.8 mL or more was independently associated with higher disease specific mortality. Therefore, [^{68}Ga]Ga-DOTA-SSA-avid TV should be considered as a prognostic factor, but to establish a potential role for PRRT patient stratification, further studies in PRRT patient populations only are warranted.

An elevated baseline IBI was independently associated with worse survival, in line with our

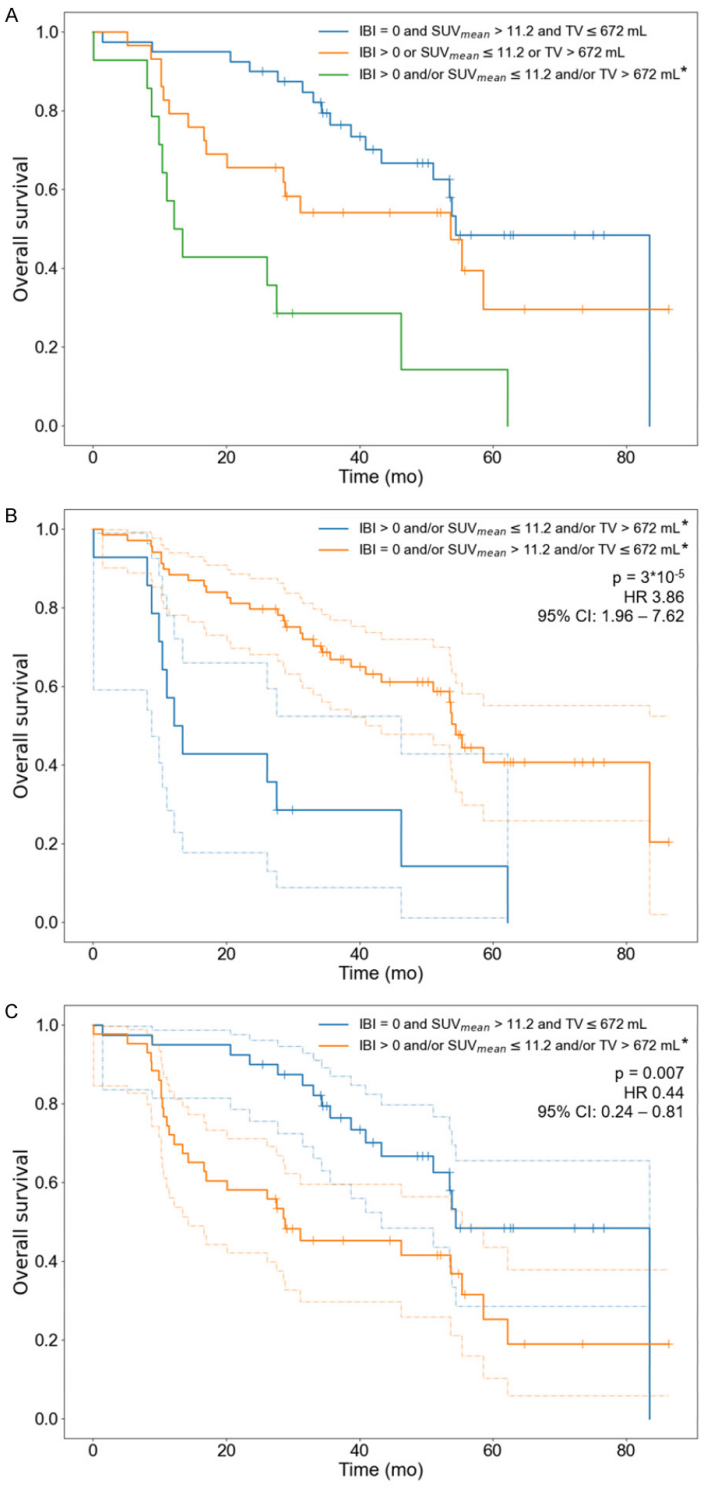

Figure 3. Survival analysis according to a composite score based on baseline inflammation-based index (IBI), mean standardized uptake value (SUV_{mean}) and [^{68}Ga]Ga-DOTATATE-avid tumor volume (TV). Dashed lines represent the 95% confidence interval (CI). HR: hazard ratio. *At least two out of three conditions have to be met.

previous findings [14] and those of Black et al. [5]. Patients with a persistently abnormal IBI after four treatment cycles showed worse survival compared with patients with normalized IBI. No significant differences were observed after two PRRT cycles, in contrast to Black et al. [5] who reported that persistently elevated IBI after the second and fourth cycle were correlated with worse PFS and OS. Therefore, we recommend not to use this parameter as the sole basis for treatment discontinuation. Nevertheless, because of the accessibility of this biomarker and its ease of use, it can be readily included in the pre-therapeutic assessment.

Tumor grade and location of the primary tumor were not associated with survival. However, the small number of patients in several subgroups might have masked correlations. For instance, in a large retrospective study in 610 patients treated with [^{177}Lu]Lu-DOTATATE, patients with pancreatic NETs showed the longest OS [20]. Moreover, regarding tumor grade, histological data for most patients dated from several years before PRRT treatment. As tumor grade may evolve over time, it is likely that several patients were classified into a lower grade that no longer reflected their disease state at the time of PRRT.

Finally, we evaluated an alternative composite score based on results from the current patient cohort, combining baseline IBI with an SUV_{mean} cut-off of 11.2 and [^{68}Ga]Ga-DOTATATE-avid TV with a cut-off of 672 mL. This new score showed significant improvement compared to our original score based on the [^{68}Ga]Ga/[^{90}Y]Y-DOTATOC dataset, as it was not only able to identify a patient group with the worst survival, but also a group with the best survival. However, when only comparing patients from the groups with score 0 and score 1, survival was no longer significantly different. Although baseline IBI, SUV_{mean} and [^{68}Ga]Ga-DOTATATE-

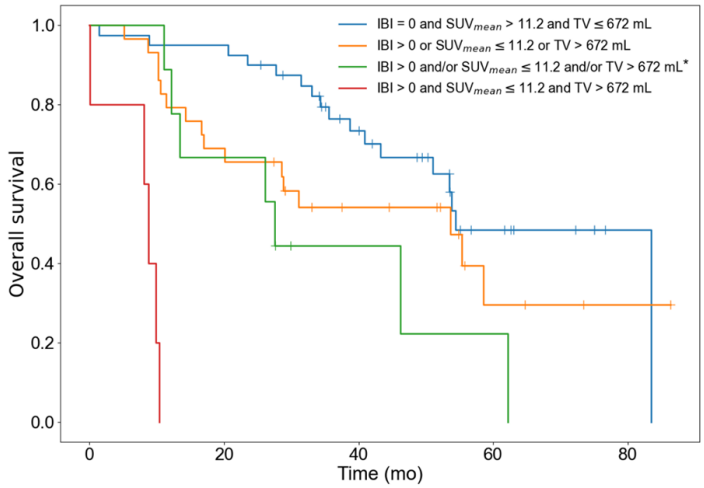

Figure 4. Survival analysis according to a four-point composite score combining baseline inflammation-based index (IBI), SUV$_{mean}$ and [^{68}Ga]Ga-DOTATATE-avid TV. *Two out of three conditions have to be met.

avid TV show prognostic utility, based on these findings, we would not suggest to use cut-off values for these parameters as threshold to withhold patients from PRRT treatment. Nevertheless, taking these factors into account within the complete pre-therapeutic work-up could improve the process of making PRRT treatment decisions. For instance, in patients showing a combination of low baseline SUV$_{mean}$, high [^{68}Ga]Ga-DOTATATE-avid TV and elevated IBI, survival is likely limited even if PRRT is started and rapidly moving to chemotherapy or, if logistics allow it, to chemo-PRRT treatment regimens [21], should be discussed in a multidisciplinary setting. Furthermore, after further validation, they could be used as stratification factors in future randomized controlled trials.

Limitations of this study include the retrospective nature of the analyses and the heterogeneity of the study population. However, the latter may also be considered as a reflection of actual clinical practice. Another important limitation is the fact that [^{68}Ga]Ga-DOTATATE PET images were obtained with three different PET cameras using slightly different reconstruction protocols. This is again a reflection of actual clinical practice as new PET cameras came into use at our nuclear medicine facility, but it might have induced some minor variability in tumor delineation and derivation of quantitative PET parameters. More importantly, as has come to attention by Bailey et al. [22], systemic miscalibrations of PET systems occur, with SUV deviations of around 15%. Such miscalibrations from the PET systems in the past at our center may not be excluded. It is therefore reasonable to take into account a conservative potential error on reported SUV values of around 15%. However, as we already advised against using strict SUV cut-off values for deselecting PRRT candidates, the effect of such a potential quantitative error is deemed negligible. Nevertheless, one might expect that a standardized approach, e.g. in terms of calibration and reconstruction protocols, may have the potential to enhance the accuracy and statistical power of such an analysis.

Conclusion

Elevated baseline IBI, low baseline SUV$_{mean}$ (≤ 11.2) and high [^{68}Ga]Ga-DOTATATE-avid TV (> 672 mL) were independently associated with worse survival in NET patients treated with [^{177}Lu]Lu-DOTATATE. The information obtained from these parameters combined may be useful to include in the pre-therapeutic assessment to help guide decisions for PRRT treatment and might be used to stratify patients in prospective PRRT trials. The utility of dichotomized PET uptake and TV cut-off values alone for patient stratification is limited.

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This study was approved by the Ethics Committee Research UZ/KU Leuven (S64247). The need for written informed consent from each

patient was waived because of the retrospective design.

Disclosure of conflict of interest

Chris Verslype has received research grants and performed consultancy services for Novartis, Ipsen and Bayer outside the submitted work. Paul M Clement has received study budget funds from AstraZeneca and was advisory board member for AbbVie, AstraZeneca, Bayer, BMS, Daiichi-Sankyo, Leo Pharma, Merck Serono, MSD, Rakuten, Takeda, and Vifor Pharma outside the submitted work. Eric Van Cutsem has received research grants and personal fees for consultancy from Amgen, Bayer, Boehringer Ingelheim, Celgene, Ipsen, Lilly, Roche, Merck Sharp & Dohme, Merck KGaA, Novartis, Roche and Servier outside the submitted work. Christophe M Deroose has been a consultant for Terumo, Ipsen, Sirtex, Bayer and PSI CRO outside the scope of the submitted work. There are no other conflicts of interest.

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