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^{68}Ga-DOTATATE Positron Emission Tomography-Computed Tomography Quantification Predicts Response to Somatostatin Analog Therapy in Gastroenteropancreatic Neuroendocrine Tumors

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. ^{68}Ga-DOTATATE • Positron emission tomography • Computed tomography • Octreotide • Lanreotide • Gastroenteropancreatic neuroendocrine tumor

Abstract

Background. Somatostatin analogs (SSAs) are the frontline antitumor therapy in advanced well-differentiated gastroenteropancreatic neuroendocrine tumors (GEP-NETs). A subset of patients demonstrate early disease progression on SSA therapy, yet the currently known predictors for treatment failure lack specificity to affect therapeutic decision. SSAs target tumor somatostatin receptors, the level of which can be quantitatively assessed with ^{68}Ga-DOTATATE positron emission tomography-computed tomography (PET/CT). We investigated the ability of ^{68}Ga-DOTATATE PET/CT to predict response to SSA therapy.

Materials and Methods. The records of 108 consecutive patients with well-differentiated grade 1–2 GEP-NETs on SSA monotherapy who received ^{68}Ga-DOTATATE PET/CT scans were retrospectively reviewed to obtain baseline characteristics, ^{68}Ga-DOTATATE maximum standardized uptake value (SUVmax), and progression-free survival (PFS) data. The optimal SUVmax cutoff for patient stratification was obtained with receiver operating characteristic curve analysis. PFS in the high versus low SUVmax groups was compared with Kaplan-Meier survival analysis. The effects of baseline characteristics and SUVmax on PFS were examined with univariate and multivariate Cox regression.

Results. ^{68}Ga-DOTATATE SUVmax predicted therapeutic failure with sensitivity and specificity of 39% and 98%, respectively. SUVmax of <18.35 was associated with shorter PFS, which was reproduced in the subgroup analysis of SSA-naïve patients. Low SUVmax was the only predictor of early treatment failure (hazard ratio, 6.85) in multivariate analysis, as well as in the subgroup analysis of grade 2 GEP-NETs.

Conclusion. Low SUVmax on ^{68}Ga-DOTATATE PET/CT independently predicts early failure on SSA monotherapy in patients with well-differentiated grade 1–2 GEP-NET. Patients with lack of expected benefit from SSA therapy can be readily identified using routine ^{68}Ga-DOTATATE PET/CT with very high specificity. ***The Oncologist*** 2021;26:21–29

Implications for Practice: Based on ^{68}Ga-DOTATATE positron emission tomography-computed tomography imaging, clinicians can better inform patients on the expected benefit of somatostatin analog therapy for gastroenteropancreatic neuroendocrine tumors, especially when access to the therapy is difficult, and offer proactive discussion on alternative management options.

Introduction

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) represent approximately two thirds of neuroendocrine tumors (NETs) in adults, and 40%–50% of patients initially present with metastatic disease [1, 2]. Somatostatin analogs (SSAs), including octreotide and lanreotide, are used for treatment of advanced well-differentiated GEP-NETs and

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currently remain as the standard frontline antitumor therapy in this patient population despite the evolving role of peptide receptor radionuclide therapy (PRRT) and other therapeutics [3]. Although the response rate of SSA therapy remains low, treatment with these agents leads to disease stabilization in approximately two thirds of patients [4, 5]. There is, however, a subset of patients who demonstrate early disease progression on SSA therapy [6]. Previous studies for characterization of such patients identified several factors predictive of early treatment failure, including pancreatic primary tumor or fast tumor growth rate [7, 8], but none of the factors was specific enough to describe more than a tendency toward lack of response [6].

Because SSAs target tumor somatostatin receptors for their antitumor effect, it is common to perform baseline somatostatin receptor imaging such as ^{111}In-pentetreotide scintigraphy or ^{68}Ga-DOTATATE positron emission tomography-computed tomography (PET/CT) before SSA therapy is initiated. The literature supporting this practice includes the placebo-controlled PROMID and CLARINET trials, which demonstrated the efficacy of SSA therapy with patients with mostly ^{111}In-pentetreotide–positive GEP-NET [4, 5], as well as a previous study that showed a higher response rate to SSAs in patients with GEP-NET with positive ^{111}In-pentetreotide scan [9].

^{68}Ga-DOTATATE PET/CT scan, approved by the U.S. Food and Drug Administration in 2016, has revolutionized somatostatin receptor imaging with its superior spatial resolution and reduced scan time, as well as high sensitivity and specificity compared with the ^{111}In-pentetreotide imaging, with impact on patient management [10–13]. Along with its analogs ^{68}Ga-DOTATOC and ^{68}Ga-DOTANOC, it has become the current gold standard of functional imaging for well-differentiated NETs [14]. In contrast to ^{111}In-pentetreotide scintigraphy, ^{68}Ga-DOTATATE PET/CT provides quantitative information on tumor somatostatin receptor status in the form of standardized uptake values (SUVs), which correlate with somatostatin receptor expression levels on pathology [15].

SUVs on ^{68}Ga-DOTANOC PET/CT have overall prognostic value in the general GEP-NET population [16–18]. More recently, higher SUVs on ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE PET/CT were found to predict response to PRRT [19, 20]. However, the role of quantitative radiotracer uptake measurements in predicting response to SSA therapy remains unclear. In the present study, we hypothesized that tumor uptake on ^{68}Ga-DOTATATE PET/CT measured by SUV can predict response to SSA therapy in well-differentiated GEP-NETs.

Materials and Methods

Study Population

Approval from the University of Pennsylvania Institutional Review Board was obtained prior to the study, and the requirement for informed consent was waived. The medical records of 528 consecutive patients who received ^{68}Ga-DOTATATE PET/CT scans at the University of Pennsylvania Health System from December 2016 to September 2018 were retrospectively reviewed. A final 108 patients with a pathologically confirmed diagnosis of well-differentiated grade 1–2 GEP-NETs treated with long-acting depot SSA monotherapy (octreotide long-acting release or lanreotide) were included in the study. At least 3 months of clinical follow-up involving cross-sectional imaging was required for enrollment. Patients managed with active surveillance, surgery, PRRT, liver-directed therapy, or other systemic antitumor therapy for GEP-NET were excluded from the study. Patients with active secondary malignancy, including NET from non-gastroenteropancreatic origin, were excluded.

Review of ^{68}Ga-DOTATATE PET/CT

At least 3 weeks after the last SSA therapy, patients were given intravenous administration of ^{68}Ga-DOTATATE at a dose of 2 MBq/kg up to 200 MBq. No patients received short-acting SSA around the time of their scan. Static positron emission tomography images were acquired from the skull base to midthigh 60 minutes after the radiotracer administration. An accompanying low-dose non–contrast-enhanced computed tomography was performed for attenuation correction and anatomic colocalization. Image processing and SUV measurements were performed retrospectively using MIM version 6 (MIM Software Inc., Cleveland, OH). SUV was corrected for total body weight. The maximum SUV (SUVmax) for each patient was defined as the highest SUV among primary and metastatic lesions.

Patient Assessments

The baseline clinical, pathologic, and laboratory characteristics of eligible patients were collected. Patients were then stratified based on gender, age, primary tumor site, tumor grade, Ki67 index, mitotic count, germline mutation status, tumor functionality, serum chromogranin A level, 24-hour urine 5-hydroxyindoleacetic acid (5-HIAA) level, and exposure to SSA therapy prior to the ^{68}Ga-DOTATATE scan. Ki67 index cutoff of 5% was used as described previously [16, 17, 21]. Tumor functionality was determined based on presence of carcinoid syndrome for gastrointestinal tumors and overproduction of functionally active peptides for pancreatic tumors.

Progression-free survival (PFS) was measured from the time of ^{68}Ga-DOTATATE scan for patients with prior SSA exposure and from the time of SSA therapy initiation for SSA-naïve patients. PFS was evaluated radiologically according to RECIST version 1.1 [22].

Statistical Analysis

The patients were grouped according to their baseline characteristics, and the mean SUVmax among the groups was compared using one-way analysis of variance (ANOVA). Log transformation of SUVmax was used for ANOVA to induce normality. The magnitude of difference in SUVmax was estimated by taking the antilog transformations of the ANOVA results and expressing them as percentages.

A receiver operating characteristic (ROC) curve was then constructed to determine the optimal SUVmax cutoff for predicting disease progression by 12 months. The area under the curve (AUC) was computed, and the optimal cutoff value was identified using the maximum likelihood estimation method [23]. Based on the cutoff, all

108 patients were stratified into high SUVmax and low SUVmax groups.

PFS in the high versus low SUVmax groups was compared with Kaplan-Meier survival analysis using the Mantel-Cox test. In addition, the effects of baseline characteristics and SUVmax on PFS were examined using univariate and multivariate Cox regression with 5% entry probability and 10% removal probability.

Using the same SUVmax cutoff, the PFS analysis was repeated on the subgroup of SSA-naïve patients. In another subgroup analysis of patients with grade 2 tumors, the predictive value of SUVmax was compared with that of Ki67 index cutoff of 10% as proposed previously [5, 21, 24].

All statistical tests were two-sided, and *p* values less than .05 were considered statistically significant. The statistical analyses were performed using GraphPad Prism 7 (GraphPad Software, San Diego, CA), except for Cox regression, which was performed with SPSS Premium 25 (SPSS Inc., Chicago, IL).

Results

Patient Characteristics

The baseline characteristics of the study population are summarized in Table 1. Eighty-one patients (75%) were men, and twenty-seven (25%) were women, with a median age of 60 (range, 27–85). All patients had metastatic disease, and there were more patients with gastrointestinal (75%) than pancreatic (25%) primary tumors. There were a similar number of patients with grade 1 (54%) versus grade 2 (46%) tumors. The median Ki67 index and mitotic count were 1% and 0 per 10 high-power fields (HPFs) for grade 1 tumors and 5.6% and 1 per 10 HPFs for grade 2 tumors, respectively. Nine patients (8%) harbored NET-related germline mutations, all of which involved the *MEN1* gene. Forty-nine patients (45%) had functioning tumors, six of which were pancreatic in origin (four gastrinomas, one glucagonoma, and one VIPoma). Serum chromogranin A and 24-hour urine 5-HIAA levels were elevated in 68% and 34% of patients, respectively. Thirty patients (28%) were SSA naïve at the time of the ^{68}Ga-DOTATATE scan.

Effect of Baseline Characteristics on SUVmax

The means and SDs of SUVmax among different groups of patients are shown in Table 1. SUVmax was 72.1% higher (95% confidence interval [CI], 57.1%–88.4%; $p < .001$) in pancreatic compared with gastrointestinal NETs. However, SUVmax did not vary with any other baseline characteristics, including gender ($p = .56$), age ($p = .72$), tumor grade ($p = .36$), Ki67 index ($p = .97$), mitotic count ($p = .58$), germline mutation status ($p = .89$), tumor functionality ($p = .16$), tumor marker levels ($p = .24$–0.87), and prior SSA therapy ($p = .69$).

Follow-Up

From the time of ^{68}Ga-DOTATATE scan, the median duration of clinical follow-up was 16 months (range, 3–24 months). Probability of freedom from progressive disease at 6, 12, and 18 months, reported as mean ± SEM, was 90.9 ± 2.9%, 80.0 ± 4.3%, and 60.8 ± 6.3%, respectively (Fig. 1A). There was no difference in PFS between gastrointestinal and pancreatic primary tumors ($p = .50$; Fig. 1B). Overall, 30 patients (27.5%) demonstrated disease progression by the last follow-up, with median PFS of 8.5 months among them.

ROC Curve Analysis

The ROC curve of ^{68}Ga-DOTATATE SUVmax for predicting disease progression is shown in Figure 2 (AUC = 0.66, $p = .043$ for AUC $\neq 0.5$). The optimal SUVmax cutoff determined was 18.35, yielding the maximum likelihood ratio of 21.4. The sensitivity and specificity for disease progression within 12 months based on SUVmax <18.35 were 38.9% (95% CI, 22.7%–58.0%) and 98.2% (95% CI, 92.3%–99.8%), respectively.

Progression-Free Survival Analysis

The Kaplan-Meier survival analysis revealed significantly shorter PFS in the low SUVmax group compared with the high SUVmax group ($p < .0001$; Fig. 3A) in the overall study population, with median PFS of 6.6 versus >24 months, respectively (median follow-up, 6.4 vs. 13.3 months). This trend was reproduced in the subgroup analysis of 30 SSA-naïve patients ($p = .019$; Fig. 3B), with median PFS of 5.7 versus >19 months, respectively (median follow-up, 4.4 vs. 10.7 months).

On univariate Cox regression analysis, higher tumor grade ($p = .002$), Ki67 index ($p = .010$), and mitotic count ($p = .007$), as well as low SUVmax ($p < .001$) and no prior SSA therapy ($p = .034$), were identified as predictors of early failure on SSA monotherapy (Table 2). However, only SUVmax <18.35 remained statistically significant on multivariate analysis with hazard ratio (HR) of 6.85 (95% CI, 2.10–22.34; $p = .001$). When the multivariate analysis was repeated with a different ^{68}Ga-DOTATATE SUVmax cutoff of 21.6, which was previously demonstrated to predict response to PRRT [19], similar results were obtained with an HR of 5.31 (95% CI, 1.63–17.33, $p = .006$).

In the subgroup of 46 patients with grade 2 tumors, Kaplan-Meier survival analysis also revealed shorter PFS with SUVmax <18.35 ($p = .006$; Fig. 4A), with median PFS of 6.7 versus 17.3 months in low versus high SUVmax groups, respectively (median follow-up, 6.4 vs. 11.2 months). In contrast, there was no statistically significant difference in PFS when the patients with grade 2 tumors were stratified based on Ki67 index cutoff of 10% ($p = .38$; Fig. 3B). Similarly, univariate Cox regression showed that SSA therapy failure was associated with SUVmax <18.35 (HR, 3.65; 95% CI, 1.35–9.87; $p = .011$), but not with Ki67 index cutoff of 10% ($p = .380$). Therefore, Ki67 index had no further value in predicting response to SSA monotherapy among patients with grade 2 GEP-NET, whereas SUVmax remained informative.

Discussion

In the present study, we evaluated the utility of SUV measurements on ^{68}Ga-DOTATATE PET/CT for predicting progression-free survival on SSA therapy in patients with well-differentiated GEP-NET. SUVs in pancreatic NETs were

Table 1. SUVmax among different groups of 108 patients with gastroenteropancreatic neuroendocrine tumors on SSA monotherapy

Baseline characteristics	Patients, *n*	Mean SUVmax ± SD	*p* value[a]	Effect size[b] (95% CI)
Gender				
Male	81	57.9 ± 39.5	.56	
Female	27	55.0 ± 40.5		
Age, years				
≤50	20	63.8 ± 45.1	.72	
<50 and ≤60	38	56.0 ± 39.2		
<60 and ≤70	32	53.2 ± 39.2		
>70	18	53.7 ± 38.8		
Tumor site				
Gastrointestinal tract	81	45.8 ± 28.4	<.001	72.1% (57.1–88.4%)
Pancreas	27	87.6 ± 52.0		
Tumor grade				
1	53	57.7 ± 38.2	.36	
2	46	56.1 ± 44.3		
Ki67 index				
≤5%	61	52.8 ± 35.6	.97	
>5%	26	59.8 ± 49.2		
Mitotic count				
<2 per 10 HPFs	55	55.5 ± 39.8	.58	
≥2 per 10 HPFs	22	59.9 ± 39.0		
Germline mutation				
Yes	9	53.5 ± 36.9	.89	
No	99	56.5 ± 40.3		
Functioning tumor				
Yes	49	62.7 ± 31.7	.16	
No	59	48.5 ± 44.9		
Chromogranin A				
Normal (≤95 ng/mL)	34	63.0 ± 46.0	.87	
Elevated (>95 ng/mL)	71	53.4 ± 37.0		
Urine 5-HIAA				
Normal (≤15 mg/day)	39	53.6 ± 38.2	.24	
Elevated (>15 mg/day)	20	40.8 ± 20.8		
SSA naïve				
Yes	30	53.0 ± 36.1	.69	
No	78	57.5 ± 41.4		

[a]Comparisons among groups were made using one-way analysis of variance (ANOVA) on log-transformed SUVmax data.
[b]Effect size was estimated by taking antilog transformations of the ANOVA results.
Abbreviations: 5-HIAA, 5-hydroxyinidoleacetic acid; CI, confidence interval; HPF, high-power field; SSA, somatostatin analog; SUVmax, maximum standardized uptake value.

higher than those of gastrointestinal NETs, as previously found with both ^{68}Ga-DOTANOC and ^{68}Ga-DOTATATE [16, 24]. The finding is in accordance with the higher expression levels of somatostatin receptor subtype 2 (SSTR2) in pancreatic NETs [25], as ^{68}Ga-DOTATATE is a specific ligand for SSTR2 and its degree of uptake is strongly correlated with tumor SSTR2 content [26, 27]. The lack of variation in SUVmax with the other baseline characteristics suggests that ^{68}Ga-DOTATATE PET/CT is an independent source of clinical information in the patient population.

The high specificity (98.2%) for treatment failure predicted by low SUVmax illustrates that a sufficient level of SSTR2 expression is a requirement for successful SSA therapy even among SSTR2-positive tumors, as previously found histopathologically [28]. On the other hand, the relatively lower sensitivity (38.9%) of the SUVmax cutoff can be explained by two factors. First, the SUVmax only takes into account the tumor with the highest SSTR2 level in a given patient, and heterogeneity of SSTR2 expression may lead to local SSA therapy failure even in the setting of high

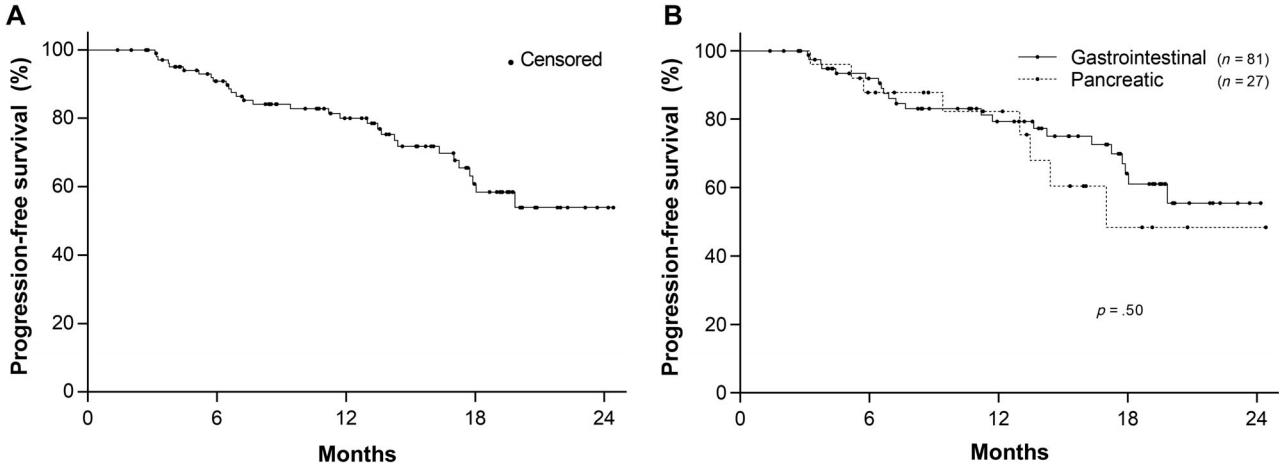

Figure 1. Kaplan-Meier plot of progression-free survival in 108 patients with grade 1–2 gastroenteropancreatic neuroendocrine tumors on somatostatin analog monotherapy. **(A):** Probability of progression-free survival at 6, 12, and 18 months was 90.9% ± 2.9%, 80.0% ± 4.3%, and 60.8% ± 6.3%, respectively (mean ± SEM). **(B):** There was no significant difference in progression-free survival between the primary tumor sites (p = .50).

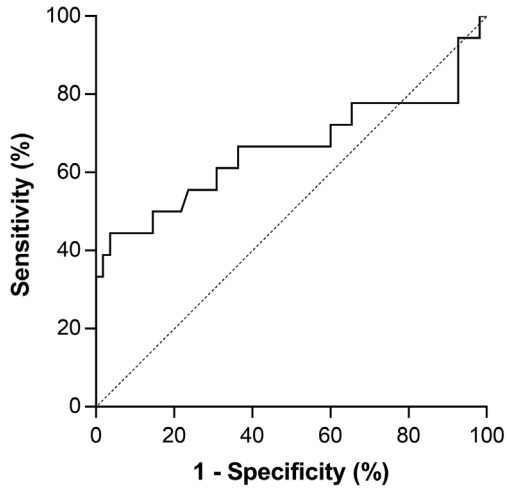

Figure 2. Receiver operating characteristic curve of ^{68}Ga-DOTATATE maximum standardized uptake value (SUVmax) for predicting disease progression within 12 months. Sensitivity and specificity obtained using the best cutoff value (SUVmax <18.35, likelihood ratio = 21.4) were 38.9% and 98.2%, respectively. Area under the curve (AUC) = 0.66 with p = .043 for AUC ≠ 0.5.

SUVmax. Second, resistance to SSA therapy may result from multiple biological mechanisms downstream of receptor-ligand binding, which would decouple tumor ^{68}Ga-DOTATATE uptake and efficacy of SSA therapy [29]. Therefore, the biological basis of SSA therapy explains the observation that meeting the threshold SUVmax is a necessary, but not sufficient, condition for response to SSA therapy.

We found a statistically significant difference in PFS based on the SUVmax cutoff, and a closer look at the PFS suggests potential futility of SSA therapy in the low SUVmax group. The PFS of 5.7 months we found in the low SUVmax group is comparable to or shorter than the placebo arm PFS of 6 months and 18 months in the PROMID and CLARINET studies, respectively [4, 5]. On the other hand, the PFS of >24 months in the high SUVmax group is longer than or comparable to the treatment arm PFS of the two studies (14.3 months and >24 months). Hence, the short PFS in the low SUVmax group we found may represent complete lack of response to SSA therapy rather than early treatment failure.

SSA therapy is generally well tolerated, with relatively minor side effects mostly involving the gastrointestinal system, such as diarrhea and flatulence [5, 30]. However, serious adverse events related to SSA therapy and subsequent study withdrawal were noted in both PROMID and CLARINET studies [4, 5]. A perhaps larger drawback of SSA therapy is the associated cost. A 2017 U.S.-based analysis estimated the total cost of SSA therapy, including management of adverse effects, at $74,566 for octreotide and $84,856 for lanreotide during the first year of treatment [31]. Such prohibitive cost makes access to SSA therapy difficult. Furthermore, because it takes about 6 months to detect progression on a futile therapy in this relatively indolent disease, typically at least half of the first year's cost will be incurred even without any clear benefit. Therefore, in the setting of likely lack of benefit, the time and resources required for initiation, maintenance, and monitoring of SSA therapy may be directed toward proactive discussion of alternative therapy options. Therefore, identifying the group of patients with minimal to no expected benefit from SSA therapy has critical value in the management of patients with GEP-NET.

The results of the multivariate regression analysis suggest that the best estimator for identification of such a group of patients is SUVmax on ^{68}Ga-DOTATATE PET/CT. Although the pathologic variables (tumor grade, Ki67 index, and mitotic count) were also able to predict response to SSA on univariate analysis, their statistical significance was lost on multivariate analysis. Similarly, SUVmax on ^{68}Ga-DOTANOC PET/CT was previously identified as an independent overall prognostic marker superior to the pathologic variables [16, 17]. Interestingly, lack of prior SSA therapy also predicted early failure on SSA therapy on univariate analysis. This finding is likely attributed to

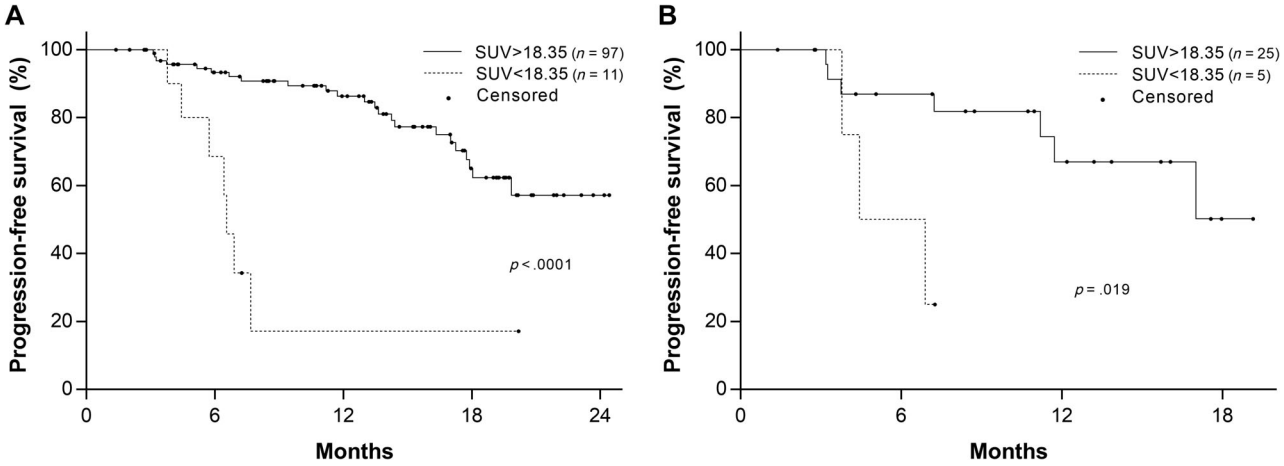

Figure 3. Kaplan-Meier plots of progression-free survival in patients with grade 1–2 gastroenteropancreatic neuroendocrine tumors on somatostatin analog (SSA) monotherapy based on ^{68}Ga-DOTATATE maximum SUV (SUVmax) cutoff of 18.35. Progression-free survival was significantly shorter in the low SUVmax group, both among all 108 patients (p < .0001 on Mantel-Cox test) **(A)** and among 30 SSA-naïve patients (p = .019) **(B)**.
Abbreviation: SUV, standardized uptake value.

Table 2. Risk/protective factors for disease progression in patients with gastroenteropancreatic neuroendocrine tumors on SSA monotherapy

	Univariate		Multivariate[a]	
Parameter	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
Gender (male vs. female)	1.35 (0.66–2.77)	.412		
Age (increasing)	1.07 (0.75–1.53)	.695		
Site of primary tumor (GI vs. pancreas)	0.76 (0.34–1.70)	.499		
Grade (1 vs. 2)	0.27 (0.12–0.61)	.002		
Ki67 (≤5% vs. >5%)	0.37 (0.17–0.81)	.010		
Mitotic count (<2 vs. ≥2 per 10 HPFs)	1.17 (1.04–1.31)	.007	NA	
Germline mutation (yes vs. no)	1.63 (0.49–5.47)	.428		
Functioning tumor (yes vs. no)	0.64 (0.31–1.32)	.220		
Chromogranin A (normal vs. elevated)	0.91 (0.42–1.97)	.805		
Urine 5-HIAA (normal vs. elevated)	1.32 (0.43–4.06)	.627	NA	
SSA naïve (yes vs. no)	2.33 (1.06–5.12)	.034		
SUVmax (<18.35 vs. ≥18.35)	4.15 (1.88–9.15)	<.001	6.85 (2.10–22.34)	.001

[a]Only statistically significant (p < .05) results are reported for multivariate analysis.
Abbreviations: 5-HIAA, 5-hydroxyinidoleacetic acid; CI, confidence interval; GI, gastrointestinal; HPF, high-power field; HR, hazard ratio; NA, not applicable (not included in multivariate analysis because of inconsistent reporting); SSA, somatostatin analog; SUVmax, maximum standardized uptake value.

selection bias, because the patients already on SSA therapy represent those without prior evidence of treatment failure. The unique role of ^{68}Ga-DOTATATE PET/CT in predicting response to SSA therapy was also demonstrated in comparison with Ki67 index in the subgroup analysis of patients with grade 2 GEP-NET.

The most notable clinical implication of the present study is prediction of treatment failure with very high specificity, which has not been possible with previously known predictive factors [6]. With increasing integration of ^{68}Ga-DOTATATE PET/CT into the initial workup of patients with well-differentiated GEP-NET, SUVmax for a given patient can be easily obtained without demand for additional resources. The subgroup analysis of SSA-naïve patients demonstrates the utility of using ^{68}Ga-DOTATATE PET/CT as a screening measure prior to initiating SSA therapy, as is routinely done for PRRT currently. We also found that ^{68}Ga-DOTATATE SUVmax can be used to guide therapy for all patients including those currently on SSA, in accordance with a previous study that demonstrated no significant change in mean and maximum ^{68}Ga-DOTATATE SUVs with SSA therapy in both primary and metastatic lesions [32].

A major limitation of using SUVmax cutoff to predict response to SSA therapy is variability in SUV measurements. Previously, somatostatin receptor–targeted PET/CT in patients with GEP-NET showed temporal variability in tumor SUVmax measurements within 25% [33, 34]. Across imaging sites, ^{18}F-fluorodeoxyglucose–based studies revealed practical

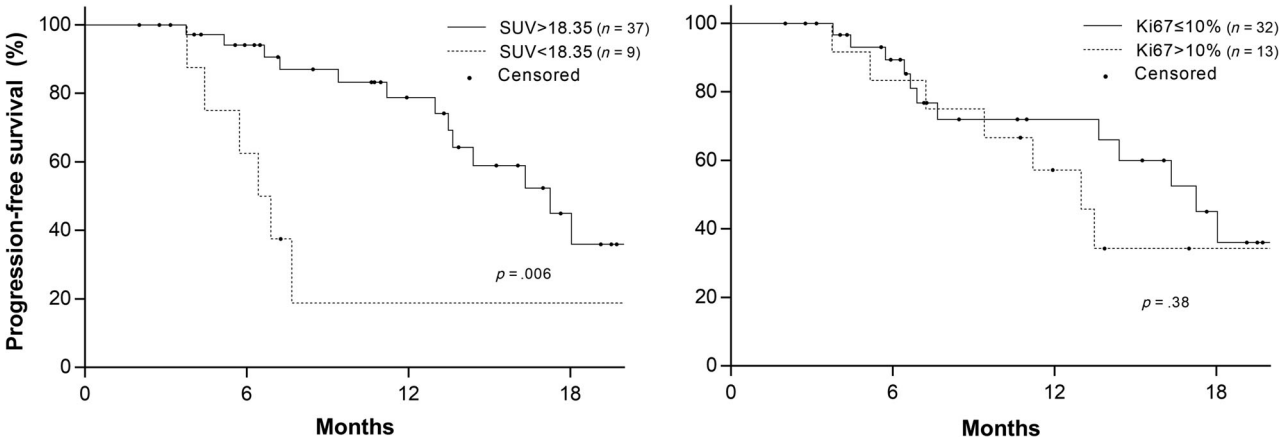

Figure 4. Kaplan-Meier plots of progression-free survival among 46 patients with grade 2 gastroenteropancreatic neuroendocrine tumors on somatostatin analog monotherapy. **(A):** Maximum SUV (SUVmax) <18.35 predicted early disease progression (p = .006 on Mantel-Cox test) with hazard ratio of 3.65 (95% confidence interval: 1.35–9.87, p = .011) on univariate Cox regression. **(B):** Stratification according to Ki67 index cutoff of 10% (excluding one patient with missing value) did not reveal statistically significant differences in progression-free survival (p = .38).
Abbreviation: SUV, standardized uptake value.

variability in SUVmax measurements of at least 15%–20% [35]. Therefore, the SUVmax cutoff used for possibly withholding SSA therapy should include a margin of safety to account for this variability. In addition, the treatment risk-benefit discussion with patients based on ^{68}Ga-DOTATATE uptake should involve disclosure of the variability in SUVmax measurements.

Despite the variability, the SUVmax cutoff of 18.35 we found is similar to those of previous studies for prediction of overall prognosis and response to PRRT. Campana et al. and Sharma et al. each found the best ^{68}Ga-DOTANOC SUVmax cutoff of 17.9–19.3 and 14.5, respectively, to be an overall prognostic marker in the general GEP-NET population [16, 17]. Previously proposed cutoff for predicting response to PRRT was 16.4 for ^{68}Ga-DOTANOC and 21.6 for ^{68}Ga-DOTATATE [19, 20]. Although Koch et al. reported a relatively higher SUVmax cutoff of 29.35 for predicting response to octreotide therapy [36], the difference is mainly attributed to the ROC curve analysis method. In our study, we prioritized specificity over sensitivity in order to minimize withholding of potentially beneficial SSA therapy, whereas Koch et al. aimed to maximize the overall accuracy of response prediction. By minimizing the distance to the upper left corner of the ROC curve, we can also obtain a similar SUVmax cutoff of 33.10 with sensitivity and specificity of 61% and 69%, respectively. Overall, we believe clinical implementation of SUVmax cutoff would be feasible, especially considering routine use and clinical utility of Ki67 index despite its substantial variability at intralesional, interlesional, temporal, and interlaboratory levels [37–40].

SUVmax measurements are also significantly affected by tumor volume. Partial volume effects in small lesions results in falsely low SUVmax measurements and therefore compromise the specificity of predicting SSA therapy failure. However, we were able to maintain very high specificity in our study, likely because of the limited role of small lesions in radiologic response assessment and sufficient number of large lesions in the patients to capture the overall tumor behavior with SUVmax, especially because we considered only the single highest SUV value in each patient [41]. Also, uptake in normal organs can be falsely low in patients with large tumor burden because of sink effect [42]. Nevertheless, global tumor SUVmax in a given patient increases with the total ^{68}Ga-DOTATATE avid tumor volume [43], explained by the wider range of SUVs offered by the larger number of lesions. The patients with larger tumor volume and SUVmax progress faster naturally [43], but the longer PFS we observed in our study suggests efficacy of SSA therapy that trumps natural disease progression in this group of patients. Because tumor volume remains as a potential source of bias, combined use of tumor volume and SUVmax cutoffs in a larger number of patients may lead to more accurate response prediction to SSA therapy.

Although the present study was conducted retrospectively, stratification of patients into low versus high SUVmax groups cannot be random, and the patients were enrolled consecutively in the order they were scanned. Therefore, a prospective study design is not required to validate the differences we found between the two groups, as evidenced by the similarity of our study design to previous prospective studies [16, 17]. On the other hand, the main confounder of our study is the possibility that shorter PFS in the low SUVmax group merely depicts aggressive tumor phenotype rather than lack of response to SSA therapy. Demonstrating lack of therapeutic benefit in the low SUVmax group will require validation in a placebo-controlled prospective study involving only the patients with low SUVmax. The generalizability of our results to the general GEP-NET population also remains to be investigated.

Conclusion

A subset of patients with grade 1–2 GEP-NETs demonstrate early disease progression on SSA monotherapy. Low SUVmax on ^{68}Ga-DOTATATE PET/CT independently identifies such patients with very high specificity, whereas

conventional clinicopathologic parameters such as Ki67 index provide only limited information on response to SSA. We present quantitative use of somatostatin receptor–targeted PET/CT for predicting response to SSA therapy, which can aid clinicians in the risk-benefit analysis regarding initiation and maintenance of SSA therapy.

Author Contributions

Conception/design: Hwan Lee
Provision of study material or patients: Hwan Lee
Collection and/or assembly of data: Hwan Lee
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Manuscript writing: Hwan Lee, Jennifer R. Eads, Daniel A. Pryma
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Disclosures

Jennifer R. Eads: Novartis (SAB), Lexicon (C/A), Pfizer (H), Bristol-Myers Squibb (E); **Daniel A. Pryma:** Siemens AG, 511 Pharma, Progenics Pharmaceuticals Inc. (RF), Progenics Pharmaceuticals Inc., 511 Pharma, Siemens AG, Actinium Pharmaceuticals Inc., Bayer. (C/A). Hwan Lee indicated no financial relationships.

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For Further Reading:
Nicole Brighi, Francesco Panzuto, Roberta Modica et al. Biliary Stone Disease in Patients with Neuroendocrine Tumors Treated with Somatostatin Analogs: A Multicenter Study. ***The Oncologist*** 2020;25:259–265.

Implications for Practice:
The results of this study confirm an increased rate of gallstones development and related complications in patients with neuroendocrine tumors (NETs) treated with somatostatin analogs (SSAs). NETs of the gastrointestinal (GI) tract and related surgery are independent risk factors for biliary stone disease development. Therefore, all patients with primary GI-NET or undergoing abdominal surgery should be considered for prophylactic cholecystectomy. Data on other subgroups are not exhaustive, and management also evaluating additional clinical features (life expectancy, surgical and anesthesiological risks) should be considered. Prophylactic treatment with ursodeoxycholic acid does not seem to be a protective factor for SSA-related biliary stone disease.