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RESEARCH ARTICLE

The Correlation Between [^{68}Ga]DOTATATE PET/CT and Cell Proliferation in Patients With GEP-NENs

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Abstract

Purpose: Objectives of the study are to analyze the correlation between [^{68}Ga]DOTATATE positron emission tomography (PET)/X-ray computed tomography (CT) measurements and various biological characteristics of gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs), and to determine optimal cutoff value of SUVmax (standard uptake value) to differentiate neuroendocrine tumors (NETs) and neuroendocrine cancers (NECs).

Procedures: Of the GEP-NEN cases (73 males, 53 females; age 18–77 years) with pathologically proven primary and/or metastatic lesions, 126 were studied. All of the short axes of lesions were larger than 0.5 cm in order to avoid the partial volume effect. Patients fasted for 6 h before the PET/CT scans. The dose of [^{68}Ga]DOTATATE was 100–200 MBq and the acquisition began at 1 h after injection. The lesion with the highest SUVmax in each patient was analyzed.

Results: In the total sample, the sensitivity of [68Ga]DOTATATE was 69.05 %. The sensitivities were significantly different among G1, G2, and G3 groups (72.22 %, 91.53 %, and 40.82 %, respectively; $p < 0.01$). The SUVmax of the G3 group was lowest. We also found that the sensitivity and SUVmax were significantly higher ($p < 0.05$) in patients with pancreatic NENs (Pan-NENs) than in patients with gastrointestinal NENs (Gi-NENs) and unknown primary NENs (Up-NENs). A significant negative correlation between SUVmax and Ki-67 was found ($r = -0.429$, $p < 0.01$). Using SUVmax to differentiate neuroendocrine tumors (NETs) and neuroendocrine cancers (NECs), the area under the ROC curve (AUC) was 0.771 and the cutoff value of SUVmax was 11.25 (sensitivity 79.2 %, specificity 65.3 %). However, Pan-NENs did not show any statistical significance results in correlation and ROC analysis.

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Conclusion: [^{68}Ga]DOTATATE PET/CT results showed a negative correlation with GEP-NEN cell proliferation and were complementary to Ki-67. Pan-NENs were different from Gi-NENs and Up-NENs when compared to somatostatin receptor expression.

Key words: Neuroendocrine tumor, Somatostatin receptor, PET/CT, [^{68}Ga]DOTATATE, Cell proliferation

Introduction

Gastroenteropancreatic neoplasms (GEP-NENs) are a heterogeneous group of neoplasms that arise from diffuse neuroendocrine cells of the digestive system, and they occur most commonly in the gastrointestinal tract and the pancreas [1]. The diagnosis of GEP-NENs mainly depends on pathology. Nuclear-associated antigen Ki-67 is the gold standard for GEP-NENs grading in the 2010 World Health Organization (WHO) classification [2]. Three grades are defined as follows: G1 (Ki-67 $\leq$ 2 %), G2 (Ki-67 3–20 %), and G3 (Ki-67 > 20 %). In our research, G1 and G2 GEP-NENs are defined as neuroendocrine tumors (NETs), while G3 GEP-NENs are neuroendocrine cancers (NECs). Ki-67 is a nuclear protein associated with cellular proliferation. It is the most common tissue-based marker used in GEP-NENs worldwide and plays a prominent role in diagnosis and prognosis. But it is not without its pitfalls. Firstly, the accuracy of this current gold standard is dependent on the skill and expertise of the reporting pathologist [3]. Secondly, significant discordance is detected between biopsy and surgical resection specimens [4]. Finally, the Ki-67 index may vary in same patient over the course of the disease, including the development of metastases [5] or following treatment [6, 7].

A unique feature of GEP-NENs is their overexpression of somatostatin receptors (SSTRs) on the tumor cells, which has established the basis for both diagnostic imaging and peptide receptor radionuclide therapy. Positron emission tomography (PET)/X-ray computed tomography (CT) with Ga-68-labeled somatostatin analogues plays a crucial role in diagnosis, staging, and management of GEP-NENs. In June 2016, the US Food and Drug Administration (FDA) approved a kit for synthesis of [^{68}Ga]DOTATATE (Fig. 1), and it has been used more and more widely.

With this study we aimed to analyze the correlation between [^{68}Ga]DOTATATE results and biological and pathological characteristics of GEP-NENs, especially the correlation with Ki-67. We hypothesized that [^{68}Ga]DOTATATE PET/CT results should be complementary to pathology. We also explored the cutoff value of SUVmax (standard uptake value) to differentiate NETs and NECs.

Materials and Methods

Patients

One-hundred-twenty-six GEP-NENs patients with pathologically proven primary and/or metastatic lesions, who underwent [^{68}Ga]DOTATATE PET/CT between June 2013 and December 2016, were retrospectively included in the study. All of the short axes of lesions were larger than 0.5 cm in order to avoid the partial volume effect. The study has been approved by ethics committee of Beijing Cancer Hospital and all subjects signed an informed consent form.

Ki-67 Staining

The Ki-67 proliferative index was determined in all cases on formalin-fixed paraffin-embedded tissue sections using a mouse anti-Ki-67 monoclonal antibody (1:50, clone MIB-1; Dako). Five hot spots, i.e., areas of highest proliferation, were counted. A total of 500 cells in each spot were counted and results were expressed in percentage.

All the patients had Ki-67 indexes in our research. Of the pathological results, 56.3 % (71/126) were obtained from primary lesions, while the others (44.7 %, 55/126) were obtained from metastases. The percentages of biopsy and surgical resection specimens were 64.3 % (81/126) and 36.7 (45/126), respectively.

[^{68}Ga]DOTATATE PET/CT Acquisition

Patients fasted for at least 6 h before PET/CT scan. Images were acquired 1 h post-injection of 100–200 MBq [^{68}Ga]DOTATATE. A whole-body scan (upper thigh to mid-skull) was performed with the patient in the supine position (Philips Gemini TF16, the Netherlands). A low-dose, non-contrast CT was used for attenuation correction and anatomic localization. Following the CT, a PET image was obtained with an acquisition time of 1 min per bed position.

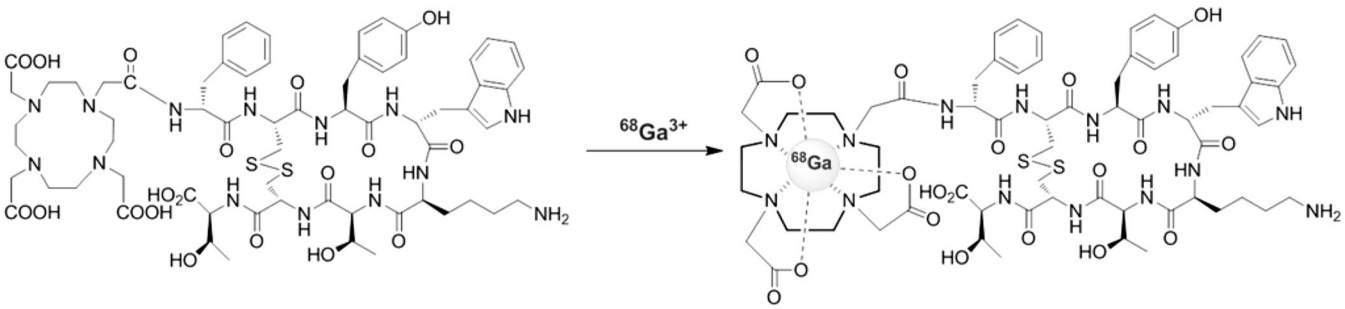

Fig. 1 Radiolabeling of [^{68}Ga]DOTATATE.

Imaging Analysis

Reconstructed attenuation-corrected PET images, CT images, and fused images of matched pairs of PET and CT slices were evaluated by two experienced nuclear medicine physicians. A PET-positive lesion was defined as any area with uptake greater than normal liver background that could not be identified as physiological uptake. The maximum standardized uptake value (SUVmax) was measured for metastatic and primary lesions, and the lesion with the highest SUVmax generated from each patient was used in the final analysis.

Statistics

Continuous variables were reported as mean ± SD, whereas categorical data was expressed as number and percentage. Statistical analyses were performed using SPSS (version 22.0; IBM). Sensitivities and SUVmax values in different groups were compared by the chi-squared test, one-way ANOVA analysis, and independent sample *t* test. Spearman's correlation coefficient and ROC curves were used to evaluate the correlation between SUVmax and the Ki-67 index. $p < 0.05$ was considered as statistically significant.

Results

Patient Characteristics

Of the GEP-NEN cases (73 males, 53 females; age 18–77 years) with pathologically proven primary and/or metastatic lesions, 126 were studied. The primary sites originated from pancreas (35.72 %), gastro-intestinal tract (46.82 %), and unknown primary (17.46 %). The percentages of G1, G2, and G3 groups were 14.29 %, 46.82 %, and 38.89 %, respectively. At [^{68}Ga]DOTATATE PET/CT evaluation, 121 (96.03 %) patients showed metastases, including lymph nodes ($n = 75$), liver ($n = 73$), bone ($n = 24$), peritoneum ($n = 15$), lung ($n = 7$), spleen ($n = 3$), and brain ($n = 1$). The clinical characteristics of the study cohort are summarized in Table 1.

Sensitivities and Mean Values of SUVmax Among Different Groups

Sensitivities and mean values of SUVmax among different groups of patients are reported in Table 2.

The sensitivities were significantly different among G1, G2, and G3 groups ($\chi^2 = 32.31$, $p < 0.01$). It indicated that better differentiated GEP-NENs had higher [^{68}Ga]DOTATATE sensitivities. The SUVmax of the G3 group was lower than the other two groups ($p < 0.05$).

Table 1. Clinical characteristics of participants in the study

Characteristic	Value
No. of patients	126
Male-to-female ratio	1.38:1 (73:53)
Mean age ± SD, years (range)	54 ± 12 (18–77)
Primary tumor site no. (%)	
Pancreas	45 (35.72 %)
Stomach	25 (19.84 %)
Small bowel	11 (8.73 %)
Large bowel	23 (18.25 %)
Primary unknown	22 (17.46 %)
Grade no. (%)	
G1	18 (14.29 %)
G2	59 (46.82 %)
G3	49 (38.89 %)
Metastasis no. (percent of total patients in the study)	
Total	121 (96.03 %)
Lymph node	75 (59.52 %)
Liver	73 (57.94 %)
Bone	24 (19.05 %)
Peritoneum	15 (11.90 %)
Lung	7 (5.56 %)
Spleen	3 (2.8 %)
Brain	1 (0.79 %)
Clinical use no. (%)	
Staging	40 (31.75 %)
Restaging	57 (45.24 %)
Detecting unknown primary sites	29 (23.01 %)
Previous treatment no. (%)	
No treatment	63 (50.00 %)
Surgery	28 (22.22 %)
Chemo, SSAs-LAR, and intervention	35 (27.78 %)

SSAs-LAR somatostatin analogues–long-acting release

Table 2. Sensitivities and mean values of SUVmax among different groups

	Sensitivity	SUVmax
Total	69.05 % (87/126)	21.31 ± 18.54
Grade		
G1	72.22 % (13/18)**	29.17 ± 28.64
G2	91.53 % (54/59)**	25.95 ± 16.20
G3	40.82 % (20/49)**	12.78 ± 12.29*
	$\chi^2 = 32.31$, $p < 0.01$	$p < 0.05$
Origin		
Pancreas	84.44 % (38/45)*	28.25 ± 21.50*
Gastrointestinal tract	61.02 % (36/59)	17.93 ± 16.73
Primary unknown	59.09 % (13/22)	16.18 ± 11.86
	$\chi^2 = 7.79$, $p < 0.05$	$p < 0.05$
Stage		
Without distant metastases	45.71 % (16/35)*	15.50 ± 20.36*
With distant metastases	78.02 % (71/91)*	23.55 ± 17.39*
	$\chi^2 = 12.35$, $p < 0.01$	$p = 0.028 < 0.05$
Treatment		
No treatment	69.84 % (44/63)	22.55 ± 20.36
Surgery	64.29 % (18/28)	17.83 ± 13.64
Chemo, LAR, and intervention	71.43 % (25/35)	21.88 ± 18.61
	$\chi^2 = 0.41$, $p > 0.05$	$p = 0.305 > 0.05$

Sensitivities and SUVmax values in different groups were compared by the chi-squared test, one-way ANOVA analysis, and independent sample *t* test (**$p < 0.01$, *$p < 0.05$). The sensitivities were significantly different among G1, G2, and G3 groups, and the SUVmax of the G3 group was lower than the other two groups. pan-NENs showed significantly higher sensitivity and SUVmax than the other groups. Patients with distant metastases showed higher sensitivity and SUVmax than local disease

We also found that the sensitivity and SUVmax were significantly higher ($p < 0.05$) in patients with pancreatic NENs (pan-NENs) than in patients with gastrointestinal NENs (Gi-NENs) and unknown primary NENs (Up-NENs). Otherwise, there was no significant difference in sensitivity or SUVmax between Gi-NENs and Up-NENs. Patients with distant metastases showed higher sensitivity and SUVmax than local disease ($\chi^2 = 12.35$; $p < 0.01$, $p < 0.05$). Previous treatment did not affect the [^{68}Ga]DOTATATE imaging results.

Correlation Between SUVmax and Ki-67

In the total sample there was a significant negative correlation between SUVmax and Ki-67 ($r = -0.429$, $p < 0.01$). The correlation was also significant in both the Gi-NENs ($r = -0.415$, $p < 0.01$) and Up-NENs groups ($r = -0.544$, $p < 0.01$). However, in Pan-NENs no statistical significance result was found ($r = -0.241$, $p > 0.05$) (Fig. 2).

Using SUVmax to differentiate NETs and NECs, the area under the ROC curve (AUC) was 0.771 and the cutoff score of SUVmax was 11.25 (sensitivity 79.2 %, specificity 65.3 %). In subgroups, the AUCs were 0.772 for Gi-NENs and 0.871 for Up-NENs, and the most appropriate SUVmax cutoffs were 8.85 (sensitivity 84.8 %, specificity 69.2 %) and 14.95 (sensitivity 90.0 %, specificity: 83.3 %). However, in Pan-NENs there was still no statistical significance in ROC analysis ($p > 0.05$) (Figs. 3 and 4).

Furthermore, the distributions of Ki-67 in Pan-NENs, Gi-NENs, and Up-NENs are indicated in Fig. 5. The Ki-67 value of Pan-NENs was significantly lower than Gi-NENs and Up-NENs, respectively ($p < 0.01$, $p < 0.05$).

Discussion

[^{68}Ga]DOTATATE can specifically bind to somatostatin receptors that are overexpressed on the surface of NEN cells, especially in subtypes 2 and 5. It was approved by the FDA for evaluation of patients with GEP-NENs and has used widely worldwide. [^{68}Ga]DOTATATE PET/CT can allow for accurate delineation of the extent of disease at both initial

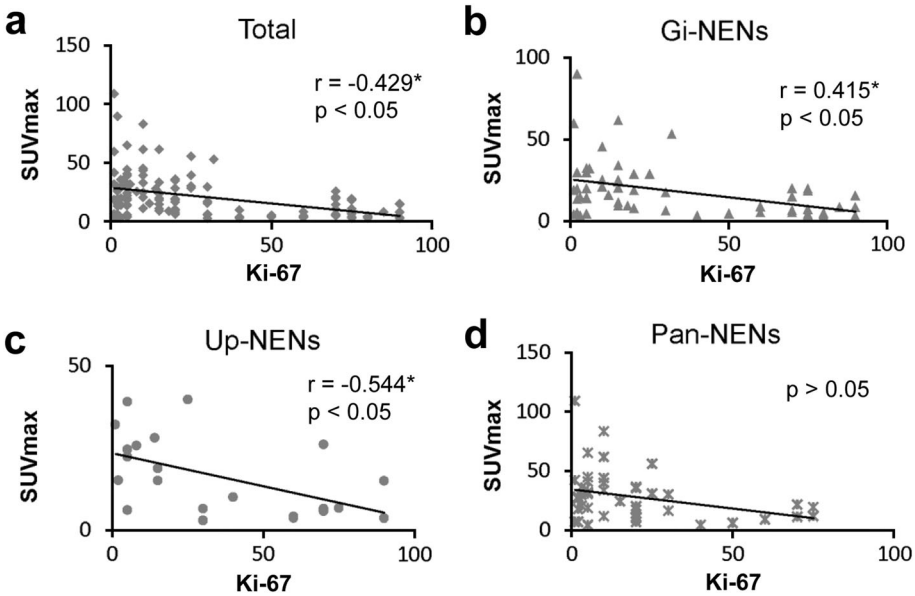

Fig. 2 There were significant negative correlations between SUVmax and Ki-67 in **a** the total sample, **b** Gi-NENs, and **c** up-NENs. However, in **d** pan-NENs, no statistical significant result was found. *$p < 0.05$.

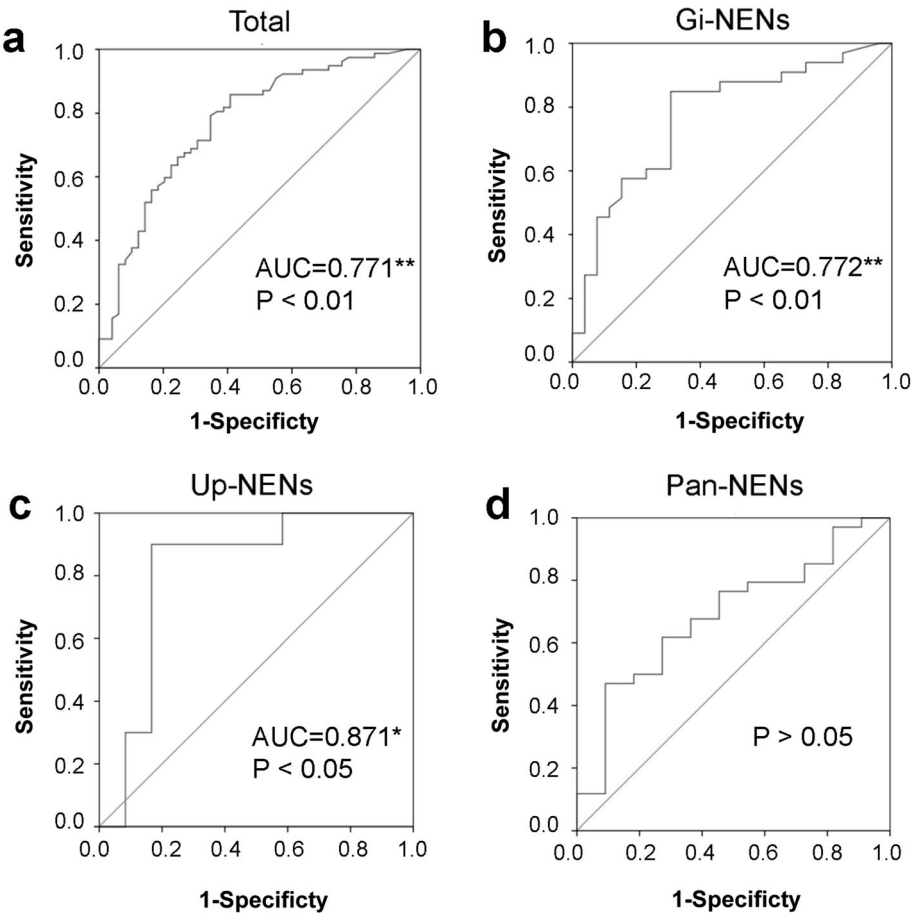

Fig. 3 When using SUVmax to differentiate NET and NEC, the values of AUC were 0.771, 0.772, and 0.871 for **a** the total sample, **b** Gi-NENs, and **c** up-NENs. **d** pan-NENs did not show any statistical significance in ROC analysis. $^{**}p < 0.01$, $^{*}p < 0.05$.

staging and follow-up and can identify an occult primary lesion. Some researches indicate that it can also provide prognostic information [8, 9]. As a functional imaging modality, [^{68}Ga]DOTATATE PET/CT can be used to evaluate the character of somatostatin receptor status noninvasively, based on analysis of the intensity of uptake of target-specific radiotracers. This bio-characteristic is associated with tumor differentiation and treatment strategy [10, 11].

Ki-67 is a nuclear associated antigen which reflects the cellular proliferation [12]. It can be characterized by immunohistochemistry and is expressed in S, G1, G2, and

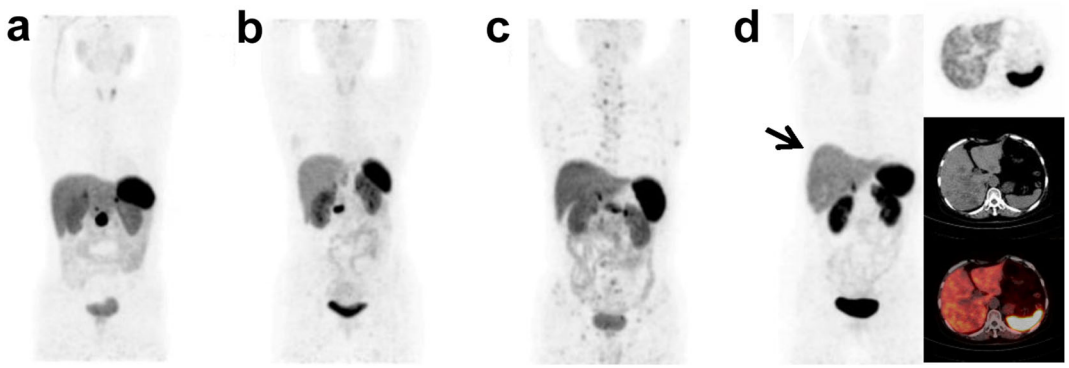

Fig. 4 Different differentiation cases showed different [^{68}Ga]DOTATATE uptake characteristics. **a** Pancreatic NET, G1, Ki-67: 1 %, SUVmax: 109.1. **b** Primary unknown, G2, Ki-67: 14 %, SUVmax: 28. **c** Rectal NEC, G3, Ki-67: 30 %, SUVmax: 17.3. **d** Duodenal NEC with multiple liver metastases, G3, Ki-67: 70 %, SUVmax: 6.2.

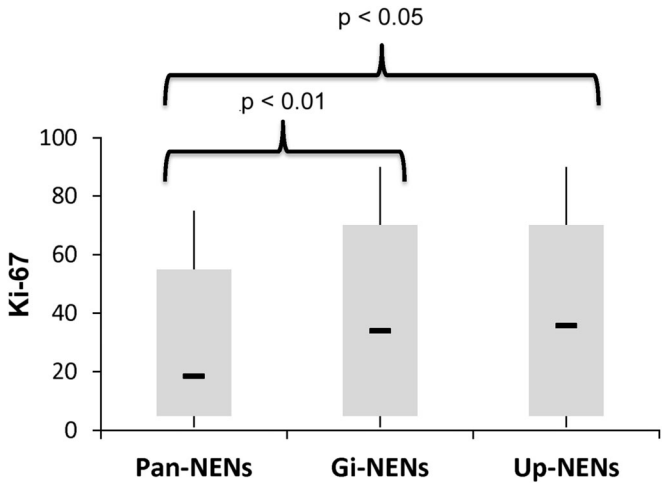

Fig. 5 The Ki-67 value for pan-NENs was significantly lower than for Gi-NENs and up-NENs, respectively ($p < 0.01$, $p < 0.05$).

M phases of the cell cycle except G0 phase [13, 14]. As a marker of proliferation, its expression has been correlated with survival in many cancers [15, 16], and it is also the gold standard for grading in GEP-NENs according to WHO classification [2].

Ki-67 is the most common tissue-based marker used in GEP-NENs worldwide and plays a prominent role in diagnosis and prognosis, but it is not without its pitfalls. The measurement resulting in the greatest accuracy consists of counting 2000 cells, including the most highly proliferative region ("hot spots") which is obviously dependent on the skill and expertise of the reporting pathologist [3, 17]. Heterogeneity of GEP-NENs is the main factor that limits the accuracy of Ki-67. Nearly half of metastatic well-differentiated NETs to the liver show intratumoral heterogeneity in Ki-67 labeling that is sufficient to change grades from G1 to G2 [4]. Some studies [5, 18] reported high variance of Ki-67 between the primary tumor and the metastatic sites. Miller showed that the discordance was present in 35.3 % of cases [19]. When multiple pathology specimens were available, Ki-67 varied throughout the course of NET disease. A majority of cases were upgraded to a higher WHO class [7]. Treatment was also associated with a decrease in Ki-67 among patients who underwent optional paired pre- and post-treatment biopsy [6].

A unique feature of GEP-NENs is their overexpression of somatostatin receptors, and this biological behavior is more common in well-differentiated NETs. The images of [^{68}Ga]DOTATATE PET/CT show the density and distribution of SSTRs of whole body, and also reflect the proliferation of lesions. In our research, SUVmax of [^{68}Ga]DOTATATE PET/CT shows a negative correlation with the Ki-67 index. This functional imaging modality not only describes the somatostatin receptor status of GEP-NENs but also reflects the cell proliferation. This means that [^{68}Ga]DOTATATE PET/CT is complimentary to Ki-67 in addition to staging and identifying the primary. Furthermore, we also use SUVmax to differentiate NETs and NECs, and we concluded that the cutoff score was 11.25 with a sensitivity of 79.2 % and a specificity of 65.3 %.

Another interesting finding of this study is that Pan-NENs showed different somatostatin receptor expression compared to Gi-NENs and Up-NENs. Sensitivity and SUVmax of Pan-NENs were significantly higher than the other two subgroups. This finding is in agreement with Campana's study using [^{68}Ga]DOTANOC as the PET tracer [8]. O'Toole also found a higher messenger RNA level of somatostatin receptors in pancreatic than in gastrointestinal NENs [20]. In Pan-NENs the correlation with Ki-67 and the ROC curves showed no statistical significance. The Ki-67 value of Pan-NENs was lower than the other two groups. These results reflect the unique bio-characteristics of Pan-NENs and would be the evidence for different treatment approaches.

The present study has several limitations. This is a retrospective single-center research study. In order to analyze the relationship between [^{68}Ga]DOTATATE results and cell proliferation more precisely we need to clarify the methods of specimen collection and specimen locations (primary lesions or metastases) in detail. Since GEP-NENs exhibit heterogeneity, we plan to design a multi-center prospective study in the near future.

Conclusion

[^{68}Ga]DOTATATE PET/CT results show a negative correlation with cell proliferation in GEP-NEN, so it is complementary to Ki-67. When using SUVmax to differentiate NETs and NECs, the area under the ROC curve is 0.771 and the cutoff score of SUVmax was 11.25 (sensitivity 79.2 %, specificity 65.3 %). Interestingly, Pan-NENs are different from Gi-NENs and Up-NENs in both SSTR expression and cell proliferation characteristics. Further study of [^{68}Ga]DOTATATE PET/CT and SUVmax will add to a greater understanding of GEP-NENs and more effective ways to treat these tumors.

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Compliance with Ethical Standards

Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. Garcia-Carbonero R, Capdevila J, Crespo-Herrero G, Diaz-Perez JA, Martinez del Prado MP, Alonso Orduna V, Sevilla-Garcia I, Villabona-Artero C, Beguiristain-Gomez A, Llanos-Munoz M, Marazuela M, Alvarez-Escola C, Castellano D, Vilar E, Jimenez-Fonseca P, Teule A, Sastre-Valera J, Benavent-Vinuelas M, Monleon A, Salazar R (2010) Incidence, patterns of care and prognostic factors for outcome of gastroenteropancreatic neuroendocrine tumors (GEP-NETs): results from the National Cancer Registry of Spain (RGETNE). Ann Oncol 21:1794–1803
2. Rindi G, Petrone G, Inzani F (2014) The 2010 WHO classification of digestive neuroendocrine neoplasms: a critical appraisal four years after its introduction. Endocr Pathol 25:186–192
3. Rindi G, Klöppel G, Couvelard A, Komminoth P, Körner M, Lopes JM, McNicol AM, Nilsson O, Perren A, Scarpa A, Scoazec JY, Wiedenmann B (2007) TNM staging of midgut and hindgut (neuro) endocrine tumors: a consensus proposal including a grading system. Virchows Arch 451:757–762
4. Yang Z, Tang LH, Klimstra DS (2011) Effect of tumor heterogeneity on the assessment of Ki67 labeling index in well-differentiated neuroendocrine tumors metastatic to the liver: implications for prognostic stratification. Am J Surg Pathol 35:853–860
5. Adesoye T, Daleo MA, Loeffler AG et al (2015) Discordance of histologic grade between primary and metastatic neuroendocrine carcinomas. Ann Surg Oncol Suppl 3:S817–S821
6. Yao JC, Phan AT, Chang DZ, Wolff RA, Hess K, Gupta S, Jacobs C, Mares JE, Landgraf AN, Rashid A, Meric-Bernstam F (2008) Efficacy of RAD001 (everolimus) and octreotide LAR in advanced low- to intermediate-grade neuroendocrine tumors: results of a phase II study. J Clin Oncol 26:4311–4318
7. Singh S, Hallet J, Rowsell C, Law CH (2014) Variability of Ki67 labeling index in multiple neuroendocrine tumors specimens over the course of the disease. Eur J Surg Oncol 40:1517–1522
8. Campana D, Ambrosini V, Pezzilli R, Fanti S, Labate AMM, Santini D, Ceccarelli C, Nori F, Franchi R, Corinaldesi R, Tomassetti P (2010) Standardized uptake values of (68)Ga-DOTANOC PET: a promising prognostic tool in neuroendocrine tumors. J Nucl Med 51:353–359
9. Tirosh A, Papadakis GZ, Millo C et al (2018) Prognostic utility of Total ^{68}Ga-DOTATATE-avid tumor volume in patients with neuroendocrine tumors. Gastroenterology 154:998–1008
10. Reubi JC, Kvols L, Krenning E, Lamberts SW (1991) In vitro and in vivo detection of somatostatin receptors in human malignant tissues. Acta Oncol 30:463–468
11. Kvols LK, Reubi JC, Horisberger U et al (1992) The presence of somatostatin receptors in malignant neuroendocrine tumor tissue predicts responsiveness to octreotide. Yale J Biol Med 65:505–518
12. Gerdes J, Schwab U, Lemke H, Stein H (1983) Production of a mouse monoclonal antibody reactive with a human nuclear antigen associated with cell proliferation. Int J Cancer 31:13–20
13. Gerdes J, Lemke H, Baisch H et al (1984) Cell cycle analysis of a cell proliferation-associated human nuclear antigen defined by the monoclonal antibody Ki-67. J Immunol 133:1710–1715
14. Scholzen T, Gerdes J (2000) The Ki-67 protein: from the known and the unknown. J Cell Physiol 182:311–322
15. Martin B, Paesmans M, Mascaux C, Berghmans T, Lothaire P, Meert AP, Lafitte JJ, Sculier JP (2004) Ki-67 expression and patients survival in lung cancer: systematic review of the literature with meta-analysis. Br J Cancer 91:2018–2025
16. Inwald EC, Klinkhammer-Schalke M, Hofstädter F, Zeman F, Koller M, Gerstenhauer M, Ortmann O (2013) Ki-67 is a prognostic parameter in breast cancer patients: results of a large population-based cohort of a cancer registry. Breast Cancer Res Treat 139:539–552
17. Klimstra DS (2013) Pathology reporting of neuroendocrine tumors: essential elements for accurate diagnosis, classification, and staging. Semin Oncol 40:23–36
18. Dhall D, Mertens R, Bresee C, Parakh R, Wang HL, Li M, Dhall G, Colquhoun SD, Ines D, Chung F, Yu R, Nissen NN, Wolin E (2012) Ki-67 proliferative index predicts progression-free survival of patients with well-differentiated ileal neuroendocrine tumors. Hum Pathol 43:489–495
19. Miller HC, Drymousis P, Flora R, Goldin R, Spalding D, Frilling A (2014) Role of Ki-67 proliferation index in the assessment of patients with neuroendocrine neoplasias regarding the stage of disease. World J Surg 38:1353–1361
20. O'Toole D, Saveanu A, Couvelard A, Gunz G, Enjalbert A, Jaquet P, Ruszniewski P, Barlier A (2006) The analysis of quantitative expression of somatostatin and dopamine receptors in gastro-entero-pancreatic tumours opens new therapeutic strategies. Eur J Endocrinol 155:849–857