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·临床研究·

^{68}Ga-DOTANOC PET/CT 在寻找转移性神经内分泌肿瘤患者原发灶中的价值 *

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摘要 目的：评估 ^{68}Ga-DOTANOC PET/CT 显像在寻找不明原因转移性神经内分泌肿瘤(neuroendocrine neoplasms, NENs)患者原发灶中的价值。**方法：**回顾性分析西京医院于 2016 年 6 月 ~2018 年 6 月经病理确诊为转移性 NENs，为寻找原发灶而行 ^{68}Ga-DOTANOC PET/CT 的 32 例患者[男 20 例、女 12 例，年龄 33~78(57.95± 13.34)岁]的相关资料。原发灶诊断以手术或活组织检查获得组织病理学结果为金标准。计算 ^{68}Ga-DOTANOC PET/CT 对转移性 NENs 患者原发灶的检出率；用 Spearman 秩相关检验分析 ^{68}Ga-DOTANOC PET/CT 显像中真阳性原发灶 SUVmax 与已知病理确诊转移灶 SUVmax 的相关性，并用配对 t 检验比较二者 SUVmax。比较 ^{68}Ga-DOTANOC PET/CT 显像与传统影像学检查(CT、MRI 或超声)对转移性 NENs 患者的诊断结果。**结果：** ^{68}Ga-DOTANOC PET/CT 准确发现转移性 NENs 患者原发灶者 19 例，其检出率为 59.4%。^{68}Ga-DOTANOC PET/CT 显像中真阳性原发灶 SUVmax=15.36± 15.02(4.17～45.9)，病理确诊转移灶 SUVmax=8.46± 7.80(1.7~27.5)，二者显著相关(r=0.776，*P*=0.003)，真阳性原发灶 SUVmax 显著高于病理确诊转移灶 SUVmax，差异具有统计学意义(t=2.594，*P*=0.025)。相比于传统影像学检查，除了真阳性原发灶及病理确诊转移灶，^{68}Ga-DOTANOC PET/CT 发现 10 例(31.3%)NENs 患者存在额外转移灶，以骨转移及淋巴结转移为主。**结论：** ^{68}Ga-DOTANOC PET/CT 显像在寻找转移性 NENs 患者原发灶中有较高的应用价值，可发现更多的转移灶，为临床提供更准确的信息。

关键词：神经内分泌肿瘤；原发灶不明；正电子发射断层成像术；^{68}Ga-DOTANOC；最大标准摄取值(SUVmax)

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Value of ^{68}Ga-DOTANOC PET/CT in Detecting Primary Site for Patients with Metastatic Neuroendocrine Neoplasms*

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ABSTRACT Objective: To evaluate role of ^{68}Ga-DOTANOC PET/CT imaging in detecting primary site in patients with metastatic neuroendocrine neoplasms(NENs) of unknown origin. **Methods:** 32 patients (20 males, 12 females, age 33~78(57.95± 13.34)years) with histopathologically proven metastatic NENs in Xijing Hospital from June 2016 to June 2018, who underwent ^{68}Ga-DOTANOC PET/CT for detecting primary site were retrospectively analyzed. The histopathological results obtained by surgical or biopsy were considered as the gold standard of primary tumor diagnosis. The detection rate of ^{68}Ga-DOTANOC PET/CT in finding the primary lesion of metastatic NENs were calculated; Spearman rank correlation test was used to analyze the SUVmax correlation between the true positive primary sites and histopathological confirmed metastases in ^{68}Ga-DOTANOC PET/CT imaging, the SUVmax of which were compared using paired t test. Compared the results of ^{68}Ga-DOTANOC PET/CT imaging and conventional imaging (CT, MRI, or ultrasound) in patients with metastatic NENs. **Results:** ^{68}Ga-DOTANOC PET/CT accurately identified primary sites in 19 patients with the detection rate of 59.4%. Mean SUVmax of true positive primary sites was 15.36± 15.02 (4.17～45.9), and of histopathologically confirmed metastases was 8.46± 7.80 (1.7～27.5) in ^{68}Ga-DOTANOC PET/CT imaging. Significant positive correlation was found between SUVmax of true positive primary sites and of histopathologically proven sites of metastasis (r=0.776, *P*=0.003), and the former was significantly higher than the latter (t=2.594, *P*=0.025). Compared with traditional imaging, additional metastases were observed by ^{68}Ga-DOTANOC PET/CT in 10 cases (31.3%), mostly in bones and lymph nodes. **Conclusions:** ^{68}Ga-DOTANOC PET/CT is an accurate method of identifying pri-

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mary sites in patients with metastatic NENs of unknown origin. It can detect more metastases and provide more accurate information to clinicians.

Key words: Neuroendocrine neoplasms; Unknown primary; Positron-emission tomography; ^{68}Ga-DOTANOC; Maximal standardized uptake value (SUVmax)

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前言

原发灶不明转移癌 (Carcinoma of unknown primary, CUP)是指经病理学证实为转移癌,而全面、仔细的常规检查(包括临床查体、实验室检查、传统影像学检查如 CT、MRI、超声等)均无法确定原发灶的一类肿瘤。约 10%-13%的神经内分泌肿瘤(neuroendocrine neoplasms, NENs) 为以转移灶为首发表现的 CUP[1]。NENs 可发生于全身多个部位,以消化道多见,且异质性显著[2]。原发灶不明的 NENs 预后较差,10 年生存率仅略高于 20%[3]。手术切除是目前 NENs 首选的治疗方式[4],即使无法完全切除,减瘤手术也有助于部分患者的症状控制[5]。因此,准确定位 NENs 原发灶对患者的诊断、治疗及预后至关重要。

传统影像学检查在 NENs 原发灶体积较小或解剖位置多变时诊断效能受限[6]。正电子核素标记生长抑素 PET/CT 显像在 NENs 的诊断、分期及寻找原发灶中均具有较高应用价值[7],其灵敏度明显优于奥曲肽 SPECT 显像[8,9]。本研究旨在初步评估 ^{68}Ga-DOTANOC PET/CT 显像在寻找转移性 NENs 患者原发灶中的应用价值。

1 材料与方法

1.1 一般资料

回顾性分析西京医院于 2016 年 6 月 ~2018 年 6 月病理确诊为转移性 NENs，为寻找原发灶而行 ^{68}Ga-DOTANOC PET/CT 检查的患者 32 例。纳入标准:1)既往无肿瘤病史;2)病理确诊为转移性 NENs，建议查原发灶者;3) 通过详细病史采集、体格检查、传统影像学(CT、MRI 或超声)及血液学检查均未发现原发灶;4)^{68}Ga-DOTANOC PET/CT 检查后取得组织病理学结果。本研究通过本院伦理委员会审查（批准号:第 20131218-6 号),全部患者均签署检查前知情同意书。

1.2 ^{68}Ga-DOTANOC 的合成及 PET/CT 显像

1.2.1 ^{68}Ga-DOTANOC 合成 以 4 mL 0.05 M 的盐酸淋洗 ^{68}Ge-^{68}Ga 发生器(德国 ITG 公司),收集全部淋洗液;100℃加热淋洗液与已预热的 DOTA-NOC(30 μg,德国 ABX 公司)及醋酸钠(1.1 mL 0.25 M)混合溶液 10 min 进行标记,反应结束后经 C18 纯化,以 1 mL 80%的乙醇淋洗产物,用 5 mL 盐水稀释,过 0.2 m 无菌滤膜,得到注射液;放化纯 >95%方符合标准。

1.2.2 ^{68}Ga-DOTANOC PET/CT 扫描仪器及方法 采用德国 Siemens 公司 Biograph 40 型 PET/CT 扫描仪。检查前患者无需禁食及控制血糖，经静脉注射显像剂 ^{68}Ga-DOTANOC 约 132-222 MBq (4-6 mCi)后 45-60 min 开始显像。首先行螺旋 CT 扫描,扫描范围自颅顶至大腿根部,采集条件:管电压(120 kV),管电流(250~350 mA),螺距(0.80),扫描层厚(3.0 mm),层间距(1 mm)。然后进行 PET 3D 扫描，采集 5~6 个床位，采集时间 2 min/ 床位,用有序子集最大期望值迭代法(OSEM; 4 次迭代、8 个子集)重建 PET 图像,并利用 CT 数据对 PET 图像进行衰减校正、图像重建及融合，将 PET/CT 图像传送到 MI(Medical Imaging, 医学影像)后处理工作站(Simens Healthcare, Germany)进行帧对帧图像对位融合,获得横断面、冠状位和矢状位图像。

1.3 图像分析

由两位或以上经验丰富,熟悉患者临床资料、转移灶病理结果的高年资核医学医师或影像放射学医师共同阅片,意见不同时由多位专家会诊讨论后达成一致意见。扫描范围内 ^{68}Ga-DOTANOC 非生理性摄取或摄取程度高于本底,均认为异常摄取,结合同机 CT 及 PET/CT 融合图像,确定是否为可疑原发灶。结合相应层面 CT 及 PET/CT 融合图像,由同一位操作者在放射性浓聚灶最明显的层面沿病灶范围勾画感兴趣区(region of interest, ROI)，由工作站根据患者体重、显像剂注射剂量、注射时间等自动计算最大标准摄取值(maximum standardized uptake value, SUVmax)。依据相应诊断标准回顾性分析传统影像学检查诊断结果。

1.4 诊断标准

全部可疑原发灶以手术切除 / 穿刺活检获得活组织病理学检查结果为诊断金标准。定义 ^{68}Ga-DOTANOC PET/CT 显像 " 真阳性原发灶 " 为 ^{68}Ga-DOTANOC PET/CT 显像中发现的真阳性原发灶 ";^{68}Ga-DOTANOC PET/CT 显像 " 病理确诊转移灶 " 为检查前已知的病理确诊的 NENs 转移灶。

1.5 统计学方法

数据分析采用 SPSS 25.0 统计分析软件包。符合正态分布的计量资料用 $\bar{x}\pm s$(平均数± 标准差)和范围表示;分类变量用数字和百分比表示。计算 ^{68}Ga-DOTANOC PET/CT 对转移性 NENs 患者原发灶的检出率；用 Spearman 秩相关检验分析 ^{68}Ga-DOTANOC PET/CT 显像中真阳性原发灶 SUVmax 与已知病理确诊转移灶 SUVmax 的相关性；用配对 t 检验比较 ^{68}Ga-DOTANOC PET/CT 显像中真阳性原发灶与病理确诊转移灶 SUVmax。比较 ^{68}Ga-DOTANOC PET/CT 显像与传统影像学检查对转移性 NENs 患者的诊断结果。$P<0.05$ 认为差异具有统计学意义。

2 结果

2.1 一般资料

32 例确诊转移性 NENs 患者 (男 20 例，女 12 例,33～78 岁)的一般资料见表 1。参照 2017 年 WHO 神经内分泌肿瘤病理分级系统 [10],32 例确诊转移性 NENs 患者病理分级 G1 级、G2 级、G3 级分别为 15 例、8 例、9 例。^{68}Ga-DOTANOC PET/CT 发现真阳性原发灶 19 例(手术切除 6 例、穿刺活检确诊 13 例),分别为胰腺 4 例(图 1)、小肠 6 例(图 2) (其中 1 例为十二指肠、空肠双原发)、胃 2 例、直肠 2 例、肺 2 例、胆囊 1 例、纵隔 1 例、卵巢 1 例。

表 1 患者一般资料

Table 1 Patients' characteristics

Characteristics	n (%)
Total patients	32
Male	20(62.5%)
Female	12(37.5%)
Age (y)	
M± SD	57.95± 13.34
Range	33～78
Histopathologically confirmed metastatic sites	
Liver	24(75.0%)
Lymph node	5(15.6%)
Bone	2(6.3%)
Cerebellum	1(3.1%)
Histopathological grades of NENs	
Grade 1	15(46.9%)
Grade 2	8(25.0%)
Grade 3	9(28.1%)
Primary tumor	
Localized	19(59.4%)
Not localized	13(40.6%)

2.2 ^{68}Ga-DOTANOC PET/CT 显像价值评价

^{68}Ga-DOTANOC PET/CT 准确发现转移性 NENs 患者原发灶者 19 例，其检出率为 59.4%(19/32 例)。其中胃肠胰原发 NENs (gastroenteropancreatic neuroendocrine neoplasms, GEP-NENs) 患者 13 例(13/19 例,68.4%),消化道原发 NENs 患者 14 例,(14/19 例,73.7%)。

^{68}Ga-DOTANOC PET/CT 显像中真阳性原发灶 SUVmax=15.36± 15.02 (4.17~45.9),病理确诊转移灶 SUVmax=8.46± 7.80 (1.7~27.5),二者显著相关(表 2)。真阳性原发灶 SUVmax 高于病理确诊转移灶 SUVmax,差异具有统计学意义(表 2)。

相比于传统影像学检查,除了发现真阳性原发灶及病理确诊转移灶，^{68}Ga-DOTANOC PET/CT 显像发现 10 例(10/32,31.3%)NENs 存在额外转移灶,分别为 5 例骨转移＋淋巴结转移,4 例骨转移,1 例肝＋肺＋淋巴结转移。

3 讨论

原发灶不明的转移性 NENs 预后较差[11],早期、准确地发现原发灶有助于指导临床医师合理治疗、改善患者预后[12]。^{68}Ga-DOTA- 奥曲肽 PET/CT 显像利用正电子核素标记的生长抑素类似物与 NENs 细胞表面高度表达的生长抑素受体(somatostatin receptors, SSTR)特异性结合,其对 NENs 的诊断效能明显优于传统影像学 [13]。既往文献报道,^{68}Ga-DOTA- 奥曲肽 PET/CT 显像发现转移性 NENs 患者原发灶的灵敏度约 38%

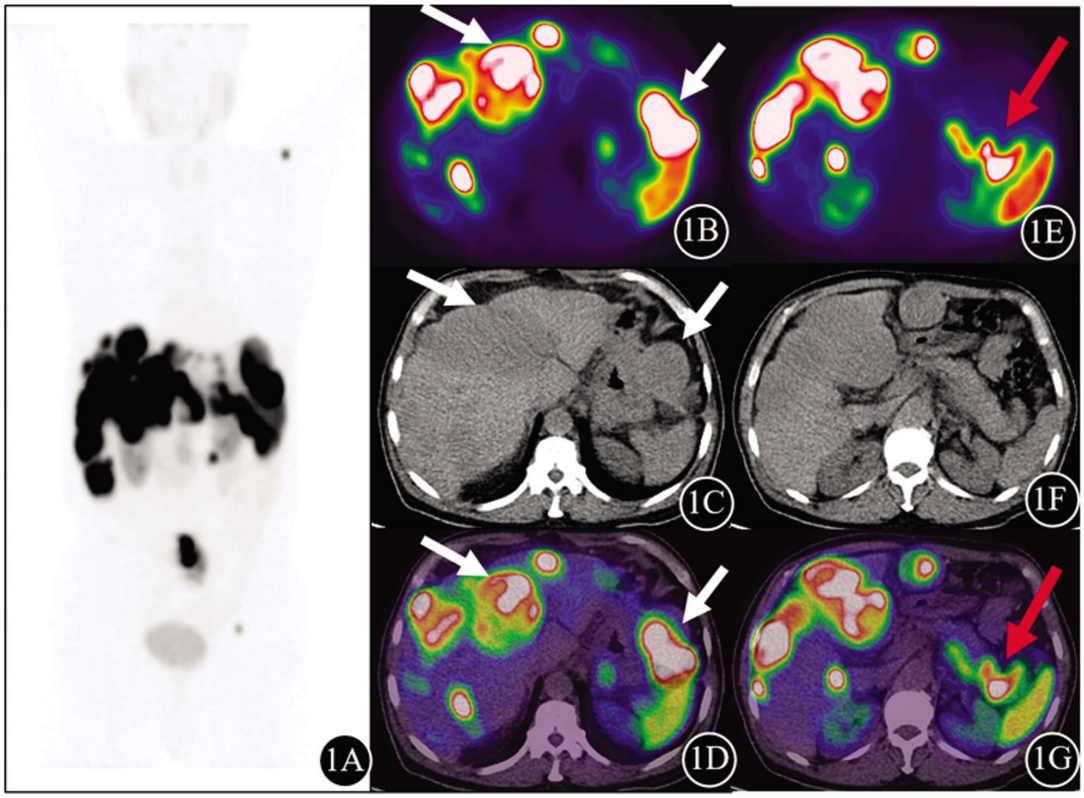

图 1 因上腹部不适行 " 肝占位 " 穿刺活检示神经内分泌瘤(G1 级:Ki-67+,约 2%)患者(男,59 岁)^{68}Ga-DOTANOC PET/CT 显像图。PET(1B)及 PET/CT(1D)示:肝脏、脾 - 胃间隙多发结节状 ^{68}Ga-DOTANOC 摄取增高灶(白箭头示),SUVmax 介于 9.9-27.5;PET(1E)及 PET/CT(1G)示:胰尾部 ^{68}Ga-DOTANOC 结节状异常摄取灶(红箭头示),大小约 4.3× 3.6× 3.6 cm,SUVmax 44.7,后经超声内镜及穿刺活检证实为原发灶

Fig.1 ^{68}Ga-DOTANOC PET/CT images of a 59-year-old man who presented with NEN(G1: Ki-67+, about 2%) of "liver-occupied" biopsy due to upper abdominal discomfort. PET(1B) and PET/CT(1D) images show multiple areas of focal tracer uptake in the liver and spleen-gastric space(white arrow), SUVmax 9.9-27.5; PET(1E) and PET/CT(1G) images show the primary tumour was in the tail of the pancreas(red arrow), 4.3× 3.6× 3.6cm, SUVmax 44.7, and later confirmed by endoscopic ultrasound and biopsy

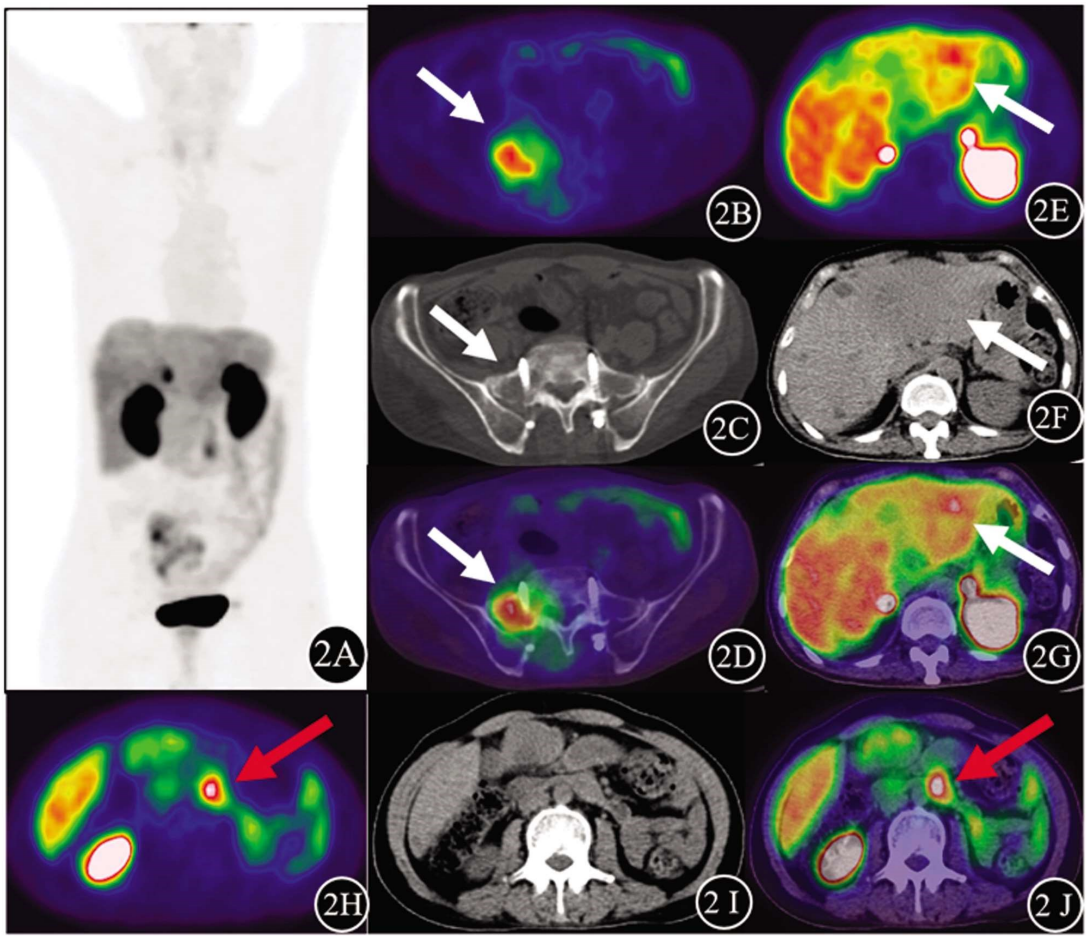

图 2 因右臀部疼痛行右骶骨穿刺活检示神经内分泌癌(G3 级:Ki-67+,约 25%)患者(男,59 岁)^{68}Ga-DOTANOC PET/CT 显像图。PET(2B)及 PET/CT(2D)示:骶 1-3 椎体右侧病变呈 ^{68}Ga-DOTANOC 异常摄取(白箭头示),SUVmax1.7;PET(2E)及 PET/CT (2G)示:肝脏内多个结节状 ^{68}Ga-DOTANOC 摄取增高灶(白箭头示),SUVmax 4.4;PET(2H)及 PET/CT (2J)示:十二指肠水平部 ^{68}Ga-DOTANOC 结节状异常摄取灶(红箭头示),大小约 1.9× 1.9× 2.2 cm,SUVmax 9.6,后经肠镜活检确诊为原发灶

Fig. 2 ^{68}Ga-DOTANOC PET/CT images of a 59-year-old man who presented with NEC, G3(Ki-67+, about 25%) of tibia biopsy for right hip pain. PET (2B) and PET/CT(2D) images show focal tracer uptake in the right side of 1-3 vertebral(white arrow), SUVmax1.7; PET(2E) and PET/CT (2G) images show multiple areas of increased tracer uptake in the liver(white arrow), SUVmax 4.4; PET(2H) and PET/CT (2J) images show the primary tumour was in the horizontal part of duodenum(red arrow), 1.9× 1.9× 2.2 cm, SUVmax 9.6, and finally diagnosed by duodenoscopy and biopsy

表 2 ^{68}Ga-DOTANOC PET/CT 显像病理确诊转移灶与真阳性原发灶 SUVmax 相关性及 t 检验比较

Table 2 SUVmax correlation and t test comparison of histopathologically confirmed metastases and true positive primary tumors in ^{68}Ga-DOTANOC PET/CT imaging

	SUVmax	SUVmax correlation	T test comparison
True positive primary tumors	15.36± 15.02	r= 0.776,	t=2.594,
Histopathologically confirmed metastases	8.46± 7.80	*P*=0.003	*P*=0.025

~60%[14,15],本研究结果与既往结果基本一致。NENs 可发生于全身多个器官和组织，以 GEP-NENs 最常见,其约占所有 NENs 的 55%~70%,而肝脏为 NENs 最常见的转移部位[1]。Pruthi[16]等报道 ^{68}Ga-DOTANOC PET/CT 可诊断 59%转移性 NENs 的原发灶,其最常见的 NENs 原发灶位于小肠、胰腺,Screiter[17]等的研究中转移性 NENs 最常见的原发部位也为小肠。本组病例中,73.7%的转移性 NENs 原发灶位于消化道,68.4%的转移性 NENs 原发于 GEP-NENs，而肝转移性 NENs 约占全部病例的 75.0%,与以往文献报道类似。

Catena[18]等研究发现分化良好的原发灶不明 NENs 通常伴有肝转移。本组病例中,病理确诊转移性 NENs 的病理分级 G1 级、G2 级、G3 级分别为 15 例（46.9%）、8 例（25.0%）、9 例（28.1%),主要以分化较好的 G1 级居多,基本与文献报道的结论相符合。既往文献证实[19],NENs 细胞表面 SSTR 表达率与肿瘤分化程度成正比,肿瘤分化程度越差(高级别),与生长抑素的亲和性越弱,^{68}Ga- 奥曲肽摄取率越低；本组病例中,^{68}Ga-DOTANOC PET/CT 显像中真阳性原发灶 SUVmax 为 15.36± 15.02,而病理确诊转移灶 SUVmax 为 8.46± 7.80,考虑可能与本组病例中不同病理级别的转移性 NENs 病例数有限有一定关系。Prasad[20]等研究发现原发灶未知的胰腺原发 NENs

平均 SUVmax 为 18.6± 9.8，而原发灶已知的胰腺原发 NENs 平均 SUVmax 为 26.1 ± 14.5，表明原发灶未知的胰腺原发 NENs SSTR 表达率更低；本组病例 SUVmax 较低也可能与原发灶未知有关。Sharma[21]等指出胰腺 NENs 原发灶 SUVmax 明显高于转移灶，与本研究结果相同。其原因可能与转移灶更加去分化，SSTR 表达率更低，从而导致 ^{68}Ga-DOTANOC 摄取程度更低有关[22]。

相比于传统影像学检查，除了发现真阳性原发灶及病理确诊转移灶，^{68}Ga-DOTANOC PET/CT 显像发现 31.3%的 NENs 患者存在更多额外转移灶，以额外发现骨转移及淋巴结转移为主，这也可能与 ^{68}Ga-DOTANOC PET/CT 显像扫描范围为全身有关。但无论对于原发灶阳性或阴性的转移性 NENs，查明原发灶或发现更多的转移灶都可以为临床制定治疗方案、控制症状、延长生存期提供更准确的信息。

综上，本研究初步表明 ^{68}Ga-DOTANOC PET/CT 显像在寻找转移性 NENs 患者原发灶中有较高的应用价值。相比于传统影像学检查，^{68}Ga-DOTANOC PET/CT 可发现更多的转移灶，为临床提供更多、更加准确、有用的信息。

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