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Context. The reliable localization of insulinoma is critical for the successful surgical treatment.
Objective. This study compared the accuracy of ^{68}Gallium (Ga)-DOTATATE PET/CT to anatomic imaging modalities, selective arterial secretagogue injection (SASI), and intraoperative ultrasound (IOUS) and palpation for localizing insulinoma in patients who were biochemically cured.
Design, Setting, and Patients. We conducted a retrospective analysis of 31 patients who had an insulinoma confirmed on histology and were biochemically cured. The results of CT, MRI, transabdominal US, IOUS, ^{68}Ga-DOTATATE PET/CT, SASI, and operative findings were analyzed.
Intervention, Main Outcome Measures, Results: The insulinomas were correctly localized in 17 out of 31 (55%) of patients by CT, in 17 out of 28 (61%) by MRI, in 6 out of 28 (21%) by US, and in 9 out of 10 (90%) by ^{68}Ga-DOTATATE. IOUS was performed in 31 patients, and 29 of them had an insulinoma successfully localized (93.5%). Thirty patients underwent SASI, and the insulinoma was regionalized in 28 out of 30 patients (93%). In 19 out of 23 patients (83%), manual palpation identified insulinoma. In patients who had all four noninvasive imaging studies, CT was concordant with ^{68}Ga-DOTATATE in 6 out of 9 patients (67%); MRI in 8 out of 9 (78%); US in 0 out of 9; and in 1 out of 9 patients (11%) the lesion was only seen by ^{68}Ga-DOTATATE.
Conclusions: ^{68}Ga-DOTATATE PET/CT identifies most insulinomas and may be considered as an adjunct imaging study when all imaging studies are negative and when a minimally invasive surgical approach is planned.

PRECIS: We studied 68Ga-DOTATATE PET/CT imaging in patients with insulinoma and found it identifies most tumors and should be considered as an adjunct imaging study.

Introduction

Insulinoma is the most common functional pancreatic neuroendocrine tumor, with an incidence of 0.1–0.3 cases per 100,000 persons per year[1]. In over 90% of cases, they are solitary and benign. Patients present with symptoms of hypoglycemia, with blood glucose in the range of 40–

50 mg/dL, and show resolution of symptoms with glucose administration, otherwise known as the Whipple triad[2]. The diagnosis is confirmed by the demonstration of inappropriately elevated insulin and proinsulin levels associated with serum glucose values of less than 50 mg/dL during 48 hour fast period.[3,4] Insulinoma may be associated with a hereditary syndrome in nearly 10% of patients, the most common being multiple endocrine neoplasia type 1 (MEN1)[5].

Insulinomas are evenly distributed throughout the pancreas and are usually less than 2 cm in size in approximately 90% of cases[1]. This makes them challenging to localize by traditional imaging techniques such as transabdominal ultrasound (US), contrast enhanced CT, and MRI. Preoperative invasive localizing studies for insulinoma include endoscopic ultrasound (EUS) with sensitivity of 75%[6], or selective arterial secretagogue injection (SASI) of the major pancreatic arteries with hepatic venous sampling for insulin to regionalize the insulinoma within the pancreas, which has a sensitivity of up to 88%[7]. Exploratory laparotomy with intraoperative ultrasound (IOUS) and bimanual palpation of the pancreas is the most sensitive way to detect insulinoma(s)[7,8]. In cases when intraoperative evaluation fails to localize an insulinoma, blind pancreatic resection is not recommended[9]. Detection of insulinoma using ^{68}Ga-DOTA peptide has been previously reported. Different radioligands targeting somatostatin receptors, including ^{68}Ga-DOTATATE, ^{68}Ga-DOTATOC, and ^{68}Ga-DOTANOC, have been evaluated for detection of neuroendocrine tumors with promising results[10,11]. ^{68}Ga-DOTATATE/DOTATOC PET/CT has been described in the detection of insulinomas[12]. The aim of this study was to evaluate the accuracy of ^{68}Ga-DOTATATE PET/CT as compared to other anatomic imaging modalities, SASI, and IOUS and palpation for localizing insulinoma in patients who were biochemically cured of their insulinomas.

Materials and Methods

Patients were evaluated at the National Institutes of Health (NIH) Clinical Center for insulinoma and underwent a resection of their insulinoma. We included patients who had insulinoma confirmed by histopathology in our cohort. Patients with insulinoma were enrolled in a clinical protocol evaluating the accuracy of ^{68}Ga-DOTATATE PET/CT (NCT01967537) after written informed consent was obtained. This prospective study was performed under an investigational new drug protocol approved by the United States Food and Drug Administration. The study was reviewed and approved by the National Cancer Institute (NCI) review board and the NIH Radiation Safety Committee.

We performed a retrospective analysis of 31 patients who underwent surgery at the NIH clinical center for insulinoma between November 4, 2009 and August 24, 2016, and had insulinoma confirmed by histology and were biochemically cured. Patients' laboratory evaluations included measurements of fasting glucose, insulin, proinsulin, and C-peptide, as well as the duration of the fast until hypoglycemia was documented. The imaging results for CT, MRI, and US, and ^{68}Ga-DOTATATE, SASI, and intraoperative findings were correlated to the histopathology finding.

^{68}Ga-DOTATATE scans were performed in 10 patients as previously described[13,14]. Five mCi of ^{68}Ga-DOTATATE was administered through a peripheral vein. After approximately 60 minutes, the patient was placed in a supine position in a PET/CT scanner (Siemens Medical Solutions USA, Inc. Malvern, PA), and images from the upper thighs to mid-skull (including pituitary gland) were obtained. A low-dose, non-contrast CT was used for attenuation correction and anatomic localization. Maximum standardized uptake value (SUVmax) levels were measured based on patient total body weight.

Data Analyses

We analyzed the ^{68}Ga-DOTATATE PET/CT uptake status by patient demographic, clinical characteristics, familial vs. sporadic insulinoma, and laboratory data. Spearman's correlation coefficient, Student's t-test, and Chi-square tests were used to test for associations between clinical, pathology, and operative variables in patients who did and did not have ^{68}Ga-DOTATATE PET/CT imaging in order to evaluate ^{68}Ga-DOTATATE PET/CT imaging's impact on patient care. A P value < 0.05 was considered statistically significant. IBM SPSS Statistics Data Editor (New York, NY) and Microsoft Excel (Redmond, WA) were used for statistical analyses.

Results

Clinical Characteristics

All patients (n=31) had a supervised fast with a median duration of 12.5 hours (range: 3–41 hours) and the median fasting end glucose was 38 mg/dL (range: 27–49). Twenty-seven patients had sporadic insulinoma and 4 patients had MEN1-associated insulinoma. The demographic and clinical characteristics of the study cohort are summarized in Table 1. Thirteen patients (42%) underwent an open resection of the insulinoma, 10 patients (32%) had a hand-assisted laparoscopic resection, and 8 patients (26%) had a laparoscopic resection. All patients, at the last follow up, were biochemically cured of their insulinoma. A comparison of patients who had ^{68}Ga-DOTATATE imaging to those who did not revealed no significant difference in age, body mass index, glucose, C-peptide, insulin, and proinsulin before and after supervised fasting between those patients (Table 1). There was also no significant difference in the type of operation and duration of the operation, and perioperative outcomes based on having a positive ^{68}Ga-DOTATATE PET/CT scan as compared to patients who did not have the imaging study (Figure 1 and Table 1).

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

Ten patients underwent a ^{68}Ga-DOTATATE scan, and 9 out of 10 (90%) had an insulinoma successfully localized. In 9 patients, the tumor was regionalized using SASI, and the median size of insulinoma was 1.5 cm (range of 0.7–2.5 cm). The gold standard for defining a positive localization result was histology. In all 10 patients, the tumors stained positive for insulin and were well-differentiated. Eight out of 9 tumors had Ki-67 of less than 2% (World Health Organization (WHO) grade I); one had Ki-67 of 3–5% (World Health Organization (WHO) grade II) (^{68}Ga-DOTATATE positive). In 4 patients, the tumor was localized to the distal pancreas; in 3 patients, to the head of the pancreas; and in 3 patients, to the body of the pancreas. Other imaging modalities performed in the 10 patients included CT, MRI, and US. Transabdominal US did not identify an insulinoma in any of the 10 patients. A CT scan accurately localized the insulinoma in 6 out of the 10 patients, and an MRI localized the insulinoma in 8 of the 10 patients. The patient with negative ^{68}Ga-DOTATATE underwent an enucleation of an uncinate process insulinoma. The tumor measured 1.5 cm in the greatest dimension and stained positive for insulin, chromogranin, and synaptophysin. The Ki-67 (MIB-1) labeling index was 1-2% and the mitotic count was 1/10 high power fields. One patient had negative anatomic imaging studies (CT, MRI, and US), and no lesion was identified using intraoperative US. The patient underwent an extended distal pancreatectomy and was biochemically cured. Pathology evaluation demonstrated multiple well differentiated neuroendocrine tumors, largest measuring 4 mm. The neuroendocrine tumors present stained

positively for chromogranin and insulin, and negative for gastrin, glucagon, pancreatic polypeptide and somatostatin.

Accuracy of imaging modalities in entire study cohort

Out of the 31 patients with pathology-confirmed insulinoma, CT accurately localized the lesion in 17 out of 31 patients (55%, average tumor size of 1.37 cm) (Table 2). MRI localized the insulinoma in 17 out of 28 patients (61%, average tumor size of 1.37 cm). In 12 patients, both CT and MRI were positive. Abdominal US accurately localized the insulinoma in 6 out of 28 (21%) of the patients. Intraoperative US was performed in 31 patients, and 29 of them had insulinoma successfully localized (93%). In 23 patients who had an open or hand-assisted laparoscopic exploration, manual palpation identified 19 out of 23 (83%) of the insulinoma. In patients who had all 4 noninvasive imaging studies (CT, MRI, US, and ^{68}Ga-DOTATATE), CT was concordant with ^{68}Ga-DOTATATE in 6 out of 9 patients (67%), MRI in 7 out of 9 (78%), and in 1 out of 9 patients (11%) the lesion was only seen by ^{68}Ga-DOTATATE (Table 3). Transabdominal US was performed in eight patients and did not localize the tumor in any of them.

Discussion

In this study, we compared the results of ^{68}Ga-DOTATATE PET/CT to other preoperative anatomic imaging and SASI to determine the accuracy of ^{68}Ga-DOTATATE. It was positive in 9 out of 10 patients. In 1 of the 10 patients in whom insulinoma was regionalized with SASI, ^{68}Ga-DOTATATE PET/CT was the only positive imaging study, as the other 5 imaging studies were negative. When we compared clinical, biochemical, treatment, patient outcome, and tumor histology, there was no significant difference between patients who underwent ^{68}Ga-DOTATATE PET/CT imaging versus those patients who did not have this imaging.

Insulinomas are associated with significant morbidity and mortality when not treated. The only curative treatment for this tumor is surgical resection. However, localization of insulinoma can be challenging, as most tumors are often less than 2 cm and may be present in any part of the pancreas. Multiple preoperative imaging modalities may be used to localize insulinoma in addition to endoscopic ultrasound, but in most studies, SASI is the most accurate test for regionalizing the tumor. While it is neither necessary nor cost-effective to perform multiple imaging studies in patients with insulinoma, this was done at our institution under a clinical investigation protocol and allowed for a head-to-head comparison to evaluate the clinical utility, if any, of ^{68}Ga-DOTATATE scanning.

^{68}Ga-DOTATATE has a high affinity to somatostatin receptors 2 (SSTR2), which are commonly expressed in neuroendocrine tumors[15]. Prasad and colleagues found that SSTR2 expression in insulinomas is present in up to 80% of cases[12]. ^{68}Ga-DOTATATE PET/CT has been reported to detect neuroendocrine tumors as small as 6 mm in size[11]. One possible advantage of ^{68}Ga-DOTATATE is to exclude the presence of additional pancreatic neuroendocrine tumors not detected by anatomic imaging in inherited syndromes such as MEN1. Although SASI is more accurate for regionalizing insulinomas, it's a costly and invasive test that requires a skilled interventional radiologist, who may not be readily available, and it may be associated with complications. ^{68}Ga-DOTATATE was shown to be safe with total radiation exposure less than that of ^{111}In-DTPA-octreotide and ^{18}F-FDG[16]. To our knowledge, there have been no prospective studies to evaluate the accuracy of ^{68}Ga-DOTATATE PET/CT to localize insulinoma. Prasad and colleagues analyzed the sensitivity of ^{68}Ga-DOTATATE/DOTANOC in a retrospective study for the localization of insulinoma. Seven patients underwent a ^{68}Ga -

DOTANOC, which successfully localized the insulinoma in 6 patients. Six patients underwent ^{68}Ga-DOTATATE, and an insulinoma was localized in 5 of them. Of these 5 patients, one had a benign insulinoma, 2 had malignant insulinomas, and 2 had nesidioblastosis[12]. ^{68}Ga-DOTA-Exendin-4 PET/CT has also been evaluated in patients with insulinoma. Wild and colleagues detected all insulinomas in 2 prospective studies, consisting of 4 patients[17] and 6 patients[18]. Kumar and colleagues evaluated ^{68}Ga-DOTANOC PET/CT imaging in 35 patients suspected to have insulinoma and reported a sensitivity of 25.8% and a specificity of 25%[19].

As the incidence of insulinoma is 0.1–0.3 cases per 100,000 persons per year[1] one of the limitations of our study are low number of patients. In addition, not all of the patients had all of the imaging modalities performed, and only 10 patients underwent ^{68}Ga-DOTATATE PET/CT.

In summary, ^{68}Ga-DOTATATE PET/CT is a non-invasive imaging modality that identifies most insulinomas. It appears to offer limited additional information when other anatomic imaging studies localize the tumor and should be considered an adjunct when all imaging studies are negative in a patient with an insulinoma, especially if a focused or minimally invasive surgical approach is preferred.

Disclosure Statement: The authors have nothing to disclose.

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Figure 1 Representative images of an insulinoma. A. Axial ^{68}Ga-DOTATATE fused PET/CT arrow pointing to the uptake in the pancreas. B. ^{68}Ga-DOTATATE anterior 3D maximum intensity projection (MIP); arrow pointing to the uptake in the pancreas. C. Axial arterial phase CT; arrow pointing to the arterially enhancing lesion in the tail of the pancreas. D. MRI axial 3D with arterial contrast imaging; arrow localizing an arterially enhancing lesion in the tail of the pancreas.

Table 1 Study cohort clinical and biochemical characteristics and treatment

Variables	DOTATATE	No DOTATATE	*P* value (Fisher's exact test)*
Gender			0.68
male	4	7	
female	6	14	
Type of operation			1.0
Open	5	8	
Laparoscopic (+/- hand assist)	5	13	
Complications^			0.42
Pancreatic leak	2	10	
No pancreatic leak	8	11	
Sporadic	7	19	
MEN1	1	3	
Intraoperative findings			
Palpation	5/8	14/15	
Ultrasound	9/10	20/21	
SASI correlated with pathology	9/10	19/20	
	Median	**Range**	***P* value (t-test)#**
Age (years)	57.5	21-75	0.65
BMI (kg/m2)	31	20-49	0.86
Case duration (min)	241	116-508	0.16
Size of insulinoma (cm)	1.5	0.7-2.5	0.08
Fasting end glucose (mg/dL)	38	27-49	0.15
Fasting end insulin (mcU/mL)	23.2	2.7-154	0.24
Fasting end proinsulin (pmol/L)	120	11-890	0.23
Fasting end C-peptide (ng/mL)	3.1	1.4-10.3	0.48
Duration of fasting (hours)	13	3-41	0.62

^All Grade A - self-limited requiring no intervention

***** Comparison between patients with positive ^{68}Ga-DOTATATE scans and those who did not have a ^{68}Ga-DOTATATE scan.

#Mann-Whitney U test was used for the fasting end C-peptide as these values were not normally distributed.

Table 2 Accuracy of localizing studies and intraoperative palpation and ultrasound for insulinoma.*

Imaging modality	^{68}Ga-DOTATATE	CT	MRI	US	SASI	Intraoperative US	Intraoperative Palpation
Rate of detection	9/10 (90%)	17/31 (55%)	17/28 (61%)	6/28 (21%)	28/30 (93%)	29/31 (93%)	19/23 (83%)

*Total number is not the same as not all patients had all of the localizing studies.

Table 3 Concordance between ^{68}Ga-DOTATATE anatomic imaging studies

	^{68}Ga-DOTATATE	Concordance
CT (+)	**6/9**	**67%**
MRI (+)	**7/9**	**78%**
US (+)	**0/9**	**0%**