Diagnostic Performance of Noninvasive Imaging Modalities for Localization of Insulinoma: A Meta-Analysis

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Abstract

Background

Insulinomas is the most common functional neuroendocrine tumor found only in the pancreas. The early detection of insulinoma is of importance. Studies comparing the performance of noninvasive modalities were limited by sample size and heterogeneity between studies. The aim of this meta-analysis was to evaluate the diagnostic performance of PET/CT, SPECT/CT, CT and MRI for the localization of insulinoma, and to provide evidence for clinical practice.

Methods

PubMed, Embase, Cochrane Library, Wanfang Data and China National Knowledge Infrastructure were searched from inception to May 31, 2021. Pooled sensitivity, specificity, positive Likelihood Ratio (+LR) and negative Likelihood Ratio (-LR), diagnostic odds ratio (DOR), and concordance rate were calculated.

Results

A total of 19 studies including 708 patients of insulinoma reached the inclusion criteria. PET/CT imaging demonstrated a pooled sensitivity of 0.79 (95% CI: 0.54–0.92) and a pooled specificity of 0.84 (95% CI: 0.20–0.99). The pooled sensitivity and specificity of SPECT/CT were 0.77 (95% CI: 0.46–0.93) and 0.45 (95% CI: 0.22–0.70). CT showed an overall sensitivity of 0.54 (95% CI: 0.35–0.72) and specificity of 0.75 (95% CI: 0.54–0.88). The pooled sensitivity and specificity for MRI were 0.54 (95% CI: 0.31–0.75) and 0.65 (95% CI: 0.39–0.84), respectively. The concordance rates of PET, SPECT, CT, and MRI were 78% (95% CI: 66%–90%), 74% (95% CI: 52%–97%), 56% (95% CI: 41%–72%), and 53% (95% CI: 33%–73%), respectively.

Conclusion

Results of this study indicate that PET/CT demonstrated superior performance than SPECT/CT, CT and MRI for the localization of insulinoma. GLP-1R based PET/CT manifested better diagnostic performance in comparison with SSTR based PET/CT imaging modality.

Background

Insulinomas is also called insulin β cell tumor, which is a relatively rare tumor found only in the pancreatic tissue [1, 2]. The incidence of sporadic insulinoma is 1–4 cases/per million/per year [3, 4]. It is a major cause of endogenous hyperinsulinemic hypoglycemia (EHH) in nondiabetic individuals [5]. Approximately 90% of these tumors are solitary and benign, 10% of them are malignant [6]. In the presence of metastases, insulinoma is often considered malignant [7], accurate diagnosis is essential due to the severe hypoglycemia that may lead to life-threatening consequences [8]. Pancreas-preserving surgery remains the only curative treatment of insulinoma, nearly 95% – 100% of cases can be cured by surgery [9, 10]. Unfortunately, surgery is unlikely effective in malignant insulinomas which are often diagnosed with liver metastases [11–14]. In addition, the first problem is the exact preoperative location of the tumor, because in about 10% of cases of insulinoma, conventional diagnostic modalities such as computed tomography (CT), magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS) manifested low sensitivity (CT: 33% – 64%, MRI: 33% – 64%, EUS: 82% – 94%) [15–18].

Molecular imaging technology has developed rapidly and plays an important role in the diagnosis of insulinoma in recent decades [1]. Somatostatin receptor (SSTR), glucagon-like peptide-1 receptor (GLP-1R), 6-[^{18}F]-l-fluoro-l-3,4-dihydroxyphenylalanine (^{18}F -FDOPA), and 2-[^{18}F] fluoro-2-deoxy-d-glucose (FDG) are commonly used as targets of

these methods, radioactively labelled peptide analogues targeting SSTR and GLP-1R are the most described in previous studies [19]. Unfortunately, because the low expression of SSTR on the surface of tumor cells, the sensitivity of radiolabeled somatostatin analogues scintigraphy varied from 20–85% [20–22]. Interestingly, almost all insulinoma tissues expressed GLP-1 receptor at high level [23, 24]. Nevertheless, there are two pitfalls in the detection of insulinomas with GLP-1R, such as low stability and fast deiodination, which confine its clinical application [25]. Exendin-4 is a natural GLP-1 analog, its half-life is longer than 20 min [26]. GLP-1R targeted radioligands (^{111}In -DOTA-exendin-4, ^{111}In -DTPA-exendin-4, ^{68}Ga -NODAGA exendin-4, ^{68}Ga -DOTA-exendin-4) have been used as a potential method for insulinoma localization with small sizes, which showed higher sensitivity than conventional imaging modalities [27–30]. With regard to the type of molecular imaging modalities, PET possesses a higher spatial resolution and sensitivity over SPECT and provides accurate quantification of tracer uptake [31].

Previous studies with small sample-sizes have investigated the efficacy of PET/CT and SPECT/CT over conventional imaging techniques for insulinoma localization. The results of these studies were heterogeneous. Therefore, the purpose of this study was to conduct a meta-analysis by synthesizing the published evidence to generate an accurate comparison of the diagnostic performance of PET/CT, SPECT/CT, CT and MRI for the localization of insulinoma, and secondly to provide evidence and hints for clinical decision-making and implement.

Materials And Methods

Data source and study selection

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) [32]. We searched online databases PubMed, Embase, Cochrane Library, Wanfang Data and China National Knowledge Infrastructure to retrieve published articles in both English and Chinese languages from the earliest date to May 31, 2021. Search terms were used as follows: PET, SPECT, CT, MRI, positron emission tomography, single photon emission computed tomography, computerized tomography, magnetic resonance imaging, and insulinoma. The reference lists of all primary studies were manually searched to retrieve potentially eligible articles. Inclusion criteria were as follows: PET/CT, SPECT/CT, CT and MRI are used in the detection of patients with suspected insulinoma; histopathology was used as the gold standard to evaluate diagnostic performance; studies reported the exact numbers of participants evaluated as true positive (TP), false positive (FP), true negative (TN), false negative (FN) under respective imaging modalities or these parameters could be calculated based on the other results in the articles. If studies recruited participants over the same period of time or from the same study center, only the researches with the most pertinent outcomes was included to avoid duplications. The types of research included prevalence surveys, case-control studies, longitudinal studies and randomized controlled trials (RCTs). Case reports, conference abstracts, and successive cases seen in a unit were excluded. Two independent investigators conducted the process of literature search and study inclusion. When disagreement occurred, they discussed their arguments, and a third reviewer was involved while no consensus was achieved.

Data Extraction And Quality Assessments

Data were extracted by two independent investigators from each included article. Name of the first author, year of publication, total number of participants, duration of insulinoma, age, gender of patients, type of insulinoma, absolute numbers of participants with TP, FP, TN, and FN outcomes were collected. The QUADAS-2, a revised tool for the quality assessment of diagnostic accuracy studies, was used for the assessment of methodological quality, risk of bias and applicability concerns of the included studies [33, 34].

Statistical analysis

The Stata 16.0 software and Review Manager 5.3 software were utilized for statistical analysis in this study. A P value less than 0.05 was considered to be statistically significant. We calculated pooled sensitivity, specificity, positive Likelihood Ratio (+ LR) and negative Likelihood Ratio (-LR), diagnostic odds ratio (DOR), concordance rate (number of patients detected by imaging modalities compared reference standard) and the 95% confidence intervals (CIs) using maximum likelihood estimates. Summarized receiver operating characteristic (SROC) curves were used for comparison of diagnostic performance of different modalities. The Cochran Q and the I^2 statistics were used to assessed the heterogeneity of results between studies included. I^2 values in the ranges of 0–25%, > 25–50%, > 50–75%, and > 75% reveal insignificant, low, medium, and high heterogeneity, respectively [35]. Moreover, funnel plots were created to assess publication and related bias. We used a Deeks' method to statistically examine the asymmetry of the funnel plot so as to detect potential publication bias.

Results

Study selection and characteristics

A total of 482 articles were identified from the databases searched. One hundred and seventeen duplicates were removed and 264 studies were excluded through an initial screening. After a full text assessment for eligibility of the remaining 101 articles, 19 studies were identified for inclusion in this meta-analysis. No additional studies were found through reference screening of the included papers. Figure 1 shows the flow of the literature search and study selection process. The included 19 studies containing a total of 708 patients with diagnosed or suspected insulinoma, provided relevant detection results of PET/CT, SPECT/CT, CT and MRI in those participants. These articles were published from 1996 to 2020. Table 1 showed details of the studies included.

Table 1
Characteristics of studies included

Study	Year of publication	Country	No. of patients	Mean Age, y (SD)	Male, No. (%)	Type of radiotracer	Patient selection
Zimmer	1996	Germany	10	58.4(14.0)	20	¹¹¹ In-pentetreotide	Patients with suspected insulinoma
Proye	1998	France	10	46(2.7)	33	¹¹¹ In-pentetreotide	Patients with confirmed insulinoma
Schillaci	2000	Italy	14	46.5(15.5)	57.1	¹¹¹ In-pentetreotide	Patients with suspected insulinoma
Christ	2013	Germany, Switzerland, and the UK	25	55	37	¹¹¹ In-DTPA-exendin-4	Patients with suspected insulinoma
Antwi	2015	Switzerland	5	54.0 (10.6)	40	⁶⁸ Ga-DOTA-exendin-4, ¹¹¹ In-DOTA-exendin-4	Patients with suspected insulinoma
Luo	2016	China	52	NR	44.2	⁶⁸ Ga-NOTA-exendin-4	Patients with confirmed insulinoma
Prasad	2016	Germany	13	53.1	30.8	⁶⁸ Ga-DOTATATE/DOTATOC	Patients with confirmed insulinoma
Sharma	2016	India	35	38.4(16.5)	NR	⁶⁸ Ga-DOTANOC	Patients with suspected insulinoma
Sowa-Staszczak	2016	Poland	25	65.5(12)	37.5	^{99m} Tc-GLP1	Patients with suspected insulinoma
Wei	2016	China	33	48	30.3	NR	Patients with confirmed insulinoma
Nockel	2017	USA	31	57.5	35.5	⁶⁸ Ga-DOTATATE	Patients with confirmed insulinoma

NR, not reported.

Study	Year of publication	Country	No. of patients	Mean Age, y (SD)	Male, No. (%)	Type of radiotracer	Patient selection
Zhu	2017	China	70	46	47.1	NR	Patients with suspected insulinoma
Antwi	2018	Switzerland	52	49	23	⁶⁸ Ga-DOTA-exendin-4	Patients with suspected insulinoma
Luo	2018	China	69	43.2	53.6	⁶⁸ Ga-NOTA-exendin-4	Patients with suspected insulinoma
Nakuz	2018	Austria	10	53	20	¹⁸ F-FDOPA	Patients with confirmed insulinoma
Leroy-Freschini	2019	France	24	52.5(14.2)	25	¹⁸ F-FDOPA	Patients with suspected insulinoma
Pallvi	2019	India	8	30	62.5	⁶⁸ Ga-DOTA-exendin-4	Patients with suspected insulinoma
Garg	2020	India	14	34.1(15.8)	50	⁶⁸ Ga-DOTATATE, ⁶⁸ Ga-NODAGA-exendin-4	Patients with suspected insulinoma
Kalff	2020	Australia	24	52.6(19.2)	54.2	⁶⁸ Ga-DOTA-Exendin-4	Patients with suspected insulinoma
NR, not reported.							

Quality Of Studies

Quality assessment by QUADAS-2 scale showed that 13 studies had low risk of bias for patient selection, 1 study had high risk of bias and 5 studies had unclear risk. 13 studies had low risk of bias for index test, risk of bias for others were unclear. Twelve studies had low risk of bias for reference standard, 1 study had high risk of bias, and 6 had unclear risk of bias. In the part of flow and timing, 3 studies had unclear risk of bias, 2 had high risk and 14 had low risk. Clinical applicability concerns of each study included were also evaluated (Fig. 2).

Diagnostic Performances Of Imaging Modalities

Eight studies reported outcomes of PET/CT imaging in the detection of insulinoma. They demonstrated a pooled sensitivity of 0.79 (95% CI: 0.54–0.92, $I^2 = 91.5\%$, $p < 0.01$) and a pooled specificity of 0.84 (95% CI: 0.20–0.99, $I^2 =$

76.3%, $p < 0.01$). The pooled sensitivity and specificity of SPECT/CT were 0.77 (95% CI: 0.46–0.93, $I^2 = 87.4\%$, $p < 0.01$) and 0.45 (95% CI: 0.22–0.70, $I^2 = 0$, $p = 0.79$). CT showed an overall sensitivity of 0.54 (95% CI: 0.35–0.72, $I^2 = 80.2\%$, $p < 0.01$) and specificity of 0.75 (95% CI: 0.54–0.88, $I^2 = 0$, $p = 0.48$). The pooled sensitivity and specificity for MRI were 0.54 (95% CI: 0.31–0.75, $I^2 = 75.0\%$, $p < 0.01$) and 0.65 (95% CI: 0.39–0.84, $I^2 = 0$, $p = 0.53$), respectively (Fig. 3). The AUC values for PET, SPECT, CT and MRI were 0.86 (95% CI: 0.83–0.89), 0.49 (95% CI: 0.44–0.53), 0.74 (95% CI: 0.70–0.78) and 0.65 (95% CI: 0.60–0.69) (Fig. 4).

The concordance rates of PET, SPECT, CT, and MRI were 78% (95% CI: 66%–90%, $I^2 = 75.0\%$, $p < 0.01$), 74% (95% CI: 52%–97%, $I^2 = 92.8\%$, $p < 0.01$), 56% (95% CI: 41%–72%, $I^2 = 85.1\%$, $p < 0.01$), and 53% (95% CI: 33%–73%, $I^2 = 88.4\%$, $p < 0.01$) (Fig. 5).

Subgroup Analysis Of Molecular Imaging Modalities

The number of studies on GLP-1R or GLP-1R analog-based PET/CT was 7, the pooled sensitivity and specificity were 0.87 (95% CI: 0.62–0.97, $I^2 = 87.5\%$, $p < 0.01$) and 0.94 (95% CI: 0.24–1.00, $I^2 = 75.6\%$, $p < 0.01$). Two studies reported the results of somatostatin receptor-based PET/CT in the detection of insulinoma, the overall sensitivity and specificity were 0.39 (95% CI: 0.24–0.56, $I^2 = 89.4\%$, $p < 0.01$) and 0.14 (95% CI: 0–0.58, $I^2 = 19.5\%$, $p = 0.265$). With regard to SPECT/CT, the pooled sensitivity and specificity for GLP-1R or GLP-1R analog-based imaging were 0.83 (95% CI: 0.73–0.91, $I^2 = 79.8\%$, $p = 0.007$) and 0.40 (95% CI: 0.12–0.74, $I^2 = 0$, $p = 0.394$), respectively. For somatostatin receptor-based scanning, the pooled sensitivity and specificity were 0.53 (95% CI: 0.36–0.69, $I^2 = 87.6\%$, $p < 0.001$) and 0.50 (95% CI: 0.12–0.88, $I^2 = 0$, $p = 0.962$) (Table 2).

Table 2
Results of subgroup analysis of molecular imaging modalities

Modalities	Sensitivity	Specificity	+LR	-LR	DOR	AUC
PET/CT	0.79	0.84	5	0.25	20	0.86
GLP-1R analog-based	0.87	0.94	15	0.14	111	0.95
SSTR-based	0.39	0.14	-	-	-	-
SPECT/CT	0.77	0.45	1.4	0.51	3	0.49
GLP-1R analog-based	0.83	0.4	-	-	-	-
SSTR-based	0.53	0.5	-	-	-	-

Publication Bias

Deeks' funnel plot asymmetry tests yielded p-values of 0.02, 0.36, < 0.01 and 0.09 for PET/CT, SPECT/CT, CT and MRI, respectively.

Discussion

The application of cancer imaging has been involved in the entire process of the management of patients with confirmed insulinoma for decades [36]. Different imaging modalities (MRI, CT and ultrasonography) have been used for insulinoma localization, but they showed low accuracy and sensitivity in previous studies [37–39], the main reason

may be that the size of insulinomas are evenly distributed throughout the pancreas and less than 2 cm in size in most cases [40]. With the development of SPECT and PET imaging, this issue can be addressed owing to improved spatial resolution and more accurate quantification in the localization of insulinoma [25, 41]. In this meta-analysis, we evaluated the diagnostic performance of PET/CT, SPECT/CT, CT and MRI for the localization of insulinoma, which were not researched in previous meta-analyses. In addition, we compared the diagnostic performance of GLP-1R based PET/CT and SSTR based PET/CT imaging modalities in this meta-analysis. These are the We had planned to conduct a meta-analysis based on individual data, unfortunately, these data were not easy to obtain, thus all statistical analyses were conducted on study level. The number of studies on PET or SPECT were small according our preliminary research, so we included studies on PET/CT, SPECT/CT, CT and MRI which are used in the detection of insulinoma. Nineteen studies with a total of 708 patients with diagnosed insulinoma were enrolled in the meta-analysis. Results of pooled analyses showed that PET/CT exhibited higher pooled sensitivity over conventional noninvasive imaging techniques (CT and MRI). The AUC value of PET/CT imaging superior to other modalities. PET/CT showed the highest concordance rate compared to gold standard. GLP-1R based PET/CT manifested better diagnostic performance in comparison with SSTR based PET/CT imaging modality.

In this meta-analysis, we did a detailed literature search in both Chinese and English language to enhance the probability to retrieve all relevant studies as we can. Data extraction was conducted by two independent investigators using a pre-designed form. Besides, we assessed the heterogeneity between studies included, quality of each study along with publication bias. Heterogeneity for between studies included was detected, the results of studies can be consolidated with caution. The potential source of heterogeneity between studies may be the demographic characteristic of participants, study design, duration of insulinoma, type of radiotracers, and type of imaging equipment. We intended to conduct the meta-regression to statistically investigate the reason for the heterogeneity between studies included, unfortunately, the numbers of studies in each subgroup were inadequate for meta-regression due to the inclusion criteria of this study. It is hoped that with the increased of the number of studies or the adjustment of inclusion criteria, this analysis can be carried out in the future. Furthermore, Deeks' funnel plot asymmetry tests indicated that publication bias may not affect the pooled results between studies.

Based on the outcomes of this meta-analysis, we may conclude that GLP-1R based PET/CT imaging for localization of insulinoma demonstrates favorable imaging results and diagnostic accuracy. It is suggested that this method should be utilized in patients with inconspicuous or inconclusive results on conventional imaging to improve diagnostic accuracy and avoid misdiagnosis in clinical practice. Furthermore, potentially powerful tracers with high availability are in need for development.

Abbreviations

EHH, endogenous hyperinsulinemic hypoglycemia

GLP-1R, glucagon-like peptide-1 receptor

SSTR, somatostatin receptor

EUS, endoscopic ultrasound

US, ultrasonography

MRI, magnetic resonance imaging

SPECT, single photon emission computed tomography

PET, positron emission tomography

CT, computerized tomography

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analysis

TP, true positive

FP, false positive

TN, true negative

FN, false negative

+LR, positive likelihood ratio

-LR, negative likelihood ratio

DOR, diagnostic odds ratio

CI, confidence interval

SROC, summary receiver operating characteristic

AUC, area under the SROC curve

QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies-2

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' Contributions

YY and JZ conceived and designed this study. YY and JS were responsible for the collection, extraction, and analysis of the data. YY and JS was responsible for data analysis and writing the paper. YY and JS performed the quality evaluation of the writing and polished the English language. All authors reviewed the paper and reached an agreement to approve the final manuscript.

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Figures

Figure 1

Flow chart of study selection

Figure 2

Methodological quality assessment of studies included

Figure 3

Forest plots for diagnostic performance of PET/CT, SPECT/CT, CT and MRI A: Forest plots for diagnostic performance of PET/CT. B: Forest plots for diagnostic performance of SPECT/CT. C: Forest plots for diagnostic performance of CT. D: Forest plots for diagnostic performance of MRI.

Figure 4

Forest plots for the concordance rates of PET/CT, SPECT/CT, CT and MRI A: Forest plot for the concordance rates of PET/CT. B: Forest plot for the concordance rates of SPECT/CT. C: Forest plot for the concordance rates of CT. D: Forest plot for the concordance rates of MRI

Figure 5

SROC curves for diagnostic performance of PET/CT, SPECT/CT, CT and MRI A: SROC curve for diagnostic performance of PET/CT. B: SROC curve for diagnostic performance of SPECT/CT. C: SROC curve for diagnostic performance of CT. D: SROC curve for diagnostic performance of MRI.