Abstract: We investigated the diagnostic performance of Somatostatin Receptor Positron Emission Tomography/Computed Tomography (SSR-PET/CT) for the detection of primary lesion and initial staging of pancreatic neuroendocrine tumors (pNETs). A comprehensive literature search up to January 2020 was performed selecting studies in presence of: sample size ≥10 patients; index test (i.e., 68Ga-DOTATOC or 68Ga-DOTANOC or 68Ga-DOTATATE PET/CT); and outcomes (i.e., detection rate (DR), true positive, true negative, false positive, and false-negative). The methodological quality was evaluated with QUADAS-2. Pooled DR and pooled sensitivity and specificity for the identification of the primary tumor were assessed with a patient-based and a lesion-based analysis. Thirty-eight studies were selected for the qualitative analysis, while 18 papers were included in the meta-analysis. The number of pNET patients ranged from 10 to 142, for a total of 1143 subjects. At patient-based analysis, the pooled sensitivity and specificity for the assessment of primary pNET were 79.6% (95% confidence interval: 71–87%) and 95% (95%CI: 75–100%), with a heterogeneity of 59.6% and 51.5%, respectively. Pooled DR for the primary lesion was 81% (95%CI: 65–90%) and 92% (95%CI: 80–97%), respectively, at patient-based and lesion-based analysis. In conclusion, SSR-PET/CT has high DR and diagnostic performances for primary lesion and initial staging of pNETs.

Keywords: pancreas; neuroendocrine tumors; positron emission tomography; somatostatin receptor analogs
1. Introduction

The incidence of pancreatic neuroendocrine tumors (pNETs) is less or equal to one case per one hundred thousand people per-year, and they account for roughly 5% of all pancreatic cancers. However, in the last few decades, their incidence has risen [1,2].

Many biological features make these tumors clinically heterogeneous, including mutational status [3,4], hormone production, and histopathological grade. Among them, NETs grading, which is mainly related to Ki-67 expression and mitotic index, has several diagnostic, therapeutic, and prognostic implications. In well-differentiated pNETs (G1, G2, and well-differentiated G3) the slow cancer growth is related to good long-term survival even in the presence of liver metastases [5], while poorly differentiated G3 neuroendocrine carcinomas (NECs) show higher proliferation rates and lower overall survival [6]. Moreover, tumor grade is strictly related to the expression of somatostatin receptors (SSR1-5) on the neoplastic cellular surface [6,7]. In low-grade pNETs, the high SSR expression allows the therapeutic use of somatostatin analogs and makes these neoplasms ideal for targeted radionuclide imaging [8]. In contrast, the down-regulation of SSR makes high-grade NEC less suitable for these approaches.

Currently, three radio-labelled somatostatin analogs are used in the clinical practice for targeted SSR radionuclide imaging of pNETs: 68Ga-DOTATATE (DOTA, Tyr(3)-octreotate), 68Ga-DOTANOC (DOTA,1-Nal(3)-octreotide), and 68Ga-DOTATOC (DOTA, D-Phe1, Tyr (3)-octreotide). Although these positron-emitting radiotracers have a different affinity to the various types of SSR [9], they showed a similar diagnostic accuracy [10,11].

Targeted SSR molecular imaging with positron emission tomography and computed tomography (PET/CT) plays a significant role in pNETs clinical management, particularly in the staging phase. Indeed, surgery is the only curative treatment approach, and an accurate assessment of both tumor detection and disease widespread is of utmost importance to avoid unsuccessful procedures. In the present systematic review and meta-analysis, we investigate the diagnostic performance of SSR-PET/CT for the detection of the primary lesion and initial staging of pNETs.

2. Materials and Methods

2.1. Literature Search

Four researchers (G.S., A.B., A.M., and A.V.) performed a bibliographic analysis until 1 January 2020, by including PubMed, Scopus, Embase, and Google Scholar databases. The terms “pancreas”, “neuroendocrine”, “NET”, “Positron Emission Tomography”, “Positron Emission Tomography/Computed Tomography”, “68Gallium”, “DOTA”, “somatostatin receptor”, “staging”, “diagnosis”, and “detection” were used for the bibliographic search, in each database. Additional filters, such as English language, original article and research article, and study including only humans, were used. Reviews, clinical reports, meeting abstracts, and editor comments were excluded. Four independent reviewers (A.G.N., V.F., P.G., and C.F.) evaluated the full texts of the selected papers. Furthermore, to improve the selection of the papers, the references of the studies included were assessed and included in the research strategy.

The systematic review was carried out using the standard methods [12], and graphically showed in accordance with the PRISMA guidelines [13]. All studies that fulfilled the inclusion criteria were considered eligible for the systematic review and meta-analysis: (a) a sample size ≥10 patients; (b) 68Ga-DOTATOC, 68Ga-DOTANOC, or 68Ga-DOTATATE PET/CT as index tests; (c) detection rate (DR), true positive (TP), true negative (TN), false positive (FP), and false-negative (FN), which allowed us to construct 2 × 2 contingency tables. In case of studies from the same group of researchers, only the report with the highest number of enrolled patients was considered for the meta-analysis.

2.2. Quality Evaluation and Statistical Analysis

The overall quality of the studies was assessed by using the Quality Assessment of Diagnostic Accuracy Studies tool (QUADAS-2) [14]. Meta-Analyist (version Beta 3.13) [15] and Comprehensive
meta-analysis software were used to carry out the meta-analysis. Heterogeneity was tested using the $\chi^2$ and the I$^2$ tests. The heterogeneity was considered low, moderate, or high in case of a value equal to 25%, 59%, and 75%, respectively [12]. The meta-analysis was carried out with the random-effects model, in accordance with the recommendation of the Cochrane Oral Health Group. The pooled detection rate was calculated for the identification of the primary pNETs. Pooled sensitivity, pooled specificity, positive and negative likelihood ratio ($LR^+$ and $LR^-$), and diagnostic odds ratio (DOR) with 95% confidence intervals (95%CIs) for the evaluation of primary pNET were also computed. Patient-based and lesion-based analyses were carried out. Publication bias was assessed using a funnel plot.

3. Results

3.1. Search Results

The literature search revealed 132 articles. Reviewing titles, abstracts, and full texts, we excluded 94 articles. Therefore, 38 studies were selected and included in the qualitative analysis, while 18 articles were considered for the meta-analysis (Figure 1).

![Figure 1. PRISMA flow-chart. Selection process of studies included in the qualitative and quantitative analysis according to the PRISMA flow diagram [13].](image)

3.2. Study Characteristics

The clinical and technical characteristics of included studies are detailed in Tables 1 and 2, respectively, while the study quality assessment is reported in Figure 2. Selected articles were published by researchers from Europe, USA, and Asia. Twenty-two studies were retrospective and 16 studies were prospective. The number of enrolled pNET patients ranged from 10 to 142, and a total of 1143 pNET patients were included. The mean and median age of the patients ranged from 40 to 65 years. Among studies that analyzed tumor grading ($n = 18$), early grading (G1-G2) was more frequent than advanced (G3), despite deriving this data for pNET was not possible. SSR-PET/CT imaging was performed exclusively in the staging or preoperative setting in 18 studies. While most studies were conducted on pNET patients irrespectively to the tumor function, the study by Nockel et al. [16] was focused on patients affected by insulinoma. Similarly, a few studies were focused on hereditary pNETs, including Von Hippel-Lindau (VHL) syndrome [17,18] and Multiple Endocrine Neoplasia Type 1 (MEN-1) [19–21].
Table 1. Characteristics of included studies.

| Reference | Year | Journal | Country | Study Design | Setting | N Pancreas/N Patients | Mean Age (Range) | Grading | Type of Treatment (n) | Detection of Suspected pNET-Diagnosis | Staging |
|-----------|------|---------|---------|--------------|---------|-----------------------|-----------------|---------|----------------------|----------------------------------------|---------|
| [22]      | 2007 | J Nucl Med | Austria | prospective | diagnosis, staging, restaging | 18/84 | 58 (28–79) | nr | 6 surgery | 16 surgery + long-acting somatostatin analogs | 13 36 |
| [23]      | 2009 | J Nucl Med | Austria | retrospective | staging and restaging | 11/51 | Nr (32–87) | nr | 7 surgery + chemotherapy | 16 surgery + long-acting somatostatin analogs | 0 11 |
| [24]      | 2010 | Clin Nucl Med | Italy | retrospective | diagnosis | 11/19 | 56 (21–80) | 9 WDET 4 WDEC | none | 11 0 |
| [25]      | 2010 | J Nucl Med | UK | retrospective | staging, restaging | 13/51 | 55.5 | 28 G1 19 G2 4 G3 | 9 surgery 27 long-acting somatostatin analogs | 0 13 |
| [26]      | 2010 | Ann Surg | Germany | prospective | diagnosis, staging | 27/52 | 52 (24–76) | 51 G1-G2 1 G3 | none | 1 26 |
| [27]      | 2010 | EJNMMI | Germany-Italy | retrospective | diagnosis | 16/59 | 65 | 16 G1 2 G2 4 G3 13 nr | none | 16 0 |
| [28]      | 2010 | Neuroendocrinology | Germany | retrospective | diagnosis, staging, restaging | 18/66 | 56 (20–79) | nr | 33 surgery 4 surgery + chemotherapy 2 long-acting somatostatin analogs | nr |
| [29]      | 2011 | Eur Radiol | India | retrospective | diagnosis and staging | 20/20 | 42.5* | nr | none | 17 3 |
| [30]      | 2011 | AJR | India | prospective | staging, restaging | 26/109 | 50* (21–76) | nr | 11 surgery + long-acting somatostatin analogs 2 surgery + chemotherapy or radiotherapy | 0 26 |
Table 1. Cont.

| Reference | Year | Journal       | Country | Study Design | Setting                                                                 | N Pancreas/N Patients | Mean Age (Range) | Grading | Type of Treatment (n) | Detection of Suspected pNET-Diagnosis n | Staging n |
|-----------|------|---------------|---------|--------------|--------------------------------------------------------------------------|-----------------------|------------------|---------|----------------------|------------------------------------------|-----------|
| [31]      | 2012 | Clin Nucl Med | Israel  | retrospective | diagnosis, treatment response evaluation, detection of SSTR expression   | 40/96                | 59 (16–89)       | nr      | Nr                   | 0                                        | 40         |
| [32]      | 2012 | Eur Radiol    | Austria | retrospective | diagnosis, staging, restaging                                            | 19/55                | 62 (37–80)       | 34 G1   | 10 G2 4 G3            | 19                                        | 0         |
| [33]      | 2012 | EJNMMI        | Italy   | retrospective | staging, restaging                                                         | 10/131               | nr               | nr      | nr                   | 10                                        | 0         |
| [34]      | 2013 | EJNMMI        | Austria | retrospective | staging and restaging                                                     | 22/249               | 59.5 (15–90)      | nr      | nr                   | nr                                        | nr         |
| [35]      | 2013 | EJNMMI        | Germany | retrospective | diagnosis                                                                  | 18/18                | 56 (26–80)       | nr      | 6 surgery other nr   | 18                                        | 0         |
| [10]      | 2013 | Recent Results Cancer Res | Germany | prospective | before PRRT                                                                | 9/27                 | 62 (46–81)       | nr      | 7 surgery + chemotherapy + PRRT 5 surgery + long-acting somatostatin analogs 2 none 6 other | 9                                        | 0         |
| [36]      | 2014 | Clin Nucl Med | Poland  | retrospective | staging or restaging after surgery                                        | 56/245               | 56 (18–78)       | G1: 103 | G2: 142              | 35 surgery 12 PRRT 6 chemotherapy 16 long-acting somatostatin analogs | 0         | 56         |
| [37]      | 2014 | Nucl Med Comm | United Kingdom | retrospective | diagnosis, staging after surgery, treatment response evaluation, detection of SSTR expression | 38/138               | 56 (20–84)       | nr      | nr                   | 0                                        | 38         |
| Reference | Year | Journal | Country | Study Design | Setting | N Pancreas/N Patients | Mean Age (Range) | Grading | Type of Treatment (n) | Detection of Suspected pNET-Diagnosis n | Staging n |
|-----------|------|---------|---------|--------------|---------|----------------------|----------------|---------|----------------------|--------------------------------------|----------|
| [38] 2015  | Pancreas | Germany | retrospective | staging | 19/19 | 58 (33–72) | G1: 3  G2: 15  G3: 1 | Pre-operative | 0 | 19 |
| [19] 2015  | J Am Coll Surg | USA | prospective | staging, restaging | 26/26 | 42 (19–82) | nr | 10 surgery 16 none | 12 | 14 |
| [39] 2015  | Ann Surg Oncol | Germany | prospective | staging | 18/44 | 56 (32–77) | nr (but all G1-G2) | Pre surgery | 0 | 18 |
| [40] 2015  | J Nucl Med | Denmark | prospective | staging, restaging | 11/59 | 61 (32–81) | G1: 12  G2: 40  7 nr | 32 surgery ** 27 interferon ** 19 PRRT ** 16 chemotherapy ** | 0 | 11 |
| [41] 2015  | Abdom Imaging | India | retrospective | staging, restaging | 141/141 | 46 (6–81) | nr | nr | 88 | 0 |
| [42] 2015  | J Nucl Med | UK | retrospective | all | 142/728 | 54 (15–86) | G1: 260  G2: 89  G3: 63 | nr nr | nr | |
| [43] 2016  | EJNMMI | Germany | prospective | diagnosis | 20/20 | 45 (22–64) | nr | nr | 20 | 0 |
| [20] 2016  | Endocrine | Italy | prospective | diagnosis | 11/18 | 40 (16–61) | nr | nr | 11 | 0 |
| [17] 2016  | Pancreas | Italy | retrospective | staging, treatment response evaluation | 25/25 | 58 (27–84) | G1: 7  G2: 7  G3: 2  nr: 9 | 16 naive 6 SST analogs 1 PRRT1 PRRT + Chemotherapy 1 PRRT + SST analogs | 0 | 25 |
| [21] 2016  | EJNMMI | France | prospective | diagnosis and restaging | 19/19 | 47 (26–70) | nr | surgery | 4 | 15 |
| [44] 2016  | J Nucl Med | USA | prospective | diagnosis, staging, treatment response | 22/97 (gastro-entero-pancreatic) | 54 | G1: 24  G2: 37  G3: 30 nr | 51 long-acting somatostatin analogs other nr | 0 | 22 |
| [45] 2016  | Eur Radiol | Germany | retrospective | diagnosis, staging | 12/38 | 63 (34–76) | G1: 16  G2: 8 | none | 12 | 0 |
| [46] 2016  | JCO | USA | prospective | diagnosis | 31/131 | 51 (19–82) | nr | none | 31 | 0 |
| Reference | Year | Journal                  | Country | Study Design | Setting                      | N Pancreas/N Patients | Mean Age (Range) | Grading | Type of Treatment (n) | Detection of pNED-Diagnosis | Staging n |
|-----------|------|--------------------------|---------|--------------|------------------------------|-----------------------|------------------|----------|-----------------------|-------------------------------|------------|
| [47]      | 2016 | Clin Radiol              | Japan   | retrospective | diagnosis, staging, restaging | 19/54                | 55 (27–81)       | nr       | nr                    | 8                            | 20         |
| [16]      | 2017 | J Clin Endocrinol Metab  | Switzerland | retrospective | diagnosis                    | 10/31                | 57.5* (21.75)    | G1: 8   | G2: 1                 | surgery                         | 10         | 0         |
| [48]      | 2017 | Pancreas                 | Italy   | retrospective | diagnosis                    | 35/35                | 59 (41–84)       | G1: 10  | G2: 25                | surgery                         | 35         | 0         |
| [49]      | 2017 | EJSO                     | Italy   | prospective   | diagnosis, prognostication    | 124/124              | 55                | G1: 6   | G2: 7, G3: 1, 3     | None                          | 0          | 124       |
| [50]      | 2018 | J Formos Med Assoc       | Taiwan  | prospective   | diagnosis                     | 10/17                | 56 (24–84)       | G1: 6   | G2: 7, G3: 1, 3 nr  | nr                           | 10         | 0         |
| [51]      | 2019 | AOJNMB                   | Turkey  | retrospective | staging metastases detection  | 19/38                | 50* (27–80)      | G1: 18  | G2: 20                | nr                        | 0          | 19        |
| [18]      | 2019 | Eur J Radiol             | USA     | prospective   | diagnosis                     | 36/36                | 46                | nr      | nr                    | nr                        | 36         | 0         |
| [52]      | 2019 | EJNMMI Research          | Finland | prospective   | diagnosis, prognostication    | 31/31                | 60 (20–83)       | G1: 13  | G2: 8, G3: 1       | nr                        | 0          | 31        |

* median; ** possible combination of different therapies not explained in the paper; PRRT: peptide receptor radiation therapy; SSTR: somatostatin receptors; WDET, well-differentiated endocrine tumor; WDEC, well-differentiated endocrine cancer; PD poorly differentiated; nr: not reported.
Table 2. Technical features of included studies.

| Reference | Device | Radiotracer (Peptide) | Activity Injected MBq Mean (Range) | Uptake Time Min Mean (Range) | PET Analysis | Semiquantitative Parameters | SUVmax Mean (Range) |
|-----------|--------|-----------------------|-----------------------------------|-----------------------------|--------------|----------------------------|---------------------|
| [22]      | PET    | DOTATOC               | 150                               | 20, 60, 100                 | visual and semiquantitative | SUVmax           | nr                  |
| [23]      | PET/CT | DOTATOC               | 150                               | 60–90                       | visual        |                           | /                   |
| [24]      | PET/CT | DOTATOC               | 1.5–2 MBq/Kg                      | 60                           | visual        |                           | /                   |
| [25]      | PET/CT | DOTATATE              | 120–200                           | 60                           | visual        |                           | /                   |
| [26]      | PET/CT | DOTATOC               | 120–250                           | 60                           | visual and semiquantitative | SUVmax           | nr                  |
| [27]      | PET/CT | DOTANOC               | 100 (46–260)                      | 60                           | visual and semiquantitative | SUVmax           | 18.6 (7.8–34.8)     |
| [28]      | PET & PET/CT | DOTATOC | 100–120                           | 60                           | visual        |                           | /                   |
| [29]      | PET/CT | DOTATOC               | 132–222                           | 30–45                        | visual and semiquantitative | SUVmax           | 12.6 (8.8–27.6) only in pancreas |
| [30]      | PET/CT | DOTANOC               | 132–222                           | 45–60                        | visual and semiquantitative | SUVmax           | 13 * (1–125)       |
| [31]      | PET/CT | DOTANOC               | 132 (77–196)                      | 73 (50–120)                 | visual and semiquantitative | SUVmax           | 26 (5.5–165)       |
| [32]      | PET/CT | DOTATOC               | 150                               | 90                          | visual        |                           | /                   |
| [33]      | PET/CT | DOTANOC               | 120–185                           | 60                          | visual        |                           | /                   |
| [34]      | PET/CT | DOTATOC               | 119 (68–220)                      | 87 (51–148)                 | visual and semiquantitative | SUVmax           | 34.6 only in pancreas |
| [35]      | PET/CT | DOTATATE              | 200                               | 60                          | visual and semiquantitative | SUVmax           | 36.5                |
| [10]      | PET and PET/CT | DOTATOC and DOTATATE | 88 (52–111) / 102 (60–125) | 68 (29–162) / 56 (24–161) | visual and semiquantitative | SUVmax           | 37.4 / 19.6        |
| [36]      | PET/CT | DOTATATE              | 156 (120–200)                     | 60–70                       | visual and semiquantitative | SUVmax           | 24.9 only in pancreas |
| [37]      | PET/CT | DOTATATE              | 117 (51–212)                      | 24–44                       | visual and semiquantitative | SUVmax           | 32 (10–151)        |
| [38]      | PET/CT | DOTATOC or DOTANOC or DOTATATE | 122 (86–149) | 60 | visual and semiquantitative | SUVmax; SUVmean | 22.5 (5.7–100.4) |
| [19]      | PET/CT | DOTATATE              | 185                               | 60                          | visual and semiquantitative | SUVmax           | 72.8 (19.2–191)    |
| [39]      | PET/CT | DOTATATE              | 200                               | 60                          | visual        |                           | /                   |
| Reference | Device | Radiotracer (Peptide) | Activity Injected MBq Mean (Range) | Uptake Time Min Mean (Range) | PET Analysis | Semiquantitative Parameters | SUVmax Mean (Range) |
|-----------|--------|-----------------------|-----------------------------------|-----------------------------|--------------|-----------------------------|-------------------|
| [40] PET/CT | DOTATOC and DOTATATE<sup>°</sup> | 150–200 | 45–60 | visual and semiquantitative | SUVmax; TBR | 44.5 (5–32.5) |
| [41] PET/CT | DOTANOC | 132–222 | 45–60 | visual and semiquantitative | SUVmax | 14.7 (5–32.5) |
| [42] PET/CT | DOTATATE | 250 | 45–60 | visual | / | / |
| [43] PET/CT | DOTATOC | 1.7 MBq/Kg | 45–60 | visual and semiquantitative | SUVmax | 18.9 (5–65.6) |
| [20] PET/CT | DOTATATE | 120–220 | 45–60 | visual and semiquantitative | SUVmax | 28 (3.9–85.8) |
| [17] PET/CT | DOTANOC | 2.5 MBq/Kg | 60 | visual and semiquantitative | SUVmax | 14.6 (4.2–82.9) |
| [21] PET/CT | DOTATOC | 97 (74–124) | 60 | visual | / | / |
| [44] PET/CT | DOTATATE | 196 | 55–93 | visual | / | / |
| [45] PET/CT | DOTATATE | 206 (127–302) | 60 | visual and semiquantitative | SUVmax; tumor to spleen ratio | 26.5 (5.7–77.9) |
| [46] PET/CT | DOTATATE | 185 | 60 | visual and semiquantitative | SUVmax | 65.4 (6.9–244) |
| [47] PET/CT | DOTATOC | 11–185 | 64 (55–75) | visual and semiquantitative | SUVmax; tumor to pancreas ratio | 31.7 |
| [16] PET/CT | DOTATOC | 185 | 60 | visual and semiquantitative | SUVmax | nr |
| [48] PET/CT | DOTATOC | 1.5 MBq/Kg | 60 | visual and semiquantitative | SUVmax | 45.6 (2–178) |
| [49] PET/CT | DOTANOC | nr | nr | visual | / | / |
| [50] PET/CT | DOTATOC | 74–185 | 60 | visual and semiquantitative | SUVmax; SUVmean, MTV; TLG | 53.8 (23.8–96) G1 11.5 (4.1–61.8) G2–3 |
| [51] PET/CT | DOTATATE | 2 MBq/Kg | 60 | visual and semiquantitative | SUVmax | 18.5 |
| [18] PET/CT | DOTATATE | 185 | 60 | visual and semiquantitative | SUVmax | nr |
| [52] PET/CT | DOTANOC | 143 | 64 | visual and semiquantitative | SUVmax | (8.7–104.7) |

MTV: metabolic tumor volume; nr: not reported; TBR: tumor to background ratio; TFFV: total functional tumor volume; TLG: total lesion glycolysis; ° radio-labelled with 64Cu; * median.
Figure 2. Study quality assessment. Overall quality assessment of the studies included in the systematic review according to QUADAS-2 tool [14].
PET/CT was employed without CT contrast media injection in all research papers except for the studies by Mayerhoefer et al. [32] and by Kazmierczak et al. [45], whereas no studies employed hybrid PET/magnetic resonance imaging (MRI) scanner.

All three SSR-targeted tracers were employed (68Ga-DOTATOC in 13, 68Ga-DOTANOC in seven, and 68Ga-DOTATATE in 14, respectively), while mixed tracers were used in two studies [38,40]. Only in the study by Poeppel et al. [10], two of these radiotracers (68Ga-DOTATOC and 68Ga-DATOTATE) were compared in terms of diagnostic accuracy, showing that maximal uptake of 68Ga-DOTATOC tended to be higher than its 68Ga-DOTATATE counterpart, thus encouraging the application of different SSR ligands in order to personalize imaging and therapy. Similarly, in one study [40], 68Ga-labeled SSR imaging was compared to 64Cu-labeled SSR-PET on a per-lesion and per-patient basis, showing promising results for 64Cu-labeled SSR, both for diagnostic and therapeutical implications.

The injected radiopharmaceutical activity was similar across all studies (Table 2). In contrast, considerable variability in the time interval between radiotracer injection and image acquisition was observed (ranging 20–162 min). However, in the paper by Nakamoto et al. [47], in which two acquisition time points (60 and 90 min post-injection) were tested, no relevant differences in terms of accuracy were reported in either the detection of primary lesion nor in the metastasis identification. Analysis of PET images was exclusively performed using visual analysis in 10 studies [21,23–25,28,32,39,42,44,49]. Additional semiquantitative criteria, mainly maximum standardized uptake value (SUVmax), were also used.

3.3. Qualitative Analysis

Most of the selected studies used conventional imaging as the reference standard to assess SSR-PET/CT accuracy in the detection of primary lesions [17,21,24–30,32,35,41,46,50]. Histopathology was used as a reference only by Cingarlini et al. [48] and Kaemmerer et al. [38]. In the former study, SSR-PET/CT showed high sensitivity (equal to 94.3%) in detecting the primary lesion of G1-2 pNETs [48]. In the latter [38], the authors used the histopathological reference combined with reverse transcriptase-quantitative polymerase chain reaction gene-expression data to evaluate the correlation between Dotapeptides accumulation and SSR2A expression in both primary and metastatic pNET lesions. Reported data showed that SUVmax and SUVmean are reliable ex vivo parameters for in vivo quantification of SSR expression in pNET.

Considering the studies that evaluated semiquantitative parameters in pNETs [17,19,20,29,30,33–36,38,41,43,48,51], average lesion SUVmax was 25.4 (range 2–191). Of note, high heterogeneity in SUVmax between the primary lesion and distant metastases was observed. While some studies reported higher SUVmax values for the primary lesion [29,30], in some others [41] the opposite finding was observed. Moreover, a variable site-specific diagnostic accuracy was observed for metastatic lesions when SSR-PET/CT was compared with conventional imaging as the reference standard [22,23,27–30,32,41,44,46,50,51]. In most studies, SSR-PET/CT was superior to CT for the detection of lymph node, bone, liver, and other organ metastases, while CT overcame SSR-targeted imaging for the assessment of pulmonary metastases.

In a few studies, the diagnostic potential of SSR-PET/CT imaging was also measured in terms of impact on the therapeutic decisions [26–28,39,42,50]. Considering all patient cohorts of these studies (n = 1513), SSR-PET/CT influenced the therapeutic plan in 597 cases, resulting in a management change in approximately 39% of patients. However, only the study by Ilhan et al. [39] specifically addressed this point in a study cohort of pNET patients, in which imaging results altered the surgical management in 6/18 cases (33%), while the remaining studies contained mixed NET patients’ cohorts. In contrast, fewer studies explored the prognostic relevance of SSR-targeted imaging at staging in pNETs [20,52]. Majala et al. [52] showed that 68Ga-DOTANOC integrated with 18F-Fluorodeoxyglucose (FDG) PET/CT can predict tumor grade and clinical outcome in non-functioning pNETs. The authors showed that not only FDG but also 68Ga-SSR imaging has prognostic value in the preoperative setting, being able to predict the histopathological grade.
3.4. Quantitative Results

As shown in Table 3, the pooled sensitivity and specificity of SSR-PET/CT for the assessment of primary pNET were 79.6% (95%CI: 70.5–87%) and 95% (75–100%) with a heterogeneity of 59.6% and 51.5%, respectively (both ps = ns). Moreover, the pooled diagnostic odds ratio (DOR) value was 35.579 (95%CI: 4.673–270.90), with a heterogeneity of 21%. Pooled detection rates for the primary tumors were 81% (95%CI: 65–90%) and 92% (95%CI: 80–97%), respectively, at patient-based and lesion-based analysis (Figures 3 and 4). A slight asymmetry in the forest plots was found for each analysis; therefore, publication bias may be present in the lesion-based and patient-based analyses (see also the corresponding Funnel Plots in Figure S1A-B).

Table 3. Results from the meta-analysis.

| Study name | Event rate (95%CI) | Lower limit | Upper limit | Z-Value | p-Value |
|------------|--------------------|-------------|-------------|---------|---------|
| Morgat [21] | 0.943 | 0.798 | 0.966 | 3.860 | 0.000 |
| Farchione [17] | 0.880 | 0.697 | 1.061 | 3.257 | 0.001 |
| Lastoria [20] | 0.999 | 0.650 | 0.998 | 2.390 | 0.17 |
| Kumar [29] | 0.976 | 0.713 | 0.999 | 2.594 | 0.009 |
| Nawa [20] | 0.945 | 0.493 | 0.568 | -0.996 | 0.024 |
| Ifhan [39] | 0.974 | 0.690 | 0.988 | 2.519 | 0.0012 |
| Versari [24] | 0.909 | 0.561 | 0.987 | 2.195 | 0.0028 |
| Frilling [26] | 0.982 | 0.770 | 0.999 | 2.808 | 0.005 |
| Prasad [43] | 0.971 | 0.664 | 0.998 | 2.436 | 0.015 |
| Nakamoto [47] | 0.975 | 0.702 | 0.998 | 2.658 | 0.011 |
| Ruf [26] | 0.611 | 0.379 | 0.839 | 0.835 | 0.03 |
| Majala [52] | 0.968 | 0.804 | 0.995 | 3.346 | 0.001 |
| 0.921 | 0.803 | 0.971 | 4.586 | 0.000 |

LR+: positive likelihood ratio; LR–: negative likelihood ratio; DOR: diagnostic odd ratio; I²: heterogeneity.

Figure 3. Detection rate at a per-lesion analysis. Plots of individual studies and pooled detection rate of SSR-PET/CT in patients with pNET on a per-lesion-based analysis, including 95%CI.

Figure 4. Detection rate at a per-patient analysis. Plots of individual studies and pooled detection rate of SSR-PET/CT in patients with pNET on a per-patient-based analysis, including 95%CI.
4. Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis specifically addressing the identification of the primary lesion and initial staging by using SSR-PET/CT in patients with pNETs. Several studies have used SSR-PET/CT imaging to achieve this aim, reporting variable results. However, most of these studies have limited power due to the relatively small number of enrolled patients, and the lack of specific studies precisely focused on pNETs. To derive more robust estimates on the SSR-PET/CT diagnostic accuracy in this clinical setting, we have pooled the published studies.

Heterogeneity of selected studies may represent a limitation in a meta-analysis. Differences among patients’ selection criteria, diversity in methodological aspects, and variable study quality are the most common potential sources of bias. We detected only a moderate heterogeneity among the studies included in the pooled analysis. However, due to the relatively low number of selected studies for the quantitative analysis, subgroup analyses aiming to explain this heterogeneity was not performed. For the same reasons, subgroup analyses, including functioning or non-functioning pNETs as well as hereditary or sporadic pNETs, were not performed.

Obtained data confirm that SSR-PET/CT represents a robust diagnostic tool in pNETs showing a high pooled true positive rate both at patient-based and lesion-based analysis, due to the low number of the observed false-negative findings.

We observed high accuracy in the diagnosis of the primary lesion. However, when compared with similar meta-analyses conducted on mixed gastroenteropancreatic (GEP)-NET populations, a reduction in sensitivity was observed. Indeed, in the meta-analysis by Geijer and Breimer [53], which included 2105 GEP-NET patients, a pooled sensitivity of 93% (95%CI: 91–94%) was reported. Obviously, this difference may be related to the spatial resolution of PET/CT hampering the detection of smaller pancreatic lesions and the inclusion of higher histopathological grades pNETs, which might have increased the occurrence of some false-negative findings due to the lower SSR expression [8]. However, the inclusion of patients affected by insulinoma in many of analyzed studies might have also contributed. Indeed, compared to carcinoids (the commonest GEP-NET histopathological subtype), insulinomas have limited SSR expression, thus potentially reducing SSR-PET sensitivity [54]. On the other hand, pancreatic SSR expression might represent a potential source of false-positive results in the primary lesion detection by SSR-targeted molecular imaging (thus reducing specificity). Indeed, particularly the head and uncinate process, represent a site of physiological SSR overexpression [55–57]. Previous studies proposed a cutoff value of SUVmax for differentiating between physiologic and neoplastic pancreatic uptake [57], but there is some overlap of SUV reported in the literature for these two different conditions. This topic was assessed by three of the selected studies [31,34,37]. Overall, they showed that caution is suggested when dismissing foci of enhanced uptake seen on functional but not on anatomic imaging as false positive, especially in patients with repeat PET findings on follow-up period.

Of note, a wide heterogeneity in SUVmax values was observed between primary pancreatic lesions and distant metastases. This is coherent with the heterogeneity in SSR-2A expression between the primary site and distant metastases, since metastatic lesions, being comparatively new as compared to the primary, may be subject to less intense down-regulation of SSR [58]. This difference may theoretically impact the SSR-PET/CT diagnostic accuracy, introducing in a site-specific detection rate heterogeneity. However, contradictory findings were reported in the analyzed studies. The use of different SSR tracers, the variable sample size, the inclusion of a mixed patient population of pNET and GEP-NET, and the variability of histopathological tumor subtypes are possible reasons behind this contradictory finding. The combined use of FDG and SSR-PET/CT imaging may at least partially solve this clinical issue [59].

When compared with conventional imaging, SSR-PET/CT offered a relevant advantage in the detection rate of most metastatic sites. These additional findings have prompted therapeutic interventions in some patients, as shown by Ilhan et al. [39]. They also have a prognostic implication because unknown distant bone metastases are considered as a negative prognostic...
factor, possibly requiring a more aggressive treatment regime [60]. Therefore, this method is now the choice to fully stage and localize the extent of disease in patients with non-insulinoma pNETs in the preoperative setting by the current guidelines of the European Neuroendocrine Tumor Society (ENETS) [61].

Only in a few cases, the SSR-PET/CT approach was integrated with contrast-enhanced (ce) CT [32,45]. In the study by Kazmierczak et al. [45], this combination resulted in an improvement in sensitivity of 50% and an improvement in accuracy of 30% in primary tumor detection. However, Mayerhoefer et al. [32] showed that sensitivity improvement is only moderate while hardly affecting specificity, concluding that unenhanced images may be enough for routine PET/CT in NET patients. Moreover, none of these studies was conducted exclusively in pNET patients. Similarly, combining PET with MRI may take the theoretical advantage of the combination of high soft-tissue contrast for MRI with metabolic data from PET, helping to recognize small lesions. Moreover, MRI is a tool-free of ionizing radiation. However, only a few studies demonstrated a positive impact of PET/MRI in studying NETs [62–65], and evidence specifically addressing pNETs is still anecdotal [66,67]. Further studies are needed to understand better the potential role of this tool in this field.

5. Conclusions

SSR-PET/CT has a high detection rate and diagnostic performances for primary lesion and initial staging of pNETs. Further studies are needed to validate the integration of SSR-PET with contrast-enhanced CT or MRI in this clinical setting.

Supplementary Materials: The following are available online at http://www.mdpi.com/2075-4418/10/8/598/s1, Figure S1A,B Funnel Plots for publication biases at the lesion-based and patient-based analyses.

Author Contributions: Substantial contributions to the conception or design of the work: R.L., M.B., D.A. and L.E.; Literature search: G.S., A.B., A.M. and A.V.; Article selection: A.G.N., V.F., P.G. and C.F.; QUADAS analysis: S.A. and R.L.; Meta-analysis: R.L. and L.E.; Manuscript preparation: M.B., D.A., L.E., S.A., R.L. and P.A.; Drafting the work or revising it critically for important intellectual content: all authors. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

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