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# Meta-analysis of 68Ga-PSMA-11 PET Accuracy for the Detection of Prostate Cancer Validated by Histopathology

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**Abstract**

*Background*: 68Ga-PSMA-11 PET is used to stage patients with prostate cancer. We performed an updated meta-analysis, which separates imaging at the time of diagnosis and that at the time of biochemical recurrence, and focuses on pathology correlation in both populations.

*Methods*: We searched MEDLINE and EMBASE databases using the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement. Quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 tool. 1,811 studies were screened, 58 were analyzed, 41 included for qualitative synthesis and 29 included for quantitative analysis. A random effect model and a hierarchical summary receiver operating characteristic model was used to summarize the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy for pelvic lymph nodes in initial staging compared to pathology at prostatectomy, and the PPV for lesions with pathologic correlation in those with biochemical recurrence. We also summarized the detection rate of 68Ga-PSMA-11 in those with biochemical recurrence stratified by PSA at time of imaging.

*Results*: The meta-analysis of 68Ga-PSMA-11 at initial staging demonstrated a sensitivity and specificity using nodal pathology at prostatectomy as a gold standard was 0.74 (95% confidence interval: 0.51, 0.89), 0.96 (0.85, 0.99). At biochemical recurrence, the PPV was 0.99 (0.96, 1.00). The detection rate was 0.63 (0.55, 0.70) with a PSA less than 2.0, and 0.94 (0.91, 0.96) with a PSA greater than 2.0.

*Conclusions*: 68Ga-PSMA-11 performed well for the localization of metastatic prostate cancer at initial staging patients and at the time of biochemical recurrence.

## Introduction

Staging of patients with prostate cancer using conventional imaging, typically magnetic resonance imaging, computed tomography and bone scans, is limited by a low sensitivity for metastatic disease. Imaging using small molecules targeting the Prostate Specific Membrane Antigen (PSMA) has demonstrated higher detection sensitivity compared to conventional imaging and other radiotracers such a choline based agents (1-3). Although there is a large number of radiotracers that target PSMA, 68Ga-PSMA-11 (or PSMA HBED-CC) constitutes the majority of the literature.

Paralleling its widespread clinical adoption, a large number of publications on 68Ga-PSMA-11 PET emerged over the past four years. Several meta-analyses have been performed. However, prior meta-analyses are limited by the heterogeneity of included studies: Patients at initial diagnosis and biochemical recurrence were combined, and reference standard for lesion validation range from clinical experience and imaging without predefined criteria to surgery/biopsy in few cases (4,5). However, aiming at the approval of PSMA ligands for PET imaging, systematic analysis of categorized evidence employing histopathology validation is needed. Additionally, since the publication of initial meta-analyses, nearly three times as many patients have been reported in the literature.

We therefore focused on the two indications where 68Ga-PSMA-11 PET is most likely to be used clinically: initial staging of those with intermediate- to high-risk prostate cancer and localization of metastatic disease in those with biochemical recurrence after definitive therapy, and performed an updated meta-analysis, separating such patients and correlated findings with pathologic validation. We have specifically focused on

lesions with pathologic validation in order to provide support for potential approval of this drug.

## Materials and Methods

### *Search strategy*

The aim of this systematic review and meta-analysis was to summarize studies of staging and restaging 68Ga-PSMA PET/CT or PET/MRI in patients with either localized or metastatic prostate cancer. The second aim was to determine the imaging test accuracy of the new PET/CT and PET/MRI method using tissue samples obtained through biopsy or surgery as the reference standard. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (6). The protocol for this meta-analysis was registered with PROSPERO (CRD temporary ID: 99828).

Scientific literature databases of MEDLINE and EMBASE were systematically searched in April 2018. Our systematic review included original research studies of initial staging and biochemical recurrence patients with 68Ga-PSMA-11 PET. The search used several keywords including: ‘‘prostate’’ or ‘‘prostate cancer’’ or ‘‘prostate neoplasm’’ or ‘‘prostate malignancy’’; ‘‘positron emission tomography’’ or ‘‘PET’’; and ‘‘prostate specific membrane antigen’’ or ‘‘PSMA’’ and “PSMA PET” with “Prostate.” The search and article selection were performed by two independent evaluators. Each screened the titles and abstracts of the reports and selected appropriate original research articles that were published in English. Papers that were excluded included those published prior to 2012, studies of laboratory results, studies of neoplasms other

than prostate cancer, studies of radiotracers that were not 68Ga-PSMA-11, bioavailability studies, case studies, and studies with small samples sizes (less than 20 patients). Risk for bias in the studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 methodology (7).

*Outcome Measures*

We looked at several outcomes measurements from the papers reviewed. We calculated imaging test characteristics (sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy) for the detection of lesions in the prostate and pelvic lymph nodes and compared those values to the histopathological biopsy or radical prostatectomy lymph node dissection results. Sensitivity is defined as true positives (TP) divided by TP plus false negatives (FN). Specificity is defined as true negatives (TN) divided by TN plus false positives (FP). PPV is defined as TP divided by TP plus FP. NPV is defined as TN divided by TN plus FN. Accuracy is defined as TP plus FP divided by the population. We also calculated detection rate in patients by PSA cutoff values that had positive imaging by 68Ga-PSMA-11. Detection rate is defined as the percentage of patients who have focal uptake on 68Ga-PSMA-11 PET that is interpreted as being consistent with cancer.

*Data Collection*

Two reviewers independently extracted from the studies the radiation dose and uptake time for 68Ga-PSMA PET/CT and PET/MRI imaging. The reviewers also extracted the number of patients in each study, their age (median/mean), PSA (median and range),

Gleason scores, initial treatment (Androgen deprivation therapy, radiation therapy or radical prostatectomy). The number of patients detected with PET imaging as well as the location of the metastases were also extracted.

*Meta-analytic methods*

In our meta-analysis, we used a random effect model (8) and a hierarchical summary receiver operating characteristic (HSROC) model (State 14.0; StataCorp, College station, TX, USA). We summarized the sensitivity, specificity, PPV, NPV and accuracy for pelvic lymph nodes in initial staging using pathology at prostatectomy as a gold standard, and for any lesion with pathologic correlation in biochemical recurrence patients. We also summarized the detection rate of 68Ga-PSMA-11 in those with biochemical recurrence stratified by PSA at time of imaging. All point estimates from the meta-analysis regression are reported as the mean and 95% confidence interval.

**Results**

*Eligible studies*

Electronic searching of PubMed and EMBASE resulted in 2,178 articles (**Figure 1**). 367 were duplicates, and 1,811 articles were reviewed at the abstract level of which 1,763 articles were excluded. Subsequently 59 papers were reviewed in full text and 18 studies were excluded. 41 articles were deemed eligible for inclusion in the meta-analysis (**Table 1**). Nearly all papers imaged patients roughly 60 minutes after injection with a dose 120 to 230 MBq. Risk for bias and applicability was assessed using the QUADAS-2 tool (**Supplemental Figure 1**). Significant biases existed in the majority of

papers reviewed. Bias in the included papers included those related to the selection of patients, as nearly all studies reported retrospective cohorts without predefined inclusion criteria. The lack of histologic reference standard was a significant bias, with again most papers reporting only detection rates, and only a few reporting results compared to histology. Overall the performance of 68Ga-PSMA-11 PET was fairly consistent across papers, with uptake times and doses in similar ranges. The majority of the papers included were retrospective studies which included patients not enrolled based on defined inclusion criteria, and only four of the included studies were prospectively acquired (**Table 1**),

*Initial staging*

Six studies included in the meta-analysis included patients imaged at initial staging, of which five papers correlated pelvic nodal disease to pathology at radical prostatectomy reporting a total of 266 patients between the five studies (**Table 2**). The majority of the papers included only patients who were classified as intermediate to high risk by the D'Amico classification (**Table 2**). Across the five studies, the meta-analysis of the sensitivity, specificity, PPV, NPV and accuracy were 0.74 (0.51, 0.89), 0.96 (0.85, 0.99), 0.93 (0.86, 0.99), 0.85 (0.75, 0.93), 0.86 (0.79, 0.92), respectively (**Figure 1**).

*Biochemical recurrence*

34 studies in the meta-analysis included patients imaged at biochemical recurrence. First, we reviewed all included papers to determine if results were reported using pathology as a gold standard, and selected all patients where a pathology correlation

was reported. The majority of papers in patients with biochemical recurrence did not have pathologic correlation for PSMA avid lesions, and only detection rates were reported. In total, 256 patients were included across 15 studies with pathologic correlation, of which 233 were reported as true positive lesions (**Table 3**)**.** The meta-analysis of the sensitivity, specificity, PPV, NPV and accuracy in all patients with pathology correlation were 0.99 (0.96, 1.00), 0.76 (0.02, 1.00), 0.99 (0.96, 1.00), 0.76 (0.02, 1.00) and 0.98 (0.94, 1.00), respectively. Given that only PSMA positive lesions were biopsied and the resultant low number of true and false negative lesions, the most relevant measurement in this population is the PPV (**Figure 2**).

The reporting of detection rate was heterogeneous across PSA levels, and comparisons across all papers is limited within specific PSA ranges. We grouped papers that reported results with a PSA < 2.0 ng / dL, between 2.0 and 5.0 ng / dL, and PSA > 5.0 ng / dL (**Table 4**). The meta-analysis for the detection rate for PSAs < 2.0 was 0.63 (0.55, 0.70), for PSAs between 2.0 and 5.0 the estimate was 0.89 (0.85, 0.93), and for PSAs > 5.0 the estimate was 0.95 (0.92, 0.97). We grouped papers who reported detection rates above and below PSAs of 2.0 ng/mL, and provided a Forest plot of the results (**Figure 3**).

Six papers reported detection sensitivity in patients with a PSA < 0.2 ng/mL, although little data was reported on pathology correlation in these papers (9-14). In these papers, 61 of 153 patients were reported as having positive disease on PSMA PET, and the meta-analysis for the detection rate for PSAs < 0.2 was 0.4 (0.24, 0.57). The largest study reported 32 out of 68 with positive disease when the PSA level was less than 0.2 nd/dL (13).

## Discussion

This meta-analysis reaffirms the utility of 68Ga-PSMA-11 PET for imaging of intermediate- to high-risk patients prior to definitive therapy and in those who develop subsequent biochemical recurrence. In initial staging patients with pathology as a gold standard, 68Ga-PSMA-11 had a sensitivity and specificity of 0.74 (0.51, 0.89), 0.96 (0.85, 0.99), and in biochemical recurrence, the positive predictive value was 0.99 (0.96, 1.00). For those patients with biochemical recurrence, the detection rate was 0.63 (0.55, 0.70) with a PSA less than 2.0, and 0.94 (0.91, 0.96) with a PSA greater than 2.0.

The sensitivity and specificity results in our study can be difficult to compare to other studies. Perera et al reported a sensitivity and specificity of 0.86 (0.37, 0.98) and 0.86 (0.03, 1.00), but merged data from both biochemical recurrence and initial staging patients (5). A second more recent meta-analysis performed only in the initial staging population closely mirrored our results with estimated sensitivity and specificity of 0.71 (0.59, 0.81) and 0.95 (0.87–0.99) (15). Von Eyben et al reported the sensitivity and specificity in initial staging patients alone: 0.70 (0.53, 0.83) and pooled specificity was 0.84 (24, 99) (4). The point estimates from von Eyben more closely mirror our results although our confidence intervals are narrower due to more patients published since the von Eyben article. Von Eyben et al did not perform a meta-analysis compared to histopathology in the biochemical recurrence setting.

In biochemical recurrence, we chose to report a positive predictive value and not the sensitivity and specificity, as only PSMA avid lesions are typically biopsied and therefore the subsequent calculated sensitivity and specificity are not relevant. Given that the all patients with biochemical recurrence are considered to have disease, the

detection rates may be used to approximate the sensitivity for metastatic disease in these patients. It is not possible to biopsy numerous nodes in patients, and therefore it is unknown the accuracy of 68Ga-PSMA-11 PET outside of biopsied lesions. It is possible that 68Ga-PSMA-11 PET only sees the “tip of the iceberg” in a large number of patients and that there may be a number of negative lesions that are not detected and not biopsied.

We chose to limit our analysis to lesions that have a biopsy correlate as the definition of reference standards varied across the papers that used a composite endpoint of clinical and imaging follow-up. One of the main reasons for the lack of pathology correlation is the difficulty in obtaining a biopsy of lesions in patients with biochemical recurrence at low PSAs. The absence of gold-standard verification makes measurements of accuracy in this population very difficult. Given that there is no agreed follow-up composite gold standards, it is not possible to pool data from patients who do not have pathologic validation. Nonetheless there was a relatively large number of patients (256) reported in the literature with pathologic correlation.

When reporting the results of research radiopharmaceuticals, it is important to consider how the data included may be used to support the subsequent radiopharmaceutical approval. In some cases, literature based meta-analysis can be used in lieu of a second registration trial, and therefore the quality of studies is critical in support of future approvals. There are a number of things that are frequently not reported, including safety, inclusion and exclusion criteria, radiopharmaceutical synthesis methods and quality control used. Using multiple readers and reporting inter-reader variability is also important in strengthening the value of the results. Dose

ranges and uptake times are frequently reported by what is defined in the imaging protocol and not what was occurred in individual patients. Another factor that is frequently under-described in the literature is the chemistry process (source of the precursor, synthesis module used, generator type, and quality assurance process used), which are important in the registration process so that regulatory bodies know that identical compounds were used across studies. There may be value in developing standard reporting guidelines for studies that evaluate the role of radiopharmaceuticals moving forward to ensure high-quality data in the literature moving forward. Furthermore, there may be value in developing harmonized release criteria across sites using the same compound in the research setting to help keep radiopharmaceutical products consistent across sites.

In addition to improved harmonization of reporting in PSMA PET articles, what would greatly strengthen the results in the literature are well designed prospective studies that include a well-defined gold standard that can be used to measure accuracy. Although this is an optimistic goal, we readily admit that in the setting of biochemical recurrence, this may be difficult given the general frequent inability to obtain histologic verification.

The main limitation of our study is the heterogeneity that exists within the included studies. For example, patients are grouped by varying PSA ranges in the literature, which makes determining the reported sensitivities within various PSA ranges difficult to pool across articles. Additionally, the majority of studies assessing imaging in those with biochemical recurrence did not include pathology correlation, and simply reported detection sensitivities. Finally the interpretive criteria are not defined in all

papers, and in the past year reporting standards have been proposed which may limit variability in reads (16,17). One of the main reasons for the heterogeneity across studies using 68Ga-PSMA-11, is that the majority of reports are from institutions using the compound under a compassionate use setting, and so no formal prospective protocols were developed or followed.

**Conclusion**

68Ga-PSMA-11 performed well for the localization of metastatic prostate cancer. In initial staging, with pathology as a gold standard, 68Ga-PSMA-11 had a sensitivity and specificity of 0.74 (0.51, 0.89), 0.96 (0.85, 0.99). In biochemical recurrence, with pathology as a gold standard, the positive predictive value was 0.99 (0.96, 1.00). The detection rate was 0.63 (0.55, 0.70) with a PSA less than 2.0, and 0.94 (0.91, 0.96) with a PSA greater than 2.0.

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**Tables**

**Table 1**: Characteristics of studies included. Means provided when available, otherwise medians reported. BCR = biochemical recurrence, IS = initial staging, R = retrospective, PR = prospective, NR = not reported.

| Study | Year | Patients (n) | Indication | Age (yr) | PSA (ng/mL) | PSA range | Design | PET Protocol | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Injected activity | Uptake time (min) |
| Afaq (18) | 2018 | 100 | BCR | 67.9 | NR | NR | R | 159 MBq | 60 |
| Afshar-Oromieh (19) | 2013 | 37 | BCR | 70 | 3.3 | (0.01-148) | NR | 121.0 MBq | 60 |
| Afshar-Oromieh (3) | 2014 | 37 | BCR | 69.3 | 11.1 | (0.01-116) | R | 132.0 MBq | 60 |
| Afshar-Oromieh (20) | 2014 | 20 | BCR | 69.6 | 2.62 | (0.51-73.60) | NR | 149.0 MBq | 60 |
| Afshar-Oromieh (14) | 2015 | 319 | IS + BCR | 68 | 4.59 | (0.01-41395) | R | 168 MBq | 60 |
| Afshar-Oromieh (13) | 2017 | 1007 | BCR | 68 | 12.1 | (0.01-1237) | R | 227 MBq | 68 |
| Afshar-Oromieh (21) | 2017 | 112 | IS + BCR | 70 | 6.39 | (0.01-176.0) | R | 207 MBq | 60 |
| Bluemel (22) | 2016 | 32 | BCR | 69 | 5.4 | (0.2-126.65) | R | 133 MBq | 60 |
| Budaus (23) | 2015 | 30 | IS | 62 | 38.9 | (1.4-376) | R | 169.4 MBq | 60 |
| Byrne (24) | 2018 | 81 | BCR | 63 | 0.87 | (0.22-8.7) | NR | 2 MBq/kg | 60 |
| Ceci (25) | 2015 | 70 | BCR | 67 | 3.5 | (0.2-32.2) | R | 146.3 MBq | 60 |
| Demirkol (26) | 2015 | 22 | BCR | 68 | 4.15 | (0.2-191.5) | R | 166.0 MBq | 45 |
| Eiber (1) | 2015 | 248 | BCR | 70 | 1.99 | (0.2-59.4) | R | 155 MBq | 54.2 |
| Einspieler (27) | 2017 | 118 | BCR | 72 | 6.4 | (2.2-158.4) | R | 2 MBq/kg | 60 |
| Fendler (28) | 2016 | 21 | IS | NR | NR | NR | R | 192 MBq | 58 |
| Giesel (29) | 2015 | 21 | BCR | 70 | 6.84 | (0.6-45) | NR | 176 MBq | 60 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Grubmüller (30) | 2017 | 117 | BCR | 74 | 1.04 | (0.58-1.87) | R | 2 MBq/kg | 60 |
| Gupta (12) | 2017 | 179 | BCR | 70 | 4.7 | (0.01-963) | R | 149 MBq | 50 |
| Habl (31) | 2017 | 100 | BCR | 64 | 1 | (0.12-14.7) | R | 146 MBq | 56 |
| Henkenberens (32) | 2017 | 23 | BCR | 80 | 2.75 | (0.52-8.92) | R | 79 MBq | 60 |
| Herlemann (33) | 2016 | 34 | IS + BCR | NR | NR | NR | R | NR | 60 |
| Herlemann (34) | 2017 | 35 | BCR | 64 | 4.1 | NR | R | NR | NR |
| Hope (10) | 2017 | 126 | BCR | 69 | 5.9 | NR | PR | 199.8 MBq | 63 |
| Hruby (35) | 2017 | 48 | BCR | NR | 5 | (2.04-39) | NR | 2.0 MBq/kg | 60 |
| Kranzbuhler (9) | 2018 | 56 | BCR | 69 | 0.99 | (0.05-30) | R | 123 MBq | 60 |
| Lake (36) | 2017 | 55 | BCR | 68.3 | 11.2 | (4-88) | R | 201.5 MBq | 65 |
| Maurer (37) | 2016 | 130 | IS | 66 | 11.5 | (6.85-24.5) | R | 1.76 MBq/kg | 59.8 |
| Morigi (2) | 2015 | 38 | BCR | 68 | 15.6 | (0.04-12.0) | PR | 2 MBq/kg | 60 |
| Pfister (38) | 2016 | 28 | BCR | 67 | 2.35 | (0.04-8) | R | 2 MBq/kg | 45 |
| Rauscher (39) | 2016 | 48 | BCR | 71 | 1.31 | (.75-2.55) | R | 154 MBq | 57 |
| Rauscher (40) | 2016 | 22 | BCR | 68 | 1.03 | (0.2-.72) | R | 147 MBq | 60 |
| Sachpekidis (41) | 2016 | 31 | BCR | 71 | 2 | (0.1-130) | NR | 236 MBq | 60 |
| Sanli (42) | 2017 | 109 | BCR | 71 | 6.5 | (0.2-640) | R | 185 MBq | 60 |
| Schiller (43) | 2017 | 31 | BCR | 64 | 2.19 | (.12-14.7) | R | 135 MBq | 60 |
| Schmidt-Hegemann (44) | 2017 | 129 | BCR | 72 | 6.04 | (0.13-150.00) | R | 189 MBq | 60 |
| Siriwardana (45) | 2017 | 35 | BCR | 67 | 0.2 | (0-1) | R | NR | NR |
| Uprimny (46) | 2017 | 203 | BCR | 68 | 1.44 | (.14-96.0) | R | 150 MBq | 60 |
| Van Leeuwen (11) | 2016 | 70 | BCR | 67 | 0.2 | (.12-.32) | PR | NR | NR |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Van Leeuwen (47) | 2017 | 30 | IS | 65 | 8.1 | (5.2-10.1) | PR | NR | 60 |
| Verburg (48) | 2015 | 155 | BCR | 70 | 4 | (0-2000) | R | 190 MBq | 60 |
| Zhang (49) | 2017 | 42 | IS + BCR | 69 | 52.31 | (7.20-348) | R | 131.7 MBq | 60 |

**Table 2**: Overview of included initial staging in five studies reporting a total of 266 patients. Papers that use intermediate to high risk by D'Amico classification for inclusion critera are noted. TP = true positive, FP = false positive, TN = true negative, and FN = false negative, NR = not reported. The number of nodes resected per patient is reported as a mean (* reported as a median).

| Study | Year | D'Amico Risk | N | nodes / patient | TP | FP | TN | FN |
|---|---|---|---|---|---|---|---|---|
| Budaus (23) | 2016 | N | 30 | 20.3 | 4 | 0 | 18 | 8 |
| Herlemann (33) | 2016 | N | 34 | 14.2 | 20 | 4 | 8 | 2 |
| Maurer (37) | 2015 | Y | 130 | 21* | 27 | 1 | 88 | 14 |
| Van Leeuwen (47) | 2016 | Y | 30 | 17.8 | 7 | 1 | 18 | 4 |
| Zhang (49) | 2017 | Y | 42 | 14.8 | 14 | 1 | 26 | 1 |

**Table 3**: Overview of included biochemical recurrence studies reporting 256 patients in total with pathology correlation. TP = true positive, FP = false positive, TN = true negative, and FN = false negative.

| Study | Year | N | TP | FP | TN | FN |
|---|---|---|---|---|---|---|
| Afaq (18) | 2018 | 11 | 10 | 1 | 0 | 0 |
| Afshar-Oromieh (19) | 2012 | 6 | 6 | 0 | 0 | 0 |
| Afshar-Oromieh (3) | 2014 | 7 | 7 | 0 | 0 | 0 |
| Afshar-Oromieh (14) | 2015 | 42 | 37 | 0 | 0 | 5 |
| Ceci (25) | 2015 | 7 | 6 | 1 | 0 | 0 |
| Demirkol (26) | 2015 | 3 | 3 | 0 | 0 | 0 |
| Einspieler (27) | 2017 | 6 | 6 | 0 | 0 | 0 |
| Morigi (2) | 2015 | 10 | 9 | 0 | 1 | 0 |
| Eiber (1) | 2015 | 12 | 12 | 0 | 0 | 0 |
| Grubmüller (30) | 2017 | 16 | 16 | 0 | 0 | 0 |
| Pfister (38) | 2016 | 28 | 22 | 6 | 0 | 0 |
| Rauscher (39) | 2016 | 22 | 22 | 0 | 0 | 0 |
| Rauscher (50) | 2016 | 48 | 42 | 3 | 3 | 0 |
| Siriwardana (45) | 2017 | 35 | 32 | 0 | 3 | 0 |
| Van Leeuwen (11) | 2016 | 3 | 3 | 0 | 0 | 0 |

**Table 4**: Overview of detection sensitivity for 68Ga-PSMA-11 PET stratified by PSA level at time of imaging in 2616 patients. (PSA = prostate specific antigen in ng/mL).

| Study | Year | N | positive patients/total | | | Detection Rate by PSA | | |
|---|---|---|---|---|---|---|---|---|
| | | | <2 | 2-5 | >5 | <2 | 2-5 | >5 |
| Afshar-Oromieh (19) | 2013 | 37 | 9/10 | 9/13 | 14/14 | 90% | 69% | 100% |
| Afshar-Oromieh (14) | 2015 | 311 | 55/90 | 64/73 | 140/148 | 61% | 88% | 95% |
| Afshar-Oromieh (13) | 2017 | 960 | 301/451 | 201/227 | 266/282 | 67% | 89% | 94% |
| Bluemel (22) | 2016 | 32 | 9/25 | 5/7 | | 36% | 71% | |
| Ceci (25) | 2015 | 51 | 17/20 | 29/31 | | 85% | 94% | |
| Demirkol (26) | 2015 | 22 | 5/7 | 15/15 | | 71% | 100% | |
| Eiber (1) | 2015 | 248 | 102/124 | 120/124 | | 82% | 97% | |
| Einspieler (27) | 2017 | 118 | NR | 36/44 | 71/74 | NR | 82% | 96% |
| Gupta (12) | 2017 | 177 | 24/56 | 117/121 | | 43% | 97% | |
| Habl (31) | 2016 | 100 | 56/80 | 20/20 | | 70% | 100% | |
| Kranzbuhler (9) | 2018 | 56 | 24/35 | 20/21 | | 69% | 95% | |
| Lake (36) | 2017 | 55 | 14/18 | 35/37 | | 78% | 95% | |
| Hope (10) | 2017 | 121 | 41/55 | 20/21 | 42/45 | 75% | 95% | 93% |
| Morigi (2) | 2015 | 38 | 18/30 | 7/8 | | 60% | 88% | |
| Sachpekidis (41) | 2016 | 31 | 7/15 | 12/16 | | 47% | 75% | |
| Sanli (42) | 2017 | 25 | 5/16 | 9/9 | NR | 31% | 100% | NR |
| Van Leeuwen (11) | 2016 | 70 | 25/70 | NR | NR | 36% | NR | NR |
| Verburg (48) | 2015 | 155 | 27/46 | 97/109 | | 59% | 89% | |

**Figures**

**Figure 1**: PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) flow diagram that depicts the process of selecting papers that were included in this meta-analysis.

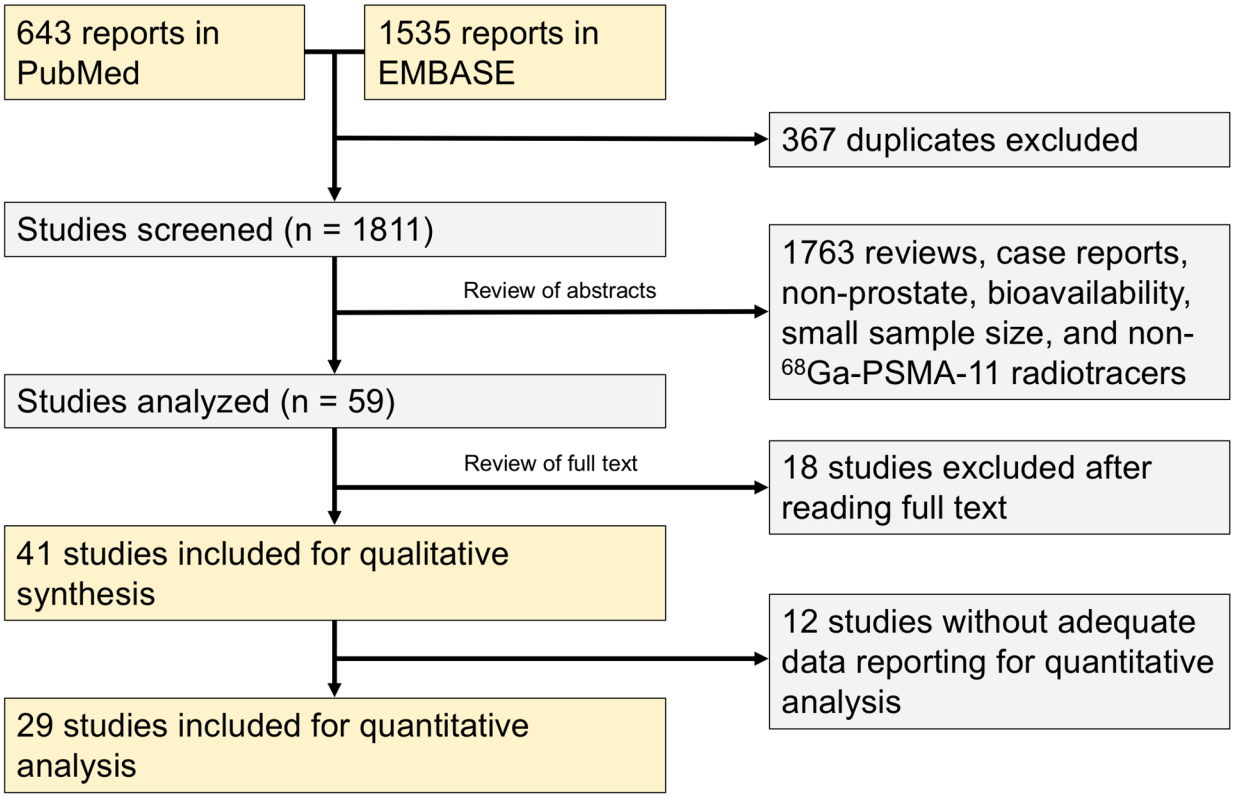


**Figure 2**: Summary of the sensitivity, specificity and Hierarchical Summary Receiver Operating Characteristic (HSROC) curve for $^{68}$Ga-PSMA-11 for initial staging of intermediate to high risk prostate cancer patients prior to prostatectomy for malignancy in pelvic nodes with pathology at time of prostatectomy as a gold standard. The meta-analysis for sensitivity and specificity was 0.74 (0.51, 0.89), 0.96 (0.85, 0.99), respectively. The size of the circles represents the size of individual studies.

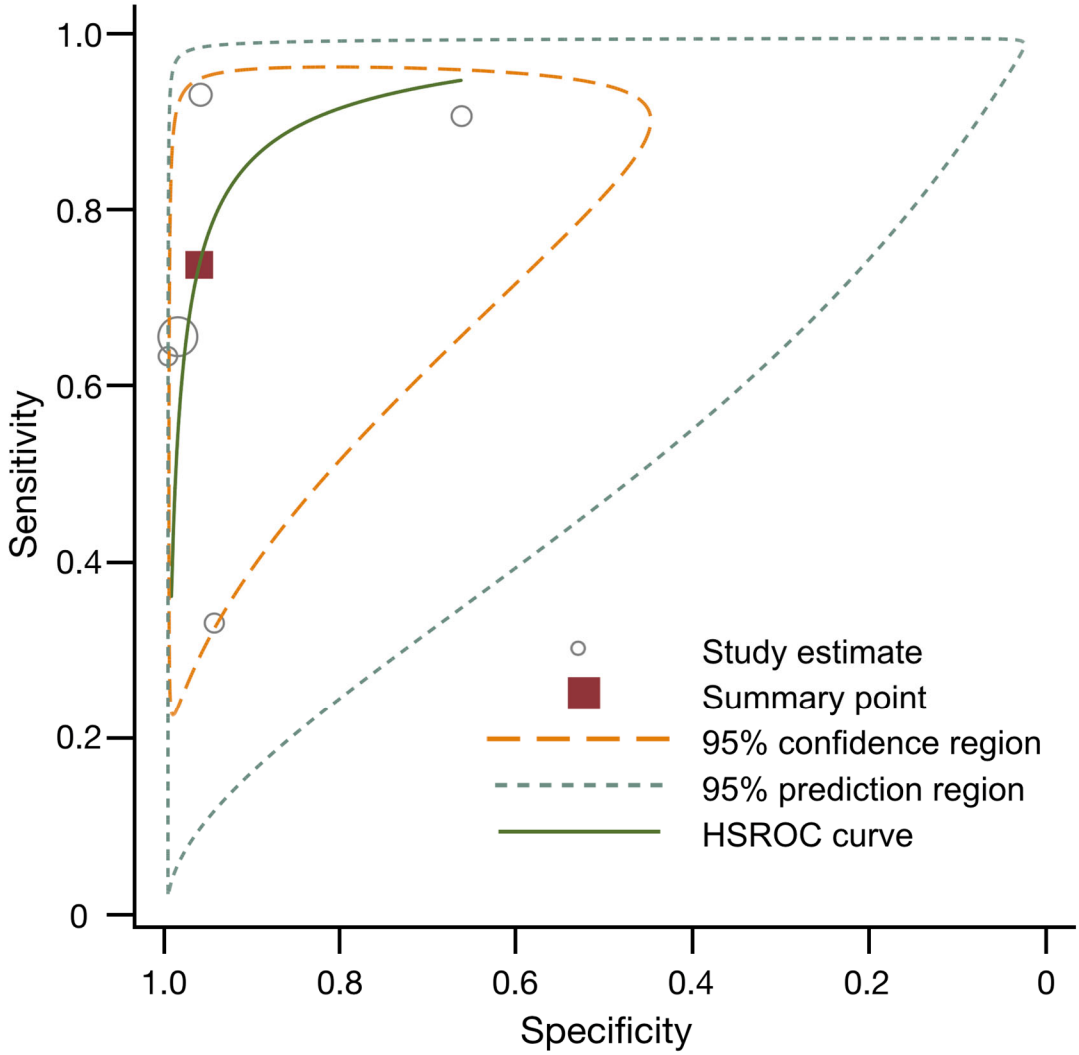


**Figure 3**: Forest plot of the Positive Predictive Value (PPV) for $^{68}$Ga-PSMA-11 in biochemical recurrence patients who have pathology correlation for gold standard comparison. The meta-analysis for PPV are 0.99 (0.96, 1.00). The size of the squares represents the size of individual studies. Reference numbers are in Table 3.

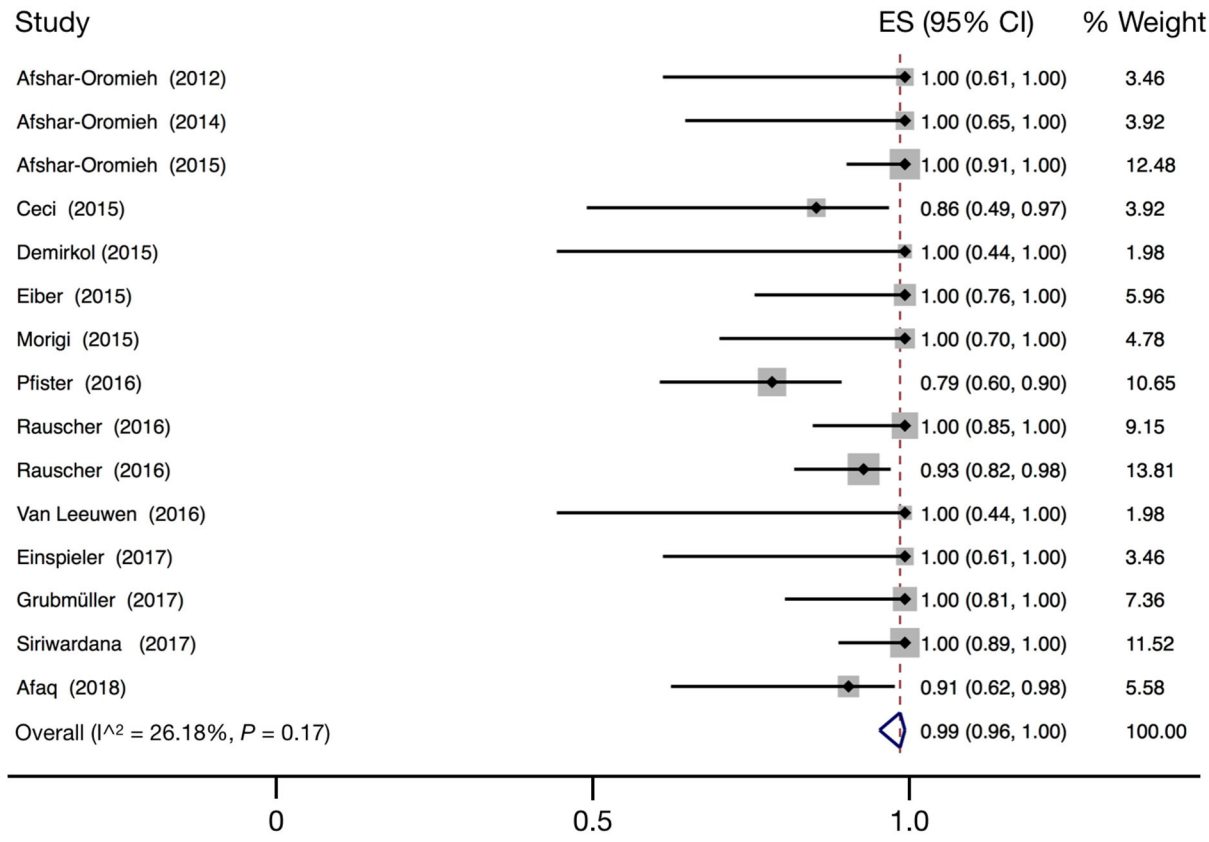
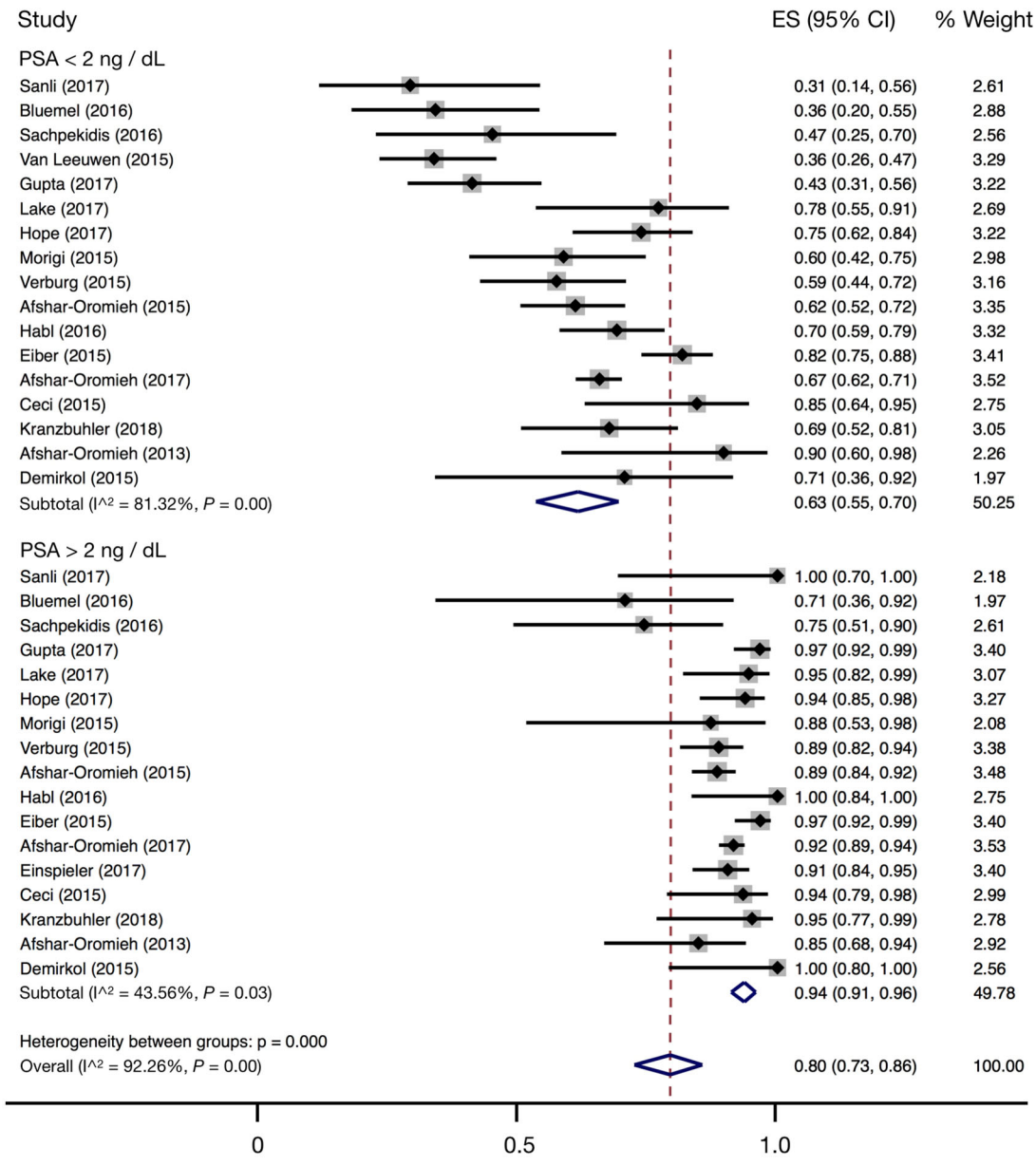


**Figure 4**: Forest plot of the detection rate for $^{68}$Ga-PSMA-11 in biochemical recurrence patients stratified by PSA > 2.0 and < 2.0 ng / dL. The meta-analysis for detection rate is 0.63 (0.55, 0.70) with a PSA less than 2.0, and 0.94 (0.91, 0.96) with a PSA greater than 2.0. The size of the squares represents the size of individual studies. Reference numbers are in Table 3.



**Supplementary Data**

**Supplementary Figure 1**: Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 evaluation for risk of bias (A) and risk of applicability (B) for the 41 studies that were included in the analysis. Red = high risk of bias, Yellow – unclear risk of bias, and Green = low risk of bias.