$^{68}$Ga-Prostate-specific membrane antigen (PSMA) positron emission tomography (PET) in prostate cancer: a systematic review and meta-analysis

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ABSTRACT

Introduction: Prostate cancer (PC) is the second most commonly diagnosed cancer in males. $^{68}$Ga-PSMA PET/CT, a non-invasive diagnostic tool to evaluate PC with prostate-specific membrane antigen (PSMA) expression, has emerged as a more accurate alternative to assess disease staging. We aimed to identify predictors of positive $^{68}$Ga-PSMA PET and the accuracy of this technique.

Materials and methods: Diagnostic accuracy cross-sectional study with prospective and retrospective approaches. We performed a comprehensive literature search on PubMed, Cochrane Library, and Embase database in search of studies including PC patients submitted to radical prostatectomy or radiotherapy with curative intent and presented biochemical recurrence following ASTRO 1996 criteria. A total of 35 studies involving 3910 patients submitted to $^{68}$Ga-PSMA PET were included and independently assessed by two authors: 8 studies on diagnosis, four on staging, and 23 studies on restaging purposes. The significance level was $\alpha=0.05$.

Results: pooled sensitivity and specificity were 0.90 (0.86-0.93) and 0.90 (0.82-0.96), respectively, for diagnostic purposes; as for staging, pooled sensitivity and specificity were 0.93 (0.86-0.98) and 0.96 (0.92-0.99), respectively. In the restaging scenario, pooled
sensitivity and specificity were 0.76 (0.74-0.78) and 0.45 (0.27-0.58), respectively, considering the identification of prostate cancer in each described situation. We also obtained specificity and sensitivity results for PSA subdivisions. Conclusion: $^{68}$Ga-PSMA PET provides higher sensitivity and specificity than traditional imaging for prostate cancer.

68 Ga-PSMA PET-CT is a non-invasive diagnostic tool to evaluate prostate cancer with increased prostate-specific membrane antigen (PSMA) expression. PSMA is a protein expressed on dysplastic prostate cells, with levels of expression of 100-1000 times that of healthy cells, which increase even further with higher stages and grades of prostate cancer (5, 6).

$^{68}$Ga is a positron emitter obtained from a $^{68}$Ge/$^{68}$Ga generator system with 68min of half-life. PSMA demonstrated to have high affinity and specific internalization into prostate cancer cells (7). $^{68}$Ga-PSMA-11 was first synthesized and evaluated by the Heidelberg group in Germany, and its accumulation is proportional to the expression level of PSMA (8). Other PSMA ligands, such as $^{68}$Ga-PSMA-617 and $^{68}$Ga-PSMA-I&T, showed similar distribution and image properties to $^{68}$Ga-PSMA-11 (6, 8), the reason why all three are known as $^{68}$Ga-PSMA.

To date, the use of $^{68}$Ga-PSMA has been well reported, and initial staging revealed superior sensitivity and specificity profiles compared to conventional choline-based tracers (7). Not only diagnosis but also among the management changes observed in the studies, the proportion of inter and intra-modality was relatively similar, indicating that $^{68}$Ga-PSMA-PET may help better plan the optimal dose, site, and volume of radiation in the case of salvage radiotherapy. We systematically reviewed the literature outlining the use of $^{68}$Ga-PSMA PET imaging in prostate cancer. Our primary objective was to perform a literature review to determine $^{68}$Ga-PSMA PET accuracy in prostate cancer, and our secondary objective was to identify predictors of positive $^{68}$Ga-PSMA PET.
MATERIALS AND METHODS

Bibliographic search
A systematic review was performed under the Cochrane Collaboration and Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines (9, 10).

We performed a comprehensive literature search of PubMed, Cochrane Library, Embase, Web of Science, Scielo, Scopus and Lilacs database, without date restriction up to 05/04/2019, using the following MeSH vocabulary key words and free text words: ((Prostate Neoplasms OR Prostate Neoplasm OR Prostatic Neoplasm OR Prostate Cancer OR Prostate Cancers OR Prostatic Cancer OR Prostatic Cancers) AND (Positron Emission Tomography OR PET) AND (PROSTATIC SPECIFIC MEMBRANE ANTIGEN OR PSMA OR GALLIUM OR GA)).

Inclusion and exclusion criteria
Patients: patients diagnosed with prostate cancer and patients initially submitted to radical prostatectomy (RP) or radiotherapy with curative intent who showed biochemical recurrence defined as a prostate-specific antigen (PSA) elevation of $\geq 0.2$ng/mL in patients with primary prostatectomy or as a PSA above the nadir after primary radiation therapy (according to the ASTRO 1996 criteria (11)).

Index test: $^{68}$Ga-PSMA-11 PET
Target condition: Diagnostic, staging, local recurrence, lymph nodal spread, distant metastasis.

Study design: Diagnostic accuracy cross-sectional study with prospective and retrospective approaches.

Exclusion criteria: case reports, animal, and phantom studies were excluded.

No language or sample-size restrictions were used.

Reference standard
A composite standard including changing in PSA values, clinical follow-up, and histopathological findings.

Outcome measures
The outcome measures included identification of predictors of $^{68}$Ga-PSMA-PET positivity, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy.

Study selection
The titles and abstracts retrieved from bibliographic searches were independently screened by two authors (MCS and PDB). The full texts of all relevant articles were obtained and independently assessed for inclusion by the same authors aforementioned. Studies that did not fulfill the inclusion criteria were excluded.

Quality assessment
The studies were independently assessed by two authors (MCS and PDB) using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS 2) checklist tool (12). The QUADAS-2 tool assesses four domains: risk of bias in patient selection, index test, reference standard, and the timing of reference standard. Each paper was scored independently by two evaluators (MCS and PDB), and discrepancies were discussed and resolved in common agreement.

Data extraction
The following information was extracted from each study: sample size, age of the patients, indication for PET (diagnosis, primary staging or recurrent disease staging), PSA level, previous therapies, initial cancer stage, $^{68}$Ga-PSMA-11 PET characteristics, rates of positive PET, and pathology correlation data (when available). When pathology correlation data were available, numbers of true positives, false positives, true negatives and false negatives were collected as appropriate. The $^{68}$Ga-PSMA-PET for diagnosis, primary staging, and recurrent cancer staging purposes data were displayed separately, when available.

The extracted data were collected in Excel 2007 (Microsoft Corporation, Redmond, CA, USA), and analysis was performed using Meta-Disc 1.4 (13). The detection rates were pooled using the generic inverse variance approach in the random-
-effects model (14). Heterogeneity in the meta-analysis of detection rates was assessed using the $X^2$ statistic in the $I^2$ statistic (10). The $I^2$ statistic indicates the percentage of the overall variability that can be attributed to between-study (or inter-study) variability, as opposed to within-study (or intra-study) variability. An $I^2$ more significant than 50% is considered to indicate substantial heterogeneity (10).

We explored the variability in diagnostic accuracy across studies by plotting the estimates of the observed sensitivities and specificities in forest plots and receiver-operating characteristic (ROC) space. Whenever data for computing true-positive, false-negative, true-negative, and false-positive rates were available, we performed meta-analyses using the bivariate model to produce summary sensitivities and specificities (13). We remade the calculations, excluding one article at a time, to verify if one of the studies was the main responsible for the heterogeneity in the meta-analyses. If substantial heterogeneity in the prevalence among the studies was observed, we estimated PPVs and NPVs by considering their relationship in the sensitivity, specificity and prevalence, and generating different scenarios with different prevalence. The significance level was set at $\alpha=0.05$.

In patients undergoing a scan for disease recurrence, we correlated the data (sensitivity and specificity) to PSA level, in subgroups divided as follow: PSA level $<0.5$ng/mL, PSA level between 0.5ng/mL and 1ng/mL, PSA level between 1ng/mL and 2ng/mL and PSA level higher than 2ng/mL.

**RESULTS**

**Identification of Studies**

Figure-1 summarizes the process of identification and selection of studies. The electronic search was complemented by manually checking the reference lists in review papers and all included studies. Overall, we included 87 studies comprising of a total of 9046 patients (range: 6-635 patients per study): 17 studies on diagnostic (15-31), 26 studies on staging (32-57), and 45 studies on restaging (5, 23, 57-100).

**Study design and quality**

A total of 52 studies used a retrospective design (6, 15, 21-28, 31-34, 37-41, 43, 45, 46, 48, 51-56, 58-64, 67, 72-77, 79, 80, 82, 85, 92, 93, 96-98), 27 studies used a prospective design (18, 19, 29, 30, 35, 44, 47, 49, 57, 66, 68, 70, 71, 78, 81, 83, 84, 87-91, 94, 95, 99, 100), and one of them used cohort design (65). Seven studies did not indicate how data were included or obtained (16, 17, 20, 42, 50, 69, 86).

While the patient selection was generally acceptable in most of the studies included, a few studies did not report the inclusion criteria clearly. All the studies reported methodology for the index test with clarity and were, thus, not considered a significant source of potential bias. There was a broad variability in the reference test: Prostate biopsy results were used in ten studies (19, 21, 23, 32-35, 39, 54, 83), histologic results from radical prostatectomy or lymphadenectomy in 35 studies (6, 15, 16, 18, 20, 22, 24, 25, 27, 29, 31, 34, 36, 38, 41, 46, 48, 49, 52, 54, 55, 59, 62, 68, 77, 78, 83, 84, 86, 87, 90, 92, 95-97) and combined outcomes using additional imaging with magnetic resonance imaging (MRI) or bone scan and/or clinical follow-up and/or response to treatment (mostly PSA testing courses over time) in 45 studies (17, 26, 28, 30, 37, 40, 47, 50, 51, 53, 56-58, 60, 61, 63-67, 69-76, 79-82, 85, 88, 89, 91, 93, 94, 98-100) (Tables 1 a-c).

**Pooled sensitivity, specificity, and diagnostic odds ratios; likelihood ratios**

The availability of original data and the possibility of constructing a two-by-two table were minimum requirements (6, 15, 17, 18, 22-24, 32, 33, 36, 37, 39-49). We excluded studies that did not provide us with enough data in terms of sensitivity, specificity, diagnostic odds ratios, and likelihood ratios analyses to create a 2X2 Table. Overall, 34 studies met the criteria for this meta-analysis, comprehending a total of 4532 patients submitted to $^{68}$Ga-PSMA PET; among those, nine studies (287 patients) in diagnostic setting and four studies for staging purposes, and 22 studies for restaging, in a total of 4050 patients (note that 1 study included staging and restaging patients).
Figure 1- Summary of the study selection process.

Excluded 3,513 articles:
   a) Duplicate
   b) Tracer others than 68Ga-PSMA
   c) Techniques other than PET or PET-CT

Excluded 713 articles because:
   a) No original data, like reviews
   b) Case Reports
   c) Abstract/Meetings reports
   d) Editorials
   e) Letters to editor

Excluded 312 articles because:
   a) Same reason above
   b) Duplicate data
   c) No results relevant to research question

87 Articles Included

45 articles for secondary staging (biochemical recurrence)
17 articles for diagnostic
26 articles for first staging
| Author          | *D | Country | N | Scan Time | Reference text     | Age | Patient Characteristics | Results                                                                 |
|-----------------|----|---------|---|-----------|--------------------|-----|--------------------------|----------------------------------------------------------------------------|
| Eiber, et al. (15) | R  | Germany | 53 | 60       | Histology          | 62-72 | Confirmed Prostate Cancer | 68Ga-PSMA PET improves accuracy for diagnosis and localization of prostate cancer |
| Budäus, et al. (27) | R  | Germany | 30 | -        | Histology          | 44-75 | Confirmed Prostate Cancer | 68Ga-PSMA PET improves accuracy for diagnosis and localization of prostate cancer. The accuracy depends on the size of lymphnodes |
| Gupta, et al. (25) | R  | India   | 11 | -        | Histology          | 46-46 | High risk prostate cancer | 68Ga-PSMA PET improves accuracy for diagnosis and localization of prostate cancer |
| Hicks, et al. (28) | R  | USA     | 32 | 71±14'   | MRI                | 62-71 | High risk prostate cancer | 68Ga-PSMA PET sensitivity is better than MRI |
| Lopci, et al. (29) | P  | Italy   | 45 | 60'      | Histology          | 64.52 | High risk prostate cancer | 68Ga-PSMA PET is indicated to diagnose Prostate cancer when MRI is negative or contraindicated |
| Sanli, et al. (26) | R  | Turkey  | 109| 45-60'   | PSA level, Gleason score | 48-79 | Confirmed Prostate Cancer | 68Ga-PSMA PET improves accuracy for diagnosis and localization of prostate cancer |
| Wu, et al. (30)  | P  | USA     | 45 | 50-100'  | Radiotherapy response | 66-74 | Confirmed Prostate Cancer | 68Ga-PSMA PET changed radiotherapy area in 53% |
| Zhang, et al. (31) | R  | China   | 58 | 601      | Histology          | 55-85 | High risk prostate cancer | 68Ga-PSMA PET prostate cancer detection is superior than nanogram |
| Zamboglou, et al. (16) | -  | Germany | 7  | -        | Histology          | 52-74 | Patients with prostate cancer candidates with subsequent prostatectomy | 68Ga-PSMA PET and MRI have high sensitivity and specificity, the combination of techniques improves performance |
| Sachpekidis, et al. (17) | -  | Germany | 24 | 60       | PSA                | 43-84 | Confirmed Prostate Cancer | 68Ga-PSMA PET has a high detection rate |
| Fendler, et al. (18) | P  | Germany | 21 | 60       | Histopathology     | -    | Confirmed Prostate Cancer | 68Ga-PSMA PET detects the location and extent of primary prostate cancer |
| Zamboglou, et al. (20) | -  | Germany | 9  | 60       | Histology          | 49-74 | Confirmed Prostate Cancer | 68Ga-PSMA PET had a good correlation with histology |
| Sahlmann et al. (21) | R  | Germany | 35 | 60-180   | Biopsy or unequivocal CT findings | 49-78 | Confirmed Prostate Cancer | 68-Ga PSMA PET is a tool that can be used to diagnose metastases of prostate cancer |
| Rahbar, et al. (22) | R  | Germany | 6  | 65       | Histopathology     | 56-73 | Confirmed Prostate Cancer | 68Ga-PSMA PET can detect injuries and collaborate on clinical strategy |
| Hijazi, et al. (23) | R  | Germany | 35 | 60-180   | PSA and biopsy     | 49-77 | Confirmed Prostate Cancer or Patients with biochemical relapse | 68Ga-PSMA PET improves the accuracy of micro-metastases diagnosis |
| Kabasakal, et al. (24) | R  | Turkey  | 28 | 5-60     | Histopathology     | 55-85 | Confirmed Prostate Cancer | 68Ga-PSMA PET is valuable for assessing primary prostate cancer |
| Rhee, et al. (19)  | P  | Australia | 20| 90        | Biopsy             | 62±7  | Confirmed Prostate Cancer | Both PSMA and MRI failed to diagnose an expressive number of lesions |

* *D = Study design; R = for retrospective study; P = prospective study; C = cohort*
| Author                  | *D | Country | N  | Scan Time | Reference text                        | Age       | Patient Characteristics                  | Results                                                                                                                                                                                                |
|------------------------|----|---------|----|-----------|---------------------------------------|-----------|------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Uprimny, et al. (33)   | R  | Austria | 90 | 60        | Biopsy/Gleason score                  | 47-83     | Patients with untreated prostate cancer  | 68Ga-PSMA PET is correlated with PSA and Gleason score                                                                                                                                                |
| Afshar-Oromieh, et al. (43) | -  | Germany | 112 | 60-180'   | CT or MRI                             | 69.8±7.9  | Suspected prostate cancer                | PET/CT with 68Ga-PSMA-11 at 3 h after injection is a valuable method to clarify unclear findings of regular scans conducted at 1 h after injection or to find new PCa lesions because most PCa lesions present with a higher uptake and contrast in late scans. |
| Bräuer, et al. (41)    | R  | Germany | 27 | NA        | change in therapeutic management      | 67.8±8.2  | Patients referred for 223Ra-dichloride therapy | Additional 68Ga-PSMA-PET as a gatekeeper between conventional staging and 223Ra-dichloride therapy can provide valuable additional information with regard to visceral metastases and tumour manifestations without adequate bone mineral turnover. |
| Demirkol, et al. (44)  | R  | Turkey  | 22 | NA        | PSA levels, treatment response        | 43-86     | Suspected Prostate cancer               | PSMA based nuclear imaging has significantly impacted our way of handling patients with prostate cancer.                                                                                                                                                       |
| Dyrberg, et al. (45)   | P  | Denmark | 55 | NA        | NaF-PET/CT, WB-MRI                    | 54-91     | patients with biopsy-proven prostate cancer referred by the clinicians for the standard bone imaging method at our institution, NaF-PET/CT                           | The overall accuracy of PSMA-PET/CT was significantly more advantageous compared to WB-MRI, but not to NaF-PET/CT.                                                                                                                                               |
| Ergül, et al. (46)     | R  | Turkey  | 78 | 60'       | prostate-specific antigen (PSA) values, Gleason score (GS), and d’Amico risk classification | 47-88   | newly diagnosed prostate carcinoma and no previous therapy | PSMA PET/CT is well suited for detecting the intraprostatic malignant lesion in patients with newly diagnosed prostate cancer.                                                                                                                                   |
| Grubmüller, et al. (47)| R  | Austria | 117| 60'       | PSA levels                            | 68-76     | hormone-naïve BCR patients              | They confirm the high performance of PSMA-PET imaging for the detection of disease recurrence sites in patients with BCR after RP, even at relatively low PSA levels.                                                                 |
| Reference | Country | N | Min. | Procedure | Patient Characteristics | Findings |
|-----------|---------|---|------|-----------|-------------------------|----------|
| Hruby, et al. (48) | Australia | 109 | Min. 45' | conventional imaging with bone scan, CT and multiparametric MRI | Men prior to definitive EBRT for intermediate and high-risk prostate cancer | PSMA-PET/CT identified the primary in 99% of patients, and altered staging in 21% of men with intermediate or high-risk prostate cancer referred for definitive EBRT compared to CT, bone scan and multiparametric MRI. |
| Kuten, et al. (49) | Israel | 137 | - | PSA levels, clinical history, imaging reports and histopathological reports | newly diagnosed intermediate- and high-risk prostate cancer were referred for initial staging | Ga-PSMA PET/CT shows promise as a sole whole-body imaging modality for assessing the presence of soft tissue and bone metastases in the setting of prostate cancer. |
| Lengana, et al. (50) | South Africa | 113 | 60' | bone scan | patients with biopsy-proven prostate cancer | 8Ga-PSMA PET/CT is superior to and can potentially replace bone scan in the evaluation for skeletal metastases. |
| Roach, et al. (58) | Australia | 431 | 45-60' | follow-up questionnaire | Patient in primary staging of intermediate- and high-risk prostate cancer | 68Ga-PSMA PET/CT scans detect previously unsuspected disease and may influence planned clinical management in a high proportion of patients with prostate cancer. |
| Soldatov, et al. (51) | Germany | 108 | NA | PSA level | Patients with increased prostate-specific antigen levels | SMA-ligand PET/CT-guided RT for relapsed PCa with limited tumor burden allowed individualization of treatment approaches, provided effective local control, and resulted in considerably prolonged biochemical progression-free survival |
| Thomas, et al. (52) | Germany/USA | 21 | 80' | conventional plans | prostate cancer patients without previous local therapy | the use of 68Ga-PSMA-PET/CT image information allows for more individualized prostate treatment planning |
| Uprimny, et al. (53) | Austria | 203 | 60' or until 5 min | PET scans 60 min p.i | PC patients with biochemical failure | Performance of early imaging in 68Ga-PSMA-11 PET/CT in addition to whole-body scans 60 min p.i. increases the detection rate of local recurrence in PC patients with biochemical recurrence. |
| Uprimny, et al. (54) | Austria | 16 | 40-70 sec | 18F-NaF PET | metastatic PC patients with known skeletal metastases | In comparison to 68Ga-PSMA-11 PET/CT, 18F-NaF PET/CT detects a higher number of pathologic bone lesions in advanced stage PC patients scheduled for radionuclide therapy. |
| Study (Authors) | Country | Patients | Age | Imaging Method | Population | Findings |
|----------------|---------|----------|-----|----------------|------------|----------|
| Uslu-Besli, et al. (55) | Turkey | 28 | 45' | Bone scan | 67.3±7.4 prostate cancer patients | Ga-68 PSMA PET/CT has higher sensitivity, specificity, and accuracy compared to bone scan in terms of bone metastasis detection in prostate cancer patients |
| Vinsensia, et al. (42) | Germany | 147 | 60±10 | conventional CT | 44-87 prostate cancer patients | 68Ga-PSMA PET is a promising modality in biochemical recurrent prostate cancer patients for N staging. Conventional imaging underestimates LN involvement compared with PSMA molecular staging score in each GS cohort. |
| von Klot, et al. (56) | Germany | 21 | NA | Histology | 68.1±6.0 patients with prostate cancer before either open or laparoscopic radical prostatectomy | 68Ga-PSMA I&T PET/CT prior to radical prostatectomy can contribute to presurgical local staging of prostate cancer. |
| Wong, et al. (57) | Australia | 131 | NA | impacted on management | 49-84 patients with newly diagnosed prostate cancer prior to consideration of definitive treatment | The use of 68 Ga-PSMA PET scans in initial staging can have a significant impact on staging and management when compared to current conventional imaging modalities. |
| Fendler, et al. (35) | Multicentric | 50 | 54 | Histology, biopsy | 49-83 Confirmed Prostate Cancer | Interobserver correlation for staging is good when observers have medium or large experience |
| Zang, et al. (36) | China | 40 | 60 | biopsy | 53-91 Patients with biochemical recurrence of prostate cancer | 68Ga-PSMA PET has high sensitivity and specificity |
| van Leeuwen, et al. (37) | Australia | 30 | 60 | Histopathology | 65.0±8.5 Patients at Risk for Prostate Cancer | 68Ga-PSMA PET has high specificity and moderate sensitivity in seven lymph node metastases |
| Pyka, et al. (38) | Germany | 126 | 60 | "best valuable comparator" (Clinical and Imaging Information) | 68.9±7.7 Confirmed Prostate Cancer | PSMA is better than bone scintigraphy in both staging and detection |
| Herlemann et al. (39) | Germany | 34 | 60 | Histopathology | 50-80 Confirmed Prostate Cancer | 68-PSMA PET is accurate in detecting the spread of the tumor |
| Giesel et al. (40) | Germany | 10 | 60 | Biopsy | 61-74 Confirmed Prostate Cancer | MP-MRI and PSMA-PET/CT are accurate in localizing prostate cancer |
| Maurer et al. (34) | Germany | 130 | 59 | Biopsy | 45-84 Patients with suspected prostate cancer | 68Ga-PSMA PET has superior performance in detecting lymph node stage |

*D = Study design; R = retrospective study; P = prospective study; C = cohort.
Table 1c. Summary of contents of study design – Recurrence.

| Author                | D* | Country  | N  | Scan Time | Reference text                         | Age          | Patient Characteristics                                | Results                                                                 |
|-----------------------|----|----------|----|-----------|----------------------------------------|--------------|-------------------------------------------------------|------------------------------------------------------------------------|
| Schmuck, et al. (60)  | R  | Germany  | 240| 180       | PSA, Histology and follow-up            | 59.8±7.5     | Patients with recurrent prostate cancer               | 68Ga-PSMA PET had high detection rates in patients with persistent PSA or biochemical persistence of prostate cancer. |
| Uprimny, et al. (61)  | R  | Austria  | 80 | 60        | PSA                                    | 47-92        | Patients with recurrent prostate cancer               | 68Ga-PSMA PET is reliable in distinguishing lesion from bladder activity   |
| Berliner, et al. (62) | R  | Germany  | 83 | 80        | PSA                                    | 68±7         | Patients with biochemical recurrence of prostate cancer | 68Ga-PSMA PET has high rates of detection of recurrent cancer, the higher the level of PSA the greater the detection rate |
| Einspieler, et al. (63)| R  | Germany  | 118| 60        | Histology                              | 50-87        | Patients with biochemical recurrence of prostate cancer | 68Ga-PSMA PET has high levels of cancer detection                        |
| Kabasakal, et al. (64)| R  | Turkey   | 50 | 60        | Change in PSA levels posterior 171Lu-PSMA treatment | 67.3±8.7   | Patients referred for restaging                       | 68Ga-PSMA PET is accurate to reestablish patients with relapse            |
| Schwenck, et al. (65) | R  | Germany  | 123| 60        | PSA                                    | -            | Patients with recurrent prostate cancer               | PSMA is more accurate than C-choline to detect lymph nodes and bone lesions |
| Hruby, et al. (66)    | C  | Australia| 419|           | Biochemical recurrence                 | -            | Patients submitted to radiotherapy                   | 68Ga-PSMA PET detected all cases of biochemical recurrence               |
| Dietlein, et al. (67) | P  | Germany  | 129| 60-120    | PSA                                   | -            | Patients with biochemical recurrence of prostate cancer | F-DCFpYP is not inferior than 68Ga-PSMA-HBED-CC                          |
| Meredith, et al. (68) | R  | Australia| 532| 60        | PSA                                    | 44-85        | Patients with biochemical recurrence of prostate cancer | 68Ga-PSMA PET s a new imaging modality to detect prostate cancer          |
| Bluemel, et al. (59)  | R  | Germany  | 32 | 60        | PSA                                    | 69.4±6.8     | Patients with biochemical recurrence of prostate cancer and negative Choline-PET/CT | Including 68Ga-PSMA PET in Choline-PET / CT negative patients increases the ratio of positive diagnoses |
| Pfister, et al. (69)  | P  | Germany  | 28 | 45        | Histopathology                        | 46-79        | Patients with biochemical recurrence of prostate cancer | 68Ga-PSMA PET is more accurate than Fluoroethylcholine PET/CT             |
| Sachpekdis, et al. (70)| - | Germany  | 31 | 60        | PSA                                    | 54-77        | Patients with biochemical recurrence of prostate cancer | 68Ga-PSMA PET has promising and satisfactory detection levels             |
| Henkenberen, et al. (71) | P  | Germany  | 29 |           | PSA                                    | 51-86        | Patients with biochemical recurrence of prostate cancer | Radiation therapy guided by 68Ga-PSMA PET has good results               |
| van Leeuven, et al. (72) | P  | Australia| 70 | 45        | PSA                                    | 57-67        | Patients with biochemical recurrence of prostate cancer | 68Ga-PSMA PET has reasonable performance in identifying recurrence of prostate cancer in patients with low PSA |
| Verburg, et al. (73)  | R  | Germany  | 155| 60        | PSA                                    | 43-86        | Patients with biochemical recurrence of prostate cancer | 68Ga-PSMA PET is a promising and clinically useful tool                  |
| Ceci, et al. (74)     | R  | Austria  | 70 | 60        | PSA                                    | 38-91        | Patients with biochemical recurrence of prostate cancer | 68Ga-PSMA PET has the potential confirmed in patients with biochemical relapse |
| Authors | Country | Study Population | Test | Findings |
|---------|---------|------------------|------|----------|
| Afshar-Oromieh et al. (78) | Germany | 310 | PSA and Histology | 68Ga-PSMA PET can detect the recurrence of prostate cancer in a large number of patients |
| Afshar-Oromieh et al. (6) | Germany | 37 | PSA and Histology | 68Ga-PSMA PET identifies a larger number of patients than Fluoroethylcholine |
| Afaq, et al. (77) | UK | 100 | Gleason grade, stage, presence of metastatic disease, PSA velocity, or PSA doubling time | 68Ga-PSMA PET/CT altered management in 39% of patients with BCR, and changes occurred more often in patients with radical radiotherapy treatment, positive 68Ga-PSMA scan results, and higher PSA levels. |
| Akdemir, et al. (79) | Turkey | 121 | Conventional imaging | 68Ga-PSMA-PET/CT is useful for re-staging patients with RPCa and has improved performance compared with CI for disease detection. |
| Barbaud, et al. (80) | France | 42 | FCH PET-CT | Performing a PSMA PET-CT when FCH PET-CT was doubtful or negative allows the recurrence localization in more 80% of patients and this had a major clinical impact, as it resulted in treatment change in more than 70% of patients as well as a significant decrease in PSA levels in more than 60% of them. |
| Bashir, et al. (81) | UK | 28 | Follow up | Our findings show that PSMA-PET/CT has a high detection rate in the eBCR setting following RP, with a large proportion of patients found to have fewer than three lesions. |
| Calais, et al. (82) | USA | 10 | Referring physicians questionnaires | This prospective referring physician–based survey shows a significant impact (54/101; 53%) of 68Ga-PSMA-11 PET/CT on the actual management of prostate cancer patients with BCR. Importantly, intended management changes after 68Ga-PSMA-11 PET/CT were further modified in almost 50% of the patients, underlining the limitations of survey-based management assessment. |
| Calais, et al. (83) | USA | 270 | Referring physicians questionnaires | Information from 68Ga-PSMA-11 PET/CT brings about management changes in more than 50% of prostate cancer patients with BCR (54/101; 53%). However, intended management changes early after 68Ga-PSMA-11 PET/CT frequently differ from implemented management changes. |
| Study | Country | Patients | Age | PSA level | Details |
|-------|---------|----------|-----|-----------|---------|
| Caroli, et al. (84) | Italy | 314 | 50 | 44-92 | We confirmed the value of 68Ga-PSMA PET/CT in restaging PCa patients with BCR, highlighting its superior performance and safety compared with choline PET/CT. Higher PSA was associated with a higher relapse detection rate. |
| Ceci, et al. (85) | Italy | 332 | 60 | 54-83 | Our data confirmed the efficacy of 68Ga-PSMA-11 PET/CT for detecting local vs. systemic disease in PCa patients presenting PSA failure after radical therapy. Furthermore, 68Ga-PSMA-11 PET/CT detection rate is different depending on the clinical stage of BCR, and this information should be taken into consideration by referring physicians. |
| Dewes, et al. (86) | Germany | 15 | NA | 59-82 | The integration of (68)Ga-PSMA-PET imaging into the RT treatment planning process can be useful for detailed target volume planning. The performance of a (68)Ga-PSMA-PET frequently leads to changes in the TNM stage, altering the RT treatment regimen and the target volume. A prospective trial is underway to evaluate the impact of (68)Ga-PSMA-PET based treatment planning on outcome. |
| Dietlein, et al. (67) | Germany | 129 | 60-120 | 18F-DCFPyL | Our data suggest that 18F-DCFPyL is noninferior to 68Ga-PSMA-HBED-CC, while offering the advantages of 18F labeling. Our results indicate that imaging with 18F-DCFPyL may even exhibit improved sensitivity in localizing relapsed tumors after prostatectomy for moderately increased PSA levels. Although the standard acquisition protocols, used for 18F-DCFPyL and 68Ga-PSMA-HBED-CC in this study, stipulate different activity doses and tracer uptake times after injection, our findings provide a promising rationale for validation of 18F-DCFPyL in future prospective trials. |
| Fendler, et al. (88) | USA | 635 | 64+ | Histopathologic analysis | Using blinded reads and independent lesion validation, we establish high PPV for 68Ga-PSMA-11 PET, detection rate and interreader agreement for localization of recurrent prostate cancer. |
| Study                      | Country   | Sample Size | PSA Level | Follow-Up | Imaging Findings                                                                 |
|---------------------------|-----------|-------------|-----------|-----------|----------------------------------------------------------------------------------|
| Fennessy, et al. (89)     | Australia | 62          | 60        | 47-89     | men with prostate cancer undergoing clinically indicated 68 Ga-PSMA PET/CT        |
| Gauthé, et al. (90)       | France    | 33          | 60        | 55-79     | patients presenting biochemical recurrence of prostate cancer whose 18F-fluorocholine (FGH) PET/CT was non-contributive |
| Hamed, et al. (91)        | Egypt     | 188         | 60        | 56-79     | patients who exhibited rising of PSA level on a routine follow-up examination after definitive treatment of PC |
| Hijazi, et al. (24)       | Germany   | 35          | 60-180    | 49-77     | Confirmed Prostate Cancer or Patients with biochemical relapse                  |
| Hope, et al. (92)         | USA       | 150         | 63±10     | 69±6.9    | Referring physicians questionnaires                                             |
| Jilg, et al. (93)         | Germany   | 30          | 50        | -         | patients with the suspicion of exclusively nodal PCA-relapse after primary therapy underwent a template pelvic and/or retroperitoneal salvage-LND after whole body 68-Ga-PSMA-PET/CT |
| Mattiolli, et al. (94)    | Brazil    | 126         | 60        | 43-89     | prostate cancer patients submitted to the 68Ga-PSMA PET / CT due to biochemical recurrence |
| McCarthy, et al. (95)     | Australia | 238         | 60        | 46-91     | All patients had histologically confirmed Ca with biochemical relapse after definitive prostatectomy or radiation therapy. Patients with biochemical relapse at least 6 months after previous response to systemic (hormonal) treatment were also included. |

Intravenous Frusemide given with 68 Ga-PSMA reduces excretion artefact, and improves diagnostic certainty. Frusemide should be considered for all 68 Ga-PSMA PET/CT imaging protocols.

68Ga-PSMA-11 PET/CT is useful in detecting recurrence of prostate cancer, by identifying residual disease which was not detected on other imaging modalities and by changing management of 2 patients out of 3.

68Ga-PSMA PET/CT is a valuable tool for the detection of PC local recurrence or extraprostatic metastases following risin

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PSMA PET/CT is significantly more sensitive than standard restaging imaging, and it may be useful in identifying patients for subsequent targeted therapy.
| Study Reference | Country | Sample Size | Age Range | Procedure | PET/CT Description |
|-----------------|---------|-------------|-----------|------------|-------------------|
| Morigi, et al. (96) | Australia | 38 | 45 | 18F-fluoromethylcholine | A sample of men with a rising PSA level after treatment, eligible for targeted treatment, was prospectively included. In patients with biochemical failure and a low PSA level, (68)Ga-PSMA demonstrated a significantly higher detection rate than (18)F-fluoromethylcholine and a high overall impact on management. |
| Pfister, et al. (69) | Germany | 28 | 45 | Lymphadenectomy | Prostate Cancer patients who underwent sLAD after PET/CT. In the present series Ga-PSMA PET/CT shows a better performance than FEC PET/CT with a significantly higher NPV and accuracy for the detection of locoregional recurrent and/or metastatic lesions prior to salvage lymphadenectomy. |
| Rauscher, et al. (97) | Germany | 48 | 49-63 | Salvage lymphadenectomy | 68Ga-PSMA HBED-CC PET imaging is a promising method for early detection of LNM in patients with biochemical recurrent prostate cancer. It is more accurate than morphologic imaging and thus might represent a valuable tool for guiding salvage lymphadenectomy. |
| Schmidkonz, et al. (98) | Germany | 93 | 180-240 | Follow up | subjects conforming to the following criteria: histopathologically confirmed PC by needle biopsy and no primary therapy. MIP-1404 SPECT/CT has a high accuracy and low interobserver variability in the diagnosis of PC and allows detection of lymph node and bone metastases in a significant proportion of as yet untreated PC patients. |
| Schmidt-Hegemann, et al. (76) | Germany | 172 | 60 | Conventional CT | Prostate Cancer patients underwent 68Ga-PSMA PET/CT before radiotherapy. Compared with conventional CT, 68Ga-PSMA PET/CT had a remarkable impact on radiotherapeutic approach, especially in postoperative patients. |
| Walacides, et al. (99) | Germany | 25 | ? | Conventional Imaging | patients with biochemical prostate cancer recurrence after primary prostatectomy underwent 68 Ga-PSMA ligand PET/CT in addition to conventional imaging techniques such as CT and/or MR imaging for restaging. 68 Ga-PSMA ligand PET/CT is superior to conventional cross-sectional imaging for the delineation of lymph node metastases from prostate cancer. |
| Wondergem, et al. (100) | Netherlands | 65 | 60 or 120 | PSA level | prostate cancer patients who were referred to our nuclear medicine department for 18F-DCFPyL PET/CT were included. 18F-DCFPyL PET/CT images at 120 min after injection yield a higher detection rate of prostate cancer characteristic lesions than images at 60 min after injection. Further studies are needed to elucidate the best imaging time point for 18F-DCFPyL. |
| Zacho, et al. (101) | ? | 68 | 60 | 18F-NaF PET/CT | PCA patients with BCR. 68Ga-PSMA PET/CT and 18F-NaF PET/CT showed comparable and high diagnostic accuracies for detecting bone metastases in PCA patients with BCR. |

*D = Study design. R for retrospective study, P = prospective study, C = cohort.*
For diagnosis, the sensitivity was 0.90 (0.86 to 0.93), with an inconsistency of 75.1% and a specificity of 0.90 (0.82 to 0.96), not considering case-only confirmed patients (Figure-2).

We carried out a secondary analysis, withdrawing studies, one by one, in order to identify which study generated such heterogeneity. Recalling Budaus, L 2015 study, we obtained a pooled sensitivity of 0.92 (0.89 to 0.95) with 2.6% heterogeneity (Figure-3).

The group of studies that enrolled patients for staging indication, resulted in a sensitivity of 0.93 (0.86-0.98), with a low inconsistency, and a specificity of 0.96 (0.92-0.99), but with a significant inconsistency (Figure-4). After a secondary analysis, when Herlermann, the study found to be responsible for the inconsistency, was withdrawn from the pool, the specificity was 0.99 (0.96-1.00) (Figure-5). A summary ROC (sROC) curve confirmed the high value for this imaging modality in the staging setting with an area under the curve of 0.9731 (Figure-6).

The pool of studies that analyzed the power of \(^{68}\text{Ga}-\text{PSMA PET}\) in restaging recurrent prostate cancer resulted in a sensitivity of 0.76 (0.74 to 0.78), with heterogeneity of 96.7% (Figure-7). The specificity of the method, calculated based on the data available from the pool of studies, was 0.42 (0.27-0.58), and, again, a great inconsistency was noted (Figure-8). An sROC curve was plotted for those results, and the calculated area under the curve resulted in 0.73 (Figure-9).

When assessing biochemical recurrence, we observed that the higher the PSA level, the higher was the ability of the study to accurately demonstrate sites of accumulation of PSMA, positive for prostate cancer involvement. For patients with PSA LEVEL <0.5ng/mL, the positive LR pool estimation was 1.17 (0.37-3.73) and the sensitivity was 56% (0.42-0.68), increasing to 1.04 (0.38-
Figure 3 - A secondary analysis, when Budaus, L. Study was withdrawn from the pool, the inconsistency became much lower, not changing, substantially, the sensitivity of the method.

Figure 4 - Sensitivity and Specificity analysis in staging prostate cancer patients. Note in specificity analysis the high inconsistency among these studies.
Figure 5 - Specificity analysis in staging prostate cancer patients, after secondary analysis that showed Herlerrmann, A. study was responsible for the great inconsistency. Recalling the study, the specificity was 0.99 (0.96 to 1.00) with no inconsistency between the studies.

![Specificity Analysis Graph]

Figure 6 - ROC curve for 68Ga-PSMA-PET in diagnosis setting, showing an area under the curve of 0.9731.

![ROC Curve Graph]  

2.85) and 58% (0.47-0.68), respectively, in patients with PSA between 0.5 and 1ng/mL. The positive probable pool ratio is 1.44 (0.59-3.51) and the sensibility is 81% (0.74-0.87) for patients with PSA 1 to<2ng/mL and, for patients with a PSA level higher than 2ng/mL, LR ratio is 1.78 (0.66-4.77), with sensitivity of 96% (0.93-0.97).

**DISCUSSION**

Early biochemical recurrence represents the most clinically relevant subgroup of patients with relapsed prostate cancer, offering the possibility of potential curative salvage therapy concepts that might have a major impact on the outcome of patients. In bioche-
mical recurrence, traditional imaging approaches (MRI, CT, and choline-based PET-CT) often fail to localize disease, mainly when the PSA level ranges lower than 2ng/mL. In our meta-analysis, we defined 4 subgroups based on PSA level: very low (<0.5ng/mL), low (0.5-1.0ng/mL), intermediate (1-2.0ng/mL), and high (>2.0ng/mL). We confirmed the value of $^{68}$Ga-PSMA-PET in all subgroups. Detection rates are indeed higher when PSA levels are higher; however, the $^{68}$Ga-PSMA-PET may have the greatest clinical impact in very low and low PSA level subgroups. To date, choline-based PET/CT is not recommended for patients with recurrent cancer and PSA level below 2ng/mL. Compared to choline-based PET/CT, evidence suggests that the $^{68}$Ga-PSMA PET has better sensitivity in detecting prostate cancer recurrence. On pooled analysis, the $^{68}$Ga-PSMA PET sensitivity

![Figure 7 - 68Ga-PSMA-PET sensitivity for restating patients with biochemical recurrence of prostate cancer.](image)

| Study          | Sensitivity (95% CI) |
|----------------|----------------------|
| Schmuck, S. 2017 | 0.94 (0.88 - 0.97)   |
| Einspieler, I. 2017 | 0.90 (0.84 - 0.95)   |
| Kabasakal, I. 2017 | 0.76 (0.59 - 0.89)   |
| Hruby, G. 2016   | 0.99 (0.91 - 1.00)   |
| Dietlein, F. 2016 | 0.79 (0.71 - 0.86)   |
| Meredith, G. 2016 | 0.95 (0.89 - 0.98)   |
| Blumberg, C. 2016 | 0.44 (0.27 - 0.62)   |
| Pfister, D. 2016  | 0.78 (0.58 - 0.91)   |
| Sachpekitis, C. 2016 | 0.70 (0.52 - 0.85)   |
| Henkenberns, C. 2016 | 0.95 (0.80 - 1.00)   |
| van Leeuwen, P.J. 2016 | 0.54 (0.42 - 0.68)   |
| Verburg, F.A. 2016 | 0.80 (0.73 - 0.86)   |
| Hijazi, S. 2015   | 0.90 (0.76 - 0.98)   |
| Ceci, F. 2015     | 0.74 (0.62 - 0.84)   |
| Eiber, M. 2015    | 0.89 (0.85 - 0.93)   |
| Afshar-Oromieh, A. 2015 | 0.72 (0.66 - 0.77)   |
| Afshar-Oromieh, A. 2014 | 0.86 (0.70 - 0.95)   |
| Caroli, P. 2018   | 0.63 (0.57 - 0.68)   |
| Hamed, M.A. 2019  | 0.99 (0.95 - 1.00)   |
| Fendler, E.P. 2019 | 1.00 (0.98 - 1.00)   |
| Jilg, C.A. 2017   | 0.98 (0.85 - 1.00)   |
| Ceci, F. 2019     | 0.40 (0.34 - 0.46)   |
| Zacho H.D. 2018   | 0.13 (0.06 - 0.23)   |

Pooled Sensitivity = 0.76 (0.74 to 0.78)
Chi-square = 665.07; df = 22 (p = 0.0000)
Inconsistency (I²-square) = 98.7%

![Figure 8 - 68Ga-PSMA-PET specificity for restating patients with biochemical recurrence of prostate cancer.](image)

| Study          | Specificity (95% CI) |
|----------------|----------------------|
| Kabasakal, I. 2017 | 0.92 (0.62 - 1.00)   |
| Fendler, E.P. 2019 | 0.27 (0.11 - 0.49)   |
| Jilg, C.A. 2017   | 0.17 (0.00 - 0.82)   |
| Ceci, F. 2019     | 0.10 (0.00 - 0.63)   |

Pooled Specificity = 0.42 (0.27 to 0.58)
Chi-square = 19.00; df = 3 (p = 0.0003)
Inconsistency (I²-square) = 84.2%
was 56% for PSA under 0.5ng/mL. Our results for diagnostic accuracy are according to a recently published meta-analysis, reporting similar pooled sensitivity and specificity (3). To the date, most of the data outlining the utility of the \(^{68}\text{Ga-PSMA}\) PET is in the restaging for biochemical recurrence after definitive therapy.

Thus far, the value of \(^{68}\text{Ga-PSMA}\) PET in the accurate detection and delineation of intraprostatic tumor burden, which is important for diagnosis and treatment planning for patients with primary prostate cancer, is poorly explored. Although prostate cancer is mostly a multifocal disease, there is growing evidence that dominant intraprostatic lesions (DILs) may be responsible for metastatic and recurrent prostate cancer. Most of the ongoing studies use multiparametric magnetic resonance imaging (mpMRI); however, Zamboglou et al. compared seven patients who underwent mpMRI and \(^{68}\text{Ga-PSMA}\) PET before radical prostatectomy with co-registration between \(^{68}\text{Ga-PSMA}\) PET, mpMRI and histopathology. The sensitivity and specificity for \(^{68}\text{Ga-PSMA}\) PET were 75% and 87% and for mpMRI were 70% and 82%, respectively.

The present study highlights the possibility of improvement in evaluating prostate cancer, supporting the use of \(^{68}\text{Ga-PSMA}\) PET for diagnosing and staging. Traditionally, the primary staging of lymph nodes is performed using CT or MRI, but this relies on pathologic changes in lymph node morphology and size criteria. However, up to 80% of metastasis-involved nodes are smaller than the threshold limit of 8mm, typically used in clinical practice. Meta-analytical data for the traditional CT and MRI imaging approaches suggest sensitivity and specificity be 39–42% and 82%, respectively. A recent meta-analysis of choline-based tracers for PET-CT reviewed sensitivity of 49.2% and specificity of 95% for the detection of lymph nodes. Maurer et al. (34) performed a retrospective review of 130 patients undergoing high-risk prostate cancer, with a sensitivity of 65.9% and specificity of 98.9%. In our meta-analysis, the pool of studies showed the sensitivity and specificity were 93% and 87%, respectively, in detecting positive lymph nodes. As these are superior to those for traditional imaging, \(^{68}\text{Ga-PSMA}\) PET could allow complete and accurate diagnosing in primary staging compared to the current practice and potential improvement in patient care.

Figure 9 - SROC curve for the pooled sensitivities and specificities on restating scenario, showing an area under the curve of 0.73.
Despite significant advances, there is considerable scope for further research based on the use of $^{68}$Ga-PSMA PET. There is a need for more robust sensitivity and specificity data. In this meta-analysis, much of the histopathological correlation data available were not suitable for inclusion in our analysis for biopsy was performed according to clinician discretion. Selective lesion biopsy did not provide meaningful false-negative rates or specificity. Several groups reported the use of the $^{68}$Ga-PSMA PET for localization of intraprostatic malignancies, particularly in the context of focal therapies (50).

There are several limitations to this study. Firstly, most of the articles used for meta-analysis were derived from not measurable, retrospective, and single-institutional studies. The absence of more comprehensive studies could be justified as this technique is new and is still being explored for its inclusion in recent prostate cancer guidelines. Secondly, the heterogeneous nature of patient cohorts, treatment protocols, and studies used to pool sensitivity and specificity data, in particular, because most of the studies were carried with small sample size and patients were assessed in primary staging settings. Researchers should be encouraged to agree on data acquisition protocols and data analysis algorithms to increase the comparability of studies, which is one of the major issues in achieving evidence. Careful reporting of those methods may help evaluation to the extent that the results found to be applicable in other clinical settings.

$^{68}$Ga-PSMA PET seems to provide higher sensitivity and specificity compared to alternative techniques. Our results reinforce the current evidence of the usefulness of $^{68}$Ga-PSMA PET, whereby the diagnostic evidence is more substantial in restaging with biochemical recurrence. The main applicability of $^{68}$Ga-PSMA PET certainly relies on restaging patients with biochemical recurrence after local treatment with curative intent.

**CONFLICT OF INTEREST**

None declared.

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