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Finn E. von Eyben  
*Center of Tobacco Control Research*

Maria Picchio  
*IRCCS San Raffaele Scientific Institute*

Rie von Eyben  
*Stanford University*

Handoo Rhee  
*Princess Alexandra Hospital*

Glenn Bauman  
*The University of Western Ontario, glenn.bauman@lhsc.on.ca*

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Review – Prostate Cancer

# <sup>68</sup>Ga-Labeled Prostate-specific Membrane Antigen Ligand Positron Emission Tomography/Computed Tomography for Prostate Cancer: A Systematic Review and Meta-analysis

Finn E. von Eyben<sup>a,\*</sup>, Maria Picchio<sup>b</sup>, Rie von Eyben<sup>c</sup>, Handoo Rhee<sup>d</sup>, Glenn Bauman<sup>e</sup>

<sup>a</sup> Center of Tobacco Control Research, Odense, Denmark; <sup>b</sup> Department of Nuclear Medicine, IRCCS San Raffaele Scientific Institute, Milan, Italy; <sup>c</sup> Department of Radiation Oncology, Stanford University, San Francisco, CA, USA; <sup>d</sup> Department of Urology, Princess Alexandra Hospital, Brisbane, Australia; <sup>e</sup> Department of Radiation Oncology, University of Western Ontario in London, ON, Canada

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## Abstract

**Context:** <sup>68</sup>Gallium prostate-specific membrane antigen (PSMA) ligand <sup>68</sup>Ga-HBED-CC-PSMA (<sup>68</sup>Ga-PSMA) is a promising radiotracer for positron emission tomography (PET)/computed tomography (CT) of prostate cancer.

**Objective:** To conduct a meta-analysis to evaluate detection rate, diagnostic test accuracy, and adverse effects of <sup>68</sup>Ga-PSMA PET/CT or PET/magnetic resonance imaging (MRI) for staging of prostate cancer and for restaging of rising prostate-specific antigen (PSA) after initial treatment.

**Evidence acquisition:** Following the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines, our systematic review searched for articles in PubMed and EMBASE databases from 2012 to July 2016. The reference standard was pathology after biopsy or surgery. The analyses used a random effect model and a hierarchical summary receiver operating characteristic model.

**Evidence synthesis:** Fifteen <sup>68</sup>Ga-PSMA PET/CT studies with 1256 patients met the inclusion criteria. Seven studies of staging PET/CT or PET/MRI detected a regional site of cancer for 203 of 273 patients (74%). Nine studies of restaging PET/CT detected sites of recurrence in 799 of 983 patients (81%) with a 50% detection rate (74 of 147 patients) for restaging PSA of 0.2–0.49 ng/ml and a 53% detection rate (56 of 195 patients) for restaging PSA of 0.50–0.99 ng/ml. Staging <sup>68</sup>Ga-PSMA PET/CT in the studies had higher detection rates of sites in the prostate bed than restaging <sup>68</sup>Ga-PSMA PET/CT (mean 57% vs 14%,  $p = 0.031$ ,  $t$  test). Both staging and restaging <sup>68</sup>Ga-PSMA PET/CT found that a subgroup of the patients had metastatic sites in pelvic lymph nodes or distant organs. Eight studies of staging PET/CT undertook histologic correlations. We performed prostate-segment-based analysis specifically regarding the primary cancer lesion for four of these studies, and patient-based analysis specifically regarding pelvic lymph node metastases for four other studies. The pooled sensitivities for staging in the two groups of studies were 70% and 61%, and the pooled specificities were 84% and 97%. None of the studies reported complications from the PET/CT imaging.

**Conclusions:** <sup>68</sup>Ga-PSMA PET/CT has clinical relevance to detect sites of recurrence for patients with PSA recurrence after radical prostatectomy (RP) with PSA levels less than 1.0 ng/ml.

**Patient summary:** Choline positron emission tomography (PET)/computed tomography (CT) can detect sites of recurrent prostate cancer in an earlier phase of prostate-specific antigen (PSA) recurrence than bone scans and CT scans, but choline PET/CT is rarely positive for patients with restaging PSA levels under 1 ng/ml. A new radiotracer called <sup>68</sup>Ga-PSMA for PET/CT was able to detect sites of recurring cancer in up to 50% of patients who had an early rise in PSA exceeding 0.5 ng/ml after initial radical prostatectomy. The published studies did not report adverse effects of <sup>68</sup>Ga-PSMA PET/CT imaging.

\* Corresponding author. Birkevej 17, DK-5230 Odense M, Denmark. Tel. +46 66145862; Fax: +46 66145862.  
E-mail address: [finn113edler@mail.tele.dk](mailto:finn113edler@mail.tele.dk) (F.E. von Eyben).

## 1. Introduction

Prostate cancer is the most frequent cancer in men in Western societies, and in men the cancer mortality is second to that for lung cancer [1]. Localized prostate cancer is mainly treated with radical prostatectomy (RP), external beam radiotherapy (EBRT), or brachytherapy, but up to a third of patients develop a recurrence [2,3]. A rise of prostate-specific antigen (PSA) is typically the first indication of recurrence and is called PSA-only recurrence because patients with PSA <10 ng/ml typically have negative findings with conventional computed tomography (CT) scans and <sup>99m</sup>Tc bone scans. More recently, hybrid choline positron-emission tomography (PET)/CT allowed reliable detection of sites of recurrence at PSA levels >1–2 ng/ml [4,5]. Guidelines recommend a potentially curative treatment of PSA recurrence after RP in the form of salvage radiotherapy for the prostate bed (SRT) without guidance from imaging. SRT gives the best results when it is started while patients have restaging PSA of 0.2–0.5 ng/ml. Typically up to half of patients develop a second PSA recurrence during follow-up after SRT, and the development and application of new and more sensitive PET probes to guide salvage treatment is a field for ongoing investigations to improve salvage treatment.

Most prostate cancer cells express prostate-specific membrane antigen (PSMA), also denoted glutamate carboxypeptidase 2 or *N*-acetyl-L-aspartyl-L-glutamate peptidase 1 (NAALAD1) [6]. A German group developed a small-molecule inhibitor for PSMA, Glu-NH-CO-NH-Lys (Ahx)-<sup>68</sup>Ga-(*N,N'*-bis-[2-hydroxy-5-(carboxyethyl)benzyl]ethylenediamine-*N,N'*-diacetic acid) (<sup>68</sup>Ga-HBED-CC-PSMA or <sup>68</sup>Ga-PSMA-11) [7], referred to here as <sup>68</sup>Ga-PSMA. In 2012, the German group reported promising findings using this molecule as a PET/CT radiotracer for patients with prostate cancer [8], and later meta-analyses confirmed the findings and indicated that <sup>68</sup>Ga-PSMA PET/CT detects prostate cancer better than radiolabeled choline PET/CT [5,9].

## 2. Evidence acquisition

### 2.1. Research question

We aimed to summarize studies of staging and restaging <sup>68</sup>Ga-PSMA PET/CT or PET/MRI for patients with prostate cancer regarding detection of localized or metastatic prostate cancer. A second objective was to summarize imaging test accuracy of the new PET/CT method using pathology after biopsy or surgery as the reference standard. A third objective was to summarize imaging-related side effects from <sup>68</sup>Ga-PSMA PET/CT or PET/MRI.

### 2.2. Search strategy

Our systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [10]. In May 2016, two authors (FEvE and GB) registered a protocol for the

systematic review in the PROSPERO register (CRD 42016039690). Our systematic review included original research studies of staging or restaging with <sup>68</sup>Ga-PSMA PET/CT or PET/MRI. The two authors undertook an electronic search in PubMed and EMBASE databases. The PubMed search used medical subject heading (MeSH) terms and free text words: ((“prostatic neoplasm\*”) [MeSH] OR (“prostate cancer\*”) AND ((“positron emission tomography”) [MeSH] OR (“PET”)) AND ((“prostate membrane specific antigen”) [MeSH] OR (“PSMA”)) AND ((“\*Gallium”) [MeSH]) OR (“\*Ga”). Further, we searched for ongoing studies in the database ClinicalTrials (ClinicalTrials.gov).

The two reviewers independently screened the titles and abstracts of the reports and selected original research articles published in English. Our review included studies on patients with prostate cancer using <sup>68</sup>Ga-PSMA PET/CT or PET/MRI for initial staging of prostate cancer or for restaging with rising PSA after the initial treatment. We excluded articles published before 2012, the founding year for <sup>68</sup>Ga-PSMA, reviews, comments, and studies of laboratory results, studies of neoplasms apart from prostate cancer, studies of radiotracers apart from <sup>68</sup>Ga-PSMA, and studies that focused on the bioavailability of the radiotracer. Further, we excluded studies that only reported patients with a positive <sup>68</sup>Ga-PSMA PET/CT because they spuriously would have increased the pooled detection rates [9], studies that only undertook <sup>68</sup>Ga-PSMA PET/CT for patients with a negative choline PET/CT because the criterion implied selection bias, and studies with ≤20 patients owing to concerns regarding selection and publication bias and imprecision. The meta-analysis also excluded studies that combined staging with restaging, apart from one study consisting of >200 patients where the smallest patient group represented <10% of all patients, and one study that analyzed the two patient groups separately. Where a center had published several articles of its experience with <sup>68</sup>Ga-PSMA PET/CT, we based our summary of the total number of examined patients on the article with the most patients, and our summary of diagnostic test accuracy on another article because only the replicate article reported the diagnostic information.

### 2.3. Outcome measures

We calculated the detection rate as the number of patients with detected sites in relation to the total number of imaged patients [11]. We calculated imaging test accuracy for the detection of lesions in the prostate and pelvic lymph nodes based on a reference standard with histopathology after biopsy or RP and pelvic lymph node dissection. We summarized the side effects following the imaging with PET/CT or PET/MRI as they were reported in the studies.

### 2.4. Data collection

From the studies, both reviewers independently extracted the radiation activity of the <sup>68</sup>Ga-PSMA radiotracer, the uptake time between injection of the radiotracer and imaging, detection criteria, blinding of nuclear medicine

physicians for clinical information, and blinding of pathologists for the  $^{68}\text{Ga}$ -PSMA PET/CT findings. Both reviewers also registered the number of patients, median/mean age of the patients, staging or restaging, initial treatment, median/mean PSA at the time of PET, and detection rate and imaging test accuracy with  $^{68}\text{Ga}$ -PSMA PET/CT. One of the reviewers contacted all primary investigators for more information. In addition, for nine of our studies we compared our extracted information with that of a meta-analysis published by an independent team [9].

### 2.5. Quality assessment

We assessed risk of bias in the studies according to the Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2, as performed in previous reviews [11–13].

### 2.6. Meta-analytical methods

Our meta-analysis applied parametric statistic to summarize means  $\pm$  SDs of clinical characteristics, and used *t* tests to compare clinical characteristics between two groups of patients. Preplanned subgroup analysis of patients with  $^{68}\text{Ga}$ -PSMA PET/CT at staging and restaging investigated whether the two subgroups differed in overall detection rates and in the regional pattern of detected sites. We summarized the sensitivity and specificity of the  $^{68}\text{Ga}$ -PSMA PET/CT in studies that used pathology after biopsy or surgery as reference standard. Our meta-analysis used a random effect model and a hierarchical summary receiver operating characteristic (HSROC) model, carried out with Metandi software and Stata 14.0 (StataCorp, College station, TX, USA). Metandi provides a pooled estimate of the summary point with an estimate of the 95% confidence interval (CI) for the summary point together with a 95% prediction area for the

combined sensitivity and specificity in a future study. A *p* value  $<0.05$  indicated statistical significance.

## 3. Evidence synthesis

### 3.1. Bibliographic search

Searching in PubMed and EMBASE gave 257 reports including 42 duplicates (Figure 1). By screening titles and abstracts of 215 unique reports, the two reviewers independently excluded reviews, comments and replies, case reports, articles published before 2012, and studies employing radiotracers other than  $^{68}\text{Ga}$ -PSMA. The two reviewers read the full text of 37 articles and selected articles according to some of our exclusion criteria. The reading left 25 studies for qualitative analyses. Our quantitative analyses excluded all but two studies that combined staging and restaging  $^{68}\text{Ga}$ -PSMA PET/CT, and all studies consisting of  $\leq 20$  patients.

### 3.2. Description of the studies included

The meta-analysis selected 15 studies with 1256 patients (Table 1) [14–28]. Three studies were prospective cohort studies [18,23,26], seven studies were retrospective studies of consecutive selected patients [15–17,19–21,25], and five studies were retrospective studies of non-random patients [14,22,24,28]. Mean of the median/mean age for the patients was  $67 \pm 3$  yr (range, 62–71 yr). Fourteen studies only used  $^{68}\text{Ga}$ -PSMA PET/CT whereas one study reported both  $^{68}\text{Ga}$ -PSMA PET/CT and  $^{68}\text{Ga}$ -PSMA PET/MRI [20]. Mean of the median/mean total radiation activity of  $^{68}\text{Ga}$ -PSMA was  $172 \pm 27$  MBq (range, 146–236 MBq) in 11 studies [14–18,22–24,27,28], whereas one study reported the mean radiation activity normalized for body weight as 1.9 MBq/kg [20]. Mean

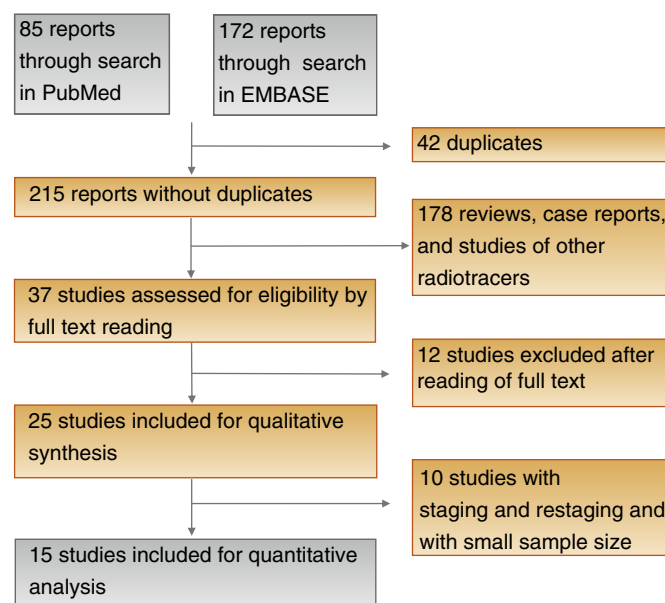


Fig. 1 – PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) flow diagram representing the selection of studies in this systematic review.

**Table 1 – Characteristics of the studies**

Study	Patients (n)	Indication for PET/CT	Median/mean age at diagnosis (yr)	Median/mean PSA and range at PET/CT (ng/ml)	PET protocol	
					Median/mean radiation activity (MBq or *MBq/kg)	Median/mean uptake time (min)
Afshar-Oromieh [14]	319	S + R	68	4.6 (0.1–41395)	161	60
Ceci [15]	70	R	67	1.7 (0.2–32)	146	60
Eiber [16]	248	R	70	2.0 (0.2–59)	155	54
Budaus [17]	30	S	62	8.8 (1.4–376)	165	NR
Fendler [18]	21	S	NR	NR	192	58
Herlemann [19]	34	S + R	67	35.1 (0.3–363)	NR	60
Maurer [20]	130	S	66	11.6 (6.9–24.5)	1.76*	60
Pfister [21]	28	R	64	2.4 (0.04–8)	NR	45
Rauscher [22]	48	R	71	1.3 (0.8–2.6)	154	57
Rhee [23]	20	S	62	6.1 (3.5–45)	150	60
Sachpekidis [24]	31	R	71	2.0 (0.1–130)	236	85
Van Leeuwen [25]	70	R	67	0.2 (0.05–1.0)	NR	45
Van Leeuwen [26]	30	S	65	8.1 (5.2–10.1)	236	85
Verburg [27]	155	R	70	4.0 (0–2000+)	190	60
Zamboglou [28]	22	S	69	11.6 (NR)	172	60
Total number	1256					

NR = not reported; R = restaging PET/CT; S = staging PET/CT.

of the median/mean uptake time for <sup>68</sup>Ga-PSMA PET/CT was 61 ± 13 min (range, 45–90 min).

The studies evaluated sites by a visual estimate of the maximum standard uptake value (SUV<sub>max</sub>), and many studies incorporated a reference tissue SUV<sub>max</sub> and reported a site as being positive when SUV<sub>max</sub> was higher than that of the reference tissue. Overall, 1002 of 1256 imaged patients had a positive site detected by <sup>68</sup>Ga-PSMA PET/CT or PET/MRI. Ten studies, including one replicate study, used a histology reference standard [17–23,26,28,29]. Two other studies [14,15] used histology or clinical judgment and follow-up as reference standard, whereas four further studies did not report a reference standard [16,24,25,27]. None of the studies reported side effects of the <sup>68</sup>Ga-PSMA PET/CT or PET/MRI imaging.

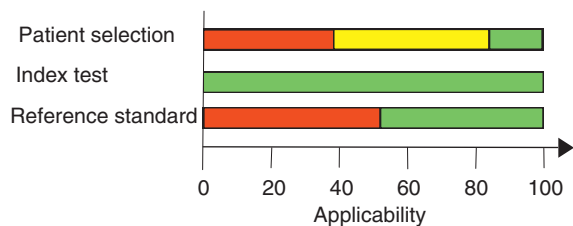
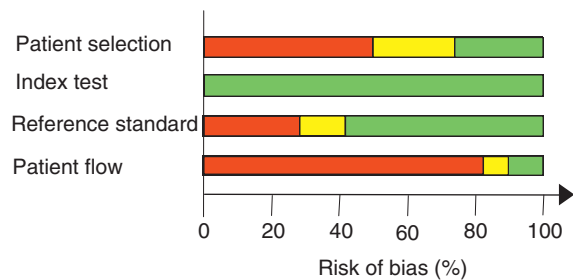
**3.3. Quality assessment**

Figure 2 summarizes our evaluation of the 15 studies regarding risk of bias as indicated by QUADAS-2 analysis.

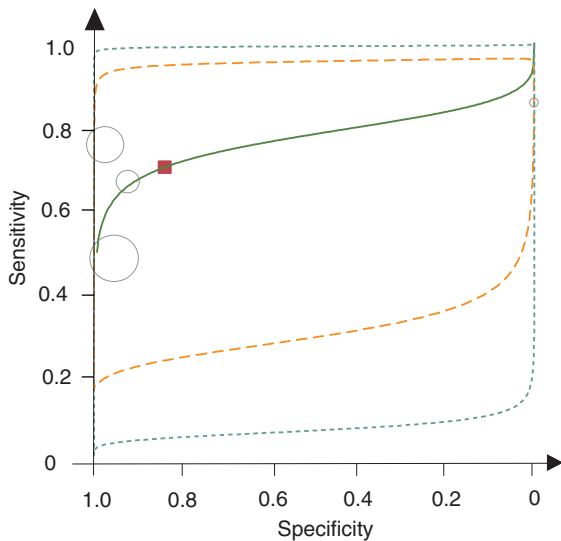
**3.4. Staging with PET/CT or PET/MRI**

Seven studies reported initial imaging with <sup>68</sup>Ga-PSMA PET/CT or PET/MRI before definitive treatment [17–20,23,26,28]. Six studies examined only <sup>68</sup>Ga-PSMA PET/CT, whereas one study examined both <sup>68</sup>Ga-PSMA PET/CT (35 patients) and <sup>68</sup>Ga-PSMA PET/MRI (95 patients) [20]. The mean of the reported median/mean PSA values in the studies was 9.3 ± 2.4 ng/ml (range, 6.1–11.8 ng/ml). <sup>68</sup>Ga-PSMA PET/CT or PET/MRI detected sites in 203 of 273 patients (74%), with 163 (60%) patients demonstrating a site in the prostate bed, 12 (4%) patients demonstrating a site in pelvic lymph nodes, and 28 (10%) patients demonstrating sites in more than one region.

Four studies [18,23,28,29] undertook lesion-based analysis and reported imaging test accuracy of staging <sup>68</sup>Ga-PSMA PET/CT to delineate intraprostatic cancer lesions based on a histopathology reference standard. One study used biopsy as the reference standard [28], and the other three studies used histopathology after RP and lymph node dissection as the reference standard [18,23,29]. Pooled sensitivity among these studies was 70% (95% CI: 53–83%) and pooled specificity was 84% (95% CI: 24–99%). Figure 3 summarizes the HSROC curve for detection of intraprostatic

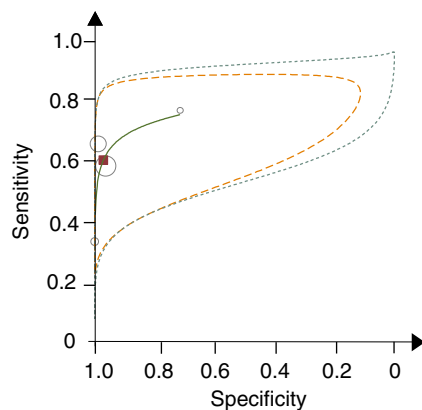


**Fig. 2 – Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 evaluation of the 15 studies. Regarding bias: proportion of studies with high risk of bias (red), unclear risk of bias (yellow), and low risk of bias (green). Regarding concerns for applicability: proportion of studies with high concerns regarding applicability (red), unclear concerns regarding applicability (yellow), and low concerns regarding applicability (green).**

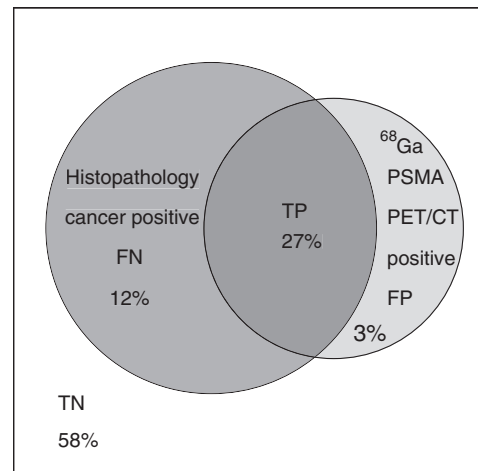


**Fig. 3** – Hierarchical summary receiver operating characteristic (ROC) analysis of staging using positron emission tomography imaging with  $^{68}\text{Ga}$ -PSMA for lesion-based analysis regarding test accuracy for intraprostatic lesions. The size of the circles shows the size of the studies, the full line shows the ROC curve, the square shows the summary operating point, the red stippled line shows the 95% confidence region for the summary point, and the black stippled line shows the 95% prediction region as a forecast of the sensitivity and specificity of a future study.  $^{68}\text{Ga}$ -PSMA =  $^{68}\text{Ga}$ -labeled ligand for prostate-specific membrane antigen.

lesions in the studies examining correlations with the histopathology reference standard. Four other studies undertook patient-based analysis and reported  $^{68}\text{Ga}$ -PSMA PET/CT imaging test staging accuracy specifically for sampled pelvic lymph node metastases [17,19,20,26]. Pooled sensitivity for lymph node detection was 61% (95% CI: 47–72%) and pooled specificity was 97% (95% CI: 85–99%). [Figure 4](#) summarizes the HSROC curve for detection of pelvic lymph node metastases in the studies, and [Figure 5](#) shows a Venn diagram that also summarized diagnostics regarding pelvic lymph node metastases.



**Fig. 4** – Hierarchical summary receiver operating characteristic of staging  $^{68}\text{Ga}$ -PSMA positron emission tomography for patient-based analysis regarding imaging test accuracy for lymph node metastases. Symbols are the same symbols as in [Figure 3](#).  $^{68}\text{Ga}$ -PSMA =  $^{68}\text{Ga}$ -labeled ligand for prostate-specific membrane antigen.



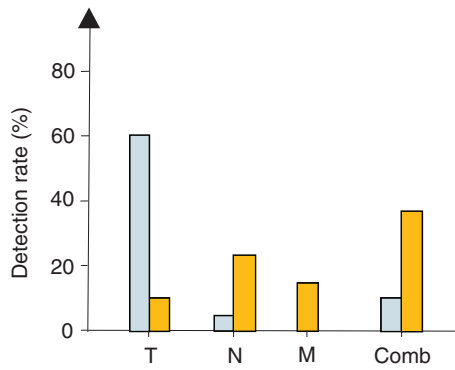
**Fig. 5** – Venn diagram for detection with staging  $^{68}\text{Ga}$ -PSMA PET of pelvic lymph node metastases. The circles indicate PET-positive and histopathology-positive patients. FN = false negative; FP = false positive; TN = true negative; TP = true positive.  $^{68}\text{Ga}$ -PSMA =  $^{68}\text{Ga}$ -labeled ligand for prostate-specific membrane antigen.

### 3.5. Restaging with PET/CT

Nine studies reported restaging with  $^{68}\text{Ga}$ -PSMA PET/CT for patients with persisting and rising PSA after initial treatment. Seven studies undertook only restaging  $^{68}\text{Ga}$ -PSMA PET/CT [15,16,21,22,24,25,27], whereas two studies included staging and restaging  $^{68}\text{Ga}$ -PSMA PET/CT [14,19]. The mean of the mean/median restaging PSA levels was  $2.3 \pm 1.4$  ng/ml (range 0.21–4.6 ng/ml). Two studies reported PSA recurrence after RP [16,26] whereas the other seven studies reported PSA recurrence after both RP and EBRT. In these studies the main treatment was RP for 87% of the patients (450 of 515) and EBRT for 13% of the patients (65 of 515).

Overall, for restaging of PSA-only recurrence,  $^{68}\text{Ga}$ -PSMA PET detected sites of recurrence in 799 of 983 imaged patients (81%). The studies reported the regional sites of recurrence for 615 of 755 patients (82%). Of these patients, 79 (10%) patients had sites in the prostate bed, 164 (22%) patients had sites in pelvic lymph nodes, 100 (13%) patients had sites in distant organs, and 272 (36%) had sites of recurrence in several regions. In eight studies [14,16,24,25,27,30–32], 74 of 147 patients (50%) with restaging PSA levels of 0.20–0.49 ng/ml had positive sites of recurrence, as had 56 of 105 patients (53%) with restaging PSA of 0.50–0.99 ng/ml. Four of the studies examined the PSA levels according to the detected sites. PET-positive patients had significantly higher PSA than PET-negative patients [14,15,24,27]. In one of the studies, PET-positive metastatic lesions in lymph nodes had a larger diameter than PET-negative metastatic lesions [26].

Two studies undertook patient-based analysis regarding  $^{68}\text{Ga}$ -PSMA PET/CT imaging test accuracy for restaging of lymph node metastases versus a histologic reference standard [21,22]. The sensitivities were 87% and 93%, and the specificities were 93% and 100%. A third study



**Fig. 6 – Detection rates for regional sites with staging and restaging  $^{68}\text{Ga}$ -PSMA PET/CT.** Grey bars show the proportion of patients with staging  $^{68}\text{Ga}$ -PSMA PET/CT or PET/MRI, and orange bars show the proportion of patients with restaging  $^{68}\text{Ga}$ -PSMA PET/CT.  $^{68}\text{Ga}$ -PSMA =  $^{68}\text{Ga}$ -labeled ligand for prostate-specific membrane antigen; PET = positron emission tomography; CT = computed tomography; MRI = magnetic resonance imaging; Comb = sites in more than one of the regions; M = sites in distant organs; N = sites in pelvic lymph nodes; T = site in the prostate bed.

undertook only lesion-based analysis and reported histologic verification for 42 patients regarding separate local, regional, and soft-tissue sites [14]. Thirteen of the patients had true-positive findings, three patients had false-positive findings, 19 patients had a combination of true-positive and true-negative sites, three patients had a combination of true-positive and false-negative sites, and four patients had true-negative findings.

$^{68}\text{Ga}$ -PSMA PET/CT for restaging at the time of PSA recurrence in the studies had higher overall detection rates than for  $^{68}\text{Ga}$ -PSMA PET/CT staging in the studies before definitive treatment, but the difference was not statistically significant (mean 78% vs mean 69%,  $p = 0.52$ ,  $t$  test). By contrast, detection rates for sites in the prostate bed were significantly higher with staging  $^{68}\text{Ga}$ -PSMA PET/CT than with restaging  $^{68}\text{Ga}$ -PSMA PET/CT (mean 57% vs 14%,  $p = 0.031$ ,  $t$  test, Figure 6).

#### 4. Discussion

This meta-analysis has added insight into the use of  $^{68}\text{Ga}$ -PSMA PET/CT and PET/MRI for patients with prostate cancer. All studies reported examinations with PET/CT, and only one study included a subgroup of patients examined with PET/MRI. The studies used a protocol for  $^{68}\text{Ga}$ -PSMA PET/CT with a radiation activity generally in the range 130–170 MBq, an uptake time of approximately 60 min, and interpretation of the imaging based on  $\text{SUV}_{\text{max}}$ . For staging PET/CT or PET/MRI, the detection rate was 70–80%. For restaging PET/CT, the restaging PSA was positively associated with the detection rate. The detection rate was 50% even for restaging PSA levels of 0.2–0.49 ng/ml, 53% for restaging PSA of 0.5–0.99 ng/ml, and was further increased for higher restaging PSA levels. Both staging and restaging PSMA PET/CT imaging were able to distinguish between single sites in the prostate bed, regional lymph nodes, and distant organs, and sites in more than one of the regions. The pooled sensitivity for primary or regional

cancer was 61–70% and the pooled specificity was 84–97%. The studies did not report adverse effects from the imaging.

For sites in the prostate bed, staging  $^{68}\text{Ga}$ -PSMA PET/CT before the initial treatment of the primary prostate cancer had a higher detection rate than restaging  $^{68}\text{Ga}$ -PSMA PET/CT after the initial treatment. This was in part because of debulking of the primary prostate cancer by the initial treatment, most often RP. A meta-analysis of choline PET/CT found the same difference between staging and restaging choline PET/CT [4]. Similarly, both the present meta-analysis of  $^{68}\text{Ga}$ -PSMA PET/CT and the meta-analysis of choline PET/CT found a subgroup of patients who had metastatic sites in pelvic lymph nodes and distant organs both at staging and restaging. Such identification of sites with PET/CT could guide treatment after surgery for men with persisting or recurrent PSA indicated by PSA monitoring. The consistency between studies with the two radiotracers for PET/CT suggests that the findings are real [33].

This systematic review has summarized detection rates and imaging test accuracy reported in the literature until July 2016. Our systematic review applied more rigid selection criteria than two previous systematic reviews [5,9]. For this reason the previous systematic reviews and our present systematic review had an overlap of only nine studies, and overlap of only one study that used histopathology as the reference standard. The different selections of studies in the three systematic reviews may have contributed to the fact that one of the previous systematic reviews found a 40% pooled detection rate in restaging with  $^{68}\text{Ga}$ -PSMA PET/CT [9].

Use of PSMA PET/CT for prostate cancer is expanding rapidly and widely. This has consequences for management. The international TNM tumor classification system classifies patients with PSA recurrence as M0 if they have no evidence of metastases on imaging, and as M1 if imaging shows evidence of metastases. Thus the distinction between M0 and M1 depends on the selection and validation of imaging methods used for the restaging.

As an alternative to SRT undertaken without guidance from imaging, a previous meta-analysis [5] proposed an algorithm that integrated PSMA PET/CT in the imaging of prostate cancer. However, because up to half the patients with PSA-only recurrence treated with SRT obtain long-term biochemical recurrence-free survival, restaging with  $^{68}\text{Ga}$ -PSMA PET/CT can only improve outcome for a subgroup of at-risk patients with PSA-only recurrence. As shown in our meta-analysis, restaging with  $^{68}\text{Ga}$ -PSMA PET/CT of such patients with restaging PSA <2 ng/ml might detect sites of recurrence that could be treated with targeted treatment with curative intent. We therefore propose that salvage treatment is individualized and guided by  $^{68}\text{Ga}$ -PSMA PET/CT for these patients also.

Our meta-analysis may have impact on research regarding  $^{68}\text{Ga}$ -PSMA PET/CT for patients with prostate cancer. Three ongoing trials are recruiting patients. Two trials address staging with  $^{68}\text{Ga}$ -PSMA PET: Evaluation of Gallium-HBED-CC-PSMA Imaging in Prostate Cancer patients (PSMA PET) (NCT02611882), and  $^{68}\text{Ga}$ -PSMA PET/MRI in Finding Tumors in Patients with Intermediate

or High-Risk Prostate Cancer Undergoing Surgery (NCT02678351). A third trial examines restaging with  $^{68}\text{Ga}$ -PSMA PET/CT:  $^{68}\text{Ga}$ -PSMA PET-CT Scan for Diagnosis and Management of Prostate Cancer (PSMA) (NCT02282137). Other studies compare PSMA and choline as radiotracers for restaging PET/CT.

Our review has limitations. We only evaluated  $^{68}\text{Ga}$ -PSMA as a radiotracer for PET/CT or PET/MRI although other PSMA radiotracers are also being investigated [34]. Because of the small number of studies, their heterogeneity, and potential selection and publication biases, external validation of the estimates of detection, sensitivity, and specificity rates will be needed. The diagnostic accuracy estimates were predominantly based on staging with  $^{68}\text{Ga}$ -PSMA PET/CT and PET/MRI, whereas we believe that the main indication for imaging is restaging of PSA-only recurrence. In addition, the review did not include analysis of studies that compared  $^{68}\text{Ga}$ -PSMA PET/CT with other imaging modalities, or of studies that reported treatment guided by  $^{68}\text{Ga}$ -PSMA PET/CT.

## 5. Conclusions

Based on published reports of staging  $^{68}\text{Ga}$ -PSMA PET/CT and PET/MRI, we found a sensitivity of 61–70% and a specificity of 84–97%. Restaging  $^{68}\text{Ga}$ -PSMA PET/CT had a detection rate of 50% for an early rise in PSA.

**Author contributions:** Finn E. von Eyben had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** F. von Eyben, Bauman.

**Acquisition of data:** F. von Eyben, Bauman.

**Analysis and interpretation of data:** F. von Eyben, Picchio, R. von Eyben, Rhee, Bauman.

**Drafting of the manuscript:** F. von Eyben.

**Critical revision of the manuscript for important intellectual content:** F. von Eyben, Picchio, R. von Eyben, Rhee, Bauman.

**Statistical analysis:** F. von Eyben, R. von Eyben.

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