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Review – Prostate Cancer

Impact of ^{68}Ga-PSMA PET on the Management of Patients with Prostate Cancer: A Systematic Review and Meta-analysis

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Abstract

Context: ^{68}Gallium prostate-specific membrane antigen positron emission tomography (^{68}Ga-PSMA PET) is an emerging imaging modality for assessment of prostate cancer. Recent studies show promising results regarding its ability to detect recurrent or metastatic prostate cancer superior to that of conventional imaging modalities. However, the impact of ^{68}Ga-PSMA PET on management of patients with prostate cancer has not been well established.
Objective: To perform a systematic review and meta-analysis to evaluate the impact of ^{68}Ga-PSMA PET on management of patients with prostate cancer.
Evidence acquisition: Pubmed and EMBASE databases were searched up to January 20, 2018. We included studies that reported proportion of management change after ^{68}Ga-PSMA PET in patients with prostate cancer. The quality of the studies was evaluated using the GRADE system. The proportion of management changes were pooled using random-effects model. Subgroup analyses and meta-regression analyses were performed to explore heterogeneity.
Evidence synthesis: Fifteen studies (1163 patients) were included. The pooled proportion of management changes was 54% (95% confidence interval 47–60%). At meta-regression analyses, PET positivity (%) was a significant factor of heterogeneity ($p = 0.0486$). For patients with biochemical failure, the proportion of radiotherapy (from 56% to 61%), surgery (from 1% to 7%), focal therapy (from 1% to 2%), and multimodal treatment (from 2% to 6%) increased, whereas that of systemic treatment (from 26% to 12%) and no treatment (from 14% to 11%) decreased with ^{68}Ga-PSMA PET.
Conclusions: ^{68}Ga-PSMA PET had a large impact on the management of patients with prostate cancer. Greater PET positivity was associated with higher proportion of management changes.
Patient summary: We reviewed all previous studies assessing the impact of ^{68}Gallium prostate-specific membrane antigen positron emission tomography (^{68}Ga-PSMA PET) in patients with prostate cancer. We found that ^{68}Ga-PSMA PET altered the management in approximately half of the patients.

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1. Introduction

Prostate cancer is one of the most common malignancies and is the third leading cause of cancer-related deaths in men [1]. As the presence and location of primary or recurrent tumors are critical for planning patient management, various imaging modalities are being assessed as a tool for the evaluation of patients with prostate cancer in primary and secondary staging [2–4]. The most recent European Association of Urology (EAU) guidelines recommend at least one cross-sectional imaging study (computed tomography [CT] or magnetic resonance imaging [MRI]) of the abdomen and pelvis along with bone scintigraphy (BS) for metastasis screening in intermediate-to-high-risk primary prostate cancer [5,6]; regarding biochemical recurrence (BCR), BS and abdominopelvic CT are recommended only in patients with serum prostate-specific antigen (PSA) >10 ng/ml or with PSA doubling time <6 mo, and multiparametric MRI may be helpful for candidates for local salvage therapy with BCR after radiotherapy (RT) [6,7]. Nevertheless, the diagnostic capability of these conventional imaging modalities is limited. Therefore, there has been an unmet need for more advanced imaging modalities that better detect loco-regional and distant metastatic lesions in order to guide the management (observation, salvage local therapy, systemic therapy) of patients with prostate cancer.

A recently developed novel radiotracer targeting prostate-specific membrane antigen (PSMA) has shown potential in this field. PSMA is a protein expressed on dysplastic prostate cells with levels of expression of 100–1000 times that of normal cells which increase even further with higher stages and grades [8,9]. Recent meta-analyses show that ^{68}Ga-PSMA positron emission tomography (PET) has excellent diagnostic performance for primary and secondary staging due to its ability to detect lesions even at very low serum PSA levels [10,11]. For instance, in the meta-analysis by von Eyben et al [11], the pooled detection rate was 50% even in a subgroup of studies assessing patients experiencing BCR with PSA levels of 0.2–0.49 ng/ml. Therefore, the most recent EAU guidelines recommend PET/CT using PSMA alongside choline in patients with BCR at low serum PSA levels (≥1 ng/ml). As such, although the diagnostic performance of ^{68}Ga-PSMA PET has been evaluated in detail, its impact on patient management has not been systematically reviewed. Therefore, the purpose of this study was to systematically review the available literature and perform a meta-analysis on the impact of ^{68}Ga-PSMA PET on the management of patients with prostate cancer.

2. Evidence acquisition

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and was registered to the International Prospective Register of Systematic Reviews (registration no. CRD42018087167) [12]. The research question for this meta-analysis was as following: "What is the proportion of patients who experience change in their management when ^{68}Ga-PSMA PET is used as compared with conventional imaging modalities (CT, MRI, and/or BS) in patients with prostate cancer?"

2.1. Literature search

A computerized search was performed using Pubmed and EMBASE databases until January 20, 2018. The search query was formulated based on keywords of "prostate cancer", "PSMA PET", and "impact" and their related terms as follows: (prostate OR prostatic) AND (PSMA OR "prostate-specific membrane antigen") AND ("positron emission tomography" OR PET) AND (impact OR change OR alter OR modif* OR influence). Bibliographies of the retrieved articles were also thoroughly checked for identification of any other relevant articles. Our search was not limited to any particular language.

2.2. Study selection

2.2.1. Inclusion criteria

Studies were included based on "Patient/Intervention/Comparator/Outcome/Study design" criteria [12]: (1) "patients" with prostate cancer, regardless of clinical setting of primary staging or biochemical failure (BCF; biochemical persistence or recurrence), (2) ^{68}Ga-PSMA PET as "intervention", (3) conventional imaging modalities (CT, MRI, and/or BS) as "comparator", and (4) proportion of patients who experience change as "outcome", and (5) "study design" of clinical trials and prospective or retrospective studies published as original articles or brief communications.

2.2.2. Exclusion criteria

Exclusion criteria were as follows: (1) small number of patients (<10), (2) other publication types including conference abstracts, review articles, editorials, and letters, (3) papers irrelevant to the research question, (4) insufficient information provided in the study to calculate the proportion of changes in management, and (5) overlapping study population. When study populations overlapped among studies, we included the study that provided more comprehensive information required for meta-analysis.

The study selection process was performed by two independent reviewers (S.H. and S.W.). In case of disagreement, a third reviewer (Y.J.K.) was consulted to reach a consensus.

2.3. Data extraction and quality assessment

The following study, clinicopathological, and ^{68}Ga-PSMA PET characteristics were extracted using a standardized form:

1. Study: origin (authors, year of publication, patient enrollment period, institution, and country), design (prospective vs retrospective; multicenter vs single center; and consecutive enrollment vs nonconsecutive), methods for data acquisition (review of medical records vs questionnaires), responding entity (referring physician vs multidisciplinary oncology committee), response rates, and type of prior conventional imaging that ^{68}Ga-PSMA PET was compared with.

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2. Clinicopathological: number of patients, age, serum PSA level at initial diagnosis and before ^{68}Ga-PSMA PET, PSA doubling time, Gleason score, D'Amico risk classification, clinical setting (primary staging vs BCF), prior treatment, and patients on androgen deprivation therapy(ADT).
3. PET: vendor, scanner model, ligands, injected dose, uptake time, acquisition time, furosemide use, and PET positivity (proportion of patients with positive ^{68}Ga-PSMA PET scans).

The quality of evidence in the included studies was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system [13,14]. The GRADE system rates the quality of evidence from very low (⊕) to high (⊕⊕⊕⊕) based on study design, risk of bias, imprecision, inconsistency, indirectness, magnitude of effect, dose-response relationship, and consideration of all plausible residual confounders. Although the studies included in our meta-analysis were cross-sectional studies and not randomized trials (comparing management before and after ^{68}Ga-PSMA PET), grading started at high (⊕⊕⊕⊕) as hypothetically, the proportion of change in the management of patients who did not undergo ^{68}Ga-PSMA PET would be "0" [15].

Data extraction and quality assessment was done by two independent reviewers (S.H. and S.W.), and disagreements were resolved by discussion with a third reviewer (Y.J.K.).

2.4. Data synthesis and analysis

The primary outcome of this meta-analysis was the "impact of ^{68}Ga-PSMA PET on the management of prostate cancer patients" in terms of the proportion of patients who had a change in the management due to imaging findings detected on ^{68}Ga-PSMA PET. The secondary outcomes were as follows: (1) subgroup analysis for studies in which change was intended and for those where the change was implemented, (2) proportion of intra- and inter-modality changes [16], and (3) explore heterogeneity.

The proportion of changes in management for each study were tabulated based on proportions reported in the study or by calculating the proportions based on total number of patients and number of patients in which the management was altered. For differentiation between inter- and intra-modality changes, the types of management were categorized as following: RT, surgery, systemic treatment, focal treatment, multimodal treatment (a combination of RT, surgery, and systemic treatment), and no treatment (eg, active surveillance and follow-up). Inter-modality change was defined as an alteration in the type of management (eg, cancellation of salvage RT due to poly-metastatic disease demonstrated on ^{68}Ga-PSMA PET), whereas intra-modality change was defined as a modification of dose/site/strategy that was indicated before ^{68}Ga-PSMA PET (eg, escalated radiation dose to local recurrence demonstrated on ^{68}Ga-PSMA PET using simultaneous integrated boost [SIB] technique). The proportions were meta-analytically pooled using the DerSimonian-Liard method for calculating weights with "meta" and "metafor" packages in R software (version 3.4.1; R Foundation for Statistical Computing, Vienna, Austria) [17]. Publication bias was evaluated using the funnel plot and Egger's test [18].

Heterogeneity was evaluated using the Cochran's Q test and Higgins I^2 test. Meta-regression analyses were done for investigating the possible causes of heterogeneity using the following covariates: study design, serum PSA level (at initial diagnosis and before PET), serum PSA doubling time, Gleason score, D'Amico risk classification, clinical setting, intended versus implemented, and responding entity.

3. Evidence synthesis

3.1. Literature search

In total, 442 articles were initially retrieved by the systematic search. With the removal of 95 duplicate articles and exclusion of 322 papers after screening the titles and abstracts, there were 25 articles to be potentially included. Full-text reviews were performed and 10 studies were excluded due to the following: endpoint of study was not change in management due to ^{68}Ga-PSMA PET (n = 5), overlapping study population (n = 4), and usage of different radiotracer (^{18}F-DCFBC; n = 1). Ultimately 15 studies comprising 1163 patients were included [19–33]. Figure 1 shows the detailed study selection process.

3.2. Characteristics of included studies

Study, clinicopathological, and PET characteristics are described in Tables 1–3, respectively. In brief, study design was prospective in five and retrospective in 10 studies. The number of patients ranged from 15 to 150, with median ages of 62–74 yr. Mean PSA levels at initial diagnosis and before ^{68}Ga-PSMA PET reported in all included studies were 6.8–27.3 ng/ml and 0.2–21.1 ng/ml, respectively. ^{68}Ga-PSMA PET was performed for BCF in 11 studies, primary staging in one, and in a mixed population in three. Various combinations of CT, MRI, BS, and choline PET/CT were used as conventional imaging modalities prior to ^{68}Ga-PSMA PET. Among the three studies with mixed population, two studies [29,31] reported outcomes separately for primary staging and BCF; therefore, they were included in the analysis for each setting. Reported management changes were implemented in 11 studies, intended in two, and both outcomes were reported in two. Data acquisition was based on the review of medical records in 12 studies, questionnaires in three, and the responding entity was the referring physician in 10 studies and a multidisciplinary oncology committee in five. PET positivity was reported in all but one study [33], with values ranging from 47% to 85% (overall, 69%).

3.3. Quality assessment

In the risk of bias domain, all studies were rated down due to the fact that blinding was virtually impossible between management decisions based on ^{68}Ga-PSMA PET versus those without ^{68}Ga-PSMA PET. In the publication bias domain, one study was rated down due to potential industry influence (from Scintomics, a company distributing PSMA-directed peptide ligands) [27]. The study by Bluemel et al [21], in which one of the authors was a shareholder of

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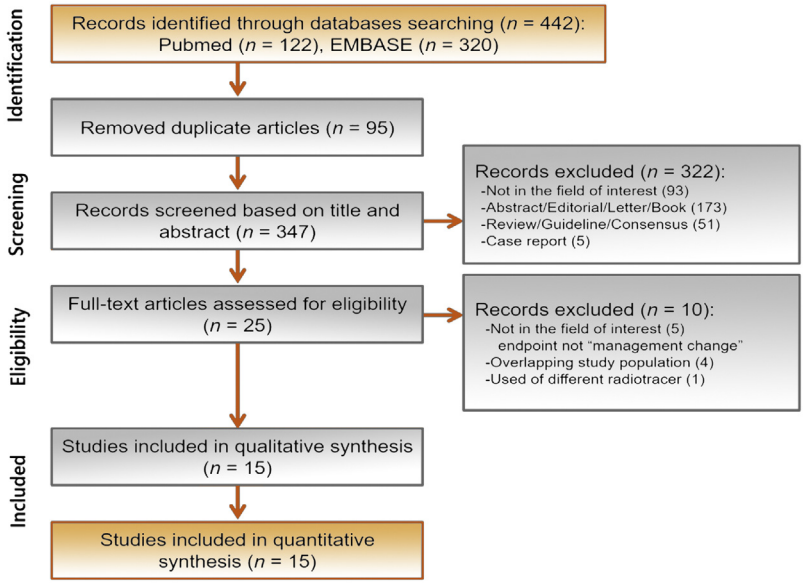

Fig. 1 – Flow diagram for study selection process.

Scintomics, was not rated down as it was explicitly mentioned that this author was not involved in data acquisition or analysis during the study. In the indirectness domain, two studies [19,28] were rated down as they only reported "intended" management changes but not changes that were actually "implemented". All but four studies [19,23,25,32] were rated up due to a large effect size (>50%). In the other domains, there were no rating up or down in the included studies. Ultimately, the quality of evidence was high (⊕⊕⊕⊕) in nine studies [20–22,24,26,29–31,33], moderate (⊕⊕⊕) in five [23,25,27,28,32], and low in one [19].

3.4. Impact of ^{68}Ga-PSMA PET on patient management

The impact on patient management due to ^{68}Ga-PSMA PET for all included studies and stratified to implemented and intended changes are illustrated in Figure 2. The proportion of change in individual studies ranged from 29% to 77%. For all the 15 studies combined, the pooled proportion of change was 54% (95% confidence interval [CI]: 47–60%). Based on the Q test ($p < 0.01$) and Higgins I^2 statistics ($I^2 = 79\%$), substantial heterogeneity was present. There was no significant publication bias according to the funnel plot and Egger's test ($p = 0.9755$; Fig. 3). The type of management change (inter- vs intra-modality) was reported in 14 of 15 (93%) studies (Fig. 4). The frequency of inter- and intra-modality changes was similar with pooled proportions of 24% (95% CI: 16–31%) and 28% (95% CI: 20–36%), respectively.

3.5. Heterogeneity exploration

The results of meta-regression analyses are summarized in Table 4. Among several variables potentially attributable to heterogeneity, PET positivity was the only significant factor ($p = 0.0486$). Specifically, meta-regression analysis demonstrated that there was a 0.55% increase in the management change for every 1% increase in PET positivity (Fig. 5). Other variables were not significant factors ($p = 0.2802$–0.9574). In studies assessing patients with BCF, there was a tendency for greater proportion of changes in management in studies with greater PSA levels before ^{68}Ga-PSMA PET (Supplementary Fig. 1). In studies with PSA level ≤1.0 ng/ml, the pooled proportion was 43% (95% CI: 28–60%), whereas greater pooled proportions of 54% (95% CI: 47–61%) and 69% (95% CI: 58–79%) were seen in subgroups with PSA levels of 1.0–2.0 and >2.0 ng/ml.

3.6. Management decisions before and after ^{68}Ga-PSMA PET in patients with BCF

Figure 6 shows the initial and modified treatment plans before and after ^{68}Ga-PSMA PET in 11 studies assessing patients with BCF. The proportion of RT increased from 56% to 61%. Specifically, conventional salvage RT to the prostate bed was the predominant choice of RT planning before ^{68}Ga-PSMA PET (95% [315/330]). However, after ^{68}Ga-PSMA PET, the number of salvage RT with increased dose and/or target volume (ie, dose escalation using SIB or sequential boost and enlarging target volume to an extent to cover PSMA-positive pelvic lymph nodes) and stereotactic body RT (SBRT) increased (24% [89/371] and 20% [73/371], respectively). The proportion of surgical resection increased from 1% to 7%. Salvage pelvic lymph node dissection consisted of 58% (25/43) surgical treatment decision. In general, the proportion of systemic treatment decreased from 26% to 12%. Among them, ADT was initially planned in 144 patients but was implemented or intended in 52 patients after ^{68}Ga-PSMA PET. The proportion of focal therapy and multimodal treatment increased from 1% to 2% and from 2% to 6%, respectively. The proportion of patients with no treatment decision decreased from 14% to 11%.

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Table 1 – Study characteristics

Origin					Design				Management plan		
First author	Publication year	Patient enrollment period	Institution	Country	Prospective	Multicenter	Consecutive enrollment	Data acquisition	Responding entity	Response rates (%)	Prior imaging
Afaq [19]	2018	June 2015–February 2017	University College London Hospital	UK	R	No	Yes	Review	Referring physician	100	NR
Albisinni [20]	2017	January 2015–December 2015	Universit e Libre de Bruxelles	Belgium	R	No	Yes	Review	Multidisciplinary oncology committee	100	NR
Bluemel [21]	2016	September 2014–May 2016	University Hospital Würzburg	Germany	R	No	Yes	Review	Multidisciplinary oncology committee	84/100[b]	CT
Calais [22]	2017	October 2016–June 2017	UCLA Medical Center	USA	P	No	Yes	Questionnaire[a]	Referring physician	55/63[b]	NR
Dewes [23]	2016	August 2013–April 2015	Technical University Munich	Germany	R	No	NR	Review	Multidisciplinary oncology committee	100	CT/MRI
Gauthe [24]	2017	April 2016–December 2016	Hôpital Tenon	France	P	No	NR	Review	Multidisciplinary oncology committee	55	CT/choline PET
Grubmuller [25]	2018	May 2014–January 2017	Medical University of Vienna	Austria	R	No	Yes	Review	Multidisciplinary oncology committee	100	CT/MRI/BS
Habl [26]	2017	March 2013–April 2016	Technical University of Munich	Germany	P	No	NR	Review	Referring physician	100	CT/MRI
Henkenberens [27]	2017	August 2014–November 2016	Hannover Medical School	Germany	R	No	NR	Review	Referring physician	100	MRI/BS
Hope [28]	2017	December 2015–October 2016	University of California San Francisco	USA	P	No	Yes	Questionnaire	Referring physician	84	CT/MRI/ BS/NaF PET
Schmidt-Hegemann [29]	2017	February 2014–August 2016	University Munich Hospital	Germany	R	No	Yes	Review	Referring physician	100	CT
Shakespeare [30]	2015	January 2015–May 2015	North Coast Cancer Institute	Australia	R	No	Yes	Review	Referring physician	100	CT/MRI/BS
Sterzing [31]	2016	NR	University Hospital Heidelberg	Germany	R	No	NR	Review	Referring physician	100	CT/MRI/BS
Van Leeuwen [32]	2016	February 2015–July 2015	St Vincent's Hospital	Australia	P	No	Yes	Questionnaire	Referring physician	100	CT
Zschaeck [33]	2017	2013–2015	Charité Universitäts-medizin Berlin	Germany	R	No	Yes	Review	Referring physician	100	CT

BS = bone scintigraphy; CT = computed tomography; HIFU = high-intensity focused ultrasound; MRI = magnetic resonance imaging; NR = not reported; P = prospective; PET = positron emission tomography; R = retrospective.

[a] Chart review/patient contact were used when questionnaire was not completed.

[b] The former for implemented, and the latter for intended changes.

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Table 2 – Patient characteristics

First author	Patients (*n*)	Mean age (yr)	Mean PSA (ng/ml)		Mean PSA-DT (mo)	Gleason ≥7 (%)	D'Amico risk classification			Clinical setting	Primary treatment			On ADT (%)
			Initial	Pre-PET			Low (%)	Intermediate (%)	High (%)		RP (%)	Definitive RT (%)	Others (%)	
Afaq [19]	100	68	NR	NR	NR	NR	NR	NR	NR	BCF	68	32	0	15
Albisinni [20]	131	69	NR	5.4	NR	82	NR	NR	NR	BCF	81	13	6	21
Bluemel [21]	45	69	22.5	1.3	7.4	NR	4	9	87	BCF	100	0	0	NR
Calais [22]	101	69*	6.8*	1.7*	NR	NR	5[b]	42[b]	52[b]	BCF	86	14	0	21
Dewes [23]	15	74*	21.1	21.1	NR	67	NR	NR	NR	Primary staging	NA	NA	NA	80
Gauthe [24]	33	67	NR	2.8	11.8	94	NR	NR	NR	BCF	85	15	0	NR
Grubmuller [25]	117	74*	NR	1.0*	NR	87	NR	NR	NR	BCF	100	0	0	NR
Habl [26]	100	64*	NR	0.9*	NR	93	0	4	91	BCF	100	0	0	NR
Henkenberens [27]	39	66*	7.5*	1.2*	10.1*	90	3	3	90	BCF	94	0	6	0
Hope [28]	150	69	NR	5.9	8.7	84	NR	NR	NR	BCF	60	33	39	5
Schmidt-Hegemann [29]	129	72*	27.3	6.0	NR	92	4	16.3	80	Primary staging/BCF	84	0	0	11
Shakespeare [30]	54	69	9.2*	1.1*	NR	NR	NR	NR	NR	Primary staging/BCF	67	17	2	NR
Sterzing [31]	57	70*	7.0*	3*	NR	NR	7	39	54	Primary staging/BCF	74	0	0	NR
Van Leeuwen [32]	70	62*	7.3*	0.2*	NR	100	NR	NR	NR	BCF	100	0	0	NR
Zschaeck [33]	22	65*	18.9	6.1	NR	NR	NR	NR	NR	BCF	100	0	0	45

ADT = androgen deprivation therapy; BCF = biochemical failure; NR = not reported; NA = not applicable; PCa = prostate cancer; PSA = prostate-specific antigen; PSA-DT = prostate-specific antigen doubling time; RP = radical prostatectomy; RT = radiotherapy.

* Median.

[a] Others include HIFU, brachytherapy, laser ablation, systemic treatment, ADT, and others.

[b] Based on NCCN risk group.

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Table 3 – PET characteristics

First author	Vendor	Model	Ligand	Mean dose (MBq)	Mean uptake time (min)	Acquisition time (min/bed)	Furosemide
Afaq [19]	NR	NR	^{68}Ga-PSMA-11	159	60	NR	NR
Albisinni [20]	GE	Discovery 690	^{68}Ga-PSMA-11	2 kg^{-1}	60	2	NR
Bluemel [21]	Siemens	Biograph mCT 64	^{68}Ga-PSMA-I&T	141	60	2–3	Yes
Calais [22]	Siemens	Biograph True Point 64 or mCT	^{68}Ga-PSMA-11	196*	62	NR	Yes
Dewes [23]	NR	NR	NR	NR	NR	NR	NR
Gauthe [24]	NR	NR	^{68}Ga-PSMA-11	2 kg^{-1}	60	4	NR
Grubmuller [25]	Siemens	Biograph TruePoint 64 Biograph mMR	^{68}Ga-PSMA-11	180*	60 (PET/CT) 90 (PET/MRI)	Pelvis: 10, WB: NR (PET/MRI) 4 (PET/CT)	Yes
Habl [26]	Siemens	Biograph mCT Biograph mMR	^{68}Ga-PSMA-11	146	56	NR	NR
Henkenberens [27]	Siemens	Biograph mCT 128	^{68}Ga-PSMA-I&T	96	60	NR	NR
Hope [28]	GE	3.0T TOF Signa PET/MR Discovery VCT	^{68}Ga-PSMA-11	199.8	63	3–5	Yes
Schmidt-Hegemann [29]	NR	NR	^{68}Ga-PSMA-11	189*	60	NR	Yes
Shakespeare [30]	NR	NR	NR	159	NR	NR	NR
Sterzing [31]	Siemens	Biograph 6	^{68}Ga-PSMA-11	175*	60	NR	NR
Van Leeuwen [32]	Phillips	Ingenuity TF 64	^{68}Ga-PSMA-11	NR	45	2	NR
Zschaeck [33]	Philips	Gemini TF 16 Astonish	^{68}Ga-PSMA-11	113	62	NR	NR

CT = computed tomography; ^{68}Ga-PSMA = ^{68}Gallium prostate-specific membrane antigen positron emission tomography; MRI = magnetic resonance imaging; NR = not reported; PET = positron emission tomography; PSMA = prostate-specific membrane antigen; WB = whole body.
* Median.

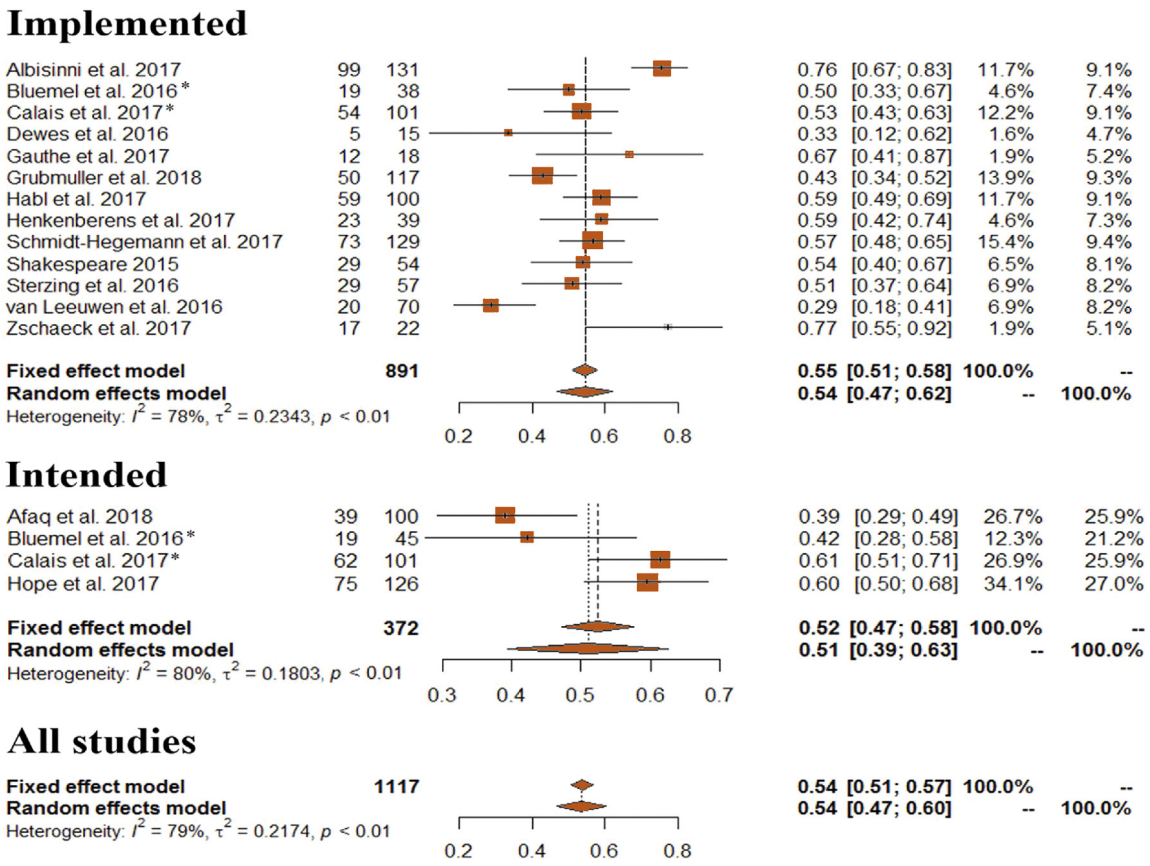

Fig. 2 – Forest plots showing pooled proportion of management changes due to 68Gallium prostate-specific membrane antigen positron emission tomography in all included studies, and stratified to implemented and intended changes. *Two studies (Bluemel et al [21] and Calais et al [22]) reported both implemented and intended changes. For these two studies, implemented changes were used for pooling all included studies.

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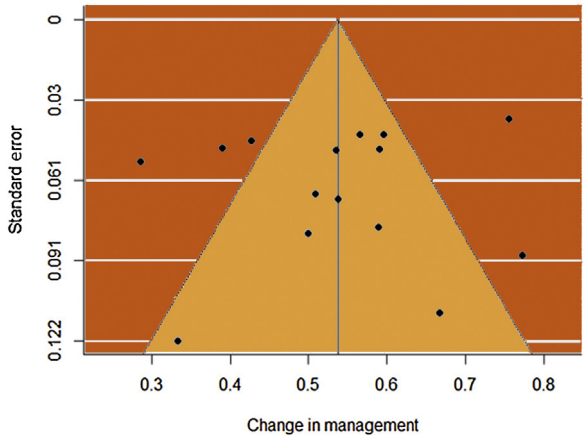

Fig. 3 – Funnel plot and Egger's test suggest that possibility of significant publication bias is low ($p = 0.9755$).

3.7. Discussion

In our meta-analysis, we evaluated the impact of ^{68}Ga-PSMA PET on the management of patients with prostate cancer. The pooled proportion of patients in which ^{68}Ga-PSMA PET led to a change in management was 54% meaning that ^{68}Ga-PSMA PET altered the decision of referring physicians or multidisciplinary oncology committees in approximately half of the patients. Even when separately assessing studies in which the change was actually implemented or just intended, the pooled proportions were similar (54% and 51%, respectively). This may be attributed to the fact that ^{68}Ga-PSMA PET has potentially superior detection rates over conventional imaging modalities. In the studies included in our meta-analysis, ^{68}Ga-PSMA PET showed an overall positive rate of 69%. Furthermore, PET positivity was a significant factor of heterogeneity, with greater PET positivity being associated with higher proportion of management changes. In addition, a previous meta-analysis demonstrated the following: (1)

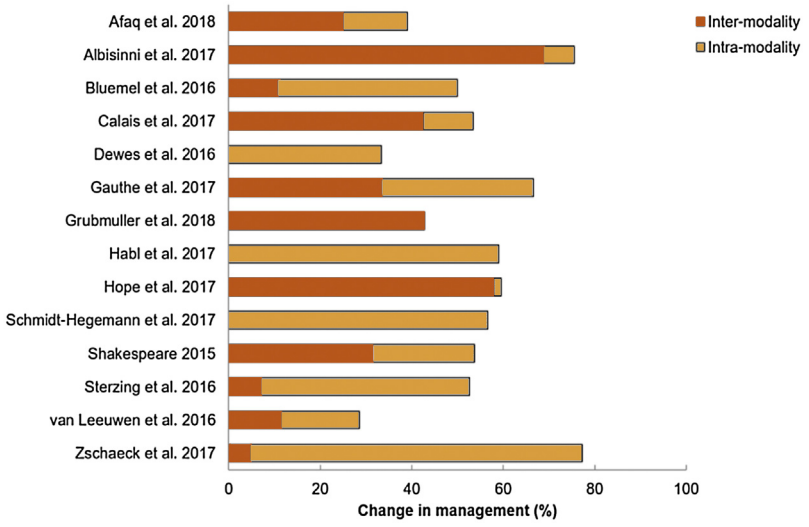

Fig. 4 – Stacked bar charts of 14 studies differentiating type of change (intra- vs inter-modality). Bars represent proportion of change in management due to ^{68}Gallium prostate-specific membrane antigen positron emission tomography, categorized as inter-modality (dark orange) and intra-modality (orange).

Table 4 – Results of meta-regression analyses for impact of ^{68}Ga-PSMA PET on management

Variable	Categories or cut-off	Regression coefficient	95% CI	*p* value
Study design	Prospective versus retrospective	−0.0156	−0.1744–0.1432	0.8474
Clinical setting	BCF versus primary staging + mixed population	−0.0474	−0.2210–0.1263	0.5928
Change type	Intended versus implemented	−0.0507	−0.2626–0.1612	0.6392
Responding entity	Referring physician versus multidisciplinary oncology committee	0.0176	−0.1422–0.1773	0.8294
D'Amico risk classification	High (%)	0.0013	−0.0015–0.0041	0.3529
	Intermediate + high (%)	0.0038	−0.0314–0.0389	0.8332
Gleason score	≥7 (%)	−0.0015	−0.0134–0.0105	0.8098
Patients on ADT (%)		−0.0013	−0.0061–0.0035	0.5877
PSA level at initial diagnosis (ng/ml)		0.0036	−0.0078–0.0149	0.5388
Pre-PET PSA level (ng/ml)		−0.0004	−0.0169–0.0160	0.9574
PSA doubling time (mo)		0.0303	−0.0247–0.0854	0.2802
PET positivity (%)		0.0055	0.0000–0.0110	0.0486

ADT = androgen deprivation therapy; BCF = biochemical failure; CI = confidence interval; ^{68}Ga-PSMA PET = ^{68}Gallium prostate-specific membrane antigen positron emission tomography; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen.

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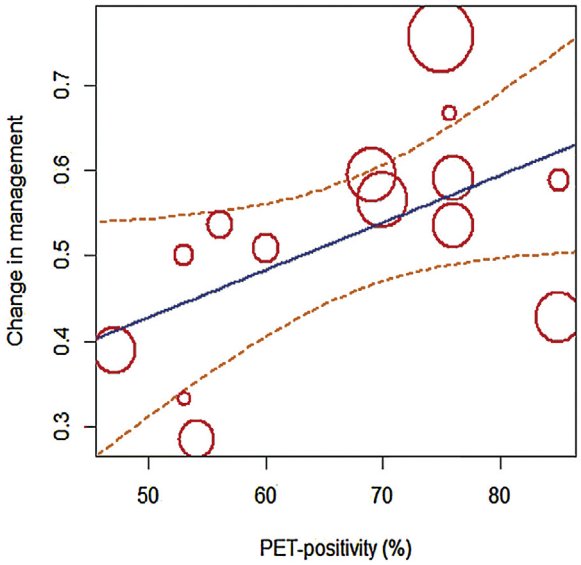

Fig. 5 – Bubble plot of meta-regression analysis for impact of ^{68}Gallium prostate-specific membrane antigen positron emission tomography using PET positivity as a covariate shows that it is a significant factor affecting heterogeneity ($p = 0.0486$).
PET = positron emission tomography.

the diagnostic performance of ^{68}Ga-PSMA PET in terms of sensitivity and specificity was high (both 86% on a per patient basis and 80% and 97%, respectively, on a per lesion basis), and (2) PET positivity was surprisingly high (42%) even in groups with very low PSA levels (<0.2 ng/ml) [10]. In contrast, currently, due to the poor detection rates using BS and CT, guidelines recommend imaging when patients become symptomatic or when PSA levels rise >10 ng/ml [7,34,35]. Even salvage RT to the prostatic fossa with or without confirmation of imaging findings is commonly performed in patients with BCF. Based on such high detectability and diagnostic performance, and the large proportion of patients who had a change in their management due to ^{68}Ga-PSMA PET, it seems plausible that this relatively novel targeted imaging modality has the potential to allow for more improvement in the management of prostate cancer patients. One study excluded after the full-text review due to the usage of ^{18}F-labelled PSMA ligand (^{18}F-DCFBC) also showed 51% change in treatment plan which is similar to our pooled estimates. This further supports that PSMA-targeted PET has a great impact on management decision.

Among the management changes observed in the studies, the proportion of inter- and intra-modality changes was relatively similar (24% and 25%, respectively). This indicates that ^{68}Ga-PSMA PET may not only help better plan the optimal dose, site, and volume of radiation in the case of salvage RT but can also change the department (ie, urology, radiation oncology, or hematology and medical oncology) in which the patient will be treated. Therefore, integration of ^{68}Ga-PSMA PET opens the possibility of personalized medicine, treating each individual patient with optimal modality and technique as opposed to a "one-size-fits-all" approach (ie, blinded salvage RT to the pelvis for all BCF patients).

It should be noted that there was substantial heterogeneity among the included studies ($I^2 = 79\%$). We speculate that this may be attributed to the differences not only in clinical settings (primary staging vs BCF), types of initial definitive treatment (radical prostatectomy vs RT), and baseline characteristics (serum PSA, Gleason score, D'Amico risk classification) but even the different practice patterns between institutions. Although we cannot directly deduct from this meta-analysis, it is well known that practice patterns regarding prostate cancer vary widely partly due to differences in country, specialty, and experience [36–38]. Among the several variables tested with meta-regression analyses in our study, we found that PET positivity was a significant factor affecting heterogeneity ($p = 0.0486$) and that there was a 0.55% increase in the proportion of management change for every 1% increase in PET positivity.

It is important to note that the number of patients who underwent RT, surgery, and focal therapy increased, whereas those that received ADT decreased with ^{68}Ga-PSMA PET in patients with BCF. This can be interpreted as the following notion that localized treatment was more possible after ^{68}Ga-PSMA PET due to its high lesion detection rate. The use of ADT can be considered in BCF patients after primary definitive treatment with negative findings on imaging studies [7]. However, the effectiveness of ADT remains controversial, and the use of ADT should be carefully balanced against potential adverse events (eg, cardiovascular events and fractures) and development of castration-resistant prostate cancer [39]. Surgical removal, focal therapy, use of increased radiation dose or stereotactic body radiotherapy to PSMA PET-positive lesions may be effective and allow reserving ADT as a potential treatment modality in the future. As surgical resection or SBRT for oligometastatic recurrence is associated with a better outcome [40,41], these findings suggest an implication that management change due to PSMA PET/CT may be associated with better prognosis. Therefore, further research regarding the effect of PSMA PET-guided therapy on patient outcome is required. In addition, with the recent advent of PSMA-targeted radioligand therapy, PSMA PET can serve as both a diagnostic imaging tool, which can modify treatment strategies, and an entryway for radioligand therapy. Recent studies demonstrated that ^{177}Lu-labeled PSMA ligand therapy is safe and effective with decline in PSA level in patients with metastatic castration-resistant prostate cancer [42–44].

Although the results of our meta-analysis are intriguing, it should be emphasized that the impact of ^{68}Ga-PSMA PET observed in our study cannot be generalized for application to all patients with prostate cancer. Upon careful examination of the study population of the included studies, it is evident that the majority (92–96%) of patients were classified as intermediate-to-high risk (in the studies [21,22,26,27,29,31] that reported risk classification) and that the clinical setting was BCF in most studies [19–22,24–28,32,33]. Although we did perform meta-regression analyses with clinical setting and D'Amico risk classification as a covariate, the results of our study are generally based on intermediate-to-high risk patients in BCF setting. This was

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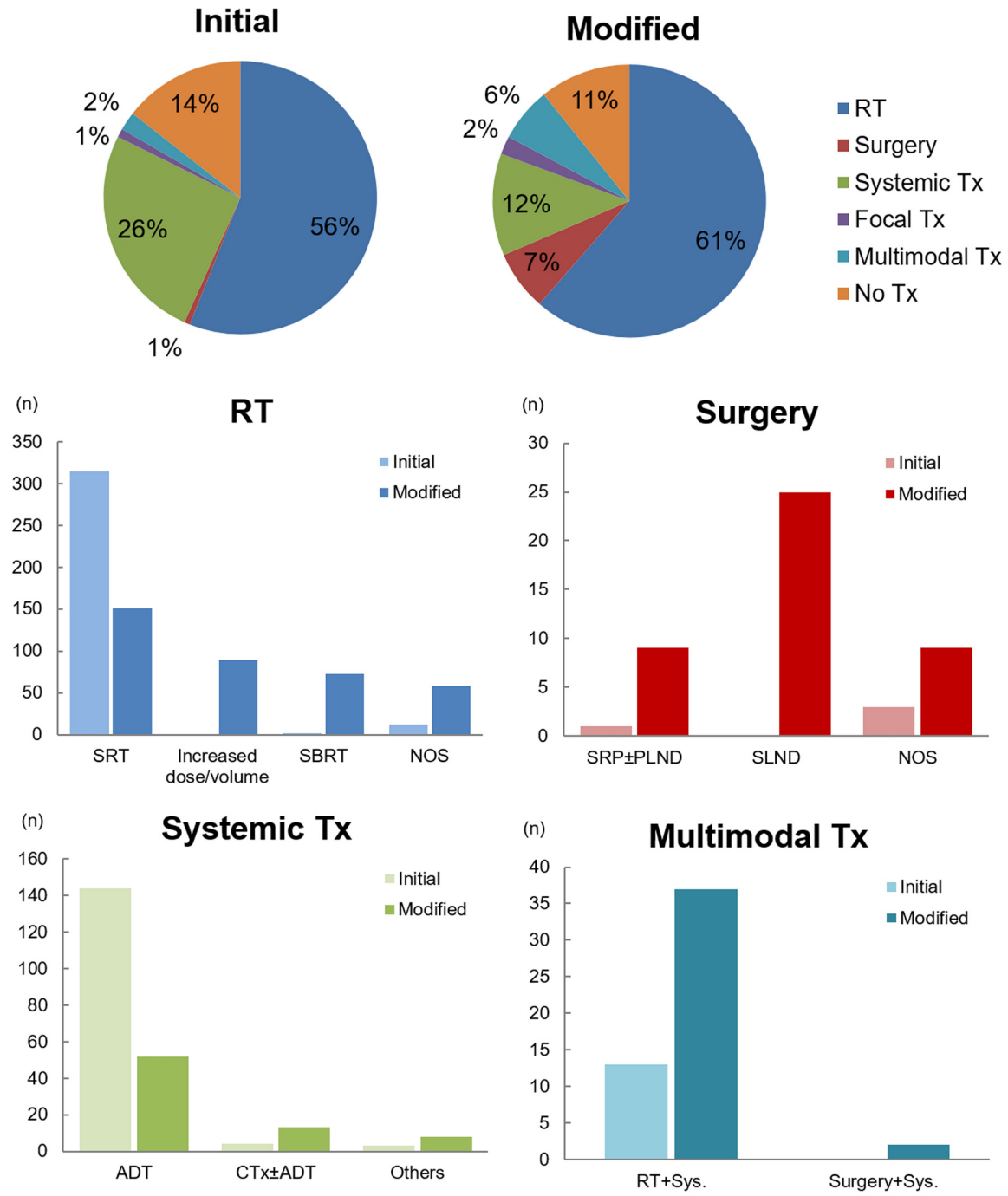

Fig. 6 – Management decisions before and after ^{68}Gallium prostate-specific membrane antigen positron emission tomography (^{68}Ga-PSMA PET) in patients with biochemical failure. (A) Pie charts show proportions of management categorized into radiotherapy, surgery, systematic treatment, focal treatment, multimodal treatment, and no treatment before (left) and after ^{68}Ga-PSMA PET (right). (B) Bar charts show comparison between pre- and post-PET management, stratified to specific type of management within each category.
ADT = androgen deprivation therapy; CTx = chemotherapy; RT = radiotherapy; Sys = systematic treatment; Tx = treatment.

due to the fact that, to date, the majority of the literature on ^{68}Ga-PSMA PET is on BCF, as PSMA protein expression increases with higher stage and grade of prostate cancer [8,9]. However, there is emerging evidence that ^{68}Ga-PSMA PET outperforms conventional imaging modalities in the primary staging of high-risk prostate cancer [45]. Future studies are warranted.

There are some limitations in our meta-analysis. First, the majority of the studies (10 of 15) were retrospective in nature. Synthesizing data from predominantly retrospective studies may overestimate the pooled estimates. However, no significant difference in management change was detected between studies being retrospective and prospective. Second, there was substantial heterogeneity

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among the studies and therefore, caution is needed in applying our pooled estimates. Although we found PET positivity as a significant factor affecting heterogeneity, some portion of heterogeneity remains unexplained. Third, there may be variation in the definition of "change" in management between the studies. Although most of the included studies provided comprehensive and detailed information regarding the pre- and post-PET management plans, a few studies were less specific on the details regarding the dose and site of radiation [19,20,22]. Nevertheless, this would have resulted in underestimation of the proportion of changes. Had such details been available, the pooled impact of ^{68}Ga-PSMA PET would have been even greater. Finally, although it was shown that ^{68}Ga-PSMA PET led to a change of management in a large proportion of patients, as of now we, do not know whether this will directly translate into better outcomes and prognoses. Further studies are warranted to elucidate this issue.

4. Conclusions

^{68}Ga-PSMA PET had a large impact on the management of patients with prostate cancer. The pooled proportion of patients experiencing change in management was 54%. Greater PET positivity was associated with higher proportion of management changes. Due to heterogeneity and paucity in studies assessing low-risk patients in the primary staging setting, caution may be needed in applying the results.

Author contributions: Sungmin Woo 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: Han, Woo, Kim.
Acquisition of data: Han, Woo, Kim.
Analysis and interpretation of data: Han, Woo, Kim, Suh.
Drafting of the manuscript: Woo.
Critical revision of the manuscript for important intellectual content: Han, Kim, Suh.
Statistical analysis: Han, Suh.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Woo, Suh.
Other: None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2018.03.030.

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