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Original Article

Radiolabelled choline versus PSMA PET/CT in prostate cancer restaging: a meta-analysis

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Abstract: Both radiolabelled choline and prostate specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) could be used in patients with biochemical recurrent prostate cancer (BRPCa). We aimed to perform a meta-analysis about the head-to-head comparison of detection rate (DR) between these methods in BRPCa. A comprehensive literature search of studies listed in PubMed/MEDLINE, EMBASE and Cochrane library databases through October 2018 and regarding the head-to-head comparison of DR between radiolabelled choline and PSMA PET/CT in BRPCa was carried out. Overall pooled DR was calculated on a per patient-based analysis; subgroup analyses taking into account different prostate-specific antigen (PSA) cut-off values were performed. Five studies (257 BRPCa patients) were included. The meta-analysis provided the following overall DR: 56% [95% confidence interval (95% CI): 37-75%] for radiolabelled choline PET/CT and 78% (95% CI: 70-84%) for radiolabelled PSMA PET/CT. Significant difference of DR was found only in patients with PSA ≤ 1 ng/ml [the DR of radiolabelled choline and PSMA PET/CT were 27% (95% CI: 17-39%) and 54% (95% CI: 43-65%), respectively]. Radiolabelled PSMA PET/CT proved to be clearly superior in detecting BRPCa lesions at low PSA levels (≤ 1 ng/ml) when compared to radiolabelled choline PET/CT. On the other hand, the superiority of radiolabelled PSMA PET/CT was less evident in patients with PSA > 1 ng/ml. More studies and in particular cost-effectiveness analyses comparing these imaging methods are warranted.

Keywords: PET, positron emission tomography, choline, PSMA, prostate, PSA

Introduction

Molecular imaging using different radiopharmaceuticals has a clear role in visualizing the presence and extent of tumor lesions [1]. Recently, the development of metabolic imaging methods has been aimed at improving diagnosis of biochemical recurrent prostate cancer (BRPCa), when an increase of prostate-specific antigen (PSA) serum values is detected following curative primary treatments as radical prostatectomy or radiation therapy [2-4]. Among the available metabolic imaging methods both radiolabelled choline positron emission tomography/computed tomography (PET/CT) and radiolabelled prostate specific membrane antigen (PSMA) PET/CT could be used for detecting tumor lesions in BRPCa patients [1-4].

Choline radiolabelled with carbon-11 (^{11}C) or fluorine-18 (^{18}F) has been shown to be useful in BRPCa patients with biochemical failure after radical prostatectomy or radiation therapy [5-7]. Radiolabelled choline is biochemically indistinguishable from natural choline; thus, it can be considered as a true radiotracer of cancer cell metabolism. As tumor cells present a high metabolic rate, choline uptake increases in tu-

mor tissue to keep up with the demands of the synthesis of phospholipids in cellular membranes [5-7].

PSMA is a transmembrane protein that is located within the apical epithelium of secretory ducts in benign prostatic tissue. During malignant transformation, PSMA is translocated to the luminal surface of the ducts; once a ligand binds to the PSMA protein, it is internalized into the cell. PSMA is overexpressed in 95% of PCa cells but the overexpression of PSMA has not been found in benign prostatic diseases such as prostatic hyperplasia; however, PSMA is not prostate specific and is found within other tissues and tumors beyond PCa [8-10]. Several PSMA ligands, differing slightly in chemical structure, are commercially available and they may be radiolabelled with several positron-emitters isotopes as Gallium-68 (^{68}Ga), Fluorine-18 (^{18}F), or Copper-64 (^{64}Cu) to obtain PET radiopharmaceuticals which can be used in the clinical practice [8-11]. ^{68}Ga-PSMA-11 is currently the most used radiotracer for PET imaging of BRPCa patients. Due to the fact that ^{68}Ga-PSMA-11 can be used only for diagnostic purposes, two modified PSMA inhibitors, PSMA-617 and PSMA I&T, have been developed. The superiority of PSMA-617 and PSMA I&T compared to PSMA-11 is that they can be efficiently labelled with both ^{68}Ga for PET, as well as, ^{177}Lu for radionuclide therapy. Therefore, both have the potential to be used as theranostic pairs [11]. More recently, PSMA ligands had been labelled with other isotopes with more favorable physical characteristics, such as ^{64}Cu. The short half-life of ^{68}Ga requires an on-site generator while longer-lived nuclides such as ^{18}F or ^{64}Cu can be produced and delivered by one production centre to several imaging centers [11].

To date, several evidence-based articles evaluated separately the detection rate (DR) of radiolabelled choline or PSMA PET/CT in BRPCa [7, 10, 11-19]. Conversely, we aimed to perform a meta-analysis about the head-to-head comparison between these two imaging methods in BRPCa to add evidence-based data in this setting.

Methods

Reporting of this systematic review and meta-analysis conforms to the "Preferred Reporting Items for a Systematic Review and Meta-Analysis of Diagnostic Test Accuracy Studies" (PRISMA-DTA statement) which describes an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses of diagnostic studies [20, 21].

Search strategy

Two authors (GT and RPM) performed a comprehensive computer literature search of PubMed/MEDLINE, EMBASE and Cochrane library databases to find relevant retrospective or prospective published articles on the head-to-head comparison of DR between radiolabelled choline and PSMA PET/CT in patients with BRPCa.

A search algorithm based on a combination of these terms was used: A) "PSMA" AND B) "choline" OR "fluorocholine" OR "F-choline" OR "C-choline" or "FCH" or "CH" or "FECH" or "FMCH" AND C) "Prostate" AND D) "PET". No beginning date limit and language restrictions were used and the literature search was updated until October 31st, 2018. To expand our search, references of the retrieved articles were also screened for additional studies.

Study selection

Studies or subsets of studies investigating the head-to-head comparison between radiolabelled choline and PSMA PET/CT in the same group of patients with BRPCa were eligible for inclusion in the qualitative (systematic review) and quantitative analysis (meta-analysis). The exclusion criteria were: a) articles not within the field of interest of this review; b) review articles, editorials or letters, comments, conference proceedings; c) case reports or small case series; d) articles without a head-to-head comparison among these two imaging methods or performing radiolabelled PSMA PET/CT only in patients with negative/inconclusive choline PET/CT; e) articles with possible patient data overlap.

Three researchers (GT, RPM, LG) independently reviewed the titles and abstracts of the retrieved articles, applying the inclusion and exclusion criteria mentioned above and rejecting articles if they were clearly ineligible. The same three researchers then independently reviewed the full-text version of the remaining articles to assess their eligibility for inclusion resolving disagreements in a consensus meeting.

Data extraction

For each study potentially eligible for the meta-analysis, information was collected concerning basic study (authors, year of publication, country of origin, study design), patient characteris-

tics (type and number of patients evaluated, mean age, mean/median PSA serum values and PSA kinetics, Gleason score), technical aspects (radiotracer used, sequence of PET/CT with different radiotracers, time interval between radiolabelled choline and PSMA PET/CT, hybrid imaging modality, mean radiotracer injected activity, time interval between radiotracer injection and image acquisition, image analysis), DR values for both radiotracers (overall and at different PSA cut-off values) on a per patient-based analysis, ratio between lesions detected by radiolabelled choline PET/CT and lesions detected by radiolabelled PSMA PET/CT, comparison of lesion uptake by using both radiotracers.

Quality assessment

The overall quality of the studies included in the meta-analysis was critically appraised based on the revised "Quality Assessment of Diagnostic Accuracy Studies" tool (QUADAS-2) [22] This tool comprises four domains (patient selection, index test, reference standard, and flow and timing) and each domain was assessed in terms of risk of bias, and the first three domains were also assessed in terms of concerns regarding applicability [22].

Statistical analysis

The DR of radiolabelled choline and PSMA PET/CT was defined as the ratio between the number of patients with at least one suspicious lesions detected by PET/CT and the total number of BRPCa patients who underwent the scan. Pooled analyses were performed using data retrieved from the selected studies and subgroup analyses taking into account different PSA serum values were planned. A random-effects model was used for statistical pooling of the data, taking into account the heterogeneity between studies. The different weight of each study in the pooled analysis was related to the different sample size. Pooled data were presented with their respective 95% confidence interval (95% CI) values, and data were displayed using plots. Heterogeneity was estimated by using the I-square index (I^2), which describes the percentage of variation across studies that is due to heterogeneity rather than chance [23], whereas the publication bias was assessed through the Egger's test [24]. Statistical analyses were performed using the StatsDirect software version 3 (StatsDirect Ltd., Cambridge, UK).

Results

Literature search

Literature search results are reported in **Figure 1**. The comprehensive computer literature search from PubMed/MEDLINE, EMBASE and Cochrane library database revealed 473 articles. Reviewing titles and abstracts, 461 articles were excluded: 449 because not in the field of interest of this review, 7 as reviews, editorials or letters, 5 as case reports. Twelve articles were selected and retrieved in full-text version [25-36]; subsequently, seven full-text articles were excluded because not performing a head-to-head comparison among these two imaging methods or performing radiolabelled PSMA PET/CT only in patients with negative/inconclusive choline PET/CT [25-31]. No additional studies were found screening the references of these articles. Finally, 5 articles including data of 257 patients with BRPCa were eligible for the qualitative analysis (systematic review) and the quantitative analysis (meta-analysis) [32-36]. The characteristics of the studies selected for the systematic review are presented in **Tables 1-3**, whereas the overall quality assessment of the studies is reported in **Figure 2**.

Qualitative analysis (systematic review)

Basic study and patient characteristics: Using the database search, 5 full-text articles performing the head-to-head comparison of DR between radiolabelled choline and PSMA PET/CT in 257 patients with BRPCa were selected (**Table 1**) [32-36]. All the selected articles were published in the last five years; different countries from Europe, America and Oceania were represented; 60% of the studies were retrospective and all were single-centre studies. Mean and median age of the patients included in these studies ranged from 64 to 72 years. Median PSA values among the included BRPCa patients ranged from 0.8 to 4 ng/ml.

Technical aspects: Technical aspects of the included studies are reported in **Table 2**. The radiolabelled choline radiotracer used was ^{11}C-choline in 40% of cases and ^{18}F-choline in 60% of cases. The radiolabelled PSMA radiotracer used was ^{68}Ga-PSMA-11 in 80% of cases and ^{64}Cu-PSMA-617 in one study. Radiolabelled choline PET/CT was performed before radiolabelled PSMA PET/CT in 60% of cases. The time

Research question: Detection rate of prostate cancer lesions by using radiolabelled choline and PSMA PET/CT using a head-to-head comparison in patients with biochemical recurrence.

Research string: ((choline) OR (fluorocholine) OR (F-choline) OR (C-choline) or (FCH) or (CH) or (FECH) or (FMCH)) AND (PSMA) AND (prostate) AND (PET)

Database screened: PubMed/MEDLINE, EMBASE and Cochrane library (until October 2018)

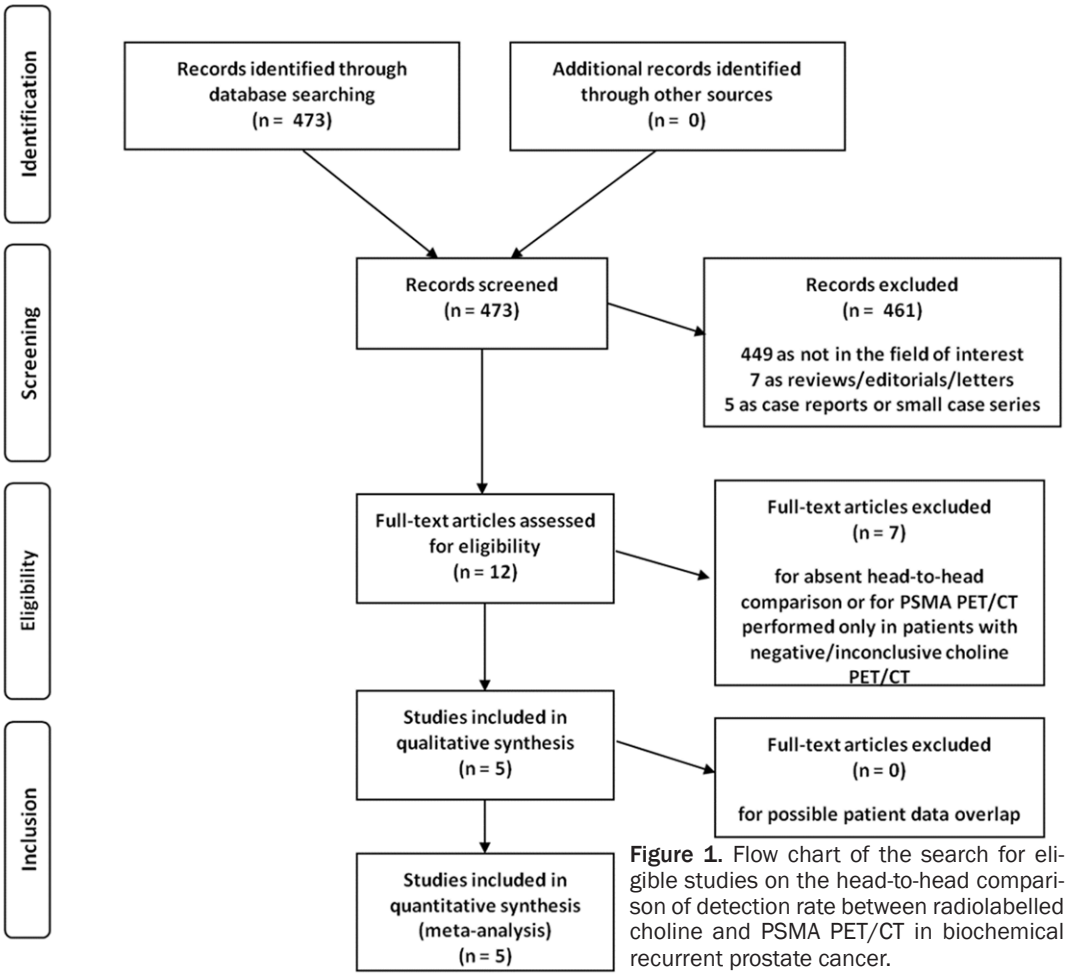

Figure 1. Flow chart of the search for eligible studies on the head-to-head comparison of detection rate between radiolabelled choline and PSMA PET/CT in biochemical recurrent prostate cancer.

interval among these imaging methods ranged between 1 to 30 days. The hybrid imaging modality was PET/CT in 100% of the studies, by using low-dose CT in 40% of cases and contrast-enhanced CT in 60% of cases. Mean injected radiotracer activity and time interval between radiotracer injection and image acquisition were quite different among the included studies. The PET image analysis was performed by using qualitative (visual) analysis in all studies and additional semi-quantitative analysis through the calculation of the maximal standardized uptake values (SUV_{max}) in most of the studies (80%). At visual analysis all foci of radiotracer uptake greater than the surrounding tissue that could not be explained by physiological activity were considered to be abnormal.

Main findings: Main findings of the included studies are listed in **Table 3**. All the studies demonstrated a higher DR of radiolabelled PSMA PET/CT compared to radiolabelled choline PET/CT on a per-patient based analysis; furthermore, more lesions were detected by radiolabelled PSMA PET/CT compared to radiolabelled choline PET/CT [32-36]. In lesions detected by both imaging modalities, all the studies found an overall higher uptake and contrast by using radiolabelled PSMA compared to radiolabelled choline [32-36]. However, in some

Table 1. Basic study and patient characteristics

Authors	Year	Country	Study design	Type of patients evaluated	No. of BRPCa patients performing PET/CT	Mean/Median age (years)	Mean/Median PSA values before PET/CT (ng/ml)	Mean/Median PSAdt (months)	Mean/Median PSAvel (ng/ml/year)	Gleason Score (percentage)
Alonso *et al.* [32]	2018	Uruguay	Prospective single-centre	Patients with BRPCa previously treated with RP (67%) or RT (33%) with or without HT.	36	Mean: 64.7±7.4 (45-77)	Median: 3.3 (0.2-138)	NR	NR	NR
Cantiello *et al.* [33]	2018	Italy	Retrospective single-centre	Patients with BRPCa previously treated with RP (100%).	43	Median: 72	Median: 0.8	Median: 4	Median: 2.6	≤ 7: 68% ≥ 8: 32%
Schwenck *et al.* [34]	2017	Germany	Retrospective single-centre	Patients with BRPCa previously treated with RP or RT with or without HT.	103	NR	Median: 2.7	Median: 4	NR	NR
Morigi *et al.* [35]	2015	Australia	Prospective single-centre	Patients with BRPCa previously treated with RP (89%) or RT (11%).	38	Mean: 68 (54-81)	Mean: 1.72±2.54 (0.04-12)	Mean: 15.6±22.1 (2.6-111.2)	NR	≤ 7: 61% ≥ 8: 39%
Afshar-Oromieh *et al.* [36]	2014	Germany	Retrospective single-centre	Patients with BRPCa previously treated with RP (76%) or RT (24%) with or without HT.	37	Mean: 69.3±7.1 Median: 70 (57-85)	Mean: 11.1±24.1 Median: 4 (0.01-116)	NR	NR	≤ 7: 64% ≥ 8: 36%

Legend: BRPCa = biochemical recurrent prostate cancer; HT = hormonal (androgen deprivation) therapy; NR = not reported; PET = positron emission tomography; PSAdt = PSA doubling time; PSAvel = PSA velocity; PSMA = prostate specific membrane antigen; RP = radical prostatectomy; RT = radiation therapy.

Table 2. Technical aspects of PET/CT in the included studies

Authors	Radiotracers	Sequence of PET/CT with different radiotracers	Time interval between radiolabelled choline and PSMA PET/CT	Hybrid imaging modality	Mean radiotracer injected activity ± SD	Time interval between radiotracer injection and image acquisition	Image analysis
Alonso *et al.* [32]	^{11}C-choline and ^{68}Ga-PSMA-11	Random	1-2 weeks	PET/CT with low-dose CT	6 MBq/Kg (choline) 2 MBq/Kg (PSMA)	Immediately (choline); 1 h (PSMA)	Visual and semi-quantitative (SUV_{max})
Cantiello *et al.* [33]	^{18}F-choline and ^{64}Cu-PSMA-617	Radiolabelled PSMA before choline	1-3 weeks	PET/CT with low-dose CT	259-370 MBq (choline); 315±55 MBq (PSMA)	5 min and 1 h (choline); 5 min, 1 h and 4 h (PSMA)	Visual and semi-quantitative (SUV_{max})
Schwenck *et al.* [34]	^{11}C-choline and ^{68}Ga-PSMA-11	Radiolabelled choline before PSMA	Within 24 hours	PET/CT with contrast enhanced CT	623±29 MBq (choline); 169±12 MBq (PSMA)	5 and 20 min (choline); 1 h (PSMA)	Visual and semi-quantitative (SUV_{avg})
Morigi *et al.* [35]	^{18}F-choline and ^{68}Ga-PSMA-11	Radiolabelled choline before PSMA	Within 30 days	PET/CT with contrast enhanced CT	3.5 MBq/Kg (choline) 2 MBq/Kg (PSMA)	Immediately (choline); 45 min (PSMA)	Visual and semi-quantitative (SUV_{max})
Afshar-Oromieh *et al.* [36]	^{18}F-choline and ^{68}Ga-PSMA-11	Radiolabelled choline before PSMA	Within 30 days	PET/CT with contrast enhanced CT	3 MBq/Kg (choline) 2 MBq/Kg (PSMA)	1 h (choline); 1 h (PSMA)	Visual and semi-quantitative (SUV_{max})

Legend: MBq = MegaBecquerel; NR = not reported; PET/CT = positron emission tomography/computed tomography; PET/MRI = positron emission tomography/magnetic resonance imaging; SD = standard deviation; SUV_{max} = maximal standardized uptake value; SUV_{avg} = average standardized uptake value.

Table 3. Main findings of the included studies comparing radiolabelled choline and PSMA PET/CT in prostate cancer restaging

Authors	Overall DR		DR in patients with PSA ≤ 2 ng/ml		DR in patients with PSA > 2 ng/ml		DR in patients with PSA ≤ 1 ng/ml		DR in patients with PSA > 1 ng/ml		Ratio of lesions detected by radiolabelled choline/lesions detected by PSMA PET/CT	Higher radiolabelled PSMA than coline uptake in lesions
	Radiolabelled choline PET/CT	Radiolabelled PSMA PET/CT	Radiolabelled choline PET/CT	Radiolabelled PSMA PET/CT	Radiolabelled choline PET/CT	Radiolabelled PSMA PET/CT	Radiolabelled choline PET/CT	Radiolabelled PSMA PET/CT	Radiolabelled choline PET/CT	Radiolabelled PSMA PET/CT		
Alonso *et al.* [32]	19/36 (53%)	27/36 (75%)	3/14 (21%)	6/14 (43%)	16/22 (73%)	21/22 (95%)	2/9 (22%)	3/9 (33%)	17/27 (63%)	24/27 (89%)	98/183	Yes
Cantiello *et al.* [33]	19/43 (44%)	32/43 (74%)	7/27 (26%)	16/27 (59%)	12/16 (75%)	16/16 (100%)	5/24 (21%)	14/24 (58%)	14/19 (74%)	18/19 (95%)	NR	Yes
Schwenck *et al.* [34]	82/103 (80%)	86/103 (83%)	29/44 (66%)	31/44 (70%)	51/57 (89%)	53/57 (93%)	8/18 (44%)	11/18 (61%)	72/83 (87%)	73/83 (88%)	554/839	Yes
Morigi *et al.* [35]	12/38 (32%)	25/38 (66%)	7/30 (23%)	18/30 (60%)	5/8 (63%)	7/8 (88%)	3/21 (14%)	10/21 (48%)	9/17 (53%)	15/17 (88%)	29/59	Yes
Afshar-Oromieh *et al.* [36]	26/37 (70%)	32/37 (86%)	5/10 (50%)	9/10 (90%)	21/27 (78%)	23/27 (85%)	2/5 (40%)	4/5 (80%)	24/32 (75%)	28/32 (88%)	56/78	Yes
Pooled values (95% confidence interval)	56% (37-75)	78% (70-84)	38% (20-58)	64% (52-75)	78% (68-87)	92% (86-96)	27% (17-39)	54% (43-65)	72% (59-84)	88% (83-92)	6/10 (5/10-7/10)	

Legend: DR = detection rate on a patient-based analysis; NR = not reported.

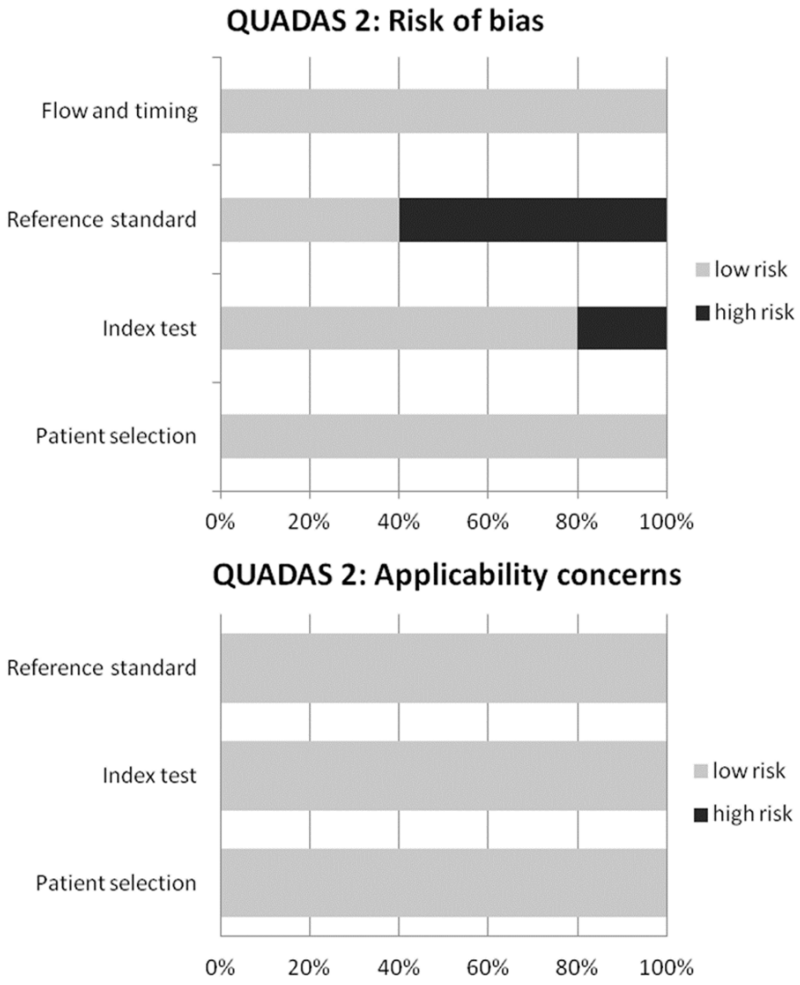

Figure 2. Overall quality assessment of the studies included in the systematic review according to QUADAS-2 tool.

cases a diverging uptake pattern was found by using both radiotracers (i.e.: choline-positive PSMA-negative lesions and choline-negative PSMA-positive lesions) [34]. One article demonstrated a 63% management impact by using both radiotracers, with 54% being due to radiolabelled PSMA imaging alone [35].

Quantitative analysis (meta-analysis)

Five studies including 257 BRPCa patients were selected for the meta-analysis on the head-to-head comparison of DR between radiolabelled choline and PSMA PET/CT [32-36]. The overall DR of radiolabelled choline PET/CT on a per patient-based analysis ranged from 32% to 80%, with a pooled estimate of 56% (95% CI: 37-75%) (**Figure 3**). The heterogeneity among the included studies was significant (I^2 = 80%). A publication bias was not detected by Egger's test (P = 0.1). The overall DR of radiolabelled PSMA PET/CT on a per patient-based analysis ranged from 66% t o 86%, with a pooled estimate of 78% (95% CI: 70-84%) (**Figure 3**). The heterogeneity among the included studies was moderate (I^2 = 40%). A publication bias was not detected by Egger's test (P = 0.1). The pooled ratio of lesions detected by radiolabelled choline PET/CT and lesions detected by radiolabelled PSMA PET/CT was 6:10.

Performing sub-group analyses taking into account different PSA cut-off values (**Table 3**; **Figures 4** and **5**), we found a statistical significant difference of DR between radiolabelled PSMA PET/CT and radiolabelled choline PET/CT in BRPCa patients with PSA ≤ 1 ng/ml (**Figure 4**). In these subgroup of patients the DR of radiolabelled choline PET/CT was 27% (95% CI: 17-39) and the DR of radiolabelled PSMA PET/CT was 54% (95% CI: 43-65). On the other hand, the superiority of radiolabelled PSMA PET/CT was less evident and not statistically significant in patients with PSA levels > 1 ng/ml (**Figure 5**).

Discussion

Several studies have used radiolabelled choline and PSMA PET/CT in BRPCa patients but only few of them have compared these diagnostic techniques in the same patients [32-36]; as these studies have limited power, due to the relatively small number of patients enrolled and assessed, we have pooled data reported in the published studies to derive more robust estimates on the DR of radiolabelled PSMA compared to radiolabelled choline PET/CT in BRPCa.

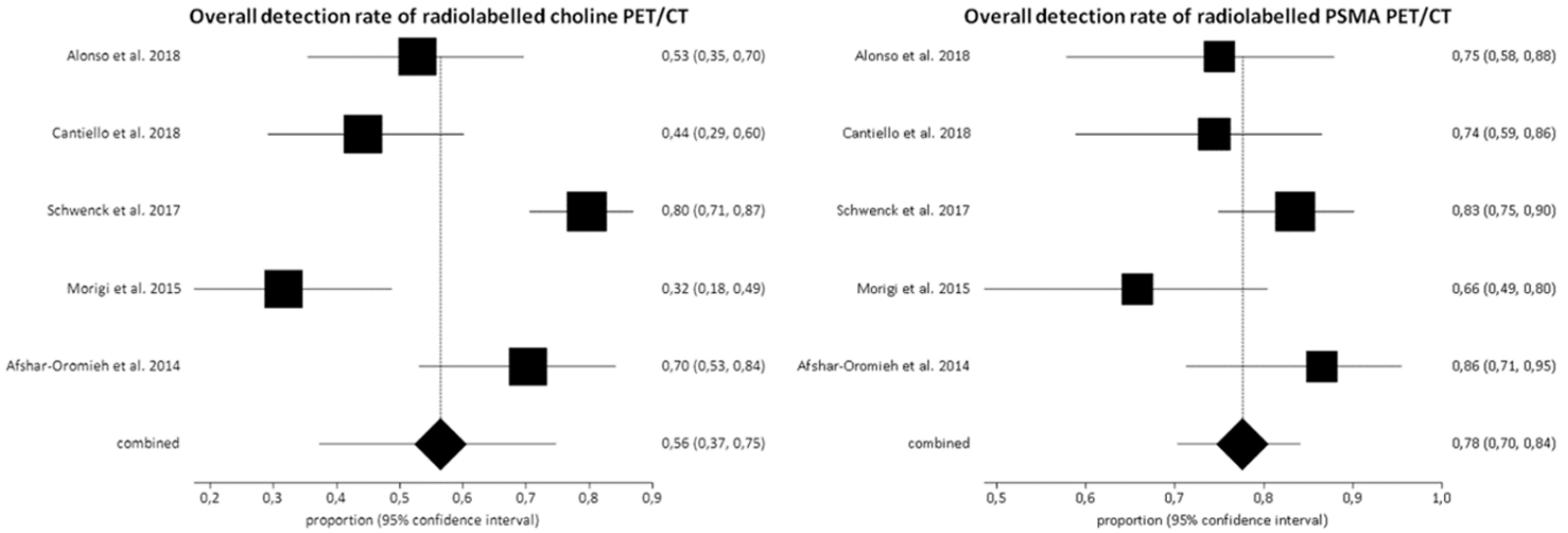

Figure 3. Plots of individual studies and pooled detection rate of radiolabelled choline and PSMA PET/CT in biochemical recurrent prostate cancer on a per patient-based analysis, including 95% confidence intervals (95% CI). The size of the squares indicates the weight of each study.

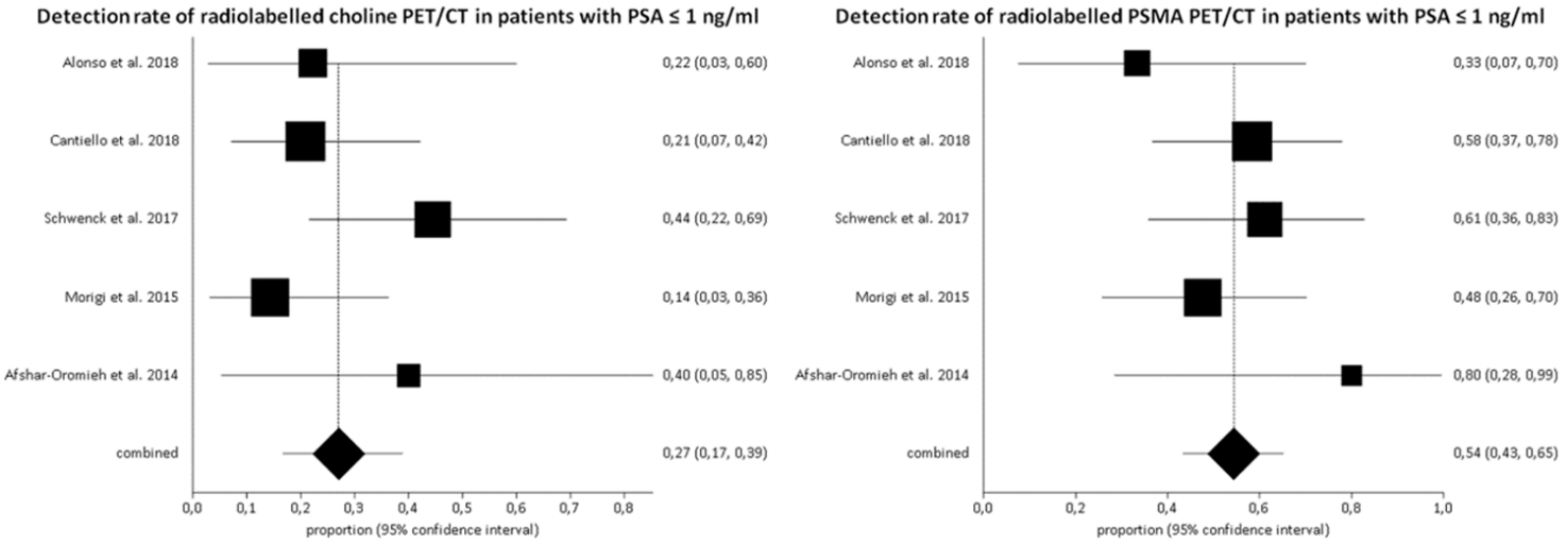

Figure 4. Plots of individual studies and pooled detection rate of radiolabelled choline and PSMA PET/CT in biochemical recurrent prostate cancer patients with PSA ≤ 1 ng/ml, including 95% confidence intervals (95% CI). The size of the squares indicates the weight of each study.

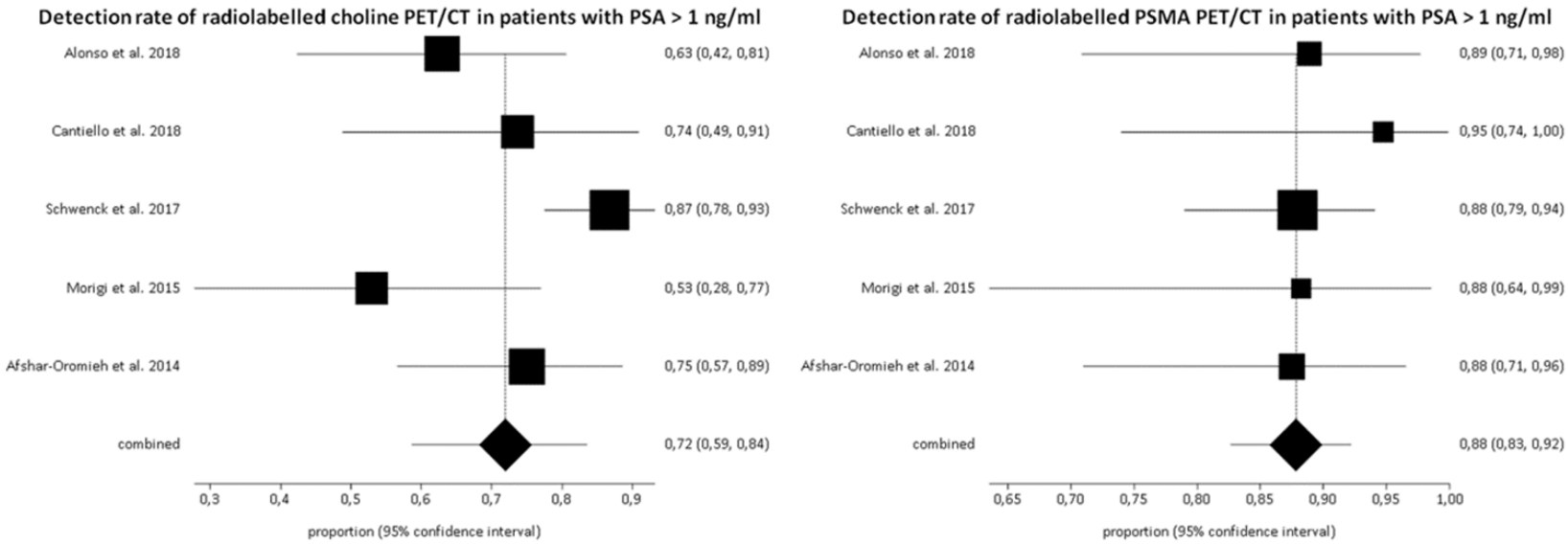

Figure 5. Plots of individual studies and pooled detection rate of radiolabelled choline and PSMA PET/CT in biochemical recurrent prostate cancer patients with PSA > 1 ng/ml, including 95% confidence intervals (95% CI). The size of the squares indicates the weight of each study.

Our systematic review and meta-analysis indicates that the overall DR of radiolabelled PSMA PET/CT on a per patient-based analysis is higher compared to that of radiolabelled choline PET/CT in BRPCa patients (78% versus 56%, respectively), but without a statistical significant difference at the pooled analysis (due to the overlap of 95% CI values). Our results are quite different compared to those reported in a recent review on the same topic [37] due to the higher number of studies included in our analysis. Overall, a significantly lower number of lesions are detected by radiolabelled choline compared to radiolabelled PSMA PET/CT (pooled ratio was 6:10); however, discordant uptake pattern applying both radiotracers can be found in some cases [34].

Performing subgroup analyses taking into account the different PSA cut-off values, we found a statistical significant difference of DR in favor of radiolabelled PSMA PET/CT in BRPCa patients with PSA ≤ 1 ng/ml (**Figure 4**). On the other hand, the superiority of radiolabelled PSMA PET/CT was less evident and not statistically significant in patients with PSA > 1 ng/ml (**Figure 5**).

A significant advantage of radiolabelled PSMA PET/CT is that PCa lesions frequently presented with higher contrast and uptake than radiolabelled choline PET/CT in all the studies evaluated, and this may have contributed to the higher DR of radiolabelled PSMA PET/CT at low PSA serum values [32-36]. Furthermore, the higher DR of radiolabelled PSMA PET/CT compared to radiolabelled choline PET/CT at low PSA levels may have important implications for the management of BRPCa patients [38] and a recent consensus document suggests radiolabelled PSMA as the preferred PET radiotracer in BRPCa patients [3].

Nevertheless, diagnostic accuracy of a test is not a measure of clinical effectiveness and high DR values do not necessarily result in improved patient outcomes. Other factors beyond the DR should influence the choice of an imaging modality in patients with BRPCa (i.e. availability, radiation dose, examination time, theranostic strategy, legal, organization and, economic aspects, and cost-effectiveness) [39]. Overall, our systematic review and meta-analysis demonstrated the higher DR of radiolabelled PSMA PET/CT compared to radiolabelled choline PET/CT in BRPCa for low PSA serum values, but large prospective studies and in particular cost-effectiveness analyses comparing these imaging methods are warranted.

Some limitations and biases of our meta-analysis should be taken into account. First of all a limited number of studies were available for the meta-analysis, because we have selected only studies that compared both imaging methods in the same patients. To reduce potential biases due to combined tests, we have also excluded studies which performed radiolabelled PSMA PET/CT only in patients with negative or inconclusive radiolabelled choline PET/CT. The major limitation of the included study was that not all positive PET/CT findings were confirmed by histology (verification bias). Confirmation was impaired by the small volume of individual lesions and the high number of biopsy-inaccessible lesions. Nevertheless, if modern imaging methods are performed in BRPCa, then confirmation of positive findings are needed only in highly selected cases and with a biopsy when findings are equivocal [3]. Theoretically the order of investigations could introduce a bias due to possible tumor progression between the first and the second PET/CT. In reality, however, it is well known that BRPCa usually presents with slow growth and noticeable changes within 30 days are very unlikely [36].

Heterogeneity among studies may represent a potential source of bias in a meta-analysis. This heterogeneity is likely to arise through baseline differences among the patients in the included studies (**Table 1**), diversity in methodological aspects between different studies (**Table 2**), and different study quality. We have detected heterogeneity among the included studies in our meta-analysis (significant heterogeneity for radiolabelled choline PET/CT and moderate for radiolabelled PSMA PET/CT), but and we tried to explain this heterogeneity performing subgroup analyses based on different PSA cut-off values. We pooled together data about ^{11}C-choline and ^{18}F-choline PET/CT without significant difference of DR among these radiopharmaceuticals. Similarly, no difference of DR was found by using ^{68}Ga-PSMA or ^{64}Cu-PSMA PET/CT, respectively. Nevertheless, longer half-life gives higher image accuracy thanks to increased uptake ratio from the late acquisitions. Furthermore, ^{64}Cu produces positrons at lower energy compared to ^{68}Ga, with lowered posi-

tron range and reduced range effect; this allows higher resolution PET images [33].

Conclusions

Radiolabelled PSMA PET/CT proved to be clearly superior in detecting BRPCa lesions at low PSA levels (≤ 1 ng/ml) when compared to radiolabelled choline PET/CT. On the other hand, the superiority of radiolabelled PSMA PET/CT was less evident and not statistically significant in patients with higher PSA levels. More studies comparing these imaging methods and cost-effectiveness analyses are warranted.

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Disclosure of conflict of interest

None.

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