Detection rates of recurrent prostate cancer: [68]Gallium (Ga)-labelled prostate-specific membrane antigen *versus* choline PET/CT scans. A systematic review

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Abstract

Background: The aim of this work was to assess the use of prostate-specific membrane antigen (PSMA)-labelled radiotracers in detecting the recurrence of prostate cancer. PSMA is thought to have higher detection rates when utilized in positron emission tomography (PET)/computed tomography (CT) scans, particularly at lower prostate-specific antigen (PSA) levels, compared with choline-based scans.

Methods: A systematic review was conducted comparing choline and PSMA PET/CT scans in patients with recurrent prostate cancer following an initial curative attempt. The primary outcomes were overall detection rates, detection rates at low PSA thresholds, difference in detection rates and exclusive detection rates on a per-person analysis. Secondary outcome measures were total number of lesions, exclusive detection by each scan on a per-lesion basis and adverse side effects.

Results: Overall detection rates were 79.8% for PSMA and 66.7% for choline. There was a statistically significant difference in detection rates favouring PSMA [OR (M–H, random, 95% confidence interval (CI)) 2.27 (1.06, 4.85), $p = 0.04$]. Direct comparison was limited to PSA < 2 ng/ml in two studies, with no statistically significant difference in detection rates between the scans [OR (M–H, random, 95% CI) 2.37 (0.61, 9.17) $p = 0.21$]. The difference in detection on the per-patient analysis was significantly higher in the PSMA scans ($p < 0.00001$). All three studies reported higher lymph node, bone metastasis and locoregional recurrence rates in PSMA.

Conclusions: PSMA PET/CT has a better performance compared with choline PET/CT in detecting recurrent disease both on per-patient and per-lesion analysis and should be the imaging modality of choice while deciding on salvage and nonsystematic metastasis-directed therapy strategies.

Keywords: choline, PET/CT, positron emission tomography, prostate cancer, PSMA

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Introduction

The role of contemporary morphological and functional imaging in the setting of recurrent prostate cancer following primary curative treatment is limited due to poor detection rates. Nuclear imaging with positron emission tomography (PET) has mitigated a number of limitations of traditional morphological and functional imaging modalities,

making PET scans of pivotal diagnostic value in this cohort of patients. Furthermore, improved detection rates with PET scans at low prostate-specific antigen (PSA) thresholds have driven recent advancements in metastasis-directed treatment strategies of oligometastatic prostate cancer.

Choline PET scans have been the traditional imaging modality of choice in restaging patients following biochemical relapse.[1] However, multiple studies have shown low sensitivity and specificity, particularly at low PSA levels,[2–7] which can result in delays in salvage therapy. Although known since the 1980s, prostate-specific membrane antigen (PSMA) has recently come to the fore in the imaging of prostate cancer due to promising preliminary data.[8–11] PSMA is a cell surface protein expressed in normal prostatic tissue, hyperplastic prostate tissue, prostatic intraepithelial neoplasia, as well as extraprostatic locations (kidney, small bowel, salivary glands), but is known to be expressed most in prostate cancer,[12–15] including in metastatic disease.[16,17] Radio-labelling of PSMA with 68Ga (amongst other tracers) has enabled its detection with PET scanning, opening a new chapter in prostate cancer imaging.[8,11]

PSMA labelled radiotracers are thought to have higher detection rates than choline-labelled tracers in the biochemical recurrence (BCR) setting, particularly at lower PSA levels.[18]

In this paper we have systematically reviewed the world literature comparing the performance of PSMA and choline-based PET/computed tomography (CT) scans in patients with biochemical recurrence following initial treatment with curative intent.

Methods

Evidence acquisition
Criteria for considering studies for this review. The inclusion criteria were all randomized trials and observational studies comparing choline and PSMA PET/CT scans in patients with suspected recurrence following initial primary curative treatment for prostate cancer.

Search strategy and study selection
The systematic review was performed in accordance with the Cochrane guidelines and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[19] Bibliographic databases searched were *MEDLINE* (2000 to March 2017), *EMBASE* (2000 to March 2017), *Cochrane Central Register of Controlled Trials* (CENTRAL; in the Cochrane Library, Issue 1, 2017), *CINAHL* (2000 to March 2017). As well as hand-searching individual urological journals, citation and reference lists were also evaluated. The search was conducted on 28 March 2017.

All studies comparing choline PET/CT scans with PSMA PET/CT scans in prostate cancer diagnostics were evaluated. No language restrictions were applied. Animal studies were excluded. Search terms included (not limited to): 'prostate cancer', 'PSMA PET', 'choline PET', 'prostatectomy', 'radiotherapy', 'lymphadenectomy', 'biochemical recurrence' and 'metastasis'. Boolean operators (AND, OR) were employed to augment the search process. Medical subjecting heading phrases included: (PSMA), (choline PET), (prostatectomy), (radiotherapy), (biochemical recurrence) and (lymphadenectomy).

Primary outcomes measures

Per-patient analysis

(1) Overall detection rates following biochemical recurrence (defined as at least one pathological lesion)
(2) Detection rates following biochemical recurrence at low PSA thresholds (defined as at least one pathological lesion)
(3) Difference in detection rates and exclusive detection (number of patients with at least one pathological lesion captured only by one of the PET scans and missed by the other PET scan)

Secondary outcome measures

Per-lesion analysis

(1) Total number of lesions in PSMA and choline PET CT/CT scans.
(2) Exclusive detection by each scan (number of lesions captured only by one of the PET Scans and missed by the other PET scan)
(3) Adverse side effects

Quality assessment of evidence

Study quality was assessed according to QUADAS-2 analysis, as detailed in the Cochrane Handbook for Systematic Review of Diagnostic Accuracy Tests.[20] The grading of recommendations assessment, development and evaluation (GRADE) approach was used to rate the quality of evidence.[20]

Data extraction and analysis

Two reviewers (MM, BR) independently identified all studies that appeared to fit the inclusion criteria for full review. Disagreement was resolved by consensus between the authors. Comparable data from each study were combined in a meta-analysis where possible. A Mantel–Haenszel Chi-square test was used for continuous data and expressed as the mean difference with 95% confidence interval (CI) and for dichotomous data an inverse variance was used and expressed as an odds ratio (OR) or risk ratio with a 95% CI. The p value was considered significant if it was <0.05. Heterogeneity was analysed using a Chi-square test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test.[19] I^2 values of 25%, 50% and 75% corresponded to low, medium and high levels of heterogeneity respectively. A fixed-effect model was used unless statistically significant high heterogeneity ($I^2 > 75\%$ was considered as significantly high heterogeneity) existed between studies. A random effects model was employed if heterogeneity existed. If the data available were deemed not suitable for a meta-analysis, they have been described in a narrative fashion. Differences in the detection rate were tested using McNemar's test. A p value <0.05 was deemed as significant.

Results

Literature search

A total of 474 papers were identified in the initial search from which 4 were evaluated for a comprehensive evaluation (supplemental Figure 1). One study was excluded as PSMA PET/CT scans were only performed on individuals who had negative choline PET/CTs.[21] Overall, three studies were included in the final review.[22–24] All three studies were observational comparative studies. Morigi and colleagues[22] was a prospective study. The other two studies were retrospective studies.[23,24] Overall 178 men with suspected recurrent prostate cancer had [68]GA-PSMA PET/CT and choline PET/CT scans. Choline tracers used were 11C-labelled choline by Schwenck and colleagues[23] and 18F-labelled choline used by Afshar-Oromieh and colleagues[24] and Morigi and colleagues[22] The demographics of individual studies are shown in Table 1.

Reference standard for individual studies

No reference standard was reported by the included studies. Histological confirmation was selectively used. In the study by Schwenck and colleagues[23] only two patients with lung metastases had histological confirmation. Both metastases were shown on the PSMA scan, and only in one patient was choline uptake shown. In the study by Morigi and colleagues[22] histopathologic confirmation was performed on 9 out of 38 patients. All nine lesions positive with PSMA were confirmed to be true-positive. Of the two lesions that were positive on the choline scan, one was true-positive the other was false-positive (but true-negative with PSMA). In the study by Afshar-Oromieh and colleagues[24] PSMA-positive lesions were confirmed with histology in seven cases.

Primary outcomes measures

Per-patient analysis

(1) Overall detection rates following biochemical recurrence

Overall detection rates for biochemical recurrence were 79.8% for PSMA and 66.9% for choline PET/CT (Table 2). All three studies reported on overall detection rates following biochemical recurrence and were suitable for meta-analysis. A random model was used for analysis as there was a moderate degree of heterogeneity ($I^2 = 51\%$). There was a statistically significant difference in overall detection rates between the choline and PSMA scans, favouring the PSMA scans. OR (M–H, random, 95% CI) 2.27 (1.06, 4.85), $p=0.04$ [Figure 1(a)].

(2) Detection rates after BCR at lower PSA values

Morigi and colleagues reported detection rates 50% and 12.5% respectively in PSA thresholds of <0.5 ng/ml for PSMA and choline scans respectively. Schwenk and colleagues reported detection rates 61% and 45% respectively at PSA thresholds of <1 ng/ml for PSMA and choline PET/CT scans respectively. Due to differing

Table 1. Individual study demographics.

	Schwenck and colleagues[25]	Morigi and colleagues[4]	Afshar-Oromieh and colleagues[26]
Type of study	Retrospective	Prospective	Retrospective
Total number of patients	103	38	37
Age (years)	• n/a	• Mean (range) = 68 (54–81)	• Mean $\pm$ SD = 69.3 ($\pm$7.1) • Median (range) = 70 (57–85)
PSA (ng/ml) at the time of scan	• Median = 2.7	• Mean $\pm$ SD = 1.72 $\pm$ 2.54 • Range 0.04–12.0	• Mean $\pm$ SD = 11.1 $\pm$ 24.1 • Median (range) = 4.0 (0.01–116)
Gleason score	• n/a	• G6–7 = 23/38 (61%) • G8–9 = 15/38 (39%)	• Mean $\pm$ SD = 7.4 $\pm$ 1.1 • Median (range) = 7 (5–9)
Initial treatment	• Radical prostatectomy or radiotherapy (no further data available)	• Radical prostatectomy = 22 • Radical prostatectomy + salvage radiotherapy = 12 • Radical radiotherapy = 4	• Radical prostatectomy = 28 • Radical radiotherapy +ADT = 9

ADT, androgen deprivation therapy; PSA, prostate-specific antigen; SD, standard deviation.

Table 2. The differences between choline PET and PSMA PET scans.

Study	*n*	Choline PET/CT	PSMA PET/CT
Overall detection rates for individual studies			
Schwenck and colleagues[25]	103	81 (78.6%)	85 (82.5%)
Morigi and colleagues[4]	38	12 (31.6%)	25 (65.8%)
Afshar-Oromieh and colleagues[26]	37	26 (70.3%)	32 (86.5%)
Total	**178**	**119 (66.9%)**	**142 (79.8%)**
Total number of lesions (per-lesion analysis)			
Schwenck and colleagues[25]		554	839
Morigi and colleagues[4]		29	59
Afshar-Oromieh and colleagues[26]		56	78
Total		**639**	**976**
Exclusive detection			
Schwenck and colleagues[25]		38	323
Afshar-Oromieh and colleagues[26]		0	22
Total		**38**	**345**

CT, computed tomography; PET, positron emission tomography; PSMA, prostate-specific membrane antigen.
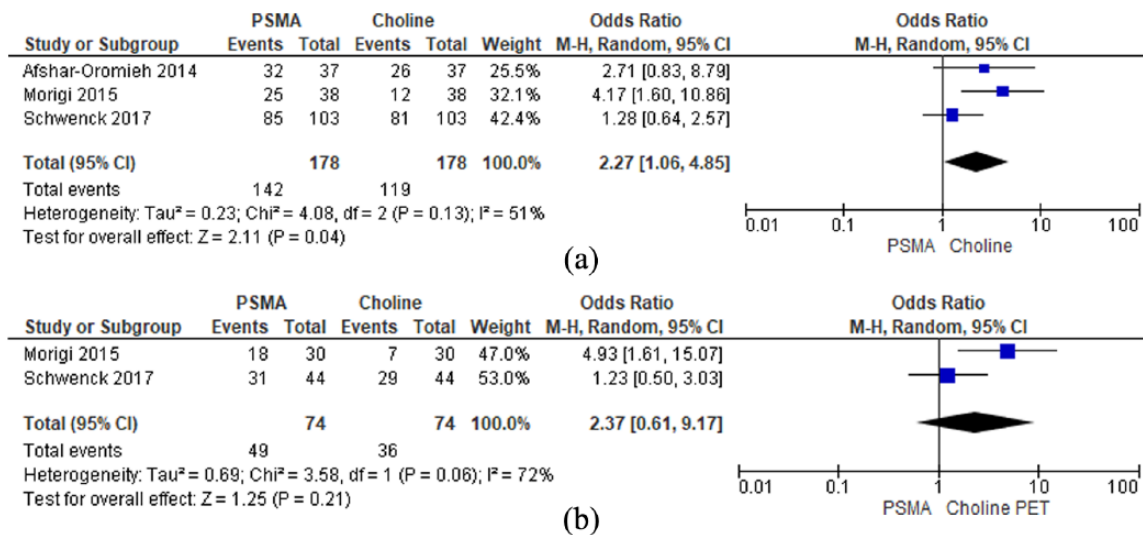
Figure 1. (a): Overall detection rates; (b): detection rates at PSA thresholds less than 2 ng/ml. PSA, prostate-specific antigen.

stratification methods used in each of the studies direct comparison was limited to PSA < 2 ng/ml in two studies. A random model was used for analysis as there was a high degree of heterogeneity ($I^2 = 72\%$). There was no statistically significant difference in detection rates between the choline and PSMA PET/CT scans at PSA thresholds <2 ng/ml. OR (M–H, random, 95% CI) 2.37 (0.61, 9.17) $p = 0.21$ [Figure 1(b)].

(3) Difference in detection rates:

The difference in detection in the per-patients analysis was significantly higher in the PSMA PET/CT scans ($p < 0.00001$). On a per-patient analysis 27 patients had lesions detected exclusively with PSMA and 4 patients had lesions detected exclusively detected with choline PET/ CT scans [Table 3(a)].

Secondary outcomes measures

Per-lesion analysis

(1) Total number of lesions in PSMA and choline PET/CT scans

On cumulative analysis, the total number of lesions detected by PSMA and choline PET/CT Scans was 976 *versus* 639 respectively (Table 2). All three studies reported higher lymph node, bone metastasis and locoregional recurrence in PSMA in comparison with choline PET/CT [Table 3(b)].

(2) Exclusive detection by each scan

All three studies individually reported higher exclusive lesions detected with PSMA as compared with choline PET/CT Scans. Cumulative analysis was possible only on data from two studies. The number of pathological lesions exclusively detected by PSMA and choline PET/CT Scans was 345 and 38 respectively (Table 2).

(3) Adverse effects with radiotracers

There were no reports of any adverse effects in any of the publications.

Quality assessment of studies

The patients in all the studies have received differing treatments and hence represent a heterogeneous cohort. All the studies were hence judged to have a high degree of risk of bias for patient selection. There was no consistent reference standard with selective use of histological confirmation to compare the outcomes of the two types of scan. There is therefore a concern with false positivity. The authors have hence judged the risk of bias for index test as unclear. The risk of bias for reference standard is judged as high. It is unclear if the timing between choline and PSMA PET/CT scans would have influenced the detection rates. The authors have therefore judged the risk of bias for flow and timing as unclear (supplemental Figure 2). There was low concern for applicability domains (supplemental Figure 2).

Table 3. (a). Difference in detection rates (per-patient analysis), ($p < 0.00001$).

	Choline −ve	Choline +ve
PSMA −ve	31	4
PSMA +ve	27	116

(b). Total number of lesions at specific sites in PSMA and choline PET-scans (per-lesion analysis).

	Bone metastasis		Lymph nodes metastasis		Local recurrence		Other sites	
	PSMA	Choline	PSMA	Choline	PSMA	Choline	PSMA	Choline
Afshar-Oromieh and colleagues[26]	23	Unclear	40	Unclear	10	Unclear	5	Unclear
Morigi and colleagues[4]	16	9	36	18	7	2	0	0
Schwenck and colleagues[25]	372	242	439	287	26	24	2	1

PET, positron emission tomography; PSMA, prostate-specific membrane antigen.

Adopting the GRADE approach, the quality of evidence for 'overall detection rates' and 'detection rates after at PSA thresholds less than 2 ng/ml' was rated as 'low' and 'very low' respectively (supplementary Table 1).

Discussion

Principal findings
The review highlights the superior performance of PSMA PET/CT scans when compared with choline PET/CT Scans in detecting recurrent prostate cancer. Overall detection rates of PSMA and choline PET/CT scans were 80% and 67% respectively. At PSA thresholds of <2 ng/ml the detection rates of PSMA and choline PET/CT scans were 66% *versus* 49% respectively. The overall detection rates on a per-patient analysis of PSMA scans was significantly better than choline scans in identifying recurrent disease in patients who have had an initial attempt at curative therapy. On a per-lesion analysis, a higher number of patients with local recurrence were detected in the PSMA cohort.

Overall, two studies in the review individually reported better detection rates of PSMA when compared with choline PET/CT scans at PSA thresholds of <1 ng/ml. The meta-analysis in the review could only analyze data at PSA thresholds

<2 ng/ml due to differing PSA stratifications by individual studies. The analysis suggested a trend towards better detection rates with PSMA at this threshold however; this did not achieve statistical significance. Additionally, the number of lesions detected by PSMA scans was significantly higher than choline scans. The exclusive detection on both per-patient and per-lesion analysis was consistently higher with PSMA. No adverse effects were reported with either scans.

Morigi and colleagues[22] reported that 54% of patients had a major to moderate change on their management in recurrent prostate cancer purely based on the findings of PSMA PET/CT, while choline PET/CT scans did not exclusively change management in any case. Bluemel and colleagues[21] reported a 43.8% increased detection rate from PSMA PET/CT in patients with choline negative scans. The exclusive detection rates both on a patient basis and lesion basis in this review were higher in PSMA PET/CT compared with choline PET/CT. These findings would affirm the suggestion that PSMA PET/CT scanning is more likely to influence management in patients with recurrent prostate cancer.

Implications in clinical practice
Salvage treatment. The timing and indications of local salvage treatment options after initial

prostatectomy or radiotherapy is an area of much contention and debate. In contemporary practice, salvage therapy is administered mostly based on PSA kinetics without an overt reliance on morphological imaging. Pfister and colleagues[27] in a pooled analysis of seven retrospective studies of early radiotherapy after radical prostatectomy reported a 5-year biochemical-free survival of 71.1% at PSA < 0.5 ng/ml and concluded biochemical-free survival rates were significantly better when salvage radiotherapy was offered at low PSA thresholds. While salvage therapy has the potential to cure if offered early, it will plausibly result in overtreatment in a cohort of patients.

Our findings strengthen the arguments made by current evidence. Castellucci and colleagues[28] reported a detection rate of 28.4% in 605 patients with BCR and PSA values <2 ng/ml. Von Eyben and colleagues[29] in a meta-analysis reported overall detection rates and detection rates at PSA thresholds < 0.5 ng/ml of 81% and 50% respectively on a per-patient analysis corroborating the findings of this review. Furthermore a meta-analysis by Perera and colleagues[30] with a total of 1309 patients showed a detection rate of 76% for BCR (PSA < 2 ng/ml).

These findings would suggest that PSMA scans, when integrated with other factors such as PSA kinetics, initial stage, grade and surgical margin state, are more likely to offer appropriate guidance on the timing of salvage treatment options than choline PET/CT Scans. In addition, if salvage radiotherapy is contemplated, accurate information on the sites of recurrence will enable clinicians to decide on the appropriate type, dose and field of salvage radiotherapy.

Nonsystemic metastatic directed therapy

Nonsystemic metastatic directed therapy (MDT) with options such as stereotactic radiotherapy or salvage lymphadenectomy in low volume oligometastatic disease is a promising and evolving treatment option for patients with recurrent prostate cancer. The potential benefits of an MDT strategy include the possibility of curing cancers previously thought to be incurable, delay hormonal manipulations and reduce treatment related toxicity. Steuber and colleagues[25] in a retrospective multi-centre study of 2079 men compared the standard of care (early *versus* delayed androgen deprivation therapy (ADT)) *versus* MDT (stereotactic radiotherapy/salvage lymphadenectomy) in

men with PET-detected nodal recurrence at PSA progression. At a median follow up of 70 months, MDT had a better cancer specific survival (CSS) in comparison with the standard of care (5-year CSS for MDT and standard of care (SOC) was 98.6% and 95.7% respectively). Ost and colleagues[26] in a phase II multi-centre randomized trial, compared surveillance and MDT in patients with three or fewer extracranial metastatic lesions on choline PET/CT with biochemical recurrence following initial prostate cancer treatment with curative intent. The trial reported significantly longer ADT-free survival in the MDT cohort in comparison with surveillance at a median follow-up time of 3 years (21 months *versus* 13 months). Despite the potential benefits of an MDT approach its success hinges on the accurate detection of all oligorecurrent lesions on imaging. In this review the overall number of metastatic lesions detected by PSMA PET/CT and choline PET/CT was 976 and 639 respectively. Also, the number of bone and lymph nodes metastasis was consistently higher in the PSMA cohort. This trend emphasizes that PSMA PET/CT scans are better equipped compared with choline-based scans to direct a MDT strategy.

Strengths and limitations

The current study has several important limitations. Due to the limited number of studies that have directly compared PSMA and choline PET/CT scans, the low number of patients included in this review impacted on some of the results. Despite this the overall statistical significance shown illustrates why there is a rapidly increasing volume of research utilizing PSMA PET/CT scans, implying there is sufficient evidence is available to convince clinicians of its merits over conventional imaging.

Each study analyzed had a heterogeneous cohort of patients that received differing treatment strategies. In the setting of recurrent prostate cancer where the evidence is often inconclusive and a variety of treatment options available, this is inevitable. The authors were also unable to perform a meta-analysis at a PSA threshold of <1 ng/ml due to differing PSA stratification used by individual studies. In the setting of recurrent prostate cancer, the diagnostic accuracy of PET/CT scans cannot be evaluated with absolute confidence due to the inability to choose a reference standard. Also, the studies have only selectively used histological evaluation to confirm

whether detectable disease was true-positive. In reality achieving histological confirmation may be impractical and potentially unethical. The quality of the evidence based on the GRADE classification was low, primarily due to the bias of individual results and the inconsistency of results. While randomized trials comparing the two radiotracers in the setting of recurrent prostate cancer may confirm the superiority of PSMA PET/CT scans with confidence; it is the author's view that the current review, despite the poor quality, provides adequate data to confirm the superiority of PSMA PET/CT scans over choline PET/CT scans.

Areas of future interest and impact on ongoing research

The authors do believe that future research in a randomized setting must concentrate on evaluating the role of PSMA PET/CT scans in defining appropriate salvage strategies in the event of recurrence following initial curative treatment. The proPSMA[31] study seeks to answer some of these questions. A possible criticism of ongoing research trials such as the Surveillance or metastasis-directed Therapy for OligoMetastatic Prostate cancer recurrence (STOMP) trial[32] and the Conventional care or Radioablation in the treatment of Extracranial metastases (CORE) trial[33] is the use of inferior imaging modalities to define oligometastatic disease. The outcomes of this review would suggest that establishing whether an individual truly has oligometastatic disease based on contemporary definitions is dictated by the imaging modality employed. In the recurrent prostate cancer setting it is therefore vital that PSMA PET/CT scans, with their superior detection rates, be used as the standard imaging modality of choice in trials evaluating the efficacy of MDT strategies.

Conclusion

PSMA PET/CT scans have a better performance compared with choline PET/CT scans in detecting recurrent disease following initial curative treatment for prostate cancer, both on a per-patient and per-lesion analysis. PSMA PET/CT scans should be the imaging modality of choice while deciding on salvage and nonsystematic metastasis-directed therapy strategies. Research trials evaluating treatment outcomes in the oligo-metastatic setting should use PSMA PET/CT scans as the imaging modality of choice to evaluate outcomes.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Supplemental material

Supplemental material is available for this article online.

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