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REVIEW Open Access

Comparison of ^{99m}Tc-PSMA SPECT/CT and ^{68}Ga-PSMA PET/CT in patients with prostate cancer: a protocol for systematic review and meta-analysis

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Abstract

Background: A wide range of nuclear imaging probes have been developed to address different metabolic processes and cell receptors in prostate cancer patients using positron emission techniques to aid diagnosis, staging, and monitoring for recurrence after treatment. While ^{68}Ga PSMA is a generator-derived PET radiopharmaceutical, SPECT/CT imaging using technetium-99m-labeled PSMA is now available as a suitable alternative. The aim of this study is to compare the pooled sensitivity, specificity, and accuracy of ^{99m}Tc-PSMA SPECT/CT and ^{68}Ga-PSMA PET/CT in patients with prostate cancer.

Main body of the abstract: A search strategy was developed using text words, MeSH, and entry terms. The following databases will be searched: PubMed, African Journals Online (AJOL), Embase, Google scholar, ResearchGate, Cochrane Library, Scopus, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Web of Science. Eligibility criteria include (a) all studies that are published or retrievable in English language, (b) observational studies, and (c) histopathology analysis or clinical and imaging follow-up or comparison with reference standards. Exclusion criteria will be interventional studies, editorials, reviews, and commentaries. Quality of the studies will be assessed using QUADAS2 Quality scores and risk of bias for individual studies will be reported. Full text of the studies will be reviewed and snowballed for any relevant literature. Assessment of methodological, clinical, and statistical heterogeneity for all the included studies will be made. Publication bias will be assessed using funnel plots. Statistical analysis and forest plots will be performed using the Open Meta-analyst software. The systematic review and meta-analysis will be reported according to PRISMA 2015 Statement.

Short conclusion: This review will provide data on diagnostic accuracy of 99mTc-PSMA SPECT/CT and 68Ga-PSMA PET/CT in patients with prostate cancer. Results from this study will help nuclear medicine service providers to make better decisions on the appropriate use of 99mTc-PSMA SPECT/CT and 68Ga-PSMA PET/CT especially with regard to the use of 99mTc-PSMA SPECT/CT which is relatively affordable and more readily available in developing countries when compared to 68-Ga PSMA PECT/CT.

Keywords: Prostate cancer, Tc-99m PSMA SPECT/CT, Ga-68 PSMA PET/CT, Sensitivity, Specificity, Accuracy

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Background

Prostate cancer is the second most common male cancer and the sixth leading cause of cancer-related deaths in males with global estimated incidence and mortality rates of 7.1% and 3.8% respectively in the year 2018 [1].

Histopathology, immunohistochemistry, and the use of International Society of Urological Pathology (ISUP) modified Gleason grading have over the years formed the bases for diagnosis, staging, risk stratification, prognosis, and clinical decision making in patients with carcinoma of the prostate [2, 3]. Recent evidence regarding the diagnostic and therapeutic roles of a transmembrane protein highly expressed in prostatic tissue known as the prostate-specific membrane antigen (PSMA) shows promise for improved diagnosis and treatment of prostate cancer. Its value and as an imaging and treatment biomarker is expected to grow as newer treatments as well as imaging systems and techniques continue to evolve [4].

Anatomic and functional/molecular imaging techniques are recommended for use in the detection and characterization of disease to select treatment or change management. Anatomic imaging techniques include plain radiography, ultrasonography, computed tomography (CT), and multiparametric magnetic resonance imaging (mpMRI), while the functional imaging methods are ^{99m}Tc methylene diphosphonate (MDP) bone scintigraphy and positron emission tomography-computed tomography (PET/CT) using different radiopharmaceuticals [5–8]. Studies have shown that the overall performance of morphological imaging techniques in the assessment primary lymph node metastases is poor and this encouraged many groups to assess molecular imaging techniques in the evaluation of prostate carcinoma [9]. A wide range of nuclear imaging probes were developed for positron emission tomography imaging addressing different metabolic processes and cell receptors including ^{18}F-FDG, ^{11}C- and ^{18}F-Choline, and ^{68}Ga-/^{18}F-prostate-specific membrane antigen (PSMA). The latter probe has shown promising results [10]. While ^{68}Ga PSMA is a PET tracer with the ^{68}Ga obtained from ^{68}Ge/^{68}Ga generator, technetium-99m-labeled PSMA (^{99m}Tc-PSMA) with the Tc-99m obtained from ^{99}Tc/^{99}Mo-generator is now available. The latter radiopharmaceutical allows imaging to be done with a SPECT/CT camera as opposed to PET/CT in the case of ^{68}Ga PSMA [11].

The aim of this systematic review and meta-analysis is to analyze and compare the sensitivity, specificity, and diagnostic accuracy of ^{99m}Tc-PSMA SPECT/CT and ^{68}Ga-PSMA PET/CT in patients with prostate cancer.

Main text

Objective

The main objective of this study is to determine and compare the pooled diagnostic accuracy of ^{99m}Tc-PSMA SPECT/CT and ^{68}Ga-PSMA PET/CT in patients with prostate cancer.

Study objectives will include:

1. To analyze the pooled estimated sensitivity, specificity, and accuracy of ^{99m}Tc-PSMA SPECT/CT in patients with prostate cancer.
2. To analyze the pooled estimated sensitivity, specificity, and accuracy of ^{68}Ga-PSMA PET/CT in patients with prostate cancer.
3. To compare the pooled estimated sensitivity, specificity, and accuracy of ^{99m}Tc-PSMA SPECT/CT and ^{68}Ga-PSMA PET/CT in patients with intermediate and high-risk prostate cancer.

Review questions

a. What are the pooled estimated sensitivity, specificity, and accuracy of ^{99m}Tc-PSMA SPECT/CT imaging in patients with prostate cancer?
b. What are the pooled estimated sensitivity, specificity, and accuracy of ^{68}Ga-PSMA PET/CT imaging in patients with prostate cancer?
c. What is the diagnostic performance of ^{99m}Tc-PSMA SPECT/CT and ^{68}Ga-PSMA PET/CT imaging in patients with intermediate- and High-risk prostate cancer?

Materials and methods

The research will study ^{99m}Tc-PSMA SPECT/CT and ^{68}Ga-PSMA PET/CT in patients with carcinoma of the prostate as two tests that use different radionuclides and imaging methods. No time restriction is assigned on eligible primary studies.

Inclusion criteria:

a) Cross-sectional studies, case-control studies, cohort studies, and historical cohort studies.
b) Studies in which histopathology analysis or clinical and imaging follow-up or comparison with reference standards were used as reference standard.
c) Only studies in which a 2 × 2 table could be constructed for true-positive, true-negative, false-positive, and false-negative values.
d) When data or subsets of data were presented in more than one article, the article with the most detail or the most recent article will be chosen.
e) Studies that are published or retrievable in the English language and are available in electronic databases.

Exclusion criteria:

a) Narrative reviews and experimental and interventional studies
b) Letters to editors, commentaries, and editorials.
c) Duplicates of same studies
d) Grey literature

This review will be reported in line with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2015 Statement) [12, 13].

Study characteristics

The PICOS is as follows:

Participants: Men with prostate cancer

Intervention: None

Comparator: 99mTc-PSMA SPECT/CT and 68Ga-PSMA PET/CT

Outcome: The primary outcome is diagnostic accuracy of 99mTc-PSMA SPECT/CT and 68Ga-PSMA PET/CT in prostate cancer patients. The measurable secondary outcomes are sensitivity, specificity, and accuracy of 99mTc-PSMA SPECT/CT and 68Ga-PSMA PET/CT in intermediate and high-risk prostate cancer patients.

Study designs: Observational/randomized controlled trials

Information sources

The search will employ topic-based strategies appropriately designed for the following databases: AJOL, CINA HL, Cochrane Library, Embase, Google Scholar, PubMed, ResearchGate, Scopus, and Web of Science.

Search strategy

This will include MeSH terms, text words, and entry terms as shown in Table 1.

Data extraction and management

Data extraction

For all eligible studies, basic characteristics which include study design, recruiting place and time, and inclusion criteria will be extracted. Details of the participants to be recorded will be age and serum prostate-specific antigen (PSA). SPECT/CT and PET/CT test details (CT technique, radiopharmaceutical uptake time, definition of positive imaging test) and details of reference standards used in the study will be summarized. Outcome data in terms of Tc-99m PSMA SPECT/CT and 68Ga-PSMA PET/CT and pathological results (positive/negative) for biopsies on the basis of per-patient or per-node, as the case may be, will be extracted into 2 × 2 contingency tables. All relevant, searched, and retrieved items will be exported to Endnote version 7 and screened before being exported to Microsoft Excel. The exported studies will then be retrieved for full-text reading to enable snowballing search on the references contained in the journal articles. Where necessary, authors may be contacted for additional information.

Selection process

Two independent reviewers will search information sources independently and assess identified studies for inclusion and exclusion. Studies for eligibility will be reviewed by another independent reviewer to check that all eligibility criteria are met.

Data items (measurable outcomes)

These will include number of cases, true-positive, true-negative, false-negative, and false-positive.

Data for subgroup analysis will include comparison of the pooled estimated sensitivity, specificity, and accuracy of ^{99m}Tc-PSMA SPECT/CT and ^{68}Ga-PSMA PET/CT in patients with intermediate and high-risk prostate cancer.

Table 1 Search strategy

S/No.	Search strategy
1.	"Hereditary prostate cancer" OR "Prostate Neoplasms" OR "Prostate Neoplasm" OR "Prostatic Neoplasm" OR "prostate Cancer" OR "Prostate Cancers" OR "Cancer of the Prostate" OR "Prostatic Cancer" OR "Prostatic Cancers" OR "Cancer of Prostate"
2.	"Prostate Specific Membrane Antigen" OR "PSMA" OR "68Ga-PSMA-11" OR "PSMA-HBED-CC Ga-68" OR "(68)Ga-PSMA" OR "Ga68 PSMA" OR "(68Ga)PSMA I and T"
3.	"Positron Emission Tomography" OR "PET Scan" OR "PET Scans" OR "PET-CT Scan" OR "PET-CT Scans" OR "PET CT Scan" OR "PET CT Scans" OR "CT PET" OR "Positron Emission Tomography-Computed Tomography" OR "PET-CT" OR "CT PET Scan" OR "CT PET Scans"
4.	"Prostate Specific Membrane Antigen" OR "PSMA99mTc-HYNIC-BBN" OR "99mTc-EDDA" OR "99m Tc-MIP 1404" OR "Tc99m PSMA"
5.	"SPECT CT" OR "SPECT" OR "SPECT CT Scan" OR "SPECT CT scans" OR "CT SPECT Scan" OR "CT SPECT Scans" OR "Single-Photon Emission Computerized Tomography" OR "Single Photon Emission Computerized Tomography" OR "Single-Photon Emission CT Scan" OR "Single Photon Emission CT Scan" OR "Single-Photon Emission-Computed Tomography" OR "Single Photon Emission Computed Tomography"
6.	1 AND 2 AND 3
7.	1 AND 4 AND 5

Quality assessment

The Quality Assessment Tool for Diagnostic Accuracy Studies (QUADAS-2) will be used to assess the quality of the studies. The domains to be assessed will include patient selection, index test, reference standard, participant flow, and timing [14].

Risk of bias

Higher scores suggest lower risk of bias in the study's methodology.

Heterogeneity and publication bias shall be assessed at study level while the method of testing or reporting shall be assessed at the outcome level. Any study with extreme bias will be excluded following consensus decision by the reviewers.

Data synthesis

a. Studies that passed the methodological quality assessment using the QUADAS-2 tool will be extracted.
b. Meta-analysis will contain the following:
   i. Diagnostic accuracy of the two imaging methods as determined by combined or pooled estimate of sensitivity and specificity, likelihood ratio (LHR), and pooled diagnostic odd ratio (DOR).
   ii. Correlation between sensitivity and specificity will be determined by performing a bivariate meta-analysis to assess the possible effect of threshold effect.
   iii. Sub-population of study subjects, i.e., the intermediate and high-risk prostate cancer groups as categorical data while the two different test methods will be used as moderators.
c. Quantitative analysis of the eligible studies will be performed using the OpenMeta (Analyst) software [15]. Sub-group estimates will be compared using a random effects meta-regression model. The degree of heterogeneity in included studies will be analyzed by Cochran chi-square statistic and its p value, I^2 and ^{2}. A random effect model will be used if a significant heterogeneity is observed (p<0.05). The pooled accuracy and subgroups analysis will be reported in forest plots.

Presentation and reporting of results

The study selection process will be summarized in a flow diagram. Tables of search strategy, quality scores, risk of bias, and list of eligible studies will be included. Quantitative data such as accuracy, 95 % CI, P values, and relative weights assigned to studies and heterogeneity tests will be included in the forest plots.

Discussion

The role of 99mTc-PSMA SPECT/CT and 68Ga-PSMA PET/CT in the management of prostate cancer patients as well as intermediate and high-risk prostate cancer patient will be discussed. The pooled diagnostic accuracy of 99mTc-PSMA SPECT/CT and 68Ga-PSMA PET/CT will be compared and discussed accordingly. The results of the sub-group analyses according to risk groups (intermediate or high risk) will be discussed. The various changes in effect size due to sensitivity test will also be discussed. Overall conclusions will be made relevant to nuclear medicine practitioners and experts that treat prostate cancer patients.

Conclusion

This review will provide important data on diagnostic accuracy of 99mTc-PSMA SPECT/CT and 68Ga-PSMA PET/CT in patients with prostate cancer. Results from this study will prompt nuclear medicine service providers to make better decisions on the appropriate use of 99mTc-PSMA SPECT/CT and 68Ga-PSMA PET/CT especially with regard to the use of 99mTc-PSMA SPECT/CT which is relatively affordable and more readily available in developing countries when compared to 68-Ga PSMA PECT/CT.

Abbreviations

^{68}Ga: Gallium-68; ^{99m}Tc: Technitium-99m; MDP: Methylene diphosphonate; PSMA: Prostate-specific membrane antigen; PET/CT: Positron emission tomography-computed tomography; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; QUADAS2: Quality Assessment Tool for Diagnostic Accuracy Studies; SPECT/CT: Single photon emission computed tomography-computed tomography

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Authors' contributions

Substantial contributions to the conception or design of the work: GHY, AUK, and ATO; literature search: GHY, ATO, ZMJ, SSM, and AK; article selection: GHY, ATO, ZMJ, and SSM; QUADAS analysis: GHY, AUK, and AK; meta-analysis: GHY, AUK, ATO, and AK; manuscript preparation: GHY, ATO, and AUK; drafting the work or revising it critically for important intellectual content: all authors. All authors have read and approved the final manuscript.

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Availability of data and materials

The final report of this study will be published in a peer-reviewed journal.

Declarations

Ethics approval and consent to participate

Ethical approval will not be required since this study will be based on published data.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflict of interest.

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