

LIMITED EVIDENCE ON IMAGING FOR DETECTING PROSTATE CANCER: A SYSTEMATIC REVIEW

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Abstract

This research aims to assess the diagnostic accuracy of imaging technology in detecting prostate cancer in patients with high PSA levels or suspicious findings in clinical examinations. The method involved searching for articles from the Medline, EMBASE, and Cochrane databases from 2011 to 2023. The selected articles used predefined inclusion criteria, and the risk of bias in individual studies was assessed using QUADAS-2. The abstracts and full texts were independently evaluated by the authors to assess the sensitivity and specificity of the imaging. The selection process followed the PRISMA 2020 guidelines. The literature search yielded 5421 abstracts, which were independently reviewed by the authors. Out of this number, 5401 abstracts were excluded due to irrelevance to the research title and abstract. Subsequently, a full review was conducted on 20 articles to assess their quality. Among the 20 articles, 14 studies were excluded because they were not original research, the PICO was not relevant, or the methods and populations used were not adequately described. Finally, six studies were included in this research, with four studies concerning MRI and two studies involving transrectal ultrasound with Doppler. Overall, the research findings indicate that the current number of imaging studies with adequate scientific quality is still limited to recommend their use beyond clinical trials for patients with high PSA levels or suspicious findings in clinical examinations. Therefore, further research is needed to strengthen and generalize these findings before imaging technology can be widely used as a diagnostic method for prostate cancer in this patient group.

Keywords: Biopsy, Diagnosis, Imaging, Prostate Cancer

1. INTRODUCTION

Prostate cancer diagnosis remains one of the greatest and most crucial challenges in healthcare today. New diagnostic techniques have been introduced, but only a few have been comprehensively evaluated before being used in clinical practice. Before the introduction of prostate-specific antigen (PSA), many cases of prostate cancer were diagnosed at a clinical stage when the disease had already caused symptoms. With the introduction of PSA, the diagnosis of prostate cancer has undergone a significant change. Currently, most tumors are detected early at stage 1 as a result of PSA testing. Although PSA screening has been shown to reduce prostate cancer-specific mortality (Schröder et al., 2009), there are still issues that need to be addressed. PSA testing has good sensitivity for prostate cancer but poor specificity (Stamey et al., 1987), meaning that a significant number of men without prostate cancer will undergo unnecessary prostate biopsies guided by ultrasound (USG). Prostate biopsy is currently the gold standard technique for diagnosing prostate cancer. Prostate biopsy with USG guidance has very high specificity but lower sensitivity (Djavan et al., 2001), resulting in repeat biopsies for men with initially negative biopsy results but persistently high PSA levels. Additionally, many men undergo prostate biopsies as an uncomfortable and painful

procedure with significant risks of complications such as infection and bleeding (Raaijmakers et al., 2002). Overall, the current diagnostic examination of prostate cancer presents substantial clinical challenges, especially with the recognition that prostate cancer is the most common non-cutaneous malignancy in the Western world. (American Cancer Society, 2007) stated that the economic costs derived from prostate cancer diagnostics imply a burden to the healthcare system and society in general.

The issues with prostate cancer diagnosis have led to the search for new and improved prostate imaging techniques that can provide simpler and valid diagnoses. Three main imaging areas have been proposed. First, transrectal ultrasound (USG) is currently used to guide systematic biopsies. Various techniques such as Doppler, Histo scanning, and elastography have been developed and marketed. Second, positron emission tomography/computed tomography (PET/CT) with new tracers has also been introduced as an imaging modality for prostate cancer. The urgent need to improve prostate cancer diagnosis has led to the widespread adoption of these techniques in clinical practice, often without a thorough evaluation of their performance in terms of sensitivity and specificity. Therefore, it is crucial to assess the diagnostic accuracy of these new imaging techniques. Hence, the objective of this systematic review is to evaluate the diagnostic accuracy of imaging techniques for prostate cancer.

2. RESEARCH METHOD

2.1. Eligibility Criteria for the Study

Only research published in the English language is included in this systematic review. The eligibility criteria for the study are assessed based on the PICO as follows:

1. Population: Men suspected of having prostate cancer, i.e., with high PSA levels or suspicious clinical findings, and without a previous diagnosis or treatment of prostate cancer.
2. Index Test: Magnetic resonance imaging (MRI), diffusion-weighted magnetic resonance imaging (DW-MRI), dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), spectroscopy, positron emission tomography (PET), positron emission tomography/computed tomography (PET/CT), transrectal ultrasound with Doppler (TRUS), contrast-enhanced ultrasound (CEUS), elastography, or Histo scanning. Regarding MRI, only articles that meet the European Consensus Statement on Minimum Requirements for Multiparametric Imaging are included (6,7). (Barentsz et al., 2012; Dickinson et al., 2011)
3. Control or Reference Test: Systematic prostate biopsy with USG guidance (≥ 10) or histopathological examination after prostatectomy.
4. Evaluated Outcome: Sensitivity and specificity for diagnostic accuracy. Sensitivity relates to the ability of a method to correctly identify truly sick individuals (in this case, prostate cancer based on biopsy results). Meanwhile, specificity is the ability of a method to correctly identify truly healthy individuals (in this case, no prostate cancer based on biopsy results).

Table 1. Inclusion criteria according to the PICO approach

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|--|--|
| Population (P) | Men with suspected prostate cancer which is elevated PSA levels (≥ 4 ng/ml) or suspicious clinical findings. |
| I (index test) | Imaging methods (MRI, transrectal ultrasonography with Doppler, or PET/CT to direct biopsy) |
| C (reference test) | Histopathologic analysis of tissue taken from prostate biopsies ($n \geq 10$) or analysis of corresponding tissue after prostatectomy |
| O (assessed output) | Sensitivity and specificity data in available or calculable patients. |
| Predefined low, medium, and high bias risk criteria | |
| Low | Prospective study. Adequately described population, sequential inclusion of patients. Reported number and experience of index test observers, reported number of biopsy observers. Blinded to both index test and reference test. Imaging performed before biopsy. |
| Medium | Retrospective study. Adequately described population, sequential inclusion of patients. Blinding was performed at the time of the index test and reference test. Number and experience of index test observers reported. Imaging was performed before biopsy or after one or more negative biopsies. |
| High | Requirements for moderate study quality were not met. |

2.2. Source of Search

An electronic literature search was conducted on the PubMed, EMBASE, and The Cochrane Library databases. The search was performed from the year 2011 to 2023. In addition to the electronic search, manual searches were also conducted, and references from narrative reviews and articles in international journals not identified in the primary search were included. Grey literature was not included.

2.3. Study Selection

The authors independently screened the titles and abstracts identified based on the predetermined search strategy. All studies with potential relevance according to the inclusion criteria were obtained in full-text form, and the authors independently assessed the studies for inclusion in the review. The reference lists were also screened for additional relevant studies. The selection process followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines.

2.4. Data Collection Process

From each included study, data were extracted and entered into a table. The authors also performed data extraction audits.

2.5. Extracted Data

Information extracted from each included article included details about recruitment (prospective, retrospective, sequential, and time and date of data collection) and characteristics of the population (age, PSA levels, previous negative biopsy or not, disease prevalence). Regarding the index tests, the type and details of the tests were recorded, the number of observers, and reporting of blinding against the reference test were also noted. For the reference test, the number of systematic biopsies was recorded, as well as the number

of observers and blinding against the index tests. Sensitivity and specificity data were extracted for the outcomes. When confidence intervals were missing, they were calculated from the data presented in the article.

2.6. Assessment of Study Bias

The authors independently assessed the risk of bias in each study using the QUADAS-2 instrument (Whiting et al., 2011). Each study was evaluated as having low, moderate, or high risk of bias based on the predetermined criteria provided in Table 1.

2.7. Quality of Evidence (GRADE)

The international GRADE assessment system was used to assess the quality of evidence related to effects and harms, according to the following four levels:

1. High quality: The authors have high confidence that the true effect is close to the estimated effect.
2. Moderate quality: The authors have moderate confidence in the estimated impact. The true effect is likely to be close to the estimated effect, but there is a possibility of substantial differences.
3. Low quality: The authors' confidence in the estimated effect is limited. The true effect may be substantially different from the estimated effect.
4. Very low quality: The authors' confidence in the estimated effect is very low. The true effect may be substantially different from the estimated effect.

Factors that can weaken the quality of evidence in research include various aspects that may introduce biases or uncertainties into the findings. Study limitations can arise from flaws in the study design, data collection, or analysis, which may affect the internal validity of the research. For example, inadequate sample size, selection bias, or confounding variables can undermine the study's credibility. Inconsistency in research results can stem from differences in methodologies, populations studied, or other contextual factors, leading to conflicting or inconclusive evidence. Additionally, imprecision may occur when the effect estimates have wide confidence intervals, making it challenging to draw definitive conclusions. Publication bias, on the other hand, occurs when studies with positive or statistically significant results are more likely to be published, while studies with neutral or negative findings may remain unpublished, skewing the overall evidence base.

To overcome these challenges and ensure the robustness of evidence, a systematic and transparent approach to evaluating the quality of evidence is essential. Researchers and experts need to engage in discussions and critical assessments of study methodologies, potential biases, and limitations. By applying standardized criteria, such as the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system, the quality of evidence can be objectively evaluated and categorized as high, moderate, low, or very low. Disagreements or uncertainties can be resolved through consensus-building processes, where the collective expertise and perspectives of researchers contribute to a more comprehensive understanding of the evidence's strengths and weaknesses. This collaborative approach enhances the credibility and reliability of research findings, ultimately aiding decision-making in healthcare and other fields.

3. RESULT AND DISCUSSION

3.1. Result

The literature search yielded 5421 abstracts, which were independently reviewed by the authors. Out of this total, 5401 were excluded due to irrelevant titles and abstracts. A total of 20 articles were reviewed in full for quality assessment. Among them, 14 studies were excluded because they were not original research, PICO criteria were not relevant, or the methods or population were not adequately described. Consequently, six studies were finally included, with four studies focusing on MRI and two studies on transrectal ultrasound with Doppler (Figure 1).

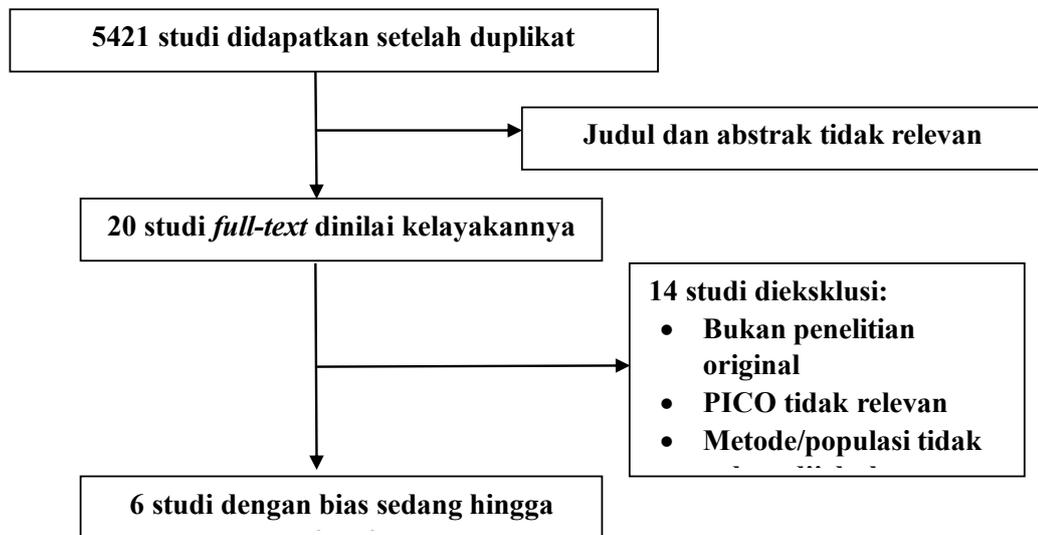


Figure 1. Research Flowchart

3.1.1. Study Characteristics

Study characteristics for the six included studies are shown in Table 2.

Table 2. Accuracy of MRI or ultrasound imaging compared to biopsy for the detection and localization of prostate cancer in patients with suspected cancer without prior biopsy or with prior negative biopsy

| Author/ Year of publication/ Country | Study Design/ Participants | Index Test | Reference test | Result (95% CI) | Quality of Study |
|---|--|-------------------------|-------------------------|--------------------|--|
| Otti et al., 2019 (Otti et al., 2019) UK | Prospective & retrospective Recruitment: 2010-2011 Participants: n=1023 Age: median 66 (mpMRI & biopsy group), | 1,5T, T2WI, DWI, DCE | Transperineal biopsy | Se: 82% Sp: 59% | Medium Methodology sufficiently explained Large sample |

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| | 68 (mpMRI only group) PSA in mpMRI group: median 5.92 PSA in mpMRI & biopsy group: 6,75 Disease prevalence: 53% | | | | |
| Gupta et al., 2020 (Gupta et al., 2020) USA | Prospective Recruitment: consecutive Participants: n=55 Age: Mean 64.34 ± 7.28 PSA: Mean 8.62 ± 5.46 6,75 Disease prevalence: 22/50 | Contrast-enhanced subharmonic transrectal ultrasound | Core systematic biopsy | Se: 80% Sp: 99% | Medium Methodology sufficiently explained Small sample |
| Girometti et al., (Girometti et al., 2012) 2012 Italy | Prospective Recruitment: consecutive with ≥1 previous negative biopsy, 2010-2011 Participants: n=26 Age: median 64 (51-74) PSA: median 6.0 (2.5-9.7) ng/ml Disease prevalence: 5/26 = 19% | 3T, T2W, DWI, DCE-MRI Observer: n = 2 Blinding: yes | ≥8 systematic biopsies Observers: not reported Blinding: not reported | T2W, DWI, DCE-MRI, MRSI Se: 5/5 = 100% (48; 100) Sp: 8/21 = 38% (21; 59) | Low Methodology poorly explained Small sample |
| Ho et al., (Ho et al., 2012) 2012 Malaysia | Prospective Recruitment: no previous biopsy, timeframe not stated Participants: n = 140 Age: not reported PSA: above 4.0 ng/ml | Transrectal ultrasound with Doppler Observer: n = 1 Blinding: yes | Biopsy according to the Vienna nomogram Observer: not reported Blinding: not reported Index and reference tests performed at the same time | Se: 29/30 = 96.7% (83; 99) Sp: 27/110 = 24.5% (18; 33) | Low Methodology poorly explained |

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| | Disease prevalence: 30/140 = 21% | | | | |
| Tamada et al., (Tamada et al., 2011) 2011 Japan | Retrospective Recruitment: 2006-2009 Participants: n=50 Age: median 70 (40-84) PSA: median 6.7 (4.1-9.9) ng/ml Disease prevalence: 35/50 = 70% | 1.5T, T2W, DWI, DCE-MRI Observers: n = 2 Blinding: yes | 12 systematic biopsies Observers: not reported Blinding: not reported | T2W, DWI, DWI, DCE-MRI Se: 29/35 = 83%; (66; 93) Sp: 12/15 = 80%, (52; 96) | Low Population not well described Possible selection bias (high prevalence of cancer) |
| Vilanova et al., (Vilanova et al., 2011) Spain | Retrospective Recruitment: no previous biopsy, 2008-2009 Participants: n=70 Age: median 64 years (43-87) PSA: median 7.4 (4.0-17.2) ng/ml Disease prevalence: 38/70 = 54% | Endorectal 1.5T, T2W, DWI, DCE-MRI, MRSI Observers: n=3 Blinding: yes | 10 systematic biopsies (n = 57) or histopathology after prostatectomy (n = 13) Observers: not reported Blinding: not reported | T2W, DWI, DCE-MRI Se: 30/38 = 79% (63; 90) Sp: 26/32 = 81% (64; 93) T2W, DWI, DCE-MRI, MRSI: Se: 36/38 = 95% (83; 99) Sp: 26/32 = 81% (65; 91) | Low Population not well explained |

According to the assessment with the QUADAS instrument combined with more specific criteria, four of the six studies were assessed as having a high risk of bias and the remaining two as having a moderate risk of bias (Table 1). The main reason for the high risk of bias was due to the study population or inadequately described parts of the methodology (Table 2).

3.2. Discussion

This systematic review supports the notion that the use of imaging for prostate cancer diagnosis remains limited and emphasizes the need for high-quality prospective trials in the field of prostate cancer detection. Overall, only six publications were considered relevant, all of which were deemed to have a moderate to high risk of bias. Methodological limitations in image evaluation and a lack of standardization with reference methods are common underlying reasons for this. Nevertheless, there is an increasing recommendation for prostate MRI examination before biopsy in various national and international guidelines, and the rapidly increasing number of prostate MRI examinations is expected in the coming years. (Cosma et al., 2019; Drost et al., 2019; Haider et al., 2016; Williams et al., 2022). The growing number of examinations conducted requires a standardized evidence-based diagnostic workflow to streamline patient management (Oerther et al., 2022).

A challenge in prostate cancer patients is that the current reference test, transrectal ultrasound-guided biopsy, only represents a small portion of the prostate and does not

provide information about the extent of tumors within the prostate. The detection rate of cancer or the number of biopsies required to reach a diagnosis is another endpoint that can be used, especially when evaluating the utility of new imaging-directed biopsy techniques, such as image fusion of ultrasound and MRI or robot-assisted MRI-guided biopsies.

One of the main strengths of this study is its rigorous methodology, conducted in accordance with international standards for systematic reviews (PRISMA). The included studies were assessed using a validated instrument (QUADAS). However, this study is considered to have a high risk of bias as it did not include all relevant aspects related to costs and outcomes. The lack of studies addressing cost-related aspects suggests a need for more knowledge in this area. To determine the cost-effectiveness of new imaging techniques, increased costs should be weighed not only against diagnostic efficacy in terms of sensitivity and specificity but also in relation to the value of achieving a non-invasive diagnosis and the potential ability to avoid costs associated with intervention complications, such as multiple biopsies. In order to ascertain the value of a technology for patients, in terms of quality of life and survival, it is also necessary to establish the clinical value of improved diagnostic accuracy.

4. CONCLUSION

In conclusion, this systematic review highlights the need for further high-quality prospective trials in the field of prostate cancer detection using imaging modalities. The limited number of relevant publications and the moderate to high risk of bias in the included studies indicate the importance of conducting rigorous research to establish the diagnostic accuracy of imaging techniques for prostate cancer. The challenges in diagnosing prostate cancer call for the development and evaluation of new imaging approaches, such as USG-MRI fusion imaging or robotic-assisted MRI-guided biopsies. While there is a growing recommendation for prostate MRI before biopsy in various national and international guidelines, the increasing number of MRI examinations necessitates a standardized evidence-based diagnostic workflow to streamline patient management.

Additionally, it is crucial to consider aspects beyond diagnostic accuracy, such as cost-effectiveness and potential benefits in terms of non-invasive diagnosis and avoiding the expenses associated with multiple biopsies. Ultimately, determining the clinical value of improving diagnostic accuracy requires an assessment of the impact on patient quality of life and survival. Overall, to enhance the diagnostic capabilities for prostate cancer, further research is needed to overcome the limitations observed in the current studies and to ensure that the use of imaging technology is appropriately targeted and evidence-based, thereby leading to improved patient outcomes.

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