Review | Pathology

Artificial Intelligence Approach in Prostate Cancer Diagnosis: Bibliometric Analysis

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Abstract

Background. Prostate cancer is one of the most common male malignancies worldwide that ranks second in cancer-related mortality. Artificial intelligence can reduce subjectivity and improve the efficiency of prostate cancer diagnosis using fewer resources as compared to standard diagnostic scheme.

This review aims to highlight the main concepts of prostate cancer diagnosis and artificial intelligence application and to determine achievements, current trends, and potential research directions in this field, using bibliometric analysis.

Materials and Methods. The studies on the application of artificial intelligence in the morphological diagnosis of prostate cancer for the past 35 years were searched for in the Scopus database using "artificial intelligence" and "prostate cancer" keywords. The selected studies were systematized using Scopus bibliometric tools and the VOSviewer software.

Results. The number of publications in this research field has drastically increased since 2016, with most research carried out in the United States, Canada, and the United Kingdom. They can be divided into three thematic clusters and three qualitative stages in the development of this research field in timeline aspect.

Conclusions. Artificial intelligence algorithms are now being actively developed, playing a huge role in the diagnosis of prostate cancer. Further development and improvement of artificial intelligence algorithms have the potential to automate and standardize the diagnosis of prostate cancer.

Keywords

Artificial Intelligence; Prostate Cancer; Gleason Score; Bibliometric Analysis

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Introduction

Prostate cancer (PCa) is one of the most common male malignancies worldwide and ranks second in cancer-related mortality [1].

Its genetic instability complicates both diagnosis and treatment. PCa may be hereditary, but in most cases, it develops through somatic mutations [2]. Late onset of PCa may indicate the accumulation of genetic changes long before clinical manifestations appeared [3]. Studies show that due to genetic or epigenetic changes, infection-induced inflammation may be associated with PCa development [4–6].

The introduction of prostate-specific antigen (PSA) improved PCa diagnosis. Prior to the widespread introduction of PSA in the late 1980s, more than 50% of patients had advanced PCa [7]. To date, with the widespread use of this test, other problems arise such as overdiagnosis and treatment, as well as PCa recurrence in more than 20% of patients after radical prostatectomy despite early intervention [8].

Artificial intelligence (AI) can reduce subjectivity and improve the efficiency of PCa diagnosis using fewer resources as compared to currently used standard diagnostic scheme. For example, in terms of the socioeconomic burden in the United States, the ten-year cost of treating patients at low and high risk of PCa is estimated at $45,957 and $188,928, respectively. Therefore, greater involvement of AI algorithms can help alleviate this burden [9].

This review aims to highlight the main concepts of PCa diagnosis and AI application and to determine achievements, current trends, and potential research directions in this field, using bibliometric analysis.

Materials and Methods

The studies on AI application in the morphological diagnosis of PCa for the past 35 years were searched for in the Scopus database years using "artificial intelligence" and "prostate cancer" keywords. The selected studies were systematized based on the year of publication, research type, subject area, and the country where the study was published, using Scopus bibliometric tools and the VOSviewer software (Leiden University, https://www.vosviewer.com/).

Results and Discussion

Diagnosis of Prostate Cancer

Determination of PSA levels is considered one of the most common laboratory tests for diagnosing PCa. PSA levels above 4 ng/ml are considered pathological for early detection, but approximately 20% of PCa patients do not reach this threshold [9].

Another standard method of diagnosing PCa is a transrectal 12-core ultrasound-guided prostate biopsy, which is most often recommended in elevated PSA levels or an abnormal digital rectal examination [10].

In recent years, the role of magnetic resonance imaging (MRI) in the diagnosis, selection of treatment strategy, and management of PCa patients has steadily grown [11]. Moreover, the use of AI algorithms has already taken its place in radiological diagnosis and creates opportunities for large-scale screening for PCa with no additional burden on radiologists [12].

In 1966, Donald Gleason developed a histological classification for assessing the stage, clinical risk, and prognosis of PCa – the Gleason scale, which has been modified several times [13]. To standardize PCa diagnosis, the International Society of Urological Pathology created a novel reference image database known as the Pathology Imagebase, which in some cases helps reach a consensus among pathologists around the world [14].

When a pathologist makes conclusion based on a subjective interpretation of a set of rules, which are still vague, the problem of the standardization of morphological diagnosis usually arises. Due to the Gleason scoring system, which contains numerous architectural descriptors and no other indicators, such as nuclear atypia, i.e., being a monoparametric system, to determine PCa aggressiveness is easier as in case of other tumors [15].

Based on the Gleason score, patients with aggressive PCa are divided into three groups: low risk (Group 1), average risk (Group 2 and 3), and high risk (Group 4 and 5). Group 1 is denoted as GS6, Group 2 as GS7 (3+4), Group 3 as GS7 (4+3), Group 4 as GS8, and Group 5 as GS9-10, respectively [9].

Different histological tissue patterns help attribute the histological image of PCa to one of five patterns, where 1 is well-differentiated pattern and 5 is poorly differentiated one (Table 1). The final Gleason score is reported as the sum of the two most predominant patterns present in the histological specimen. In modern clinical practice, the lowest Gleason score is assigned to GS6 (3+3) [16].

Table 1. Histological patterns of the Gleason score.

Pattern	Description
1	Small well-differentiated cells
2	Cells are at a greater distance from each other due to increased stroma
3	Well-formed separated glands variable in size
4	Fused glands, cribriform and glomeruloid structures, poorly formed glands
5	Poorly differentiated individual cells, solid nests, cords, and linear arrays

The Gleason scoring system helps make the final diagnosis of PCa being the basis for selecting treatment strategy. However, the manual and qualitative nature of analysis limits the speed and throughput of images, as well as reduces the accuracy due to significant differences in the assessment between pathologists [17].

The task of automating and standardizing Gleason grading is currently of great interest. This is due to the low reproducibility and significant subjectivity of the results [18].

In addition, both the global Covid-19 pandemic and the war in Ukraine have caused an even more significant shortage of pathologists in remote areas, which can be at least partially compensated by remote work and maximum automation of the diagnostic process.

Artificial Intelligence Application in Morphological Diagnosis of Prostate Cancer

In recent years, the use of AI to solve the problem of subjectivity in pathomorphological diagnosis has become widespread. Many software algorithms for image analysis are developed or tested.

Källén *et al.* developed the first learning-based approach to Gleason score prediction; however, it was limited to tissue samples with homogeneous Gleason grading [19]. Zhou *et al.* achieved an overall accuracy of 75% in differentiating GS7 (3+4) from GS7 (4+3) on The Cancer Genome Atlas [20]. Using the same image samples, del Toro *et al.* developed a binary classifier of low and medium ($\leq$7) and high ($\geq$8) Gleason score images [21].

Many machine learning algorithms are currently used to analyze histopathological images: decision tree, boosting algorithm, k-nearest neighbors (KNN) algorithm, support-vector machines, deep learning, Bayesian structural time series model, etc. [17, 22–25].

Most of these algorithms require whole slide tissue images for diagnostic software, and, therefore, applying this algorithm is limited to this criterion [26–31].

Diagnostic algorithms, which are widely developed and tested, significantly depend on the segmentation of tumor tissue into epithelial, stromal, and luminal components. For example, for differentiating benign prostate pathology from malignant one, one of the programs used the approach of comparing the ratio of tissue components [32].

Algorithm for the diagnosis of PCa proposed by Gertych *et al.* focused on quantitative assessment of the epithelial component of benign and malignant tumors [33]. Singh M *et al.* used it to evaluate glandular structural

Table 2. Examples of studies highlighting timeline of artificial intelligence approach
in prostate cancer diagnosis.

Year	Researchers	Key Findings	Ref
2015	Gertych et al.	Algorithm focused on quantitative assessment of the epithelial component	[33]
2016	Källén et al.	First learning-based approach	[19]
2017	Zhou et al.	Accuracy of 75% in differentiating GS7 (3+4) from GS7 (4+3)	[20]
2017	del Toro et al.	Algorithm trained to discriminate low and medium versus high Gleason score images	[21]
2017	Singh M et al.	Glandular structural features and patterns	[34]
2018	Nir et al.	Accuracy of 92% in detecting PCa and accuracy of 79% in its Gleason grading	[26]
2020	Nagpal et al.	Developing a deep learning algorithm; the agreement with experts did not exceed 70%	[27]

features and patterns for morphological classification of PCa [34].

Prior to automated image analysis, fragments with specific histological patterns, evaluated by an experienced pathologist, should be created. During the study, the image is divided into tiles and classified as a stroma, benign element, malignant low- or highly differentiated element [33].

In some cancers, automated qualitative and quantitative assessment of tissue components helps predict treatment outcomes: e.g., nuclear and stromal features, detected by AI algorithms when analyzing histological images, correlate with the prognosis in breast cancer patients [35]; detection of tumor infiltrating lymphocytes applying deep learning models allows for immune spatial analysis [36].

As in PCa diagnosis the main attention is paid to automatic grading the sample on the Gleason score and solving the problem of subjectivity, it is too early to talk about predictions using machine learning [37–43].

Nir *et al.* used multiple machine learning techniques combined with deep learning and demonstrated 92% of accuracy in detecting PCa and 79% of accuracy in its Gleason classification. However, there was moderately low consistency of results with pathological conclusions, probably, due to significant subjectivity in the assessment by different experts [26].

In the most extensive study to date, Nagpal *et al.* developed their deep learning algorithm and tested its effectiveness with 29 certified pathologists. Nevertheless, the agreement with experts did not exceed 70% [44].

Thus, AI algorithms are now being actively developed, playing a huge role in the diagnosis of PCa (Table 2). Even though the agreement between automated analysis results and pathological conclusions does not exceed 70%, further development and improvement of AI algorithms have the potential to automate and standardize the diagnosis of PCa.

Bibliometric Analysis of Scientific Literature

Between 1987 and 2022, the Scopus database included 670 publications with the keywords "artificial intelligence" and "prostate cancer". According to the results of bibliometric analysis, the number of publications in this research field has drastically increased since 2016, which indicates the relevance and prospects of AI application in PCa diagnosis, and publications for 2023 only confirm this (Fig. 1).

The first periodicals to appear in this research field were "Lecture Notes in Computer Science" (including sub-series "Lecture Notes in Artificial Intelligence" and "Lecture Notes in Bioinformatics"; https://www.springer.com/gp/computer-science/lncs) and "BJU International" (https://www.bjuinternational.com/), and in recent years, "Cancers" (https://www.mdpi.com/journal/cancers) and "Frontiers In Oncology" (https://www.frontiersin.org/journals/oncology) have become more popular.

The world's most productive and highly cited researcher in AI application for diagnosing PCa is Anant Madabhushi (Case Western Reserve University, Cleveland, U.S.), who has 20 publications in this research field in the Scopus database and the h-index of 58. Researchers from
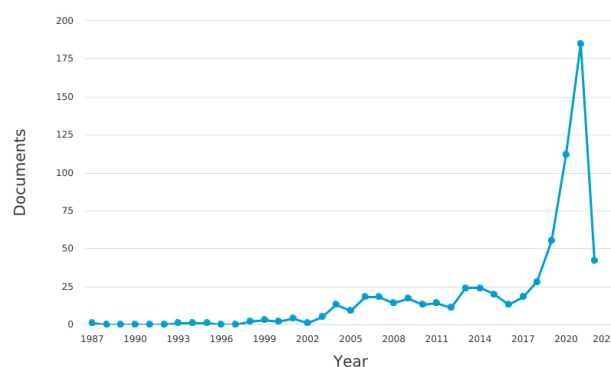

Figure 1. Timeline of publications in the research field using the tools of bibliometric analysis of the Scopus database (the graph represents data as of March 23, 2022; the decrease in the number of papers published in 2023 is due to continuation of publishing articles).
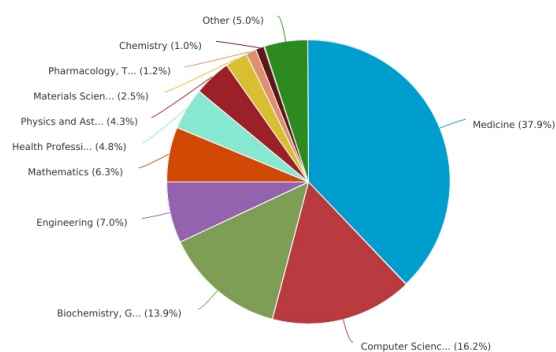

Figure 2. Distribution of publications in the research field by subject areas using the tools of bibliometric analysis of the Scopus database.
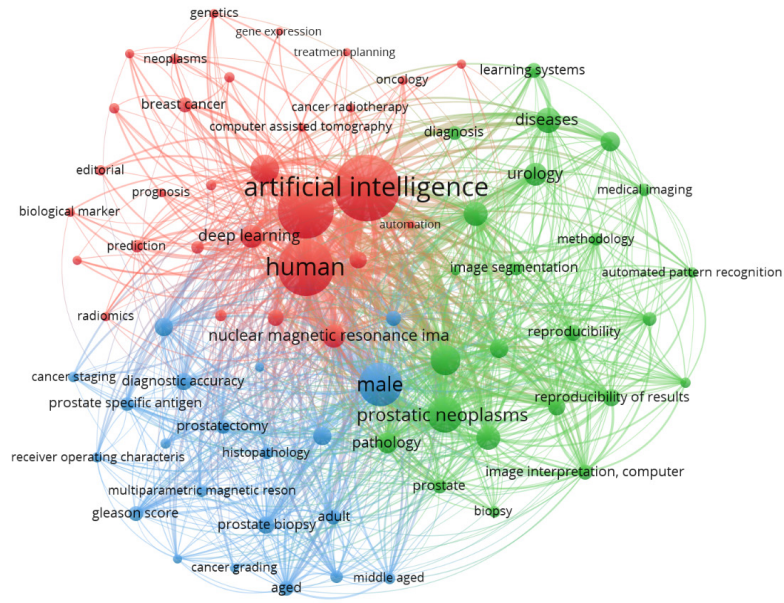
Figure 3. Thematic clusters of the research field (according to VOSviewer bibliometric analysis).
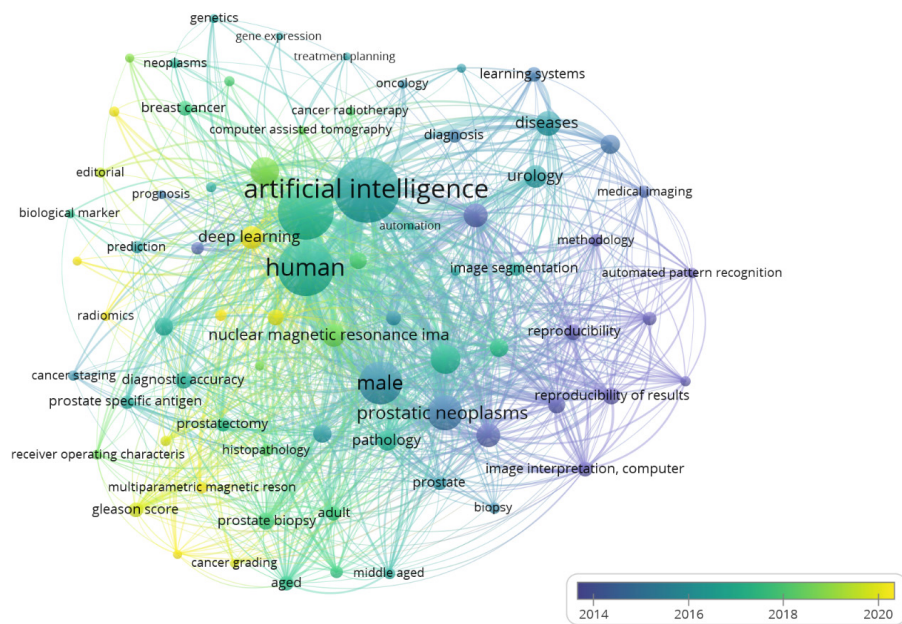

Figure 4. Chronological development of the analyzed research field (according to VOSviewer bibliometric analysis).

the United States, Canada, and the United Kingdom are dominating in the field, while the National Cancer Institute and the National Institutes of Health (United States) are the most prominent sponsors.

The publications analyzed can be divided into 21 subject areas, the vast majority of which relate to medicine, computer science, biochemistry, genetics, and molecular biology (Fig. 2).

Using VOSviewer bibliometric network visualization tools, the articles selected can be divided into three thematic

clusters: AI, imaging techniques, PCa histology (Fig. 3). In addition, there are three chronological stages: research using computed tomography and MRI, application of AI to automate imaging result analysis, application of AI in the pathomorphological diagnosis (Fig. 4).

Limitations

This research includes publications in Scopus database from 1987 to March 23, 2022 only.

Conclusions

Today, the use of AI has become widespread in automating, standardizing, and providing cost-effective pathomorphological diagnosis. Many software algorithms for image analysis are developed or tested.

A bibliometric analysis of publications in the Scopus database for 1987-2022 using the keywords "artificial intelligence" and "prostate cancer" showed that the number of papers in this research field had increased significantly over the past seven years, with most research carried out in the United States, Canada, and the United Kingdom. These publications can be divided into 21 subject areas, the vast majority of which relate to medicine, computer science, biochemistry, genetics, and molecular biology.

Applying the VOSviewer software allowed us to identify three thematic clusters (AI, imaging techniques, PCa histology) and three qualitative chronological stages in the development of this research field (research using computed tomography and MRI, application of AI to automate imaging result analysis, application of AI in the pathomorphological diagnosis).

Thus, AI algorithms are now being actively developed and playing a huge role in the diagnosis of PCa. Even though the agreement between automated analysis results and pathological conclusions does not exceed 70%, further development and improvement of AI algorithms have the potential to automate and standardize PCa diagnosis.

Ethical Statement

This study does not include any human participants and/or animals.

Conflict of Interest

The authors declare that no conflicts exist.

Financial Disclosure

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