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Review Article

THE ROLE OF MAGNETIC RESONANCE SPECTROSCOPY FOR PROSTATE CANCER DIAGNOSIS

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ABSTRACT

Prostate cancer (PC) is the most common malignancy among men and is the fifth leading cause of cancer-related death in men worldwide. The present study aims to systematically review the ability of magnetic resonance spectroscopy (MRS) to differentiate between benign and malignant prostate lesions. According to the 06-PRISMA guideline, we searched in five English databases, including Scopus, PubMed, Web of Science, EMBASE, and Google Scholar without time limitation for publications related to the role of magnetic resonance spectroscopy for prostate cancer diagnosis. The searched words and terms were: "prostate cancer", "prostatitis", "magnetic resonance spectroscopy", "benign prostate hyperplasia", "malignant prostate hyperplasia", "comparison". Totally 1927 papers were identified by database searching. Out of these papers, 261 papers were discarded because of duplication. Of the remaining 1666 papers, 1604 papers were discarded because of the inadequate information and the ones in which the abstract was submitted in congresses as preceding papers, conferences, and editorials without full text. Out of the remaining 62 papers which were studied for eligibility, 52 papers were removed for a number of reasons including inconsistency between methods with results, incorrect interpretation of the results, poor methodology, etc. Finally, 10 papers were included in this present study. In general, based on the results of the review of articles, MRS has optimal sensitivity, specificity and accuracy in diagnosing prostate cancer and differentiating it from benign prostate hyperplasia in comparison with other diagnostic and pathological methods. Due to the small number of studies related to the sensitivity and specificity of MRS, further checking was not possible to confirm these results. Therefore, further studies in this regard are recommended.

Keywords: Prostate cancer, Prostatitis, Magnetic resonance, Hyperplasia, Malignant prostate

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INTRODUCTION

Prostate cancer (PC) is the most common malignancy among men and is the fifth leading cause of cancer-related death in men worldwide, and causing 358,989 deaths (3.8% of all deaths caused by cancer in men) in 2018 [1]. The epidemiology of PC is complex and is a subject of much study and debate. The clinical heterogeneity of prostate cancer may be a hallmark of this intricacy, the severity of the disease varies from person to person; some men will have advanced disease and, notwithstanding primary treatment will experience disease progression, while others have prostate cancer and live with it with the least difficulty [2, 3]. In addition, prostate cancer remains the most common non-cutaneous malignancy and second leading cause of cancer death in men, so changes in the diagnosis and management of prostate cancer can have substantial public health consequences [4, 5]. The incidence rate of PC varies through the areas and societies. In 2018, 1,276,106 new cases of prostate cancer were recorded worldwide, demonstrating 7.1% of all cancers in men [6]. According to statistics released in 2018, the highest mortality rates were in Central America, Australia-New Zealand and Western Europe, respectively [7]. Asia and North Africa also had the lowest mortality rates [7].

Age is known as the most important risk factor for PC, the disease rarely affects young men. According to the Prostate Cancer Institute, only 1 in 10,000 men under the age of 40 gets the disease. This statistic reaches 1 in 38 men aged 40 to 59 y and 1 man out of 14 men aged 60 to 69 y. Most cases are diagnosed in men over 65 y [8, 9]. Ethnicity is also considered as another risk factor of PC. The incidence and mortality rate among white men is lower than among African and American men. However, the Asian race has always had the lowest incidence of PC, which can be due to low genetic susceptibility and multiple environmental factors [10, 11].

Family history of PC is well-established risk factor for PC risk in men so that if one of the first-degree relatives is infected, the probability of contracting this disease is doubled [12]. Other risk factors for PC include diet (rich in red skin and saturated fats and poor in fruits and vegetables), Cigarette smoking, sedentary lifestyle, overweight, Alcohol consumption and sexually transmitted infections [13-19].

PC often has no specific symptoms in the early stages. But as the disease progresses, the following symptoms appear in the patient: Frequent urination, especially during nighttime sleep, decreased urinary flow pressure or difficulty emptying the bladder, the presence of blood in the urine or semen, weakness and disorder of the urinary system. Non-cancerous prostate complications such as benign prostatic hyperplasia (BPH) and prostatitis can have the same clinical symptoms [20].

The main ways to diagnose PC include measuring the concentration of prostate-specific antigen in the serum (PSA), rectal examination, and Tran's rectal Ultrasonography biopsy [21, 22]. PSA blood tests are the most common method of early detection and diagnosis of PC; but because the specificity is low, it is not reliable [23]. In addition, rectal examination only allows the posterior surface of the prostate to be touched, and its sensitivity and specificity are not suitable for monitoring treatment [24]. If the results of PSA levels and rectal examination are suspicious, biopsy is used as an invasive and complementary method for histological examination of the prostate. Because biopsy is associated with bleeding and an increased risk of infection, it should be replaced with a non-invasive, high-sensitivity, non-invasive procedure [25]. Magnetic resonance spectroscopy (MRI) as a non-invasive imaging method without ionizing radiation, is capable of imaging PC, providing anatomical and physiological information for diagnosis, staging and treatment design [26].

Diffusion-weighted imaging (DWI) and T2-weighted imaging techniques, despite their ability to detect large tumors, have limitations in detecting small tumors, In addition, dynamic contrast-enhanced MRI is an invasive procedure [27], While magnetic resonance spectroscopy as a functional method allows non-invasive study by examining the levels of prostate metabolites including citrate, polyamine, choline, creatine and phosphocreatine content and accordingly, it provides the ability to distinguish the PC and differentiate it from other benign lesions [28]. Due to its non-invasiveness, sensitivity and specificity of magnetic resonance spectroscopy and its ability to detect small tumors in the early stages, it is considered as a suitable method in diagnosing this type of disease [29]. Therefore, the present study aims to systematically review the ability of magnetic resonance spectroscopy (MRS) to differentiate between benign and malignant prostate lesions.

METHODS

Study design

According to the 06-PRISMA guideline, we searched in five English databases, including Scopus, PubMed, Web of Science, EMBASE, and Google Scholar, without time limitation for publications related to the role of magnetic resonance spectroscopy for prostate cancer diagnosis. The searched words and terms were: "prostate cancer", "prostatitis", "magnetic resonance spectroscopy", "benign prostate hyperplasia", "malignant prostate hyperplasia", "comparison".

Studies selection

Initially, the studies were imported to the EndNote X9 software (Thomson Reuters, New York, NY, USA) and duplicate articles were removed. Next, three independent authors surveyed the title and abstract of the articles and the related papers were included for more examination.

Data extraction

As exclusion criteria, the papers with inadequate data, those are just an abstract of the article, mismatch between study method and results, and studies with unreasonable results and interpretation were excluded from the review. The extracted data in each selected paper was include type of study, control group, sample size(case/control), type of disease, measurement scale, dosage, intervention process, results, year, reference.

RESULTS AND DISCUSSION

Totally 1927 papers were identified by database searching. Out of these papers, 261 papers were discarded because of duplication. Of the remaining 1666 papers, 1604 papers were discarded because of the inadequate information and the ones in which the abstract was submitted in congresses as preceding papers, conferences, and editorials without full text. Out of the remaining 62 papers which were studied for eligibility, 52papers were removed for a number of reasons, including inconsistency between methods with results, incorrect interpretation of the results, poor methodology, etc. Finally, 10papers were included in this present study (fig. 1). The results of a review of studies on the ability to differentiate PC from benign prostatic lesions, including prostatitis and benign prostatic hyperplasia, are shown in table 1.

Table 1: Results of pathological examinations and MRS

Authors	Sample size	PC/BPH	Coil type	Magnetic field intensity	Biopsy results (Gleason score)	PSA test	Protocol type	MRS results	Ref
Cornel *et al.*	12	4 (PC)/7 (BPH)	Body coil	1.5 T	-	-	PRESS	Ability to differentiate PC from BPH based on significantly higher citrate in BPH and choline in PC	[30]
Kurhanevice *t al.*	33	14(PC)/12 (BPH)	Endorectal surface coil	1.5 T	4-8	2-38 ng/ml	STEAM	Significantly higher ratio of citrate to total of choline and creatine in BPH	[31]
Kim *et al.*	20	6(PC)/7 (BPH)	Saddle type external-body surface coil	1.5 T	7<	176.53-68.64 ng/ml	STEAM	Significantly higher ratio of citrate to total of choline and creatine and also higher ratio of citrate to lipid in BPH	[32]
Segura *et al.*	20	10(PC)/10 (BPH)	Body coil	1.5 T	7 in 5 patients/ 7<in others	231.6±178.0	STEAM	Higher levels of myoinositol in PC than inflammation/The ratio of creatine to myoinositol and citrate to choline is higher than 1 in BPH and lower than 1 in PC	[33]
Yue *et al.*	14	3(PC)/3 (BPH)	Body coil	1.5 T	-	-	2D PRESS	Decreased citrate and polyamine and increased choline in PC compared to BPH	[34]
Giskeødegård *et al.*	50	29(PC)/21 (BPH)	Body coil	3 T	6-10	11.6 (P)Ca1.2) (BPH	3D CSI	Higher choline levels and amino acid metabolism in PC compared to BPH	[35]
Meier-Schroers *et al.*	85	44(PC)/21 (chronic prostatitis)	Body coil	3 T	7<	8.6±1.1 ng/ml	STEAM	Higher citrate to choline ratio in chronic prostatitis patients	[36]
Zhang *et al.*	43	8 (PC)/35 (prostatitis)	Body coil	1.5 T	6	12.9 ng/ml	3D CSI	Higher choline levels and reduced citrate/Higher ratio of choline and creatine to citrate in PC than prostatitis	[37]
Zhang *et al.*	127	9(PC)/118 (BPH)	Body coil	3 T	2-7/ 7<in 67% of patients	10.87±4.80ng/ml	3D CSI	There is no significant difference between the amount of metabolites between the two diseases	[38]
Mazaheri *et al.*	67	34(PC)/33 (BPH)	Endorectal coil	3 T	6-9	0.1–65.8 (ng/ml)	3D CSI	Ability to differentiate PC from BPH based on significantly higher citrate in BPH and choline in PC	[39]

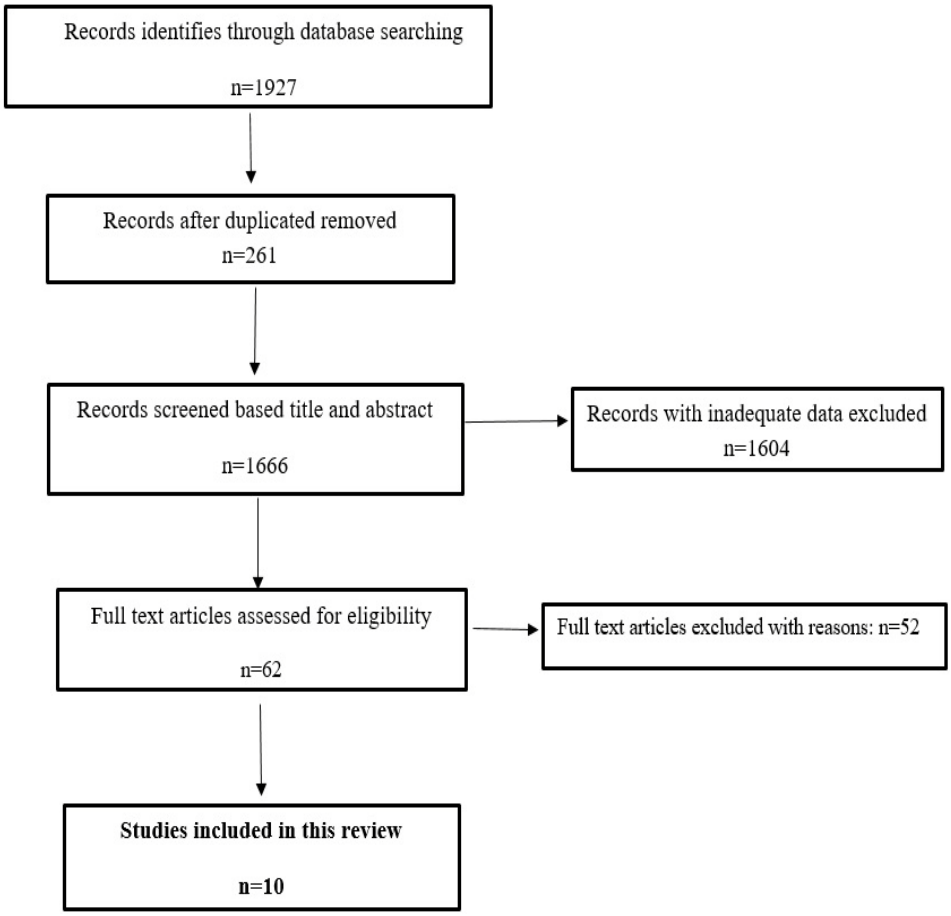

Fig. 1: Flowchart describing the study design process

MRS imaging is a non-invasive imaging technique that is used to study metabolic changes in the brain area as well as metabolic changes in other organs such as the prostate [40]. In this imaging method, various metabolic information can be obtained simultaneously and, unlike mass spectroscopy or other common methods, there is no need to isolate. Also, MRS has the ability to detect the intensification spectrum of tissue chemical compounds, which reveals information related to chemical composition as well as metabolic information of tissues [41].

Prostate MRS can be used to determine changes in signal intensity from citrate metabolites. Citrate is one of the most important metabolites produced in the mitochondria of living cells in the tricarboxylic acid cycle; Intracellular concentrations of citrate are very low, but detected citrate can indicate prostate health [28].

In TE=120=MS and in a 1.5 Tesla magnetic field in a 1.5 Tesla magnetic field, the spectrum from a healthy prostate emits a strong signal from the citrate shows; which is usually higher than the choline signal [42]. But the Cho/Citratio will be various in different areas of the prostate so the highest value of this ratio will be in the sides of a healthy prostate and this ratio will be the opposite in the urethra. A high choline signal and a weak citrate signal in prostate tissue may indicate PC, but spatial non-uniformity should also be considered. Researches also shows the effect of BPH on this signal ratio. In general, the method of detecting tumors is based on increasing the ratio of total choline and creatine to citrate [42].

With respect to the sensitivity, specificity, and accuracy of MRS in diagnosing and differentiating benign and malignant prostate masses various investigations have been done [43]. Previous studies demonstrated that the mean sensitivity, specificity, and accuracy of MRS in the diagnosis of PC and its differentiation from benign lesions was estimated at 74.52 and 74.82, and 77.74%, respectively. Todays, the conventional methods for PC diagnosis have some limitations in use; for example, a rectal examination can only detect about 55% of all cancers that are later detected by biopsy. In addition, cancers detected by this method in half of the cases are in the advanced stages of the disease. Using PSA test and considering cut-off 4 ng/ml as a sign of PC, there is a possibility that a quarter of cancers will not be diagnosed [43].

Previously Hricak *et al.* (1994) demonstrated that MRI using endorectal coils as a primary diagnostic tool is not appropriate for the diagnosis of prostate cancer due to its low specificity and positive predictive value (PPV) [44, 45]; while MRI specificity for staging in stages B and C is 77% and is very sensitive to detect tumors that extend beyond the prostate and seminal vesicles [46].

At present, the pathological and tissue biopsies test with the sensitivity of 50% and a specificity of 82% remain the gold standard methods for PC diagnosis [47]. However, since these methods have dangerous complications such as the risk of infection, bleeding, allergies, therefore, the need for an accurate and non-invasive method to diagnose prostate cancer and improve the ability to identify a group of treatable patients is strongly felt [47, 48].

According to table 2, the present study aimed to examine the uniformity of the basic information of all studies, including PSA and Gleason scoring, which may affect the evaluation of results. In a number of studies, voxel identified by biopsy sites have been identified; However, biopsy is limited due to the multifocal nature of PC and its non-uniform nature in the diagnosis, location and grading of all cancers.

In the study conducted by Kristen *et al.* [49] on the magnetic resonance imaging and the total choline and creatine to citrate ratio; the findings revealed that in the diagnosis of cancer with Gleason grade 3+3, MRS tumor imaging, has a sensitivity of 44.4% and in cancer with a grade of more than 8 with has a sensitivity of 89.5%.

Therefore, a high proportion of tumors with a Gleason score of 6 and <6 do not show abnormal metabolite ratios in the voxel. This may be due to the small size of the tumors, which allow volume averaging with noncancerous tissue. In addition, low-grade tumors (<6) may not be detected due to slow changes in citrate and choline levels [49, 50].

In total, two studies have examined the ability of PC to differentiate from prostatitis, among which the study of Zhang *et al.* [38] Showed a higher amount of choline and decrease in citrate in PC than prostatitis; also a higher total choline and creatine to citrate ratio in prostatitis compared to PC; This study is inconsistent with the results of other studies on the higher total choline and creatine to citrate ratio in cancer [38]. While the study of Meier *et al.* revealed that the citrate to choline ratio was higher in prostatitis than PC patients [36].

The general review of all these studies showed that choline and citrate are the most important diagnostic markers for PC and its differentiation from BPH; All studies showed a significant increase in choline and a decrease in citrate in PC compared to BPH. In addition to choline and citrate in the study of Kim *et al.*, [32] higher lipid levels and reduced citrate to lipid ratio were seen in PC. Segura *et al.* survey showed a decrease in myoinositol levels and a higher ratio of creatine to myoinositol and citrate to choline in BPH compared to PC [33]; and Yue *et al.*'s study displayed a decrease in polyamine in PC cases compared to BPH [34].

CONCLUSION

In general, based on the results of the review of articles, MRS has optimal sensitivity, specificity and accuracy in diagnosing prostate cancer and differentiating it from benign prostate hyperplasia in comparison with other diagnostic and pathological methods. Due to the small number of studies related to the sensitivity and specificity of MRS, further checking was not possible to confirm these results. Therefore, further studies in this regard are recommended.

ETHICAL STATEMENT

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

All data generated or analyzed during this study are included in this published article.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The authors have no conflicts of interest, financial or otherwise.

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