# Magnetic resonance spectroscopy-based prostate cancer metabolism (MRS)

**Dr Ashok Sharma[1], Dr Sumit Ghosh[2], Dr Parnita[3], Dr Ayushman[4]**

[1]Professor, Department of Radiodiagnosis and Imaging, Santosh Deemed To Be University, Pratap Vihar Ghaziabad, U.P India

[2,3&4] Senior Resident, Department of Radiodiagnosis and Imaging, Santosh Deemed To Be University, Pratap Vihar Ghaziabad, U.P India

**ABSTRACT**

It's crucial to comprehend PCa's metabolism in order to improve diagnostic methods and look into potential new therapy targets. Techniques for magnetic resonance spectroscopy (MRS) have been found to be helpful in the identification and measurement of metabolites. Citrate (Cit), a crucial molecule of oxidative phosphorylation, and changes in various metabolic pathways in PCa serve to illustrate metabolic phenotype and support tumour growth. Recent studies using dynamic nuclear polarisation (DNP) have shown that PCa has high rates of glycolysis (the Warburg phenomenon). Understanding the aberrant metabolic activity of PCa patients has been made possible by high-throughput metabolic profiling techniques using MRS on a variety of materials, including intact tissues, biofluids such prostatic fluid and seminal fluid, blood plasma/sera, and urine. An in-depth understanding of the metabolic rewiring related to cancer is possible thanks to the improved analytical capacity of these approaches in the identification and quantification of a large number of metabolites. The identification of diagnostic and prognostic biomarkers, as well as the comprehension of the altered metabolic pathways that might be addressed to slow the progression of cancer, are two benefits of metabolomics study. The prospective uses of in vivo 1 H MRS, high-resolution magic angle spinning spectroscopy (HRMAS), and in vitro MRS approaches in understanding the metabolic alterations of PCa and their utility in the therapy of PCa patients are briefly discussed in this review.

**Keywords:** Magnetic resonance spectroscopy (MRS) . In vivo . In vitro MRS. HRMAS. Prostate cancer. Biomarker.

## INTRODUCTION

It is now well acknowledged that understanding cancer metabolism is crucial for comprehending the process of carcinogenesis and creating effective treatment plans. In order to maintain a steady supply of the numerous substrates needed for the manufacture of the membranes, genetic material, and proteins essential for their fast multiplication, cancer cells change their metabolism. In older men around the world, prostate cancer (PCa) is a tumour that is regularly diagnosed (1). The prognosis for PCa differs from patient to patient; in some, the disease is indolent for years while in others, it progresses aggressively and quickly to metastases. However, its increased level has also been documented in a number of other disorders such urinary retention, inflammation, and benign prostatic hyperplasia (BPH) (2). Prostate-specific antigen (PSA) is utilised as a screening biomarker for PCa. The "gold standard" for PCa diagnosis is trans-rectal ultrasonography (TRUS)-guided biopsy; however, this procedure has low specificity because to insufficient sample (3). There is an urgent need for biomarkers with greater accuracy for improved clinical management of PCa patients because the clinical biomarkers currently in use do not have sufficient specificity and sensitivity.

Studies have linked oncogenes, which are key players in the onset and development of PCa, to altered metabolic pathways (4).

Metabolomic research that reveals a deeper understanding of metabolic reprogramming has the potential to identify novel metabolic markers for PCa that could be used for diagnosis, illness evaluation, aggressiveness, therapeutic targets, and treatment resistance (5).

One of the most popular methods for gaining insight into metabolic profiles influenced by various disease conditions and comprehending tissue metabolism is nuclear magnetic resonance (NMR) spectroscopy. The capacity to non-invasively assess tissue biochemical levels from a particular region of interest (ROI) is provided by in vivo MR spectroscopy (MRS). Another technique for metabolic evaluation of intact tissue biopsy samples is ex vivo high-resolution magic angle spinning (HRMAS) MR spectroscopy (6,7). To understand the altered metabolic pathways in PCa, in vitro NMR spectroscopy can be used with a wide range of samples, including tissue extracts and biofluids like blood plasma/sera, urine, prostatic fluids, and seminal plasma (8, 9, 10) Quantitative data on a large number of compounds originating from both catabolic and anabolic processes in the cell are provided by high-throughput metabolomics approaches based on these NMR techniques (11, 12). The changes that show up at the level of gene expression, protein expression, and metabolic abnormalities are all combined in metabolomic analysis (13, 11, 12). The benefits of metabolic profiling have been acknowledged in the identification of therapeutic targets based on altered metabolic pathways, diagnosis, prognosis, and determination of biomarkers of disease aggressiveness (11,12, 14, 15).The potential of in vivo proton (1 H) MRS, in vitro high-resolution (1 H) MRS, and HRMAS in the study of prostate cancer metabolism and its potential role in identifying biomarkers that can be used in various aspects of PCa management, such as diagnosis and therapy, are briefly discussed in this review.

## MRS techniques to study PCa metabolism and altered metabolites

### In vivo MRS techniques

The benefit of in vivo MRS is that it uses a clearly defined ROI to non-invasively identify metabolites. Due to its noninvasive nature, it has important uses in long-term studies for treatment assessments and for assessing the effectiveness of different therapeutic regimens. Researchers have used the in vivo 1 H multi-voxel spectroscopy method known as MR spectroscopy imaging (MRSI) to study the metabolism of the prostate tissue (16). For localised in vivo MRS studies, three orthogonal planes of MR imaging are used to first pinpoint the cancer lesion on the prostate MR picture. These images are then utilised to locate the tumour, localise it, and perform MRS to get in vivo metabolic data. T2-weighted MR images of the prostate from a volunteer and a PCa patient, respective.

### Dynamic nuclear polarization MRS

Dynamic nuclear polarisation (DNP) hyperpolarization has recently been employed to get $^{13}C$ spectra from PCa in vivo. This technique has been found to dramatically increase the sensitivity of in vivo MRS by enhancing nuclear polarisation by more than 10,000-fold. The metabolic fate of an appropriate intravenously administered $^{13}C$-labeled hyperpolarized substrate is subsequently observed using $^{13}C$ MRS. The polarizer,

which must be situated close to the MRS scanner for polarisation and subsequent use of the substrate, is part of the unique setup needed for the procedure. Due to the short half-lives of these polarised substrates, MRS must be completed quickly after injection of the hyperpolarized substrate to prevent considerable polarisation loss. One of the main DNP MRS limitations is this. The most frequently used substrate is $^{13}C$ pyruvate, which is a crucial molecule in the metabolic pathway glycolysis.

**HRMAS NMR spectroscopy**

According to Decelle and Cheng (2014) and Fuss and Cheng (2016), high-resolution magic angle spinning (HRMAS) 1 H MRS has the ability to reveal important metabolic data from ex vivo intact tissue samples. In contrast to in vivo MRS, a large number of metabolites can be detected and measured utilising tissue sample HRMAS. A clinical technique for PCa diagnosis and prognosis is the quantification of the levels of these metabolites since it has been demonstrated to be helpful in understanding the altered metabolism in PCa and identifying cancer metabolic markers. The benefit of HRMAS is that it maintains tissue architecture and allows for the use of the same tissue specimens in later histopathology and molecular research. A number of HRMAS investigations have concentrated on enhancing diagnosis, tracking the effects of treatment, comprehending prognostication, and comparing the biomarkers with data gathered using in vivo MRS. The Gleason score and [(tCho + creatine + spermine)/Cit] assessed by both in vivo and ex vivo MRS were found to have a significant positive connection (17).

**In vitro MR spectroscopy**

The most effective and insightful method for examining cancer metabolism in vitro has been high-resolution NMR spectroscopy-based metabolomics investigations. Its benefits include the ability to analyse a variety of materials, including tissue and cell extracts as well as body fluids such seminal fluid, prostatic fluid, blood, and urine. In addition, using a high magnetic field spectrometer (over 400 MHz) in most experiments has the benefit of high sensitivity as well as excellent resolution. Compared to other MR techniques, this permits the identification of a large number of metabolites and precise calculation of their levels. It also offers a more thorough examination of how changed metabolic pathways affect oncogenesis.

**Altered metabolism in prostate Cancer**

To comprehend the process of cancer growth and to identify fresh treatment targets, the research of prostate cancer metabolism is of major clinical interest (5). The pathways are changed by metabolic rewiring in a way that maintains supply of the biochemicals and components needed for the fast cell division required for PCa development. The MR spectroscopy investigations discussed in the sections above have demonstrated that these techniques can be used to identify and quantify a wide variety of metabolites.

The changes in these metabolic levels are proof that PCa has numerous altered metabolic pathways. The development of new diagnostic techniques and the comprehension of the underlying biochemistry of tumour aggressiveness, which can be utilised to obtain biomarkers of tumour aggressiveness, are both facilitated by knowledge of the metabolic variations between healthy cells and malignant cells. When treating PCa patients appropriately, this knowledge would be helpful. A number of metabolic processes,

including glycolysis, oxidative phosphorylation, amino acid, and lipid metabolism, have been observed to be altered during carcinogenesis, according to the data on altered metabolites utilising various MR approaches as stated above.

## SUMMARY

Several research teams have examined the utility of metabolic indicators in the clinical management of PCa during the past 20 years, including its detection, assessment, and determination of PCa aggressiveness, as well as the role of various MRS techniques in the study of PCa metabolism. Malignant PCa cells were shown to have distinct metabolic characteristics indicated by in vivo MRS, including reduced Cit, polyamine levels, and high levels of compounds containing tCho, which indicate significant proliferative activity.

It has been shown that HRMAS 1 H MRS has the ability to extract useful metabolic data from ex vivo intact tissue samples. Compared to in vivo MRS, more metabolites may be detected and measured utilising tissue sample HRMAS. The identification of anomalies in metabolic pathways associated with tumorigeneses and metastases is facilitated by high-throughput profiling techniques.

Our understanding of altered metabolic pathways in PCa has increased thanks to metabolomics technologies that involve the simultaneous identification and measurement of all the metabolites engaged in biosynthetic and catabolic activities in the cell. The citric acid cycle, oxidative phosphorylation, glycolysis, amino acid metabolism, lipid catabolism, and biosynthesis are the main metabolic pathways that are changed in PCa cells. The investigation produced biomarkers that can be used for PCa clinical care, both diagnostic and prognostic. The investigation of metabolic reprogramming of oncogenesis has enormous potential for the NMR spectroscopy techniques.

## CONCLUSION

However, the majority of PCa studies have only examined biomarkers for diagnosis or an evaluation of aggressiveness. The identification of additional biomarkers for improved diagnostic and prognostic potential as well as dysregulated metabolic pathways in PCa may be aided by an integrated strategy examining different types of samples such as blood plasma, urine, seminal fluid, and prostatic fluid. These decision-making approaches may be useful in a variety of clinical challenges related to PCa care.

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