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Role of Metabolic Imaging in Diagnosis of Primary, Metastatic, and Recurrent Prostate Cancer

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Abstract

Purpose of review: The present review describes the current role of metabolic imaging techniques such as multiparametric MRI (mpMRI), magnetic resonance spectroscopic imaging (MRSI), hyperpolarized MRSI, and positron emission tomography (PET) in the diagnosis of primary prostate cancer, surveillance of low-grade disease, detection of metastases, and evaluation of biochemical recurrence after therapy.

Recent Findings: The natural history of prostate cancer ranges from indolent disease that is optimally monitored by active surveillance, to highly aggressive disease that can be lethal. Current diagnostic methods remain imperfect in noninvasively distinguishing between silent versus aggressive tumors. Hence, there is a high demand for noninvasive imaging techniques that offer insight into biological behavior of prostate cancer cells. Characterization of prostate cancer metabolism is a promising area to provide such insights.

Summary: Metabolic imaging may allow for greater detection and ultimately characterization of tumor based on aggressiveness and spread. Hence, it has the potential to monitor tumor activity, predict prognostic outcomes, and guide individualized therapies.

Keywords

investigational; metabolic networks and pathways; metabolism; metabolomics; precision medicine; prostatic neoplasms; therapies

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Conflicts of interest

None

1. Introduction

Prostate cancer (PCa) is the most common malignancy in European and American men and second most common malignancy in men worldwide (after lung cancer) [1]. It is the second leading cause of cancer death in American men claiming an estimated 31 620 lives out of the 174 650 Americans diagnosed in 2019 [2].

PCa is an asymptomatic tumor with a long latency period. It begins in the second-third decade of life but can only be detected in the fourth-fifth decade [3]. To reduce the incidence of advanced disease and mortality, aggressive screening methods have been adopted, which have had the unintended consequence of overdiagnosis and overtreatment. This can lead to not only treatment associated complications such as incontinence and impotence, but can cause a profound impact on patients' psychological well being, life decisions, and employment [4].

Although multiple diagnostic modalities exist, currently the gold standard for definitive diagnosis of PCa is a prostate biopsy. The decision to perform a biopsy is based on parameters such as serum prostatic- specific antigen (PSA) level, digital rectal examination (DRE), magnetic resonance (MR) imaging, and family history of PCa. Prostate biopsy carries risks such as infection (causing sepsis in rare cases), bleeding, urinary retention, and erectile dysfunction [5]. Prostate biopsy has a significant rate of missed diagnosis or under diagnosis of aggressive disease [6]. Among patients diagnosed with low risk disease, there remain issues of optimal active surveillance schedules and optimal noninvasive monitoring methodologies. For patients who undergo definitive treatments for their PCa, there remain challenges of posttreatment surveillance in that approximately 15–30% of such patients can experience biochemical recurrence within 10 years [7].

An emerging area aimed at reducing the challenges associated with PCa diagnosis and surveillance is metabolic imaging. Metabolic imaging has shown considerable promise in its ability to identify metastatic and aggressive tumors requiring definitive therapy [8,9&&]. Molecular imaging is becoming increasingly important for characterizing sites of malignancy, predicting prognosis and outcome following treatment, and guiding salvage therapies after disease recurrence [10].

2. Relationship Between the Unique Metabolic Profile of Prostate Gland and Metabolic Imaging

2.1 Zinc, Citrate, and Choline

Malignant cells have unique metabolic profiles that distinguish them from the healthy tissue that they originate from. Metabolic imaging refers to a group of molecular imaging methods that exploit these unique metabolic profiles to evaluate different clinical conditions. In order to explore the metabolic processes unique to malignant prostate cells and how they are utilized in imaging, we must first understand the metabolic intricacies of healthy prostate epithelial cells. Unlike most other cells in the body, epithelial cells of the peripheral zone of the normal prostate do not oxidize citrate, a key step in the Krebs cycle catalyzed by the enzyme m-aconitase [11]. Studies show that this is because of the prostate's ability to

accumulate a large amount of zinc (Zn²⁺) in mitochondria where it exerts an inhibitory effect on m-aconitase. This is accomplished by the high concentration of zinc transporter ZIP1 and ultimately leads to accumulation of citrate [12]. However, in malignant prostate cells there are alterations to zinc transporter ZIP1 that decrease the amount of intracellular zinc and allow for oxidation of citrate and utilization of Krebs cycle. This not only increases the energy available for enhanced cell proliferation but also allows for avoidance of apoptotic checkpoints [13]. Prostatic cancer cells also exhibit abnormal choline phospholipid metabolism causing increased choline levels. Choline is necessary for synthesis of phospholipids used in the cell membrane. Therefore, increased choline levels are because of increased synthesis of new cell membranes. Increased choline levels may also be because of its role in epigenetic modification of housekeeping enzymes involved in attenuating carcinogenesis [14]. Choline is oxidized to betain, which is used to transfer a methyl group to homocysteine, ultimately leading to the synthesis of sadenosylmethionine (SAM). Glutathion S- transferase 1 is an enzymes involved in detoxification of reactive chemical species responsible for development of malignancy, however it is hypermethylated via SAM in over 90% of PCA cases [15]. Hence, choline may influence PCA carcinogenesis via its role as a methyl group donor. Magnetic resonance spectroscopy imaging (MRSI) can measure the decreased citrate and increased choline levels in malignant cells and can aid in diagnosis, staging, and surveillance of PCA.

2.2 Warburg Effect

Most solid tumors undergo a shift from oxidative phosphorylation to aerobic glycolysis, otherwise known as the Warburg effect. This causes a massive increase in rate of glucose uptake in order to satisfy the increased growth requirements [16]. Normally, the lack of citrate oxidation causes healthy prostate cells to elude oxidative phosphorylation. Early on, PCA cells do not exhibit the Warburg effect and instead utilize lipids and other energetic molecules for energy production. Lack of glucose uptake prevents visualization of cells via 18F-deoxyglucose positron emission tomography (FDG-PET); hence, other radiotracers such as 11C-choline, 18F-fluorocholine, and 11C-acetate are used. Acetate and choline are lipid precursors and thus take advantage of the fact that PCA cells upregulate de novo lipid synthesis and activity of lipogenic enzymes [17].

Prostate cancer cells eventually switch to enhanced aerobic glycolysis (Warburg effect) during further disease progression, including the metastatic stage due in part to activation of cancer associated fibroblasts that cause activation of pyruvate kinase M2 (PKM2), a rate limiting enzyme that converts phosphoenolpyruvate to pyruvate that in turn is reduced to lactate to allow glycolysis to continue in tumor cells [18]. Metabolic imaging methods such as hyperpolarized [1-13C]-pyruvate MRSI (hyperpolarized MRSI) allow for analysis of in-vivo conversion of pyruvate to lactate in real time. This conversion is illustrated by metabolic maps of transgenic adenocarcinoma of mouse prostate (TRAMP) model in Fig. 1. Thus, hyperpolarized MRSI is a noninvasive method of capturing the switch to Warburg effect in PCA cells, allowing for analysis of aggressiveness and metastatic potential of tumor cells [19].

3. Role of Metabolic Imaging in Primary Diagnosis and Surveillance of PCa

3.1 Multiparametric magnetic resonance imaging

Multiparametric magnetic resonance imaging (mpMRI) is currently the most accurate and most commonly used imaging method for the detection of clinically significant primary PCa, staging of tumor extent, and monitoring treatment response [20]. In fact, obtaining mpMRI prior to first TRUS biopsy is endorsed by European Association of Urology (EAU) and United Kingdom National Institute for Health and Care Excellence (NICE) [21,22]. Prebiopsy mpMRI has been shown to improve the detection of clinically significant PCa and reduce the over diagnosis of nonclinically significant cancer that would otherwise not warrant definitive therapy [23–25]. Furthermore, new studies have demonstrated the improved diagnostic yield of prostate cancer per biopsy core and reduced number of core biopsies taken per procedure in individuals with prebiopsy mpMRI [26&,27,28].

3.2 Magnetic resonance spectroscopy imaging

According to the American College of Radiology Prostate Imaging-Reporting and Data System (PI-RADS), mpMRI is comprised of three main imaging sequences: diffusion-weighted imaging (DWI) with high b-value images and an apparent diffusion coefficient map (ADC); multiplanar T2-weighted (T2W) imaging; and dynamic contrast-enhanced (DCE) imaging. Although not currently part of the PI-RADS guidelines and not yet widely used in routine clinical practice, MRSI can add value to the routine mpMRI sequences through its additional metabolic information. MRSI allows for spectroscopic analysis of endogenous molecules such as choline, citrate, and creatinine. The ratio between these molecules provides detail regarding tumor volume and metabolite behavior. The significance of choline and citrate in PCa has been previously discussed. Creatine remains unchanged during malignancy and can be used as an internal reference. Metabolic ratios such as [(choline ÷ creatine)/citrate] are positively correlated to tumor Gleason score [29]. Quantitative analysis of metabolic ratio provided by MRSI can be used to evaluate PCa aggressiveness and to develop a therapeutic plan [30]. A 2019 meta-analysis for the diagnosis of PCa showed that MRSI has an 86% sensitivity, 78% specificity, and a mean diagnostic odds ratio of 22 [31].

Although MRSI is not routinely included in mpMRI per PI-RADS guidelines, the addition of MRSI may be beneficial in complicated cases such as in patients with prior inconclusive MRI or patients with continuously rising PSA levels despite negative MRI findings [32].

3.3 Hyperpolarized magnetic resonance spectroscopic imaging

Another metabolic imaging tool that can evaluate disease aggressiveness is hyperpolarized MRSI. Hyperpolarized MRSI noninvasively measures metabolic substrates and their product in real time. Currently, the most promising substrate is [1–13C] pyruvate, which is taken up by tumor cells and metabolized to lactate directly reflecting the Warburg effect. Compared to MRSI which can only measure steady-state levels of endogenous metabolites, hyperpolarized MRSI can detect in-vivo flux of metabolites in real time and offers a higher

signal-to-noise ratio (SNR). However, hyperpolarized MRSI is a challenging procedure because of the necessity of short acquisition times due to the exponential decay to the non-detectable thermal equilibrium level of the hyperpolarized substrate [33]. Additionally, it requires a specialized polarizer device and MRI hardware that allows carbon imaging. Thus, there is ongoing research on the optimization and application of this technology.

At the time of initial PCa diagnosis, it is critical to determine whether the appropriate therapy is active surveillance (if the disease is more indolent) or immediate definitive treatment such as radical prostatectomy and/or radiation (if the disease is considered more aggressive). Accurate risk stratification will prevent overdiagnosis and overtreatment of potentially indolent cancers, saving the patient from unnecessary morbidity and psychological harm and saving society from immense financial burden. A study by Bok et al. demonstrated that hyperpolarized MRSI was able to differentiate low to high grade PCa in a TRAMP model. It showed that hyperpolarized lactate-to-pyruvate ratio significantly increased in high grade PCa when comparing low-grade to high-grade disease but there was no increase when comparing lowgrade PCa versus healthy tissue. Thus, hyperpolarized lactate-to-pyruvate ratio can act as a marker for PCa aggressiveness at the time of biopsy [34&&]. Similarly, Nelson et al. in the first clinical application of this technology, demonstrated that areas of the prostate that included tumor revealed four to five times higher pyruvate to lactate conversion than healthy tissue, demonstrating the ability of hyperpolarized MRSI to differentiate between high-grade versus low-grade/benign prostatic tissue. They further showed that biopsy proven tumor that had not been detected using mpMRI could be detected using hyperpolarized MRSI, establishing the potential added benefit of hyperpolarized MRI compared to routine mpMRI [35].

3.4 Positron emission tomography

PET is another metabolic imaging technique that relies on the uptake of radiotracers to visualize metabolic processes in the body and diagnose disease. It is rarely used to make initial diagnosis of PCa or to evaluate patients with localized PCa because its most useful in distant staging and detecting recurrence [36]. PET is commonly associated with CT and more recently MRI to correlate metabolic and anatomical information.

Two US Food and Drug Administration (FDA) approved metabolic PET radiotracers, ¹¹C-choline and ¹⁸F-fluciclovine, have proven effective in detection of PCa metastasis and recurrence. ¹¹C-choline takes advantage of the upregulated lipogenesis and phospholipid synthesis during early differentiation of prostate cancer cells to enhance detection of these cells. ¹⁸F-fluciclovine is a synthetic amino acid that is largely transported via sodium-dependent amino acid transporters and takes advantage of the upregulation of these channels in prostate cancer [37].

4. Role of Metabolic Imaging in Prostatic Cancer Metastasis

4.1 Metabolic Imaging in Extracapsular Tumor Spread

ECE represents a significant portion of patients with clinically localized tumors treated with radical prostatectomy, with studies reporting incidences ranging from 15 to 60% [38,39].

The survival and prognosis of patients with extracapsular disease is less favorable compared to patients with localized disease confined to the prostate, highlighting the need for accurate methods of ECE detection [40]. Studies have shown that MRSI/mpMRI has improved the local staging of disease, including the detection of extracapsular spread of disease [41]. The addition of metabolic data provided by MRSI adds incremental value in predicting organ confined PCa, with an area under the receiver operating characteristic curve of 0.726 in comprehensive clinical models to 0.854 with the addition of MRSI [42].

4.2 Metabolic Imaging in Lymph Node Metastases

Although there is significant heterogeneity based on tumor aggressiveness, at the time of diagnosis 13% of patients have cancer that has spread to regional lymph nodes and 6% have distant metastases [2]. Pelvic lymph node dissection (PLND) is the definitive method for assessing nodal spread in PCa. Even with extensive PLND, Joniau et al. [43] have shown that 13% of metastatic lymph nodes are missed. PET/CT has greater sensitivity and specificity over nonmetabolic imaging methods such as MRI in identifying nodal spread, especially in the detection of subcentimeter disease. Contractor et al. compared MRI, 11C-choline PET, and 11C-choline PET/CT and found the per nodal sensitivity to be 18.5, 40.7, and 51.9% and specificity to be 98.7, 98.4, and 98.4%, respectively [44]. 11C-Choline PET/CT showed a median true-positive LNM AQ4 size of 9.2mm and false-negative LNM of 4.7mm.

A recent study in patients with high-risk prostate cancer with negative bone scans comparing 18Ffluciclovine to conventional imaging demonstrated that the 18F-fluciclovine PET/CT has superior PLND detection rate (37.5 vs. 27.5%) and sensitivity (61.9 vs. 42.9%) and equivalent specificity of (89.5 vs. 89.5%) [45]. Another study with a similar patient population comparing 18F-fluciclovine PT/MRI to conventional MRI had equitable sensitivity in patient-based detection of PLND metastasis (40 vs. 40%) and higher specificity (100 vs. 87.5%) [36]. This study also demonstrated that the overall metastatic burden (e.g. having less than two positive PLNDs) was higher in PET positive patients compared to PET negative patients, which may be attributed to the greater anatomical clarity obtained via PET/MRI. Although the greater anatomical information obtained by PET/MRI is thought to increase efficacy, the PLND metastatic detection rate data from these studies suggests that its more complicated than previously thought [46]. Another study evaluating the efficacy of 18F-fluciclovine PET/CT in the detection of metastasis of primary PCa to small (5–10mm short axis diameter) PLNDs concluded that 18F-fluciclovine PET/CT was successful in detecting small PLND metastasis but not specific enough to avoid falsely identifying benign lymph nodes [47]. Figure 2 illustrates the ability of 18F fluciclovine PET/CT to detect metastasis in subcentimeter lymph nodes.

18F-fluciclovine PET-based studies are still in their infancy and while the current data seems promising, further studies are required to elucidate its efficacy in detecting PLND metastasis in patients with PCa.

4.3 Metabolic Imaging in Distant Metastases

Pyruvate-to-lactate conversion rate (kPL) in hyperpolarized ^{13}C -pyruvate MRI can not only differentiate prostate cancer aggressiveness as previously discussed, but it has also been shown to play a role in tumor progression and metastasis [34&&]. A pilot study evaluating the feasibility of ^{13}C -pyruvate MRI in patients with metastatic prostate cancer to the skeleton and liver demonstrated real time detection of metabolic activity within metastatic lesions [9&&]. It showed that kPL in bone and liver lesions ($0.020 \pm 0.006 \text{ s}^{-1}$ and $0.026 \pm 0.000 \text{ s}^{-1}$, respectively) were higher than in high-grade primary prostate cancer ($0.013 \pm 0.003 \text{ s}^{-1}$) measured in a previously studied cohort [48]. It also demonstrated the ability of hyperpolarized MRI to capture treatment response via a decrease in kPL from 0.026 to 0.015 (s^{-1}) in a patient with liver metastasis treated with chemotherapy for 2 months. In another study using hyperpolarized MRI to measure treatment response to androgen deprivation therapy in a patient with metastatic PCa, kPL decreased markedly from 0.025 s^{-1} at baseline to 0.007 s^{-1} 6 weeks after initiation of therapy [49]. Hence, hyperpolarized MRI is not only able to detect metastatic disease but it can potentially act as a metabolic biomarker of treatment response.

^{18}F -fluciclovine PET/CT has been shown to be superior to whole body bone scan for the detection of bone metastasis in PCa. A recent study comparing these two methods showed that sensitivity, specificity, positive predictive value, and negative predictive value for $^{99\text{m}}\text{Tc}$ -MDP were 79, 86, 45, and 96%, respectively, compared to 100, 98, 89, and 100% for ^{18}F -fluciclovine PET/CT, respectively [50&&]. This study also revealed that fluciclovine PET/CT can detect previously undiagnosed metastatic lesions on bone scan and showed that fluciclovine PET/CT did not miss any lesions that were detected by bone scan. Importantly, it demonstrated that fluciclovine PET/CT scan characterizes disease burden by providing information regarding soft-tissue and bone metastasis, thus potentially being a valuable tool in the clinical management of metastatic PCa.

These metabolic imaging modalities show promise in characterizing PCa metastases, however, further research needs to be done before they can be adopted in routine PCa staging.

5. Role of Metabolic Imaging in Prostate Cancer Recurrence after Treatment

Recurrence rate of prostate cancer after definitive local therapies varies based on aggressiveness of initial tumor and type of treatment; approximately 20–40% of patients who have undergone radical prostatectomy experience biochemical recurrence of PCa [51,52]. The current gold standard for monitoring PCa recurrence includes serial PSA testing. The threshold for defining abnormal PSA in the context of biochemical recurrence depends on the type of initial therapy. In general, PSA level more than 0.2 ng/ml is abnormal in patients treated with radical prostatectomy, whereas a rising PSA level more than 2 ng/ml from nadir is considered abnormal among patients treated with definitive radiation therapy. Bach-Gansmo et al. [53] showed that ^{18}F -fluciclovine PET/CT can detect prostate cancer recurrence across a wide range of PSA values, including PSA levels less than 0.79 ng/ml

with a detection rate of 41.4%. A retrospective study of 30 patients with PSA levels 0.5 ng/ml or less and 0.3 ng/ml or less after initial treatment for prostate cancer demonstrated that 18F-fluciclovine PET/CT can detect biochemical recurrence with a positivity rate of 55 and 53% for each PSA group, respectively [54]. Thus, fluciclovine-based PET seems to be a potentially useful metabolic imaging method to detect PCa recurrence in patients with low PSA levels allowing the site of recurrence to be detected within the windows of curability.

18F-fluciclovine is more practical to handle than 11C-choline because of a physical half-life of 110 min for the former compared to 20 min for the latter [55,56]. Moreover, 18F-fluciclovine exhibits little renal excretion or bladder uptake compared to 11C-choline, allowing for better visualization of the prostate and greater accuracy of detection of involved sites in distant lymph nodes [57]. This increase in accuracy was demonstrated by Nanni et al. [58] who showed that 18F-fluciclovine was statistically significantly superior to 11C-choline in detecting both local and distant sites of disease recurrence.

Furthermore, 18F-fluciclovine also appears to be superior to conventional imaging modalities such as MRI in evaluating patients with biochemical recurrence. Akin-Akintayo et al. [59] demonstrated that PCa detection rate for 18F-fluciclovine PET-CT in nonprostatectomy patients with biochemical recurrence after definitive therapy was 94.7% compared to 31.6–36.8% for mpMR. This comparison is illustrated in Fig. 3.

Conclusion and Future Trajectory

Metabolic imaging can aid in initial diagnosis, active surveillance, staging, and evaluation of biochemical recurrence of PCa. Hyperpolarized MRSI offers a method to distinguish relative tumor aggressiveness and thereby can potentially help make better management decisions for newly diagnosed PCa. Multimodal approaches involving MRSI and PET will become increasingly emphasized and adopted into routine management of prostate cancer. Metabolic imaging will play a major role in personalized care based on the patient's unique tumor metabolic profile to avoid invasive treatment in majority of patients who have indolent disease, and provide definitive management for the minority of patients who have higher risk disease. It will allow for personalized therapies such as targeted focal radionuclide therapy to diseased sites within the prostate gland. Finally, metabolic imaging will help reduce the need for additional imaging studies and thereby decrease overall costs associated with PCa evaluation and management.

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Key Points

1. Addition of MRSI to mpMRI protocol can increase detection of PCa in complicated cases
2. [1–¹³C] pyruvate hyperpolarized MRI allows for in-vivo real time measurement of Pyruvate-to-lactate conversion rate (k_{PL}) used to analyze PCa aggressiveness
3. ¹⁸F-fluciclovine PET/CT is a useful imaging method for the detection of metastasis in recurrent PCa

FIGURE 1.

Warburg effect within transgenic adenocarcinoma of mouse prostate (TRAMP) mouse model. (a) ^1H -MRI of a coronal slice of a TRAMP mouse with the location of the tumor indicated by a dashed circle. Metabolic maps of (b) pyruvate and (c) lactate acquired after injection of hyperpolarized $[1-^{13}\text{C}]$ pyruvate. Increased conversion of pyruvate to lactate in the tumor reflects increased glycolysis as seen in the Warburg effect.

FIGURE 2.

Identification of subcentimeter lymph node via F-18-FACBC/Fluciclovine: 72-year-old male with history of prostate cancer initially diagnosed 17 years ago status post-radical prostatectomy with biochemical recurrence. Most recent PSA of 1.6 ng/ml. Axial fused F-18-FACBC/Fluciclovine positron emission tomography (PET)/CT image shows uptake within a subcentimeter right external iliac lymph node (arrow). Uptake was also seen in another adjacent similarly sized lymph node (not shown). One major advantage of PET over conventional morphologic imaging such as CT and magnetic resonance imaging (MRI) is the detection of metastases in small, otherwise normal appearing lymph nodes.

FIGURE 3.

Local recurrence on magnetic resonance imaging (MRI) and F-18-FACBC/Fluciclovine positron emission tomography (PET) after brachytherapy: 68-year-old male with rising PSA after brachytherapy performed 4 years earlier. Most recent PSA was 4 ng/ml. Original cancer was located at the prostatic apex, Gleason score 3+3=6. Axial T2 weighted image shows heterogeneous T2 hypo-intense area at the anterior apex of the prostate (thick arrow). Note foci of susceptibility artifact related to brachytherapy seeds (thin arrows). Axial dynamic contrast enhanced image shows early enhancement at the right anterior apex (arrow), indicative of locally recurrent tumor. Axial PET image from an F18-FACBC-Fluciclovine PET shows focal tracer uptake at the right apex corresponding to the site of tumor (arrow). No abnormal uptake was seen elsewhere in the body to indicate distant metastases.