Clinical Applications of Molecular Imaging in the Management of Prostate Cancer

Michael A. Gorin, MD[a,*], Steven P. Rowe, MD, PhD[b], Samuel R. Denmeade, MD[c]

KEYWORDS

• Molecular imaging • Prostate cancer • PET • Cancer staging

KEY POINTS

- Prostate cancer is a common malignancy with a number of varied clinical states for which there are a multitude of treatment options.
- In selecting an ideal mode of treatment for a given patient, it is critical to accurately determine the locations and extent of their disease.
- Molecular imaging offers the promise of improved sensitivity over conventional imaging modalities for detecting sites of prostate cancer.
- Molecular imaging also offers to potential to determine additional information about a patient's prostate cancer such as Gleason score or the abundance of a molecular therapeutic target.

INTRODUCTION

Prostate cancer is the most common noncutaneous malignancy in men, accounting for 1 in 10 of all cancer diagnoses.[1] Worldwide, approximately 1.1 million cases are diagnosed annually.[2] Because of the widespread use of prostate-specific antigen (PSA) screening, nearly 80% of patients will be found to have clinically localized disease at the time of initial presentation.[3] Despite local treatment with either radiation therapy or radical prostatectomy, 20% to 30% of men with prostate cancer will recur biochemically within 10 years.[4–7] For patients with recurrent disease, treatment options include salvage local therapy and systemic treatment with androgen deprivation.[8,9] Fortunately, because of the slow natural history of prostate cancer, only half of all men who recur biochemically will progress to overt metastatic disease.[4–7] A proportion of these patients, however, will develop castration resistance and require secondary treatment with a novel antiandrogen or cytotoxic chemotherapy.[10–12]

Given the wide range of disease states and available treatment options for men with prostate cancer, there is a need for improved imaging techniques capable of accurately and precisely defining a patient's extent of disease. Molecular imaging with PET offers this promise. In oncology, molecular imaging is most commonly performed with 2-deoxy-2-[^{18}F]-fluoro-D-glucose PET. When performed in combination with x-ray computed

Dr M.A. Gorin has served a consultant to Progenics Pharmaceuticals.
[a] Department of Urology, Johns Hopkins University School of Medicine, 600 North Wolfe Street, Marburg 118, Baltimore, MD 21287, USA; [b] The Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA; [c] The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA
* Corresponding author.
E-mail address: mgorin1@jhmi.edu

PET Clin ■ (2016) ■–■
http://dx.doi.org/10.1016/j.cpet.2016.11.001

tomography (CT), this imaging test allows for the highly sensitive localization of rapidly dividing cells undergoing glycolysis.[13] This test, however, has offered little in the way of clinical utility for imaging prostate cancer. This lack of utility has been attributed to several factors, including the slow-growing nature of prostate cancer and its relatively low level of glycolytic activity in the castrate-sensitive state.[14,15] As a result, the field has witnessed a flurry of activity in the development of novel PET radiotracers for prostate cancer imaging. These radiotracers include agents targeting fatty-acid synthesis (eg, ^{11}C-choline, ^{18}F-choline, and ^{11}C-acetate), amino acid transport (eg, ^{18}F-FACBC), and the transmembrane protein prostate-specific membrane antigen (PSMA; eg, ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL). This article reviews the current uses of imaging in the management of men with prostate cancer and outlines potential ways in which molecular imaging can be used to improve patient outcomes.

INITIAL PROSTATE CANCER STAGING WITH CONVENTIONAL IMAGING

According to current guidelines from the National Comprehensive Cancer Network,[16] the decision to perform staging imaging of patients with newly diagnosed prostate cancer should be based on a combination of digital rectal examination findings (ie, clinical T stage), serum PSA level, and biopsy Gleason sum. Per these guidelines, staging with cross-sectional imaging, including CT or MR imaging, is only recommended for patients with clinical T3 or T4 disease or those with clinical T1 or T2 disease who have a $\geq$10% risk of lymph node involvement. Most commonly, the Partin tables[17] or Briganti nomogram[18] are used to estimate this risk. Additionally, assessment for bone metastases using technetium-99m (^{99m}Tc)-methylene diphosphonate bone scan is recommended for patients with any of the following: bone pain, Gleason $\geq$8 cancer on biopsy, clinical T1 disease with a PSA $\geq$20 ng/mL, clinical T2 disease with a PSA $\geq$10 ng/mL, or clinical T3 to T4 disease. The goal of this and similar staging guidelines is to prevent the indiscriminate and costly use of imaging in patients who are at low risk of harboring metastases. In fact, the appropriate use of staging imaging in men with prostate cancer is among the items highlighted by the American Board of Internal Medicine's Choosing Wisely Campaign.[19]

Following a complete staging evaluation, patients found to have clinically localized prostate cancer should be further substratified based on their risk of progression to systemic disease. The most current version of the National Comprehensive Cancer Network guidelines[16] includes 5 risk categories: very low risk, low risk, intermediate risk, high risk, and very high risk (defined in **Table 1**). In general terms, patients with clinically localized intermediate or higher-risk prostate cancer should be offered treatment with either radiation therapy (external beam or brachytherapy with or without androgen deprivation depending on the risk category) or surgery with radical prostatectomy. Patients in the very low and low-risk groups may also be offered these treatment options; however, given the indolent nature of their disease, these men should also be presented with the option of active surveillance with selective delayed intervention. In fact, because of the significant morbidity associated with treatment (ie, urinary incontinence and erectile dysfunction), active surveillance has in recent years emerged as the de facto standard of care in this patient population. This trend has followed the publication of several reports that have shown the safety of active surveillance in appropriately selected men with low-risk prostate cancer.[20–26]

Table 1
Risk categories of localized prostate cancer as defined by the National Comprehensive Cancer Network (Version 3.2016)

Risk Category	Clinical T Stage	Gleason Score	PSA (ng/mL)
Very low[a]	T1c	$\leq$6 (Fewer than 3 cores each with $\leq$50% cancer)	<10 (PSA density <0.15 ng/mL/g)
Low[b]	T1-T2a	$\leq$6	<10
Intermediate[b]	T2b–T2c	7	10–20
High[b]	T3a	8–10	>20
Very high[b]	T3b–T4	Primary pattern 5 or >4 cores with Gleason score 8–10	—

[a] Patients must meet all criteria to be included in the very low risk group.
[b] Patients meeting any of the listed criteria are included in the risk group.