Clinical presentation and diagnosis of prostate cancer

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INTRODUCTION

Prostate cancer is among the most common cancers in men worldwide, with an estimated 1,600,000 cases and 366,000 deaths annually [1]. In the United States, 11 percent of men are diagnosed with prostate cancer over their lifetime, with the incidence generally rising with age [2]; there are an estimated 165,000 cases and 29,000 deaths annually [3]. The overall five-year survival rate is over 98 percent.

An overview of the clinical presentation and initial diagnosis of men with prostate cancer is presented here.

Screening, risk factors, and chemoprevention of prostate cancer are described separately:

- (See "Screening for prostate cancer".)
- (See "Risk factors for prostate cancer".)
- (See "Genetic risk factors for prostate cancer".)
- (See "Chemoprevention strategies in prostate cancer".)

Laboratory, radiologic, and pathologic testing of the prostate are described separately:

- (See "Measurement of prostate-specific antigen".)
- (See "The role of magnetic resonance imaging in prostate cancer".)
- (See "Prostate biopsy".)
- (See "Interpretation of prostate biopsy".)
- (See "Molecular prognostic tests for prostate cancer".)

The prostate cancer staging system, initial staging evaluation, and management approaches based upon risk are presented separately:

- (See "Initial staging and evaluation of men with newly diagnosed prostate cancer", section on 'Introduction'.)
- (See "Localized prostate cancer: Risk stratification and choice of initial treatment".)
- (See "Initial approach to low- and very low-risk clinically localized prostate cancer".)
- (See "Initial management of regionally localized intermediate-, high-, and very high-risk prostate cancer and those with clinical lymph node involvement".)
- (See "Prostate cancer in older males".)

CLINICAL PRESENTATION

Spectrum of disease at detection — Clinical manifestations of prostate cancer are frequently absent at the time of diagnosis. The clinical behavior of prostate cancer ranges from a screen detected asymptomatic, microscopic, well-differentiated tumor that may never become clinically significant to the rarer screen detected or clinically symptomatic aggressive, high-grade cancer that causes metastases, morbidity, and death.

At the time of diagnosis, 78 percent of patients have localized cancer, regional lymph node involvement is present in 12 percent, and 6 percent have distant metastases [2]. (See "Screening for prostate cancer", section on 'Introduction' and "Initial staging and evaluation of men with newly diagnosed prostate cancer".)

Symptoms — It is rare for patients to present because of symptoms attributable to prostate cancer. Most prostate cancers are diagnosed in the local stage and are asymptomatic.

Uncommonly, prostate cancer may present with nonspecific urinary symptoms, hematuria, or hematospermia; however, these symptoms are more commonly due to nonmalignant conditions. (See "Lower urinary tract symptoms in males", section on 'Symptoms' and "Etiology and evaluation of hematuria in adults" and "Hematospermia".)

Among the six percent of patients whose prostate cancer is metastatic at the time of diagnosis, bone pain may be the presenting symptom. Bone is the predominant site of disseminated prostate cancer, and pain is the most common manifestation of bone metastases. An initial diagnosis of prostate cancer after bone metastases have already occurred has become unusual [4]. (See "Bone metastases in advanced prostate cancer: Clinical manifestations and diagnosis", section on 'Clinical manifestations'.)

Other symptoms with metastatic disease may include hematuria, inability to void, incontinence, erectile dysfunction, weight loss, weakness or pain due to spinal cord compression, pain due to pathologic fractures, fatigue caused by anemia, or symptoms associated with chronic renal failure. (See "Initial staging and evaluation of men with newly diagnosed prostate cancer", section on 'Evaluation for distant metastases'.)

Signs — Clinical signs associated with prostate cancer include an elevated prostate-specific antigen (PSA) on laboratory testing and an abnormal prostate finding on digital rectal examination.

PSA testing — On laboratory testing, PSA elevation is often present in men with prostate cancer. The likelihood of prostate cancer increases with a more elevated PSA value. However, an elevated PSA can occur in a number of benign conditions, and a PSA result in the normal range does not rule out the possibility of prostate cancer. Despite its lack of specificity for prostate cancer, PSA remains the most commonly used and most valuable test for early detection of prostate cancer

PSA testing in a man without a history of prostate cancer is most often done for screening purposes, although PSA is sometimes performed as part of an evaluation of symptoms. Measurement of PSA and recommendations regarding PSA screening for prostate cancer are discussed in detail separately. (See "Measurement of prostate-specific antigen" and "Screening for prostate cancer", section on 'Approach to screening'.)

Digital rectal examination — On physical examination, digital rectal exam (DRE) may detect prostate nodules, induration, or asymmetry that can occur with prostate cancer. However, prostate cancer is often not detectable by DRE, because DRE can only detect tumors in the posterior and lateral aspects of the prostate gland, which are the portions of the prostate that are palpable via the rectum. Tumors not detected by DRE include the 25 to 35 percent that are not reachable because they occur in other parts of the gland and the small, stage T1 cancers that are not palpable (table 1). (See "Initial staging and evaluation of men with newly diagnosed prostate cancer", section on 'Staging system'.)

DRE is generally not recommended as a routine screening test for evaluation of the prostate or rectal area in the absence of symptoms (urinary or rectal). However, when an abnormality suggestive of prostate cancer is detected on DRE, further evaluation is warranted. (See 'Evaluation' below.)

Differential diagnosis — Lower urinary tract symptoms (LUTS) such as frequency, urgency, nocturia, and hesitancy occur commonly among men and are usually related to a benign etiology such as benign prostate hyperplasia (BPH) rather than to prostate cancer. However,

patients may be concerned that these or other symptoms due to anatomic, infectious or irritative etiologies could indicate the presence of prostate cancer. Such symptoms may be due to bladder outlet obstruction (BOO), urinary tract infection (UTI), prostatitis, interstitial cystitis (IC), or chronic pelvic pain syndrome (CPPS). (See "Lower urinary tract symptoms in males".)

The differential diagnosis of an elevated PSA includes many etiologies besides prostate cancer. These include both transient (eg, prostatitis, perineal trauma) and persistent causes (eg, BPH). These causes, as well as mechanisms to assess and sometimes limit their impact on PSA measurement, are described separately.

On DRE, many men have symmetric enlargement and firmness of the prostate. These findings are more frequent in men with BPH rather than cancer of the prostate. (See "Clinical manifestations and diagnostic evaluation of benign prostatic hyperplasia".)

EVALUATION

Clinical suspicion — Findings that typically raise clinical suspicion for prostate cancer are an elevation in prostate-specific antigen (PSA) levels or an abnormality (eg, a nodule, induration, or asymmetry) on digital rectal examination (DRE). These can be signs of prostate cancer and warrant additional evaluation, although benign etiologies can also cause these findings.

There is no single threshold for defining an abnormal PSA value; there is considerable variability in normal PSA and studies do not conclusively identify a single approach applicable to every patient. We compare the patient's PSA result with the age-specific reference range for the patient's age, as well as with the prior year's PSA, if available. Some contributors to this topic evaluate further if the PSA is above the upper value for the age range, whereas others evaluate if the PSA is above the midpoint. We also evaluate if the PSA increased more than 0.75 ng/dL in one year, even if the PSA value is not above the age-specific range. (See "Measurement of prostate-specific antigen".)

Some clinicians, including other UpToDate contributors, use a single total PSA cutoff of 4.0 for all age groups as a benchmark above which to arrange evaluation for prostate cancer.

Urologic evaluation — The objective of urologic evaluation is to determine whether a prostate biopsy is warranted, whether additional testing may obviate the need for biopsy at the time, and the appropriate timing for reevaluation.

Repeating the PSA — Prior to further evaluation, we repeat an elevated or increased PSA test in a few weeks to confirm that the level remains elevated. If modifiable factors that can

temporarily raise PSA are present, these factors should be addressed prior to repeating the PSA [5,6]. If the repeated PSA is within the normal expected values for age, and is not increased more than 0.75 ng/dL compared with the prior year value, no further evaluation at that time is necessary, unless there is a palpable nodule, induration, or asymmetry on DRE. If the repeat PSA is not elevated, returning to routine screening is warranted if the patient opts for continued screening.

> Studies have found considerable variability in PSA results over the short term and in year-to-year comparisons. One-third of patients will have a decrease to baseline levels if PSA is repeated a month or so later, even in the absence of any treatment (eg, use of antibiotics for prostatitis). A retrospective analysis of stored serum from 972 men found substantial year-to-year fluctuations with 44 percent of men with a PSA above 4.0 ng/mL having normal PSA findings at subsequent annual visits [7-9]. (See "Acute bacterial prostatitis".)

Some benign factors can raise PSA persistently (eg, benign prostatic hyperplasia [BPH]), rather than transiently. Even if benign factors that can elevate PSA are present, urologic evaluation is warranted.

Molecular and genomic analysis — A number of urine- and blood-based molecular and genomic tests have been developed to help decide when a biopsy is indicated [10]. Prostate health index (PHI), the 4K score, SelectMDx, PCA3, and EPI are amongst these. They may provide information which is complementary to PSA and PSA density as well as magnetic resonance imaging (MRI) findings. How they best perform in providing prognostic information is still being evaluated.

Decision to biopsy — Results of PSA testing, DRE, and any adjunctive tests and imaging are used to inform the clinical likelihood for harboring significant disease and thus guide the decision about whether a biopsy is needed to obtain tissue for histologic diagnosis. (See "Prostate biopsy".)

After shared decision-making with the patient, we usually proceed to biopsy if:

- Life expectancy is at least 10 years (some contributors biopsy if life expectancy is >5 years)

AND

- PSA is elevated above the range for the patient's age cohort, or PSA has increased more than 0.75 ng/mL over one year, or there is a palpable concerning abnormality on DRE

Not pursuing prostate biopsy, even if PSA is elevated or increased, may be appropriate in older patients or patients who have significant comorbidities that limit their life expectancy when the

patient's goals are aligned with less aggressive diagnostics and interventions.

For men with an equivocal PSA, urologic evaluation may include certain adjunctive PSA tests or prostate imaging in an attempt to better estimate the likelihood of prostate cancer.

- **Potential adjunctive laboratory testing** – Examples of adjunctive laboratory testing for equivocal PSA results include:

  - PSA density – PSA density is the ratio of PSA level (determined by blood testing) to prostate volume (measured using transrectal ultrasound). PSA is expressed by both benign and malignant prostate tissue. Thus, an elevated PSA level may be more worrisome in a small prostate than in a larger-volume prostate in which higher levels of PSA may be expected. PSA density <0.15 ng/mL/cc is considered favorable. (See "Measurement of prostate-specific antigen", section on 'PSA density'.)

  - Free or bound PSA – Free PSA can be measured and used to calculate the ratio of free to total PSA (f/t PSA). Prostate cancer is associated with a lower percentage of free PSA in the serum as compared with benign conditions. An f/t PSA <10 to 15 percent is highly suspect for prostate cancer, whereas an f/t PSA >25 percent is highly likely to be due to BPH. F/t PSA ratios are of most value when deciding whether a repeat biopsy is necessary in an older patient who has a prior negative biopsy, but a PSA level that is still suspicious. (See "Measurement of prostate-specific antigen", section on 'Serum free and bound PSA'.)

  We do not suggest, for general use, the multiple other PSA-related analyses (eg, p2PSA) and methods developed to attempt to increase the accuracy of PSA testing. Such methods include the 4K score and the PHI. There is no consensus about the ultimate clinical utility of these tests; however, some experts do use them. The tests are described in detail separately. (See "Measurement of prostate-specific antigen", section on 'Advances in PSA testing'.)

  There is ongoing development of new strategies, biomarkers, and genomic tests to improve the accuracy of PSA based screening. (See "Measurement of prostate-specific antigen", section on 'Advances in PSA testing'.)

- **Imaging** – Prostate MRI is increasingly being used as an adjunctive tool in refining risk status for clinically meaningful prostatic disease and to inform decisions for performing biopsies. Some, but not all, contributors of this topic use MRI to help determine the need for biopsy. The role of MRI is discussed in detail elsewhere.

MRI of the prostate is used in some countries to help decide whether to do a prostate biopsy (see "The role of magnetic resonance imaging in prostate cancer", section on 'Initial presentation with no prior biopsy'). For example, in an older patient with significant comorbidities, an MRI showing either no lesion or a low risk lesion could be an argument to forgo biopsy. (See "The role of magnetic resonance imaging in prostate cancer", section on 'Prostate imaging reporting and data system (PI-RADS)'.)

Transrectal ultrasound (TRUS) is often used to evaluate abnormalities detected on DRE. However, even if TRUS does not show concerning findings, prostate biopsy is warranted if indicated based on other factors (eg, PSA results or DRE), because TRUS misses a substantial number of tumors [11,12]. Cancers typically appear hypoechoic, but some may be hyperechoic or isoechoic, leading to false negative studies. (See "Prostate biopsy", section on 'Transrectal biopsy'.)

Prostate-specific membrane antigen (PSMA) positron emission tomography (PET) scanning is become more widely available in the United States and is more sensitive and specific than other PET scan techniques. Local disease within the prostate can be demonstrated on PSMA PET in some cases. However, imaging with PSMA PET is not currently used to diagnose local disease or to direct prostate biopsy.

Use of adjunctive laboratory testing to inform the decision to biopsy varies among experts, including among contributors to this topic, and some contributors use MRI more frequently than others. As an example, for a patient with PSA above 10 mg/dL, one contributor proceeds to biopsy if prostate size is small (30 to 40 grams) on DRE but might defer biopsy if the prostate is of normal texture and symmetry but is enlarged (eg, >100 grams) on DRE, suggesting a lower PSA density. In such cases, a PSA test is repeated in four to six months, and if there is a substantial increase in PSA value (suggesting a doubling time <12 months), MRI of the prostate is obtained to inform the decision to biopsy.

Attempts have been made to create risk models to determine the likelihood of prostate cancer based on multiple variables (eg, PSA, age, family history, DRE result, prostate volume, previous negative biopsies, PSA velocity, free PSA). A meta-analysis concluded that some models improved the predictive value of PSA for detecting prostate cancer, with areas under the receiver operating characteristic curve (AUC) ranging from 0.66-0.79 [13]. Only one model was used to predict clinically significant (high-grade) cancer, with an overall AUC 0.71 (95% CI 0.67-0.75); however, estimates showed a high degree of heterogeneity. Until such models have undergone additional study for clinical effectiveness, we do not recommend using them to inform the decision to biopsy. A diagnostic strategy involving blood-based risk prediction combined with MRI-targeted biopsy has also been evaluated [14].

Biopsy technique — A transrectal biopsy is typically performed with imaging guidance (ie, TRUS or MRI). MRI targeting may be performed with initial biopsy and is a common practice in the United Kingdom, Australia, and the United States. After a negative biopsy with TRUS, if there is ongoing concern because of further increase in PSA or abnormalities on exam, a repeat biopsy with MRI targeting increases the cancer detection rate. MRI-targeted prostate biopsy is being evaluated as a method to improve accuracy, either alone or used with TRUS to do an MRI/US-fusion biopsy [15,16]. The use of imaging to guide biopsy is described separately. (See "The role of magnetic resonance imaging in prostate cancer", section on 'Clinical applications' and "The role of magnetic resonance imaging in prostate cancer", section on 'Elevated serum PSA with a prior negative TRUS biopsy' and "Prostate biopsy", section on 'Procedural details'.)

Biopsy is typically performed by a transrectal route using ultrasound guidance or via a perineal approach. The perineal route is being used increasingly because of a lower risk of infection, although it may require more sedation or anesthesia than a transrectal biopsy. MRI targeting may be considered to facilitate the diagnosis, with some experts recommending that biopsy may be avoided if the MRI is normal. If the MRI shows an abnormality, fusion software can help direct a biopsy targeted to the abnormal area and may improve the accuracy of biopsy.

The techniques involved in prostate biopsy, including preparation, extent of sampling, and complications, are discussed separately. (See "Prostate biopsy".)

DIAGNOSIS

The diagnosis of prostate cancer is based on the histology of tissue obtained on prostate biopsy. Prostate cancer cannot be diagnosed on the basis of a prostate-specific antigen (PSA) result, physical examination, adjunctive laboratory testing, imaging studies, or symptoms.

A biopsy may show prostate cancer or precancerous or benign findings. Histologic features and interpretation of a prostate biopsy are described separately. (See "Interpretation of prostate biopsy", section on 'Histologic features'.)

If the biopsy indicates prostate cancer, architectural features of the cells in the biopsy tissue are used to generate a Gleason grade that correlates closely with clinical behavior. Gleason scores can be categorized according to GRADE groups from 1 to 5, which correlate with prognosis and help determine treatment approaches. (See "Interpretation of prostate biopsy", section on 'Histologic features' and "Interpretation of prostate biopsy", section on 'Gleason grading system'.)

The biopsy may indicate a precancerous histologic finding. Clinical implications of precancerous results on prostate biopsy are described separately. (See "Precancerous lesions of the prostate: Pathology and clinical implications".)

A prostate biopsy that does not show cancer does not exclude the possibility of prostate cancer. The biopsy may indicate benign findings even if prostate cancer is present, because a prostate biopsy uses a sampling technique with a substantial potential for missing cancerous tissue, even when imaging is used to guide biopsy. Thus, repeat biopsy may be indicated if the PSA level increases further, or if findings on digital rectal examination or prostate imaging warrant rebiopsy. This is described in detail separately. (See "Interpretation of prostate biopsy", section on 'Issues related to sampling error' and "Prostate biopsy", section on 'Patient follow-up and counseling'.)

Diagnosis of prostate cancer that initially presents after becoming metastatic to bone is described separately. (See "Bone metastases in advanced prostate cancer: Clinical manifestations and diagnosis", section on 'Diagnosis'.)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Prostate cancer (The Basics)")
- Beyond the Basics topics (see "Patient education: Prostate cancer screening (PSA tests) (The Basics)" and "Patient education: Prostate cancer screening (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- Prostate cancer is among the most common cancers in men worldwide. (See 'Introduction' above.)
- Prostate cancer only rarely presents with clinical symptoms. Uncommonly, prostate cancer may present with nonspecific urinary symptoms, hematuria, or hematospermia; however, these are usually due to nonmalignant conditions. (See 'Symptoms' above and 'Clinical presentation' above.)
- Prostate cancer is suspected in patients who have an elevation of prostate-specific antigen (PSA) or an abnormal digital rectal examination (DRE). Although DRE is not recommended for screening, if DRE is performed, asymmetry, nodularity, or induration raise suspicion for prostate cancer. (See 'PSA testing' above and 'Digital rectal examination' above.)
- The risk for prostate cancer increases as the PSA level rises, although there is no specific numerical threshold that accurately determines the presence of prostate cancer. PSA changes over time are helpful in determining cancer risk. (See 'PSA testing' above.)
- The diagnosis of prostate cancer requires tissue. This is usually obtained by biopsy with imaging guidance, which should be preceded by measurement of PSA. (See "Prostate biopsy" and "Interpretation of prostate biopsy" and 'Diagnosis' above and 'Decision to biopsy' above.)
- After shared decision-making with the patient, usually we proceed to biopsy if the patient has a life expectancy of at least 10 years (some contributors biopsy if life expectancy is >5 years) and one of the following: a PSA (on initial PSA testing and on repeat a few weeks later) that is elevated above the range for the patient's age cohort, an increase in the PSA of more than 0.75 ng/mL over one year, or a nodule, induration, or asymmetry on DRE. If the PSA results are equivocal, adjunctive testing (eg, PSA density, PSA doubling time, magnetic resonance imaging [MRI]) can be useful to better estimate the likelihood of prostate cancer. If the patient has significant comorbidities that limit life expectancy, a prostate biopsy to evaluate for the possibility of asymptomatic prostate cancer is usually not warranted. (See 'Decision to biopsy' above.)

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GRAPHICS

Prostate cancer TNM staging AJCC UICC 8th edition

Primary tumor (T)	
Clinical T (cT)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor that is not palpable
T1a	Tumor incidental histologic finding in 5% or less of tissue resected
T1b	Tumor incidental histologic finding in more than 5% of tissue resected
T1c	Tumor identified by needle biopsy found in one or both sides, but not palpable
T2	Tumor is palpable and confined within prostate
T2a	Tumor involves one-half of one side or less
T2b	Tumor involves more than one-half of one side but not both sides
T2c	Tumor involves both sides
T3	Extraprostatic tumor that is not fixed or does not invade adjacent structures
T3a	Extraprostatic extension (unilateral or bilateral)
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall
Pathological T (pT)	
T category	**T criteria**
T2	Organ confined
T3	Extraprostatic extension
T3a	Extraprostatic extension (unilateral or bilateral) or microscopic invasion of bladder neck
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator

	muscles, and/or pelvic wall
NOTE: There is no pathological T1 classification. *NOTE:* Positive surgical margin should be indicated by an R1 descriptor, indicating residual microscopic disease.	

Regional lymph nodes (N)

N category	N criteria
NX	Regional nodes were not assessed
N0	No positive regional nodes
N1	Metastases in regional node(s)

Distant metastasis (M)

M category	M criteria
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional lymph node(s)
M1b	Bone(s)
M1c	Other site(s) with or without bone disease

NOTE: When more than one site of metastasis is present, the most advanced category is used. M1c is most advanced.

Prostate-specific antigen (PSA)

PSA values are used to assign this category.

PSA values
<10
≥10 <20
<20
≥20
Any value

Histologic grade group (G)

Recently, the Gleason system has been compressed into so-called Grade Groups.

Grade Group	Gleason score	Gleason pattern
1	≤6	≤3+3
2	7	3+4
3	7	4+3

4	8	4+4, 3+5, or 5+3
5	9 or 10	4+5, 5+4, or 5+5

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

Graphic 110728 Version 10.0

Contributor Disclosures

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