Chapter 2

Clinical features and diagnosis of prostate cancer

Anatomy and function of the prostate

The prostate is a compound tubuloalveolar exocrine gland that is part of the male reproductive system (Figure 2.1) [1]. The normal adult prostate is around the size of a walnut and increases in size with age. It is situated at the base of the bladder and surrounds the urethra. The rectum sits posteriorly, allowing for the prostate to be palpated via rectal examination. The gland produces approximately 20% of the fluid produced during ejaculation; the remainder is produced by the testicles and seminal vesicles. The prostate gland contains smooth muscle fibers in addition to the glandular tissues, which contracts during ejaculation.

The glandular tissue of the prostate is dependent on androgens for normal growth and development; androgens are hormones that promotes male sex characteristics, the most common being testosterone. The secretory epithelium is pseudostratified and is supported by a fibroelastic stroma. The ductal system is connected to the prostatic urethra via the ejaculatory ducts, which are formed by the junction of the prostatic ductal systems with the vas deferens. The epithelium changes to transitional type at or near the junction of the two systems. Around the prostate is a loose fibromuscular capsule, which is sheathed in the muscles of the pelvic floor. Contraction of these muscles occurs during ejaculation [1].

N. James, *Primer on Prostate Cancer*,
DOI: 10.1007/978-1-907673-82-5_2, © Springer Healthcare 2014

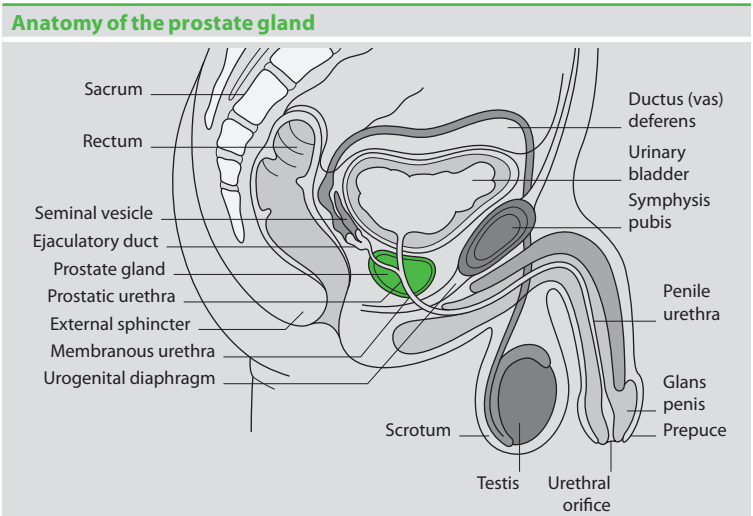

Figure 2.1 Anatomy of the prostate gland. Reproduced with permission from Theodorescu [1].

Structurally, the prostate can be divided by zone or by lobe; in clinical discussions, prostate cancer is usually described by zones. The zones described are:

- Peripheral zone (PZ): comprises of the posterior part of the gland surrounding the distal urethra. Between 80–85% of cancers arise in the PZ [2].
- Central zone (CZ): surrounds the ejaculatory ducts. Only approximately 5–10% of cancers arise in the CZ [2].
- Transition zone (TZ): surrounds the proximal urethra. The TZ enlarges throughout life and is the part of the gland where benign prostatic hypertrophy (BPH) occurs in later life. Approximately 10–15% of cancers originate from the TZ [2].
- Anterior fibromuscular zone or stroma: forms the entire anterior surface of the prostate as a thick, nonglandular apron, shielding from view the anterior surface of the three glandular regions [3].

The zonal system more closely describes the functional and pathological processes within the prostate gland. The zonal system is illustrated in Figure 2.2 [3].

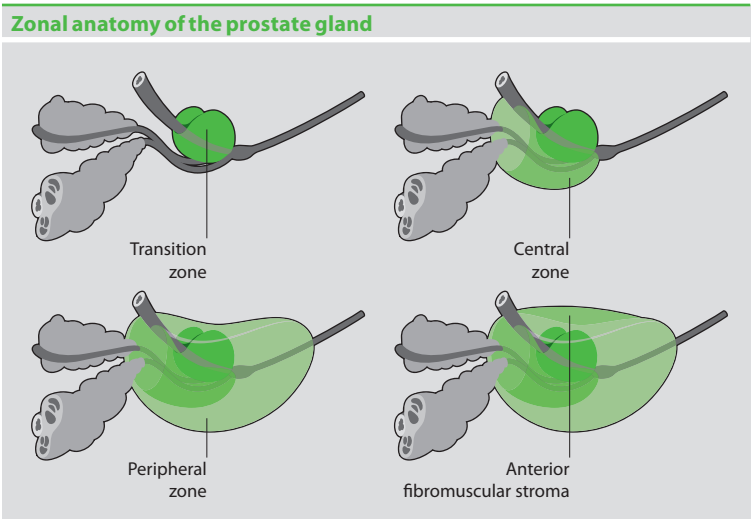

Figure 2.2 Zonal anatomy of the prostate gland. Reproduced with permission from Taylor and Albertsen [3].

Symptoms of prostate cancer

Prostate cancer symptoms can include erectile dysfunction, blood in the semen, pain in the lower back, hips, and/or upper thighs, urinary problems, or enlargement of the prostate. Enlargement of the prostate can lead to obstruction with reduced flow, hesitancy, post-micturition dribbling, or even retention, bleeding, and/or infection. An overlapping problem set appears from urinary irritation. It is important to point out that all of these symptoms occur in men with BPH as well as other disorders arising from other parts of the urinary system. Clinicians should perform standard examinations and testing to make the most appropriate diagnosis while ruling out other possible diseases.

Symptoms from metastasis

Most commonly, symptoms from metastasis occur from bone secondaries, causing pain or fracture. Occasionally, patients will present with nodal enlargement causing palpable masses, lymphedema, or venous thromboembolism.

Diagnosis

Making a diagnosis of prostate cancer generally includes investigating presenting features from prostate-specific antigen (PSA) blood testing, PSA velocity (how much a patient's PSA levels increase from year to year), digital rectal examination (DRE), blood count and biochemical profile, transrectal ultrasound (TRUS), magnetic resonance imaging (MRI), and biopsy.

Incidental diagnosis can occur during investigation for other diseases, such as bladder cancer, where biopsies may be undertaken. In many ways the issues are the same as for screen-detected cancer and will not be discussed further.

Prostate-specific antigen testing

Prostate cancer screening is done in part through the use of the PSA blood tests and is often combined with a DRE. As previously discussed in Chapter 1, the rate of PSA screenings vary from country to country, and studies have shown conflicting results as to whether PSA screening is useful when determining if biopsies are needed for patients with suspected disease [4,5]. PSA levels should be evaluated in line with other diagnostic techniques when managing a patient with prostate cancer [6,7]. Not all low or high PSA levels will necessarily indicate that a patient has or does not have prostate cancer, as PSA levels are organ specific and not cancer specific. Clinicians should administer and evaluate PSA levels with caution to avoid unnecessary subsequent biopsies and possible adverse events. Despite the inherent risk of PSA testing, PSA levels still may indicate a patient's risk for prostate cancer (Table 2.1), although

Low prostate-specific antigen levels and the risk of prostate cancer

Prostate-specific antigen level (ng/mL)	Risk of prostate cancer
0–0.5	6.6%
0.6–1	10.1%
1.1–2	17.0%
2.1–3	23.9%
3.1–4	26.9%

Table 2.1 Low prostate-specific antigen levels and the risk of prostate cancer. Reproduced with permission from © Elsevier, Heidenreich et al, 2013 [7]. All rights reserved.

those chances are small and should be evaluated with other diagnostic measures in mind [6,7].

Digital rectal examination

DREs are performed by a clinician physically examining the prostate via the rectum for any bumps, enlargements, or suspicious hard areas. As most prostate cancers are located in the PZ, a DRE may detect cancers in this zone when its volume is approximately 0.2 mL or larger; about 18% of patients with prostate cancer can be diagnosed by a DRE regardless of PSA levels [7]. As reported in the European Association of Urology (EAU) guidelines, when PSA levels of up to 2 ng/mL are taken into account, a suspect DRE has a positive predictive value of 5–30%; additionally, a DRE can indicate whether a prostate biopsy is recommended for a patient, especially in more aggressive cases [7].

However, like PSA blood testing, DREs are not absolutely conclusive. The American Urological Association (AUA) 2013 guidelines could not find evidence to support the continued use of DREs for first-line screening due to their lack of sensitivity and the high possibility of missing early prostate cancer tumors, which may not be felt during the examination [6]. Nevertheless, the AUA panel acknowledged the standard practice of DREs, and given that prostate cancer could be found with DREs, still suggests that the examination used in conjunction with other diagnostic tests could be helpful when screening patients for prostate cancer [6].

Transrectal ultrasound

A TRUS is performed by inserting a small probe in the patient's rectum; this probe emits sound waves into the patient's prostate that echoes back to the probe to ultimately create video images of the prostate. The TRUS can sometimes detect tumors that may not have been detected by a DRE, and it may also give clinicians a better idea of PSA density, which can help distinguish between BPH and prostate cancer. It should be noted that TRUS may not always be able to distinguish between normal tissue and cancer tissue; however, TRUS is an important imaging test when prostate needle biopsies are to be performed, as it gives a visual location of where possible tumors might be located.

Magnetic resonance imaging

For patients who are likely to have low-risk disease (no symptoms, low PSA [<10 ng/mL], low PSA velocity), there is a growing body of opinion that multiparametric MRI should be performed ahead of biopsy, with the possibility that patients with a low risk of cancer on imaging may be offered observation with no initial biopsy [8]. The rationale is that biopsy artifacts on an MRI persist for 3–6 months, making accurate staging difficult post-biopsy. Using multiple MRI sequences on a "clean" prostate allows for an increasingly accurate estimate of the risk of clinically significant disease. Given the low risk of death from early prostate cancer, the reduction in morbidity from avoiding biopsy is attractive as it also prevents the trauma of a cancer diagnosis.

Biopsy

A comprehensive review of the patient's history, age, ethnicity, heredity, comorbidities, and their results from PSA blood tests, DREs, and imaging tests should all be evaluated before determining if a biopsy is needed [4,7]. High PSA levels in particular should not be the sole reason to perform biopsies given the inconclusive correlation between high PSA levels and actual presentation of prostate cancer [5]. PSA levels should be validated by repeat PSA tests [7] and supported by suspicious DREs, imaging results, and the patient's overall history and risk factors [4–7].

Prostate cancer biopsies can be performed by transrectal, perineal, or transurethral method. As mentioned above, biopsies can be guided by TRUS to give clinicians a visual location of possible tumors. Once the suspicious tissue is extracted, the patient's possible prostate cancer can be examined pathologically. While biopsies and an analysis of the tumor histology can allow clinicians to appropriately determine the patient's disease and its severity, the biopsy procedure can also lead to adverse events, such as infection, bleeding, and urinary difficulties, and clinicians should take extra caution to avoid such complications [5]. In addition, with the growing use of MRI prebiopsy, targeted biopsy (usually transperineal using MRI derived information) is increasingly used.

Pathology and the Gleason system

The Gleason system was developed by Dr Donald Gleason in the early 1970s and has become the preferred histological grading system of prostate cancer [2]. The Gleason system is based upon the degree of loss of the normal glandular tissue architecture (Figure 2.3) [9]. Biopsies are graded from 1–5 and then an aggregate score incorporating the principal and major secondary score is produced (eg, 3 + 4 = 7). Scores conventionally tend to be grouped into the following broader risk categories:

- 1–5: low-grade prostate cancer
- 6–7: intermediate-grade cancer (most prostate cancers fall into this group)
- 8–10: high-grade cancer

Increasingly, however, pathologists are reluctant to use Gleason grades of 1 or 2, making 3 effectively the lowest grade cancer score. A Gleason score of 3 + 3 is thus now regarded as low risk, 3 + 4 and 4 + 3 as intermediate risk, and 8–10 as high risk. Care must therefore be taken when comparing recent with older data due to this grade migration.

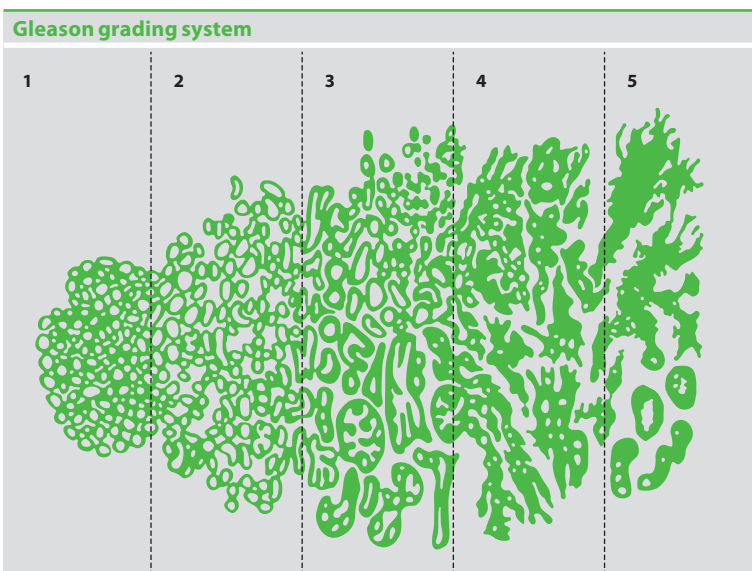

Figure 2.3 Gleason grading system. This illustration exemplifies the Gleason grading system, with five basic tissue patterns associated with five tumor grades. Reproduced with permission from Huang et al [9].

Staging

Generally, conventional staging is done using the American Joint Committee on Cancer (AJCC) TNM classification system (Tables 2.2 and 2.3) [2], which is based on:

- the evaluation of the primary tumor (T category),
- whether the cancer has spread to regional (nearby) lymph nodes (N category),
- whether there is evidence of distant metastasis (M category),

TNM staging of prostate cancer
Clinical evaluation of the primary tumor (T)
TX: Cannot evaluate the primary tumor
T0: No evidence of tumor
T1: Tumor present, but not detectable clinically or with imaging
T1a: Tumor was incidentally found in <5% of prostate tissue resected (for other reasons)
T1b: Tumor was incidentally found in >5% of prostate tissue resected
T1c: Tumor was found in a needle biopsy performed due to an elevated serum PSA
T2: Tumor can be felt (palpated) on examination, but has not spread outside the prostate
T2a: Tumor is in half or less than half of one of two lobes of the prostate gland
T2b: Tumor is in more than half of one lobe, but not both
T2c: Tumor is in both lobes
T3: Tumor has spread through the prostatic capsule (if it is only partway through, it is still **T2**)
T3a: Tumor has spread through the capsule on one or both sides
T3b: Tumor has invaded one or both seminal vesicles
T4: Tumor has invaded other nearby structures
Clinical evaluation of the regional lymph nodes (N)
NX: Cannot evaluate the regional lymph nodes
N0: There has been no spread to the regional lymph nodes
N1: There has been spread to the regional lymph nodes
Evaluation of distant metastasis (M)
M0: There is no distant metastasis
M1: There is distant metastasis
M1a: The cancer has spread to lymph nodes beyond the regional ones
M1b: The cancer has spread to bone
M1c: The cancer has spread to other sites (regardless of bone involvement)

Table 2.2 TNM staging of prostate cancer. M, metastasis; N, nodes; PSA, prostate-specific antigen; T, tumor. Reproduced with permission from © American Joint Committee on Cancer, 2013 [2]. All rights reserved. Additional information provided by Heidenreich et al [7].

- the PSA levels at the time of diagnosis, and
- the Gleason score based on a biopsy.

The use of additional staging/diagnostic tests should match the severity of disease as determined by the biopsy and prostate imaging (TRUS or MRI). Based on clinical experience, patients with low-risk disease (PSA <10 ng/mL, Gleason 3 + 3 or 3 + 4 if aged >70–75 years) probably need no further imaging. The likelihood of metastasis increases in patients with intermediate- and high-risk disease, and in these cases full staging is justified, with cross-sectional abdominal and pelvic imaging at a minimum as well as an isotope bone scan. In practice, it is in the author's opinion that it is helpful to define prostate cancer by risk group when evaluating the patient (see Table 2.4 for other classification methods) [7,10–13]; multiple risk groups may overlap, but the analysis will provide a more comprehensive view of the patient's cancer.

American Joint Committee on Cancer anatomic stage/prognostic groups

Group	T	N	M	PSA	Gleason
I	T1a–c	N0	M0	PSA<10	Gleason ≤6
	T2a	N0	M0	PSA<10	Gleason ≤6
	T1–2a	N0	M0	PSA X	Gleason X
IIA	T1a–c	N0	M0	PSA<20	Gleason 7
	T1a–c	N0	M0	PSA≥10<20	Gleason ≤6
	T2a	N0	M0	PSA≥10<20	Gleason ≤6
	T2a	N0	M0	PSA<20	Gleason 7
	T2b	N0	M0	PSA<20	Gleason ≤7
	T2b	N0	M0	PSA X	Gleason X
IIB	T2c	N0	M0	Any PSA	Any Gleason
	T1 – 2	N0	M0	PSA ≥20	Any Gleason
	T1 – 2	N0	M0	Any PSA	Gleason ≥8
III	T3a–b	N0	M0	Any PSA	Any Gleason
IV	T4	N0	M0	Any PSA	Any Gleason
	Any T	N1	M0	Any PSA	Any Gleason
	Any T	Any N	M1	Any PSA	Any Gleason

Table 2.3 American Joint Committee on Cancer anatomic stage/prognostic groups. When either PSA or Gleason is not available, grouping should be determined by T stage and/or either PSA or Gleason as available. M, metastasis; N, nodes; PSA, prostate-specific antigen; T, tumor. Reproduced with permission from © AJCC Cancer Staging Manual, 2013 [2]. All rights reserved.

Categorization by risk group

Classification	Definition
European Association of Urology [7]	
High-risk, localized prostate cancer	cT3a *or* Gleason score 8–10 *or* PSA >20 ng/mL
	T2c *or* Gleason score >7 *or* PSA >20 ng/mL
Locally advanced prostate cancer	cT3a
	T3–4, N0, M0
	T3–4, any N *or* any T, N1
European Society of Medical Oncology [10]	
High-risk localized (also locally advanced disease)	T3–4 *or* Gleason score >7 *or* PSA >20 ng/mL
National Comprehensive Cancer Center [11]	
High-risk localized	T3a *or* Gleason score 8–10 *or* PSA >20 ng/mL
Locally advanced/very high	T3b–T4
National Collaborating Centre for Cancer/National Institute of Health and Care Excellence [12]	
High-risk localized	T3–T4 *or* Gleason score 8–10 *or* PSA >20 ng/mL
Locally advanced prostate cancer	T3–T4, any N, M
STAMPEDE trial [13]	
High risk, nonmetastatic	Any 2 from: T3–4, Gleason score 8-10, PSA >40 ng/mL

Table 2.4 Categorization by risk group. M, metastasis; N, nodes; PSA, prostate-specific antigen; T, tumor. Adapted from Heidenrech et al [7], Horwich et al [10], National Comprehensive Cancer Center [11], National Collaborating Centre for Cancer [12], and STAMPEDE Trial [13].

References

1 Theodorescu D. Prostate cancer, clinical oncology. In: Schwab M, ed. *Encyclopedic Reference of Cancer*. Berlin, Germany: Springer-Verlag; 2001:720-727.

2 American Joint Committee on Cancer. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer Science+Business Media; 2010.

3 Taylor JA, Albertsen PC. Benign and malignant disease of the prostate. In: Rosenthal RA, Zenilman ME, Katlic MR, eds. *Principles and Practice of Geriatric Surgery*. 2nd ed. New York, NY: Springer Science+Business Media; 2011:1069-1082.

4 Descotes J-L, Legeais D, Gauchez A-S, Long J-A, Rambeaud J-J. PSA measurement following prostatectomy: an unexpected error. *Anticancer Res*. 2007;27:1149-1150.

5 Basch E, Oliver TK, Vickers A, et al. Screening for prostate cancer with prostate-specific antigen testing: American Society of Clinical Oncology provisional clinical opinion. *J Clin Oncol*. 2012;30:3020-3025.

6 Carter HB, Albertsen PC, Barry MJ, et al. Early detection of prostate cancer: AUA guideline. www.auanet.org/common/pdf/education/clinical-guidance/Prostate-Cancer-Detection.pdf. Accessed July 18, 2013.

7 Heidenreich A, Bellmunt J, Bolla M, et al. EAU guidelines on prostate cancer. Part I: screening, diagnosis, and treatment of clinically localised disease. *Eur Urol*. 2011;59:61-71.

8 Gupta RT, Kauffman CR, Polascik TJ, Taneja SS, Rosenkrantz AB. The state of prostate MRI in 2013. *Oncology (Williston Park)*. 2013;27:262-270.

9 Huang PW, Lee C-H, Lin P-L. Classifying pathological prostate images by fractal analysis. In: Chatterjee A, Siarry P, eds. *Computational Intelligence in Image Processing*. Heidelberg, Germany: Springer-Verlag Berlin Heidelberg; 2013:253-263.

10 Horwich A, Parker C, Bangma C, Kataja V; on behalf of the ESMO Guidelines Working Group. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2010;21(suppl 5):v129-v133.

11 National Comprehensive Cancer Center (NCCN). NCCN clinical practice guidelines in oncology (NCCN Guideline®): prostate cancer. www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed July 18, 2013.

12 National Collaborating Centre for Cancer. Prostate cancer: diagnosis and treatment. 2008. www.nice.org.uk/nicemedia/live/11924/39687/39687.pdf. Accessed July 18, 2013.

13 STAMPEDE: Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy: a multi-stage multi-arm randomised controlled trial. www.clinicaltrials.gov/ct2/show/study/NCT00268476. Accessed July 18, 2013.

http://www.springer.com/978-1-907673-81-8

Primer on Prostate Cancer
James, N.
2014, VIII, 50 p. 14 illus. in color., Softcover
ISBN: 978-1-907673-81-8