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Anatomy of the prostate gland and surgical pathology of prostate cancer

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Introduction

Urologists and pathologists have focused more and more on the anatomic structures of the human prostate gland and their relationship to prostate carcinoma development and prognosis since the resurgence of radical prostatectomy in the late 1980s. The accessibility of whole-mount slide preparation in the study of the prostate has greatly simplified this analysis.

This chapter concentrates on the anatomy of the prostate gland and analyzes how anatomic structures relate to the origin, development, and evolution of prostate carcinoma. The concept of zonal anatomy and its role in prostate carcinoma will also be described.

Anatomy and histology of the normal prostate gland

Embryology and development of the prostate gland

During the third month of gestation, the prostate gland develops from epithelial invaginations from the posterior urogenital sinus under the influence of the underlying mesenchyme [1]. The normal formation of the prostate gland requires the presence of 5 α -dihydrotestosterone, which is synthesized from fetal testosterone by the action of 5 α -reductase [2]. This enzyme is localized in the urogenital sinus and external genitalia of humans [3]. Consequently, deficiencies of 5 α -reductase will cause a rudimentary or undetectable prostate in addition to severe abnormalities of the external genitalia, although the epididymides, vasa deferentia, and seminal vesicles remain normal [4].

During the prepubertal period, the constitution of the human prostate remains more or less identical but begins to undergo morphologic changes into the adult phenotype with the beginning of puberty. The gland enlarges continuously in size to reach the adult weight of approximately 20 g by 25–30 years of age [1].

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Normal anatomy and histology of the prostate

The base of the prostate is at the bladder neck and the apex at the urogenital diaphragm [5]. The Denonvilliers' fascia, a thin, filmy layer of connective tissue, separates the prostate and seminal vesicles from the rectum posteriorly. Skeletal muscle fibers from the urogenital diaphragm extend into the prostate at the apex and up to the midprostate anteriorly [6].

In the twentieth century, several investigators maintained that the prostate gland was composed of diverse lobes by analogy with laboratory animals [1, 7]. This concept became popular even though no distinct lobes can be seen in the human. Thereupon, McNeal established the current and most widely accepted concept of various zones rather than lobes of the prostate [8, 9, 10].

The peripheral zone comprises all the prostatic glandular tissue at the apex as well as all of the tissue located posteriorly near the capsule (Figure 1.1). In this zone, carcinoma, chronic prostatitis, and postinflammatory atrophy are relatively more

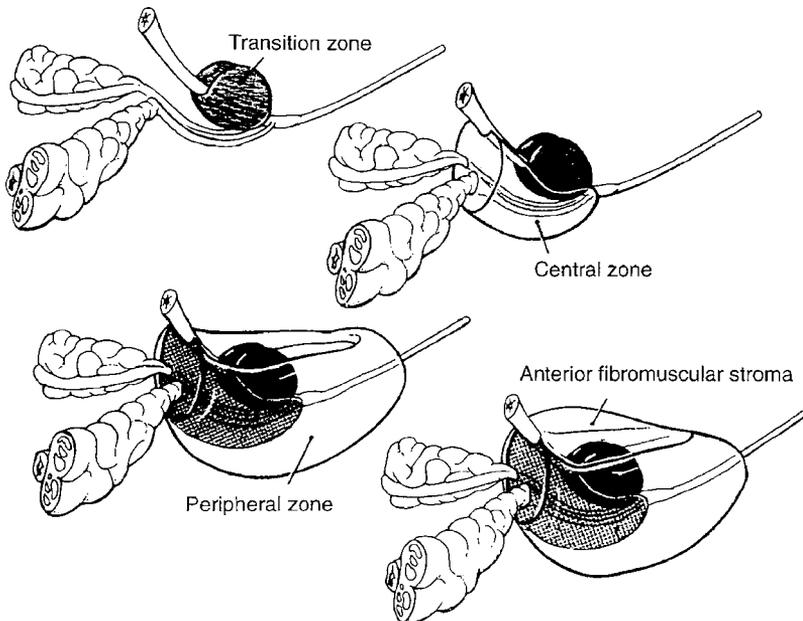


Figure 1.1. Zonal anatomy of the normal prostate as described by McNeal [8, 9, 10]. The transition zone comprises only 5%–10% of the glandular tissue in the young male. The central zone forms part of the base of the prostate and it is traversed by the ejaculatory ducts. The prostate is constituted by the peripheral zone, particularly distal to the verumontanum. (From Greene DR, Shabsigh R, Scardino PT. Urologic ultrasonography. In: Walsh PC, Retik AB, Stamey TA *et al.* eds. *Campbell's Urology*, 6th edn. Philadelphia: WB Saunders, 1992; 342–393, with permission.)

common than in the other zones. The central zone is a cone-shaped area of the adult gland, with the apex of the cone at the confluence of the ejaculatory ducts and the prostatic urethra at the verumontanum (Figure 1.1). The transition zone consists of two equal portions of glandular tissue lateral to the urethra in the midgland (Figure 1.1). This portion of the prostate is involved in the development of age-related benign prostatic hyperplasia (BPH) and, less commonly, adenocarcinoma. The anterior fibromuscular stroma (AFMS) forms the convexity of the anterior external surface. The apical half of this area is rich in striated muscle, which blends into the gland and the muscle of the pelvic diaphragm (Figure 1.1). Toward the base, smooth muscle cells become predominant, blending into the fibers of the bladder neck [11]. The distal portion of the AFMS is important in voluntary sphincter functions, whereas the proximal portion plays a central role in involuntary sphincter functions.

The histologic architecture of the prostate is that of a branched duct gland. Two cell layers, a luminal secretory columnar cell layer and an underlying basal cell layer, line each gland or duct. The lumens of otherwise normal prostatic glands and ducts frequently contain multilaminated eosinophilic concretions, termed corpora amylacea, that become more common in older men. Calculi are larger than those corpora with a predilection for the ducts that traverse the length of the surgical capsule, separating the transition and peripheral zones.

The prostatic capsule is composed of fibrous tissue surrounding the gland. Although the term “capsule” is embedded in the current literature and common parlance, there is no consensus about the presence of a true capsule [12]. This capsule is best appreciated posteriorly and posterolaterally as a layer more fibrous than muscular, between the prostatic stroma and extraprostatic fat.

The seminal vesicles are located superior to the base of the prostate. They undergo confluence with the vas deferens on each side to form the ejaculatory ducts. The ejaculatory duct complex consists of the two ejaculatory ducts along with a second loose stroma rich in vascular spaces. The utricle (when present) is located between the ejaculatory ducts. The remnants of the utricle occasionally form cystic structures in the midline posteriorly. The seminal vesicles are resistant to nearly all of the disease processes that affect the prostate. Seminal vesicle involvement (SVI) by prostate cancer (PCa) is one of the most important predictors for PCa progression (Figure 1.2) [13, 14].

Metastatic PCa oftentimes involves pelvic lymph nodes. The prognostic significance of this feature has been documented by several investigators [15]. In some individuals, periprostatic (PP) and periseminal vesicle (PSV) lymph nodes are

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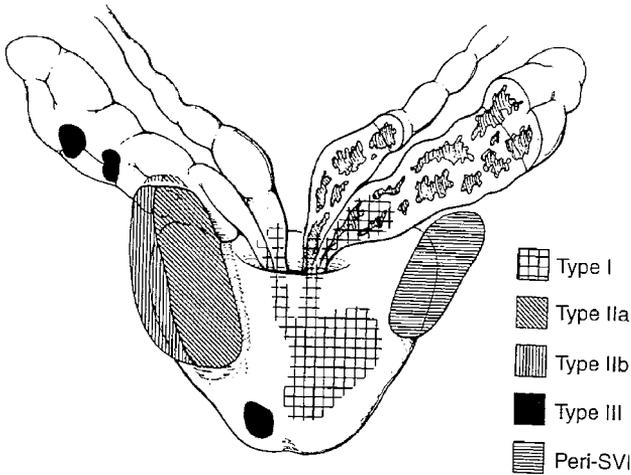


Figure 1.2. Diagrammatic representation of the three patterns of seminal vesicle involvement (SVI) and peri-SVI. The combination of types I and II is categorized as type I + II. (From Ohori M, Scardino PT, Lapin S L *et al.* The mechanisms and prognostic significance of seminal vesicle involvement by prostate cancer. *Am J Surg Pathol* 1993; 17: 1253 [14], with permission.)

present and, although uncommon, they may be involved by metastatic PCa as well, sometimes in the absence of pelvic lymph node metastases [16].

Neural anatomy

The prostate is an extraordinarily well-innervated organ. Two neurovascular bundles are located posterolaterally adjacent to the gland and form the superior and inferior pedicles on each side. These nerves are important in regulating the physiology, morphology, and growth maturation of the gland [17, 18, 19, 20]. The prostate receives both parasympathetic and sympathetic innervation, the former from the hypogastric and pelvic nerves, and the latter from a peripheral hypogastric ganglion [21]. Walsh and Donker previously demonstrated the importance of these nerves in penile erection, so urologists as well as patients have put an increasing interest on nerve-sparing surgical treatment of PCa [22].

Surgical pathology of the prostate gland

Epidemiology, clinical aspects

Prostate cancer remains the most common malignancy affecting men and the second leading cause of cancer-related death of men in the United States [23]. In 2007, there were 218 890 new cases of PCa, resulting in 27 050 deaths in the United States [23]. Adenocarcinoma accounts for about 95% of prostatic neoplasms, and

frequently has no specific presenting symptoms. More often than not, PCa is clinically silent, although it sometimes mimics obstructive symptoms of BPH. Therefore, patients may be diagnosed with advanced PCa with metastases without symptoms related to the region of prostate. Consequently, in the past two decades the diagnostic value of patient screening by using early detection programs has come to the forefront of focus. With the introduction of widespread screening with serum prostate-specific antigen (PSA), the incidence of stage IV PCa at presentation has dramatically lessened, although the number of PCa detected has increased as well [24].

Morphologic diagnosis of prostate adenocarcinoma

The identification on gross inspection of PCa diagnosed today is often difficult or impossible. Although the color of most grossly visible tumors is tan-white, a minority of PCa cases are yellow, a more specific gross feature of PCa. In prostatectomies, PCa tends to be multifocal, mainly found in the peripheral zone [25, 26], followed by the transition zone and then central zone. In the authors' experience, PCa foci must be at least 5 mm in diameter for reliable gross identification, although much larger tumor areas may be difficult or impossible to accurately identify grossly. Most grossly recognizable tumors are firm to palpation and the minority are fleshy and soft. Most tumors palpable by digital rectal examination (DRE) are visualized by ultrasound and gross inspection.

Histology of prostate cancer and Gleason grading

In both radical prostatectomy specimens and needle biopsy samples, histologic grading of PCa by the Gleason system is the strongest prognostic factor of a patient's time to progression [27, 28, 29]. The Gleason system describes the histologic appearance of PCa under low magnification (architectural as opposed to cytologic grading) (Figure 1.3). The Gleason scoring system is defined by a scale of 1 to 5. Well-differentiated PCa (Gleason grade 1 or 2) is characterized by a proliferation of microacinar structures lined by prostatic luminal cells without an accompanying basal cell layer. At least some of the neoplastic cells contain prominent nucleoli, defined as at least 1 μm in diameter by Gleason but defined as larger by other investigators [28, 30]. Gleason pattern 5 is the highest grade and includes a solid pattern with central necrosis or infiltrating individual cells.

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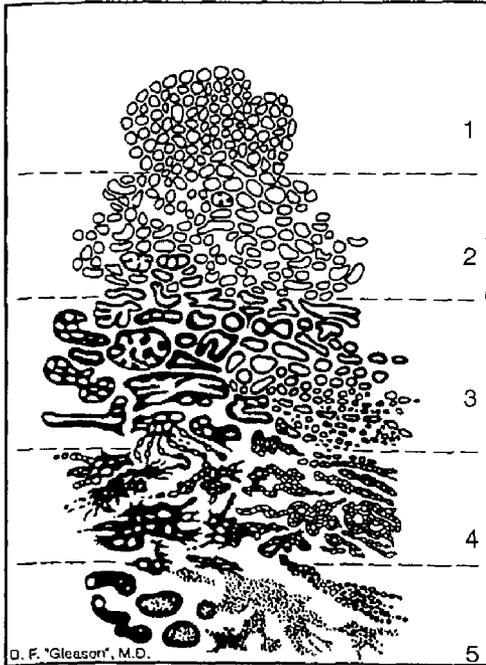


Figure 1.3. Simplified drawing of histologic patterns of prostatic adenocarcinoma, emphasizing the degree of glandular differentiation and relation to stroma. All black in the drawing represents tumor tissue, with all cytologic detail obscured except in the right side of pattern 4, where tiny structures are intended to suggest the hypernephroid pattern. (From Gleason D F. Histologic grading of prostatic adenocarcinoma. In: Tannenbaum M, ed. *Urologic Pathology: The Prostate*. Philadelphia: Lea & Febiger. 1977; 181, with permission).

As PCa is usually heterogeneous with two or more grades in a given cancer, Gleason chose to incorporate both a primary (most prevalent) and a secondary (next most prevalent) grade into the system [31]. The primary pattern is added to the secondary grade to arrive at a Gleason score. Consequently, the Gleason score possibilities range from 2 (1 + 1) up to 10 (5 + 5).

Although the Gleason system is now internationally accepted, there are several issues concerning it as a grading system. Most notably Gleason grading is observer dependent and may vary depending on the level of experience. Also, it is controversial whether to grade PCa after treatment (androgen ablation or radiation). Another limitation is that the majority of patients diagnosed today fall into the Gleason 6–7 category, an intermediate prognostic range limiting the potential usefulness of a 10-point scale. That said, several studies have confirmed that the time to progression in patients with a Gleason 4 + 3 is significantly less compared to that for Gleason 3 + 4 patients [32, 33].

Other histologic parameters such as the presence of extracapsular extension, perineural invasion, surgical margin status, lymph node status and SVI hold prognostic information and have been added to postoperative nomograms in order to optimize the prediction of time to progression (Figure 1.4).

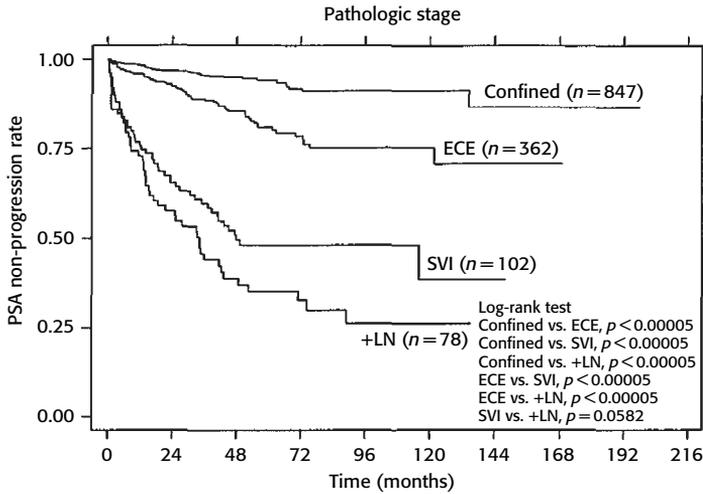


Figure 1.4. Kaplan Meier disease-free probability plot by pathologic stage. ECE, extracapsular extension; LN, lymph node; SVI, seminal vesicle involvement.

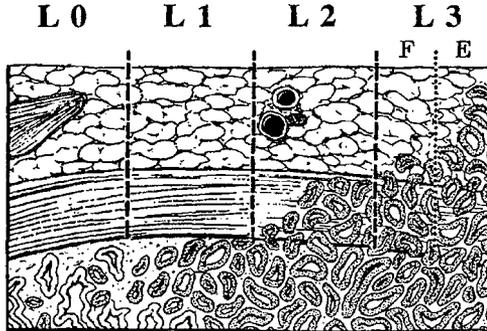


Figure 1.5. Levels of prostatic capsular invasion (see text for definitions.) Extraprostatic extension designated as L3 signifies extension of tumor into periprostatic soft tissue, which may be subclassified as focal (L3F) or established (L3E). The sharpness of the boundaries between prostatic stroma, capsule, and adipose tissue is exaggerated for clarity. (From Stamey TA, McNeal JE, Freiha FS *et al.* Morphometric and clinical studies on 68 consecutive radical prostatectomies. *J Urol* 1988; 129: 1245–1241; [34] and from Wheeler TM. Anatomic consideration in carcinoma of the prostate. *Urol Clin North Am* 1989; 16: 623–634, with permission.)

Several investigations have been done analyzing the prognostic significance of the level of PCa invasion with respect to the prostatic capsule [34, 35, 36]. According to the staging of the International Union Against Cancer (UICC) and also the American Joint Commission on Cancer (AJCC), tumors at levels 0–2 would be considered pathologically confined, whereas tumors that are at level 3 (L3), focal (L3F) or established (L3E) are considered pathologically not confined to the prostate (Figure 1.5) [37].

Various studies have demonstrated the importance of the prostatic neuroanatomy due to its relationship with PCa in the process of perineural invasion

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(PNI). Indeed, PNI is highly prevalent in PCa, being reported in about 85% of radical prostatectomy cases [38, 39, 40]. It has been shown to be the primary mechanism by which PCa penetrates the capsule and/or metastasizes [41]. One study has shown that the volume of PCa in the perineural space is closely correlated with prognosis [42].

Recently, a new system based on the quantification of intratumoral reactive stroma, also named “stromagenic cancer,” has been introduced as another way to grade PCa. Stromagenic cancer is the phenomenon of dedifferentiation of smooth muscle cells into myofibroblasts that have the capability to promote PCa growth [43, 44]. Reactive stroma (RS) was classified into four groups (Grade 0, up to 5% RS; Grade 1, 6%–15% RS; Grade 2, 16%–50% RS; and Grade 3, >50% RS). Quantification of RS Grades 0 and 3 in PCa was determined to be an independent predictor of recurrence-free survival, and correlated significantly with other clinicopathologic parameters of PCa [45, 46].

Zonal anatomy and prostate adenocarcinoma

Based upon the pioneering work of McNeal beginning in the 1960s, much has been written about the different neoplastic potential of the zones of the prostate, and of the effect of zonal origin on prognosis [47, 48]. At one time the predominant thought was that PCa arose nearly exclusively in the posterior part of the prostate (now known as the peripheral zone) close to the prostatic capsule [16, 49]. However, later studies confirmed that in prostates removed for PCa a significant minority of PCa foci arise in the transition zone and central zone [36, 50]. The periurethral portion of the prostate had been considered to be resistant to the development of PCa, although it was known to be quite susceptible to the development of nodular hyperplasia. McNeal is also credited with describing the unique well-differentiated nature of tumors arising in the transition zone (Gleason pattern 1 and 2) [26]. These tumors were characterized as having a low risk of progression and of being rarely associated with capsular invasion or SVI [26].

Treatment effects on primary prostate adenocarcinoma

Radiation and hormone therapy may cause artifactual elevation of the Gleason score due to collapse of the glandular architecture [51, 52]. At the time of writing, there is no consensus about grading results after treatment [53, 54].

Radiation therapy induces profound changes in the non-neoplastic ducts and acini as well as the prostatic stroma, and the former changes may be confused with adenocarcinoma histologically by the uninitiated [55]. Often, the individual tumor cells appear so damaged by the radiation therapy as to appear non-viable. This latter change may also be seen after endocrine therapy, which can be performed in different ways: orchiectomy, estrogen administration, or androgen deprivation [51, 56].

Other novel therapies have been utilized, such as gene therapy, for PCa. The resulting morphologic changes described associated with HSV-tk ganciclovir gene therapy have been loss of glandular architecture, increased inflammation and apoptosis/necrosis, as well as areas of degenerating tumor cells [57].

Staging systems for prostatic adenocarcinoma

In the twentieth century, several different staging systems for PCa were established. The first internationally accepted staging system for PCa was introduced by Whitmore in 1956. Stages were classified in letters (A–D) [58]. This staging system was modified by Jewett, subdividing level B. Jewett demonstrated that patients with a palpable nodule had increased cancer-free survival [59]. In the early 1950s, staging systems for solid tumors began to consider the TNM (Tumor – Lymph node – Metastasis) classification to analyze patients' prognosis and to determine the tumor's definite level of development. Within each category of TNM, there are several sublevels based on tumor volume or extent (T1–T4), amount and/or size of lymph node metastases (N0–N3), and distant metastases (M0–M1) (Table 1.1) [60]. Since its inception, several enhancements have been made to the TNM staging system to allow more precise analysis of the clinico-pathologic stage of the tumor [61]. In 1992, the AJCC staging system mirrored the TNM staging system [37, 62, 63]. The AJCC staging system is based primarily on a particular clinico-pathologic classification of each tumor, allowing for more precise stratification of patients into prognostically distinct groups [60].

Although many different areas of metastases of a PCa have been described (kidney, breast, brain, liver), metastatic spread most commonly occurs into the pelvic lymph nodes, bones, and lungs [64, 65]. Bony metastases are mainly an osteoblastic process. However, the development and improvement of staging systems is a complex procedure and, today, clinical subspecialties are focusing on the improvement of staging systems for different neoplastic disease to precisely demonstrate each patient's prognosis.

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Table 1.1. The 2002 American Joint Committee on Cancer/International Union Against Cancer TNM Staging Classification

Stage	Definition
Primary tumor, clinical (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor not palpable or visible by imaging T1a: Tumor incidental histologic finding in 5% or less of tissue resected T1b: Tumor incidental histology finding in more than 5% of tissue resected T1c: Tumor identified by needle biopsy [e.g., because of elevated prostate-specific antigen (PSA) levels]
T2	Tumor confined within the prostate ^a T2a: Tumor involves half of one lobe or less T2b: Tumor involves more than half of one lobe but not both T2c: Tumor involves both lobes
T3	Tumor extends through the prostate capsule ^b T3a: Extracapsular extension (unilateral or bilateral) T3b: Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than the seminal vesicle(s): bladder neck, external sphincter, rectum, levator muscles, pelvic wall, or all the above
Primary tumor, pathologic (pT)	
pT2 ^c	Organ confined pT2a: Unilateral, involving half of one lobe or less pT2b: Unilateral, involving more than half of one lobe but not both lobes pT2c: Bilateral
pT3	Extraprostatic extension pT3a: Extraprostatic extension pT3b: Seminal vesicle invasion
pT4	Invasion of bladder, rectum
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node or nodes