Anatomo-Pathology

4

Theodorus H. Van der Kwast

Contents

4.1 Gross Anatomy of the Prostate: Clinical Importance 39
4.1.1 The Boundaries of the Prostate 40
4.1.2 Prostate Lobes 42
4.1.3 McNeal's Four Prostate Regions 42
4.1.4 Prostate Zones and Cancer 43

4.2 Microscopic Anatomy of the Prostate 43
4.2.1 Prostate Zones: Age-Related Microscopic Changes 43
4.2.2 Androgen Deprivation-Induced Changes 44

4.3 Precursor Lesions of Prostate Cancer (H-PIN) 44
4.3.1 High-Grade Prostatic Intraepithelial Neoplasia 44
4.3.2 Intraductal Carcinoma 45

4.4 Prostate Cancer 45
4.4.1 Types and Variants of Adenocarcinoma 46
4.4.2 Gleason Grading of Prostatectomy Specimens 47
4.4.3 Staging of Prostatectomy Specimens 48
4.4.4 Surgical Margins 50
4.4.5 Anterior Prostate Cancers 51
4.4.6 Multifocality and Index Tumor 51
4.4.7 Tumor Volume and Insignificant Cancer 51

4.5 Concluding Remarks 52

References 52

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4.1 Gross Anatomy of the Prostate: Clinical Importance

For several reasons, interest in the anatomy of the prostate gland has been increasing during the last decade. The site of origin of a prostate cancer and its localization within the prostate gland may affect the diagnostic process and influence treatment considerations. Also the recent advent of focal therapy makes it more imperative to establish the exact localization and extent of the prostate cancer or cancers. For adequate pathological staging, it is important to have an understanding of the boundaries of the prostate, particular at its anterior border, at its apex where the prostate borders the skeletal muscle constituting the striated or urethral sphincter and its proximal (bladder neck) border where the prostate merges with the detrusor muscle of the urinary bladder (Hammerich et al. 2009). Finally, ongoing improvements in imaging of the prostate also have led to a more thorough analysis of the gross anatomy of the prostate gland. The official anatomic terminology of the prostate and its contiguous structures has been revised several times in the past, and current recommendations try to accommodate clinical concepts within an updated terminology (Myers et al. 2010) as highlighted in a recent authoritative and well-illustrated review of the topic (Walz et al. 2010).

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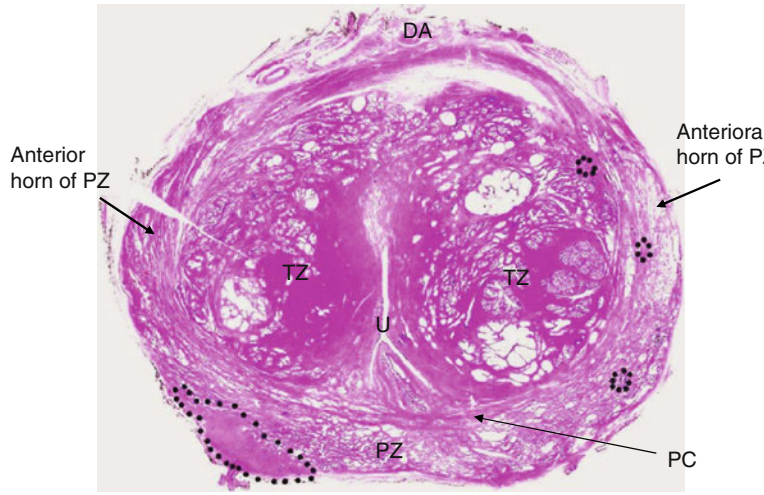

Fig. 4.1 Wholemount section of radical prostatectomy specimen, with multifocal prostate cancer (marked by *dotted line*). *DA* detrusor apron, *PC* posterior commissure, *PZ* peripheral zone, *TZ* transition zone, *U* urethra. The index tumor is located in the posterior peripheral zone, and one small cancer is located in the transition zone of the anterior prostate

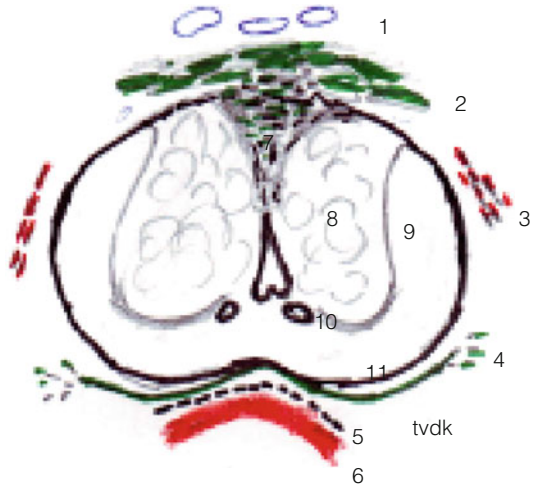

Fig. 4.2 Schematic drawing of the main structures of the mid prostate and its surroundings. The rectal fascia (*5*) is separated from Denonvilliers fascia (*4*) by the mesorectal plane. Legend: *1*=dorsal vascular complex, *2*=detrusor apron, *3*=levator ani skeletal muscle, *4*=Denonvilliers fascia, *5*=rectal fascia, *6*=rectal wall, *7*=anterior fibromuscular stroma, *8*=transition zone, *9*=anterior horn of peripheral zone, *10*=ejaculatory duct, and *11*=peripheral zone (posterior)

4.1.1 The Boundaries of the Prostate

The prostate is situated between the rectum at the posterior surface and smooth muscle fibers originating from the outer, longitudinal detrusor muscle of the bladder (detrusor apron) at its anterior surface (Figs. 4.1 and 4.2).

4.1.1.1 Denonvillier's or Posterior Prostatic Fascia

The posterior surface of the prostate is demarcated by Denonvillier's fascia, a continuous fibromuscular layer that covers the posterior surface of the prostate enveloping the seminal vesicles. Its superior (cranial) part merges with the subperitoneal connective tissue of the urinary bladder. Denonvillier's fascia has previously been referred to as rectovesical septum, although this fascia is not really a septum and it is also not belonging to the rectum or bladder wall. More recently, Denonvillier's fascia has been coined posterior prostatic and seminal vesicle fascia (Walz et al. 2010). Current consensus is that Denonvillier's fascia originates from the fusion of the two walls of the embryological peritoneal cul-de-sac, analogous to the female rectovaginal septum, but these two layers cannot be distinguished during surgery (Lindsey et al. 2000). Denonvillier's fascia consists of a single layer of fibrous tissue, loose connective tissue, and smooth muscle of variable caliber (Fig. 4.3). More laterally, the fascia becomes fragmented and disappears. The thickness of the fascia is highly variable, becoming thinner at advancing age. When a surgeon performs an interfascial or extrafascial dissection during prostatectomy, the Denonvillier's fascia will be visible in the pathology specimen. The latter dissections

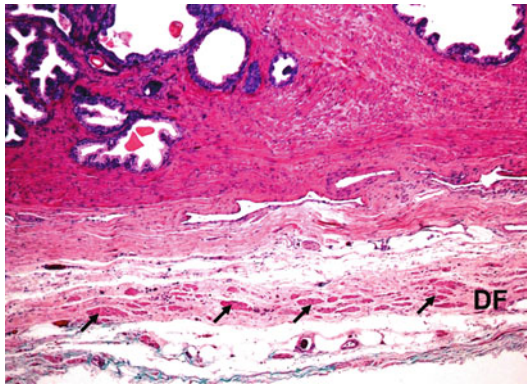

Fig. 4.3 Section of posterior margin of the prostate, displaying Denonvilliers fascia (*DF*) with small bundles of smooth muscle (*arrows*) embedded in fibrous tissue of low cellularity. Here, Denonvilliers fascia is separated from the outer prostate by a thin layer of loose connective tissue

have an optimal oncological outcome, because Denonvillier's fascia is adherent to the prostate at its mid portion. Further, prostate cancers rarely if at all extend beyond Denonvillier's fascia (Villers et al. 1993). To preserve the neurovascular bundle as good as possible, an intrafascial dissection may be chosen, obviously with an increased risk of prostate incision (Walz et al. 2010).

4.1.1.2 The Endopelvic Fascia and Pubovesical Ligaments

On the anterior (ventral) aspect of the prostate is the "endopelvic fascia," representing a sheet of tissue of variable thickness covering the prostate from its base to the apex, while extending laterally and inferiorly toward the pubic bones of the symphysis, where it connects with and is reinforced by the fibers of the puboprostatic or pubovesical ligaments (Myers et al. 2010). The latter contains fibrous tissue but also smooth muscle of longitudinal detrusor muscle origin. The composition and structure of the endopelvic fascia can display much individual variation.

Cross sections of a prostatectomy at the mid prostate at the site of the verumontanum (seminal colliculus), harboring the orificium of the ejaculatory ducts show at its anterior surface a mixture of bundles of smooth muscle (detrusor apron), skeletal muscle, likely an extension of the levator ani and fibroadipose tissue, adhered to the prostate at the midline to the anterior fibromuscular septum or anterior commissure (Fig. 4.2). More anterior, adipose tissue may be present, containing the veins and arteries of the dorsal vascular complex (Fine et al. 2007; Myers et al. 2010). The anterior fibromuscular septum, separating the left and right halves of the prostate varies in thickness and merges imperceptibly with the extraprostatic tissue in the midline (Fig. 4.2). As a consequence, it may be challenging for the pathologist to determine the presence of extraprostatic extension of an anterior localized adenocarcinoma (Fine et al. 2007; Magi-Galluzzi et al. 2011). More lateral, adipose tissue may occasionally be present between the prostate and the endopelvic fascia, facilitating the identification of extraprostatic extension of an anterior carcinoma.

4.1.1.3 The Inferior Boundary of the Prostate

The prostate apex represents the site where the intermediate or membranous part of the urethra exits the prostate. This part of the urethra is surrounded by the external urethral sphincter composed of thin caliber skeletal muscle fibers. The external urethral sphincter is a distinct muscular structure, separated from the pelvic floor musculature by a thin fibrous layer (Stolzenburg et al. 2007). The sphincter is horseshoe-shaped, with only collagenous and elastic fibrous tissue posteriorly. Historically, the terminology of urogenital diaphragm was used to describe the external striated urethral sphincter, but this was shown to be an artifact of cadaveric dissection (Myers et al. 2010). Cross sections of the prostate apex of a radical prostatectomy specimen show an intermixture of benign prostatic glandular tissue with skeletal muscle fibers at the anterior part of the specimen, obfuscating a clear demarcation between prostate and sphincter tissue. For this reason, extension of a carcinoma between skeletal muscle fibers of the apex is not considered a manifestation of extraprostatic extension.

4.1.2 Prostate Lobes

Clinically, during digital rectal examination, a lobulation of the prostate may be noted. This lobulation of the prostate may be the consequence of (1) an anatomic phenomenon, that is, the indentation of the rectal surface, and (2) the preferential growth of the transition zone in elder men, commonly referred to as benign prostatic hyperplasia (Myers et al. 2010). The degree of the furrow of the rectal surface of the prostate was found to be dependent on the closeness of the ejaculatory ducts to the posterior surface of the prostate. Thus, anatomic variations of the localization of the ejaculatory ducts may contribute to the outside appearance of the prostate. In the mid-posterior urethral position, benign prostate hyperplasia may result into median lobe hyperplasia, also known as Home's lobe, protruding as a ball valve into the bladder lumen just inferior to the trigone. Rarely, a discrete midline anterior benign prostate hyperplastic lobule may be seen mid anterior at the bladder neck. Another cause of a lobular appearance may be the development of a nodule as the consequence of a carcinoma. Although the vast majority of contemporary carcinomas do not present themselves as a nodule, prostate cancers identified by positive digital rectal examination are pathologically advanced in over 50% of men (Gosselaar et al. 2008).

4.1.3 McNeal's Four Prostate Regions

In 1988, McNeal proposed a model of zonal anatomy of the prostate gland, abolishing the previous concept of a lobular organization of the gland structure (McNeal 1988). In his model, the prostate is divided into four regions, that is, (1) the anterior fibromuscular stroma, (2) the central, (3) the transition, and (4) the peripheral zone (Figs. 4.1 and 4.2).

4.1.3.1 The Anterior Fibromuscular Stroma

The anterior fibromuscular stroma represents dense fibromuscular tissue, stretching between the anterior part of the urethra to the outer anterior margin of the prostate, merging with the internal sphincter of the bladder neck and with the striated muscle of the external sphincter at the apex. The distal (apex) portion of the anterior fibromuscular stroma is rich in striated muscle and is important in voluntary sphincter function, whereas in its more superior end, smooth muscle becomes a dominant feature with an important role in involuntary sphincter functions (Hammerich et al. 2009). The anterior fibromuscular stroma contains few if any prostatic glands. Maintenance of its integrity may be important for the outflow resistance of urine.

4.1.3.2 The Central Zone

The central zone is a cone-shaped area between the ejaculatory ducts and the bladder neck, situated posterior to the ascending prostatic urethra. Histologically, the prostatic glands in the central zone have a distinct and more complex architecture often with cribriform and papillary features as compared to those in the other zones. For pathologists, it is important to recognize central zone glands, because their nuclear features may resemble high-grade prostatic intraepithelial neoplasia (H-PIN), a precursor lesion of prostate cancer (Bostwick et al. 2004). Confusingly, radiologists may occasionally refer to "central gland" when actually describing the combined periurethral transition and central zone, while they usually do not separately report on the "central zone."

4.1.3.3 The Transition and Peripheral Zone

The transition zone is mainly located lateral and anterior of the urethra (Figs. 4.1 and 4.2) and may be separated from the peripheral zone by a band of denser fibromuscular stroma, that is, the posterior commissure (Myers et al. 2010). The largest amount of peripheral zone tissue is at the inferior (apex) and posterior part of the prostate, but it extends as the lateral horn of the peripheral zone to the anterior part of the prostate. Thus, the anterior prostate comprises both a peripheral zone (lateral) and transition zone (mediolateral) component, as well as the midline anterior fibromuscular stroma (Fine et al. 2007). It should be noted

that the definition of the anterior region, e.g., anterior to the urethra (Bott et al. 2002), varies among authors.

4.1.4 Prostate Zones and Cancer

About 70% of prostate cancers originate in the peripheral zone, most of them at a posterior or posterolateral localization (McNeal 1988). This coincides with the frequent occurrence of the cancer precursor H-PIN in the peripheral zone and its much rarer occurrence in the transition zone (Bostwick et al. 2004). In several patient series, it was shown that, in spite of significantly higher PSA levels as well as greater tumor volume when compared with those of peripheral zone cancers, tumors from the transition zone showed similar biochemical cure rates following radical prostatectomy (Van der Kwast et al. 2011). This would suggest a less aggressive phenotype for transition zone cancers when compared to tumors from the peripheral zone, but contradictory findings have also been reported. Augustin et al. (2003) reported that the zonal location was not an independent prognostic factor on multivariate analysis.

The determination of the zonal origin of prostate carcinoma by the pathologist is more challenging on standard quadrant sections of prostatectomy specimens when compared to whole-mount sections (Fine et al. 2007). Often a prostate cancer involves both the peripheral and transition zone, and presence of histological features typical for some of the transition zone cancers and/or the presence of the largest proportion of a carcinoma in the transition zone might occasionally provide an argument that the tumor has arisen within the transition zone.

4.2 Microscopic Anatomy of the Prostate

Histologically, the prostate glands and ducts in all zones share a similar cellular composition; they are lined by an inner layer of luminal or secretory cells and an outer rim of basal cells. Each of the three anatomically distinct zones of the prostate has its own set of periurethral main prostatic ducts. Their lining often displays a hyperplasia of basal cells, and here the luminal cells may display a more columnar (ductal) appearance (Pickup and Van der Kwast 2007). The periurethral ducts give off branches, with tributaries adopting the epithelial morphology of prostatic acini as they progress upstream from the urethra. Here, the ducts and acini are no longer distinguishable. Interspersed within the glandular lining of the ducts and acini are the neuroendocrine cells which secrete regulatory neuropeptides. Only the luminal cells express prostate-specific antigen, which is under androgen regulation. Androgen receptors can be found in the nuclei of luminal cells and fibromuscular stromal cells (Fig. 4.4), whereas the neuroendocrine cells and most of the basal cells lack androgen receptors (Krijnen et al. 1993).

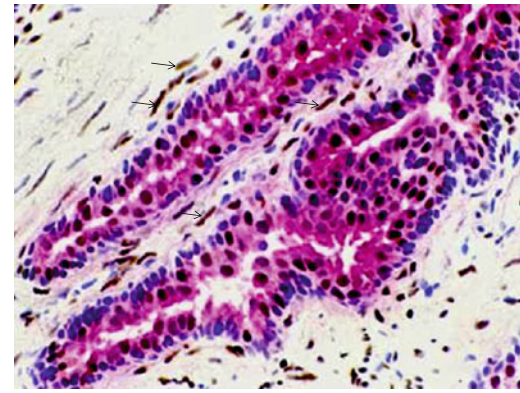

Fig. 4.4 Microscopic image of prostate tissue immunostained for PSA (*red*) and androgen receptor (*brown*). *Blue* nuclei are unstained. Both stromal cells (*arrows*) and PSA-positive luminal cells are positive for androgen receptor, while basal cells are negative for androgen receptor

4.2.1 Prostate Zones: Age-Related Microscopic Changes

Although morphologically the peripheral and transition zone show a strong resemblance, expression array studies have shown consistent differences in expression patterns (Van der Heul-Nieuwenhuijsen et al. 2006). There are also physiological differences, which become manifest during aging and under conditions of androgen deprivation

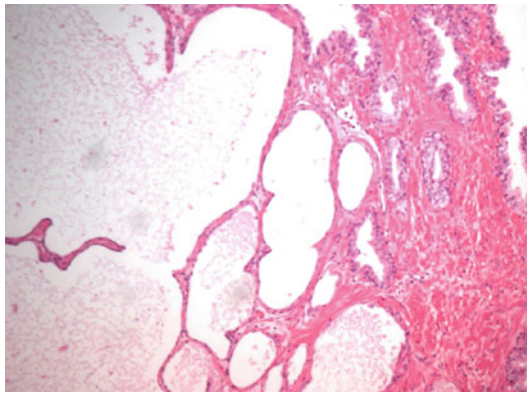

Fig. 4.5 Microscopic image of prostate glands showing cystic atrophy, adjacent to normal prostate glands at the *right*

(see Sect. 4.2.2). In aging men, hyperplasia of both the glandular and/or fibromuscular component occurs almost uniquely in the transition zone. Infarctions do also occur more frequently in the transition zone of the prostate, particularly in enlarged prostates due to benign prostate hyperplasia (Brawn et al. 1994). In comparison with the transition zone, the peripheral zone is more often subject to glandular atrophy. Aging-related atrophy as seen in the peripheral zone mostly has a focal distribution. Various histological forms of atrophy may coexist, including partial atrophy, cystic atrophy (Fig. 4.5), sclerotic atrophy, and hyperplastic atrophy or postatrophic hyperplasia. It was recently shown that partial atrophy and focal atrophy are generally not associated with chronic inflammation (Billis et al. 2010). Some postulated mainly on the basis of circumstantial evidence that chronic inflammation associated with glandular atrophy, that is, postinflammatory atrophy, is a condition underlying the subsequent development of cancer (De Marzo et al. 2004), but evidence for this view is inconclusive.

4.2.2 Androgen Deprivation-Induced Changes

It is well-established that long-term use of aromatase inhibitors, such as Dutasteride, leads to an average reduction in prostate gland volume by 17.5% after 2 years, mainly attributed to its effect on BPH (Andriole et al. 2010). Microscopic changes of the normal tissues during long-term administration of aromatase inhibitors have not been described. This is in contrast to the pronounced effects of antiandrogens and lutein hormone releasing hormone agonists. After androgen deprivation to castration levels, the entire prostate will shrink in size to about 80% of the original size within 3 months of treatment. This reduction in volume is associated with a profound remodeling of the prostate tissue (Têtu et al. 1991). This remodeling is different for the peripheral and transition zone of the normal prostate: in the peripheral zone, a general atrophy of prostatic glands is noted, that is, flattening of the luminal cells resting on a single conspicuous layer of cuboid basal cells, while the glands lose their infoldings and they have a more flattened appearance. In contrast, the transition zone glands display more prominent basal cell hyperplasia, and the glands become smaller and more rounded. Castration-level androgen deprivation is also causing periprostatic fibrosis, which may impact surgery in case of the now obsolete neoadjuvant therapy for more advanced prostate cancer (Têtu et al. 1991).

4.3 Precursor Lesions of Prostate Cancer (H-PIN)

A few histopathologically distinct glandular proliferations have in the past been proposed as a precursor lesion for prostate cancer. They include H-PIN, atypical adenomatous hyperplasia (adenosis), and intraductal carcinoma of the prostate (IDC-P). Only H-PIN is now commonly recognized as a true prostate cancer precursor lesion, while the jury is still out for IDC-P and adenosis is now considered an unlikely prostate cancer precursor.

4.3.1 High-Grade Prostatic Intraepithelial Neoplasia

H-PIN is the term used to denote the presence of dysplastic features in the luminal cells lining prostatic glands or ducts, while retaining the antecedent

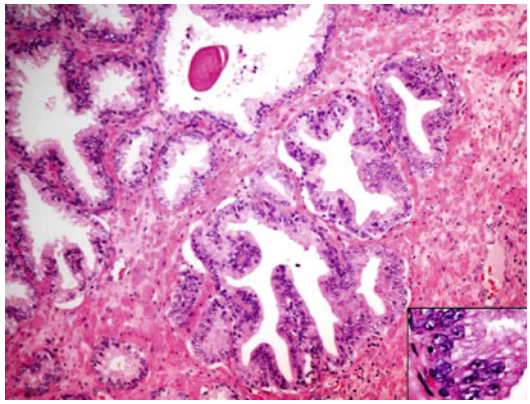

Fig. 4.6 Micrograph showing H-PIN at the *right* and benign glands *upper left*. H-PIN maintains the normal glandular architecture, but its cytoplasm is more basophilic. The *inset* illustrates the prominent nucleoli which are a hallmark of H-PIN

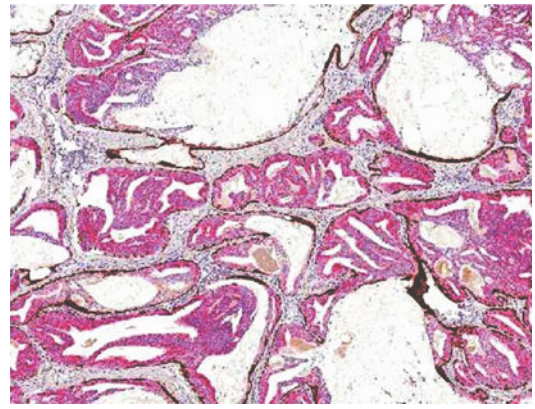

Fig. 4.7 Low-power micrograph of an extensive intraductal carcinoma of the prostate immunostained for alpha-methyl coenzyme A (*red*) racemase and the basal-cell marker high-molecular weight keratin (*brown*). Glands and ducts are distended by large numbers of neoplastic cells (*red*), but remain lined by basal cells (*brown*)

architecture of benign glands (Fig. 4.6). The hallmark of H-PIN is the presence of prominent nucleoli in cells lining prostatic glands or ducts with a luminal (but not basal) cell morphology and location (Bostwick et al. 2004). Montironi et al. (2005) reported that H-PIN was found in association with invasive carcinoma in 70% of cystoprostatectomy specimens with an incidental prostate cancer and in 50% of specimens without prostate cancer. Because of this association of H-PIN with carcinoma, their similarity in cytonuclear features, their close spatial association in the prostate, and shared specific genetic changes, H-PIN is considered as precursor for prostate cancer (Epstein 2009). It remains, however, unclear which proportion of H-PIN actually progresses over time to invasive prostate cancer.

4.3.2 Intraductal Carcinoma

Intraductal carcinoma of the prostate (IDC-P) is a histopathologically distinctive entity characterized by malignant cells expanding the lumen of prostatic ducts and acini, while at least a partial rim of basal cells continues to be present (Guo and Epstein 2006; Pickup and Van der Kwast 2007). IDC-P is commonly associated with conventional acinar prostatic adenocarcinoma, but in rare cases, IDC-P may be predominant (Fig. 4.7) or even lacking an invasive component (Robinson and Epstein 2010). Originally, it was considered most likely that IDC-P represents the intraductal spread of frankly invasive carcinoma, but the possibility that it could represent a prostate cancer precursor was also entertained (Kovi et al. 1985; McNeal and Yemoto 1996). Particularly, the occasional finding of an extensive IDC-P with no or limited invasive carcinoma would be in line with the view that IDC-P could represent a precursor lesion, developing from a subset of H-PIN. Mostly, IDC-P can be reliably distinguished by pure morphological criteria from H-PIN, mainly based on the filling up and distension of the lumen by the dysplastic cells in IDC-P (Guo and Epstein 2006).

Several studies have reported that IDC-P represents an independent prognosticator for early biochemical recurrence after radical prostatectomy (McNeal and Yemoto 1996; O'Brien et al. 2011).

4.4 Prostate Cancer

Prostate cancer is a very common finding in elder men, and its clinical course is highly variable with most cancers running an indolent course. The histopathological features of prostate cancer and its spatial extension have been shown to

be the strongest predictors of their behavior, as well as surgical margin status after radical prostatectomy.

4.4.1 Types and Variants of Adenocarcinoma

Apart from the vast majority of conventional acinar adenocarcinomas, separate types of prostate cancer may occasionally be identified as well. The latter may reveal a different behavior, or they may occur as a consequence of earlier treatment for prostate cancer. Variants of prostate cancer belong to the group of conventional acinar adenocarcinoma, and their description is of diagnostic help for the pathologist, and they also may have a distinct clinical behavior. As of yet, molecular typing has not led to the identification of distinct genotypes of prostate cancer with a clearly distinct morphologic counterpart. This stands in contrast to findings in, e.g., breast cancer.

4.4.1.1 Conventional Acinar Adenocarcinomas and Its Variants

Conventional acinar adenocarcinoma is the most common type of prostate cancer, representing over 95% of cancers. This type of adenocarcinoma displays a remarkable morphologic heterogeneity, which may coexist within the same tumor focus. Most common is the formation of small-to-medium-sized glands, but these glands may fuse or form cribriform or ragged sheets of cells. These architectural patterns are reflected in the histopathological grading of the conventional acinar adenocarcinomas. Variants of conventional acinar adenocarcinoma are mucinous or colloid carcinoma, the more rare signet ring cell carcinoma, lymphoepithelioma-like carcinoma, and the sarcomatoid variant (carcinosarcoma), as well as the pseudohyperplastic and atrophic variants (Grignon 2004). The latter two may be a diagnostic pitfall, particularly when encountered isolated in a prostate biopsy. Most of these variants occur in the context of a conventional acinar adenocarcinoma. The mucinous variant requires that at least 25% of the carcinoma displays a mucinous morphology (Epstein et al. 2004). All variants follow essentially the same Gleason grading rules (see Sect. 4.2) as the conventional acinar adenocarcinomas.

4.4.1.2 Ductal Adenocarcinoma

Although in the current WHO classification of prostate cancer, ductal adenocarcinoma is coined as a distinct type of prostate adenocarcinoma, some would consider it as a variant of the conventional adenocarcinoma. Ductal adenocarcinoma as a dominant pattern accounts for a mere 0.2–0.8% of all prostate cancers (Grignon 2004; Yang et al. 2004). They typically involve the large periurethral ducts and may become clinically manifest as an exophytic papillary mass in the prostatic urethra. Ductal adenocarcinoma is, however, more frequently (in up to 3% of prostate cancer diagnoses) found as a minor component of conventional-type (acinar) adenocarcinoma. In >80% of prostatic ductal adenocarcinomas, an associated acinar adenocarcinoma is found, usually in close proximity to the ductal component. Consistent with the features of large periurethral duct epithelium (see Sect. 4.2), the columnar neoplastic cells form a pseudostratified epithelium, often lining papillary structures with true fibrovascular cores and their nuclei are mostly elongated or oval with often a single macronucleolus. Ductal adenocarcinoma can often be found extensively growing within prostatic ducts with the morphology of intraductal carcinoma or even comedocarcinoma (Pickup and Van der Kwast 2007).

4.4.1.3 Neuroendocrine Carcinoma

Poorly differentiated neuroendocrine carcinomas of the prostate may also be referred to as small cell or large cell (undifferentiated) carcinomas (Evans et al. 2006), but the first terminology is now preferred. Notably, neuroendocrine differentiation of scattered cells and small foci of neuroendocrine cells is a common phenomenon in conventional acinar adenocarcinoma (Krijnen et al. 1993). In poorly differentiated neuroendocrine carcinoma,

large sheets of tumor cells, lacking glandular differentiation, with large nuclear/cytoplasm ratio and hyperchromatic nuclei give the tumor a basophilic appearance. In about 50% of the cases, they are admixed with a conventional adenocarcinoma (Grignon 2004). Although still rare, they are more common in patients who have been treated with androgen deprivation. A metastatic origin from another body site must be excluded when the tumor occurs in its pure form. Immunohistochemistry is helpful to demonstrate its neuroendocrine differentiation, using antibodies, e.g., against synaptophysin and chromogranin A. They generally lack androgen receptors or PSA, whereas the lung/thyroid cancer marker TTF-1 is commonly positive (Evans et al. 2006), but about 50% of them may overexpress the prostate-specific marker ERG (Williamson et al. 2011). Their clinical behavior is as aggressive as poorly differentiated neuroendocrine cancers from any other body site, whether in its pure form or admixed with conventional adenocarcinoma, and treatment is the same.

4.4.1.4 Other Rare Prostate Cancer Types

Other rare types of prostate cancer include a.o. basal cell carcinoma, squamous cell carcinoma, and adenosquamous carcinoma of the prostate (Grignon 2004). Basal cell carcinomas also referred to as adenoid cystic carcinomas are extremely rare. Some of them show features such as comedonecrosis typical of the aggressive basaloid carcinomas, and others have a more bland morphology.

Primary squamous cell carcinoma originating in the prostate is very rare, and propagation of a urothelial or squamous cell carcinoma derived from the urinary bladder or urethra should be excluded. By definition, squamous cell carcinomas do not contain glandular or urothelial components, and they may originate from the periurethral glands or from the basal cells of prostatic glandular acini differentiating into squamous cells. Adenosquamous carcinoma of the prostate is a carcinoma, composed of a blend of conventional adenocarcinoma and squamous cell carcinoma. About 50% of the reported adenosquamous carcinomas occur in prostate cancer patients subsequent to androgen deprivation therapy and/or radiotherapy. Both squamous and adenosquamous carcinomas tend to metastasize rapidly with a predilection for the bones.

4.4.2 Gleason Grading of Prostatectomy Specimens

The Gleason grading system, based on architectural and not on cytonuclear features, continues to be the strongest prognosticator of prostate cancer (Eggener et al. 2011). This system accounts for the heterogeneity of prostate cancer by identifying five grades on the basis of the tumor architecture, ranging from 1 (most differentiated) to 5 (least differentiated). Grades 1 and 2 are typical of the transition zone with grade 1 now virtually obsolete (Epstein et al. 2005). By adding the most dominant growth pattern (the primary Gleason pattern) to the next most dominant growth pattern (the secondary Gleason pattern), a nine-tiered total score of ascending aggressiveness from 2 to 10 is obtained. Figure 4.8 displays the four frequent, but distinct patterns of cancer constituting a grade 4 prostate cancer. When the high-grade (Gleason grades 4 or 5) component constitutes less than 5% of the cancer volume, it is not incorporated in the Gleason score (5% rule), but it will be reported as a tertiary grade. A meta-analysis by Harnden et al. (2007) has shown convincingly that presence of a tertiary grade 5 has an unfavorable prognostic impact. On the other hand, most studies have shown that a <5% grade 4 component in an otherwise Gleason score 6 (3+3), carcinoma does not adversely affect the prognosis. The biological behavior of a tumor is more related to the proportion of poorly differentiated (grade 4/5) components within the tumor (Vis et al. 2007; Cheng et al. 2005) than the Gleason score itself, even if by current convention the very heterogeneous Gleason score 7 category is subdivided in those with a dominant pattern 3, that is, Gleason score 7 (3+4), and those with a dominant pattern 4, that is, Gleason score 7 (4+3). Table 4.1 gives an overview of the Gleason grades for the various types and variants of prostate cancer.

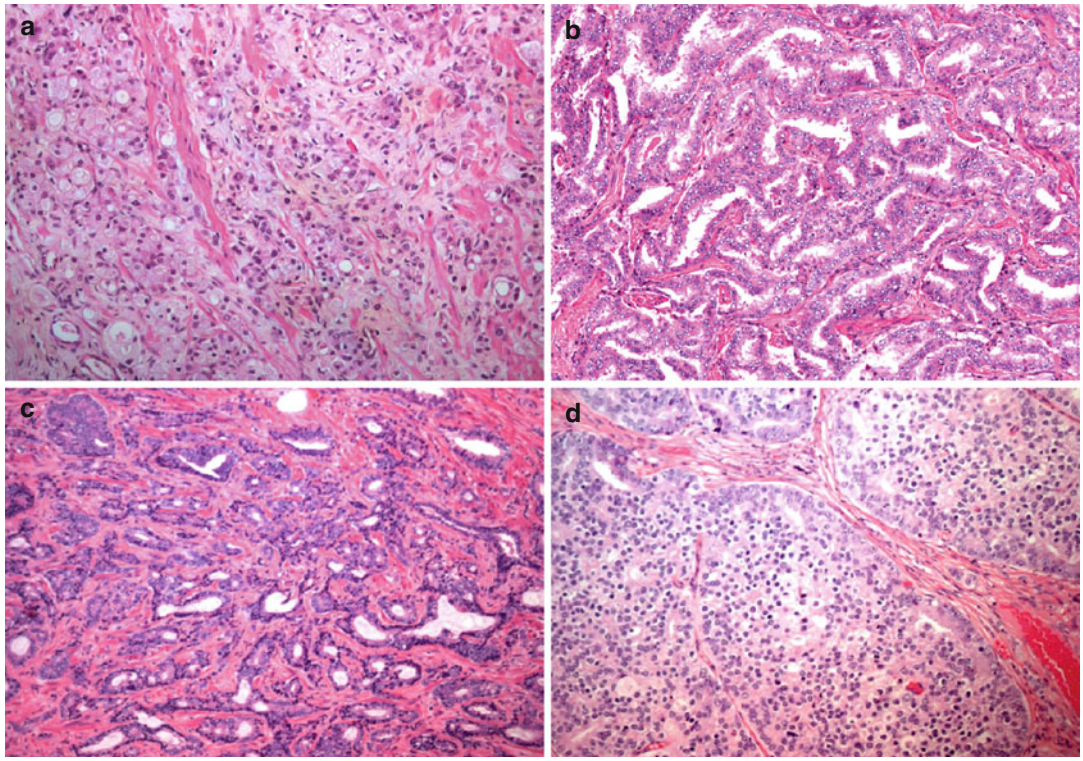

Fig. 4.8 The heterogeneity of Gleason grade 4 prostate cancer is displayed in these four micrographs: small glandular nests and strands (**a**), large fused glands (**b**), small fused glands (**c**), and large cribriform structures (**d**)

Table 4.1 Types and variants of prostate cancer and Gleason grade

	Type or variant	Gleason grade
Type	Ductal adenocarcinoma	Grade 4, if comedonecrosis grade 5
	Basal cell or adenoid cystic	Not applicable
	Squamous or adenosquamous	Not applicable
	Poorly differentiated neuroendocrine	Not applicable
Variant	Mucinous[a]	Often grade 4
	Pseudohyperplastic[a]	Mostly grade 3
	Foamy gland[a]	Mostly grade 3
	Atrophic	Grade 3
	Sarcomatoid	Grade 5
	Signet ring cell	Grade 5

[a]For these variants, the Gleason grade is determined by the architecture of the glandular neoplastic cells

4.4.3 Staging of Prostatectomy Specimens

The objective of staging is to (1) group malignancies which have an apparently similar prognosis so as to inform a uniform therapeutic approach, (2) assist clinical trials and research studies by defining homogeneous patient populations, and (3) promote the comparability of clinicopathologic data from multiple hospitals and research groups.

In general, pathologic (sub)staging of tumors should maintain symmetry with clinical (sub) staging, thus allowing direct comparison of

cases. The 2010 TNM system distinguishes organ-confined (pT2) and non-organ-confined prostate cancers (pT3a,b/pT4) to describe the extent of prostate cancer in a radical prostatectomy specimen (International Union Against Cancer (IUCC) 2009).

4.4.3.1 Stage pT2 Prostate Cancer

Organ-confined prostate cancers are stage pT2, which means they are within the confines of the prostate, including its outer fibromuscular border. Substaging of pT2 cancers is now optional, given its lack of clinical and academic value (Van der Kwast et al. 2011). Although clinical substaging of cT2 prostate cancer has clinical value, they do not correspond with the pathological substages.

4.4.3.2 Stage pT3a Prostate Cancer

Extraprostatic extension can be diagnosed unequivocally when tumor is in contact with adipose tissue, but also in the posterolateral area extraprostatic extension can be determined when tumor is within loose connective tissue or perineural spaces of the neurovascular bundles even in the absence of adipocytes. Extraprostatic extension may also be recognized as a distinct tumor nodule within desmoplastic stroma that bulges beyond the normal contour of the gland (Magi-Galluzzi et al. 2011). In the apex, benign glands are frequently admixed with striated muscle in the apex, and as a consequence, the finding of malignant glands within striated muscle does not represent extraprostatic extension. Further, in the current era of bladder-preserving prostatectomy, invasion into the bladder neck is no longer considered as stage pT4, but instead pT3a (Aydin et al. 2004).

At the anterior fibromuscular stroma, the prostate blends in with extraprostatic smooth muscle, and here, extension beyond the prostate contour or adipose tissue at the sides (Bouyé et al. 2009) should help determine the presence of extraprostatic extension (Figs. 4.9 and 4.10). Since in contemporary series, at least 50% of patients with extraprostatic extension at radical prostatectomy do not show tumor progression over a 10-year follow-up period, ways to improve the prognostication of extraprostatic extension were examined (Magi-Galluzzi et al. 2011). Accordingly, focal

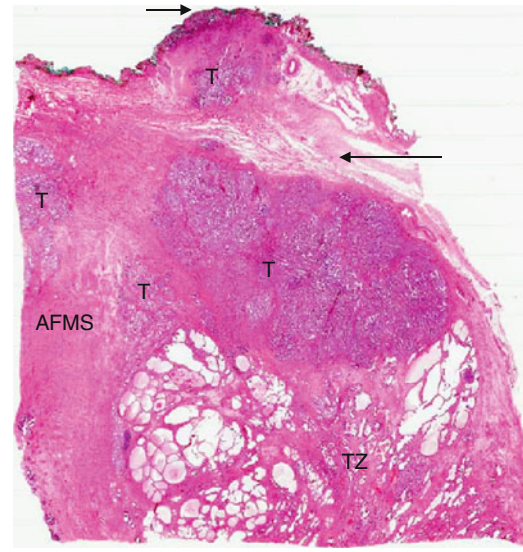

Fig. 4.9 Upper right quadrant section of prostatectomy specimen with a larger anterior cancer (*T*) of the transition zone (*TZ*), penetrating the anterior surgical margin (*short arrow*). The *long arrow* indicates the plane separating the prostate from the anterior extraprostatic tissue. The tumor is adjacent to and infiltrates the anterior fibromuscular stroma (*AFMS*)

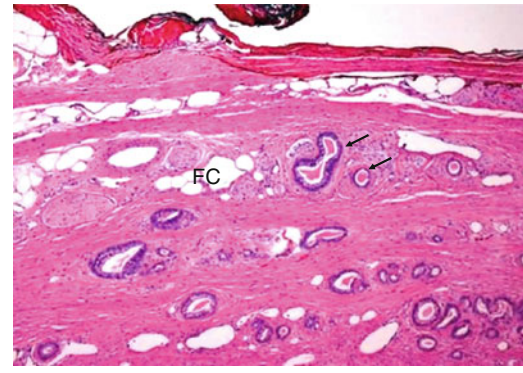

Fig. 4.10 A few tumor glands (*arrows*) are found at the level of fat cells (*FC*), indicating focal extraprostatic extension

extraprostatic extension as opposite to established or extensive extraprostatic extension has been defined as the presence of a few extraprostatic glands or 1 or 2 high-power fields in one or maximum two levels (Fig. 4.10). Each of these categorizations has prognostic significance, to the effect that focal extraprostatic extension has the same risk of progression as organ-confined prostate cancer.

4.4.3.3 Stage pT3b Prostate Cancer

Seminal vesicle invasion as defined by the invasion of the muscular wall of the extraprostatic seminal vesicles (stage pT3b) conveys a highly unfavorable prognosis. The carcinoma can invade the seminal vesicles by (1) spreading along the ejaculatory duct and/or by direct invasion at the base of the prostate and/or (2) by extending into periseminal vesicle soft tissue and then into the wall of the seminal vesicle. Rarely, discontinuous metastases in blood vessels can here be found as an isolated finding (Berney et al. 2011). As for the latter, there is no consensus whether to consider this as pT3b stage.

4.4.3.4 Stage pT4 Prostate Cancer

The designation of stage pT4 in a prostatectomy specimen is highly restricted now: pT4 urinary bladder neck involvement by prostatic carcinoma includes only prostate cancer with gross or radiographic extension into the bladder neck. It is allowable to assign a pT4 stage associated with radical prostatectomy if an associated biopsy of urinary bladder, rectum, or pelvic side wall is positive for prostatic carcinoma that is directly invading these structures, as assessed by clinical and/or radiological means (Magi-Galluzzi et al. 2011). Positive surgical margin at the bladder neck does not constitute stage pT4 cancer, but is reported as pT3a margin positive cancer (Buschemeyer et al. 2008).

4.4.4 Surgical Margins

Approximately 10–35% of radical prostatectomy specimens are reported to have positive surgical margins on pathologic evaluation. Biochemical progression free survival for men with surgical margin positivity on radical prostatectomy is about 60% as compared to 80% in patients with negative surgical margin (Ohori et al. 1995; Cheng et al. 1999). Most investigators have been able to confirm the independent prognostic impact of this parameter in multivariable analyses (Tan et al. 2011).

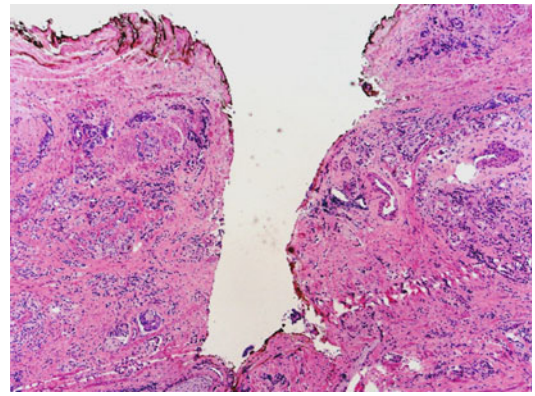

Fig. 4.11 A laceration into the prostatic tissue. Although tumor cells are here in contact with the ink, this may not be considered as a true positive margin

4.4.4.1 Definition of Positive Margins

As for surgical margins, tumor cells should really be in contact with ink in order to consider the margin positive. In a study of 278 margin-negative radical prostatectomy cases, Emerson et al. (2005) found that the closest distance between tumor and resection margin, which ranged from 0.02 to 5 mm, did not significantly predict PSA recurrence in univariate or multivariate logistic regression analysis and concluded that routine pathologic reporting of this distance was not required. This is in line with the finding of Epstein (1990) that a close margin (i.e., <0.1 mm) should not be designated as positive surgical margin since this would not impact the prognosis. Also, lacerations in the capsule should be accounted for as they may cause a false-positive diagnosis of positive margins (Chuang and Epstein 2008), even though tumor cells may be covered by ink at these sites due to leakage (Fig. 4.11). Similarly, presence of tumor cells in the outer surface of the specimen, *not* covered by ink should in general not be considered as evidence for a positive margin.

4.4.4.2 Location and Extent of Positive Surgical Margin

Published reports on the impact of location of positive surgical margins on outcome have been

conflicting (Tan et al. 2011). Several studies have shown that the extent of tumor at the surgical margin correlates with postoperative disease recurrence, but a large study by Stephenson et al. (2009) demonstrated that neither location nor extent of positive margin improved the predictive accuracy of a nomogram compared to one in which surgical margin status was modeled as positive versus negative.

4.4.5 Anterior Prostate Cancers

Transition zone cancers particularly when in an anterior location tend to be detected late, since they are generally not targeted by the standard biopsy scheme which focuses mainly on the cancers in the posterior location (Bott et al. 2002). Often, they have reached a large size and/or transformed into an aggressive higher-grade cancer before their detection, and under these circumstances, there is a greater risk of a positive margin and biochemical failure when prostatectomy is performed (Fig. 4.9). Anterior prostate cancers are not uncommon, with about 35% of the anterior prostate cancers originating from the anterior horn of the peripheral zone, thus representing peripheral zone carcinomas (Al-Ahmadie et al. 2008).

The recently proposed term acronym PEATS (i.e., prostatic evasive anterior tumor syndrome) alludes to the phenomenon of anterior cancers detected at a stage too advanced to be cured (Lawrentschuk et al. 2010). It is obvious that in patients enrolled in an active surveillance program, it remains a challenge to identify the presence of these hidden aggressive anterior tumors. Magnetic resonance imaging guided biopsies targeting anterior zone abnormalities play an increasing role in this clinical setting.

4.4.6 Multifocality and Index Tumor

Multifocality of prostate cancer (Fig. 4.1) is very common, with 2–5 tumors of variable size found in 80% of prostatectomy specimens (Wise et al. 2002). The concept of an index or dominant tumor was derived from the Stanford group who measured the volume of the largest tumor nodule in wholemount sections and demonstrated its independent clinical significance (Stamey et al. 1999). The advancement of focal therapy for treatment of prostate cancer has made this concept more relevant, but it has been challenged in the past on two grounds. Firstly, several subsequent studies have failed to demonstrate the independent prognostic significance of the tumor volume (Wolters et al. 2010) and secondly because the dominant nodule does not always represent the component of tumor having the highest Gleason score or the most advanced pathological stage (Andreoiu and Cheng 2010). Conversely, other features may influence the clinical importance of the individual tumor foci, and in particular, pT category and Gleason grade/score may need to be included in the defining characteristics. Thus, in a clinical setting in case of a multifocal cancer, the index tumor would represent the tumor with the worst prognostic features.

4.4.7 Tumor Volume and Insignificant Cancer

Although the prognostic significance of quantitation of prostate cancer volume and the proportion of prostate gland tissue involved by carcinoma is not disputed, few studies were able to provide evidence that parameters reflecting prostate cancer volume are of significance independent of Gleason score, pathological stage, and surgical margin status (Van der Kwast et al. 2011). Nevertheless, a cutoff of the index tumor volume of 0.5 ml is included in the current definition of a clinically significant prostate cancer, that is stage pT2, Gleason score 6 (3 + 3) and volume of index tumor <0.5 ml (Epstein et al. 1994). This <0.5 ml TV threshold is based on incidentally detected PC in a single radical cystoprostatectomy series, published by Stamey et al. (1993) based on a 8% lifetime risk to be diagnosed with clinically significant PC. It was recently validated on an independent

dataset, yielding the same volume threshold, if Gleason score and pathological stage were not taken into account (Wolters et al. 2011).

Imaging technology is now making such progress that visualization of most prostate cancers of a volume in the order of 0.5 ml is possible. It should be noted, however, that a potential limitation of imaging is the failure to identify "sparse" tumors, which contain less than 50% of cancer glands in their cross-sectional areas (Langer et al. 2008). This may cause an underestimation by magnetic resonance imaging of the actual tumor volume of some cancers. On the other hand, it remains unclear, whether these sparse tumor areas are clinically relevant (Ayala et al. 2011). It is envisaged that, in the future, further advances in imaging techniques will result in more accurate clinical estimations of the volume of the index tumor. This might reinforce the clinical rationale for incorporating a size-related staging parameter into pathological reporting of prostate cancers.

4.5 Concluding Remarks

As reflected in this chapter, much progress has been made in recent years in the understanding of the complex anatomy of the prostate and the appreciation of its considerable individual variation particularly with regard to its anterior and posterior boundaries. It is also becoming clearer that continuous efforts in the past to reconcile anatomic and clinical terminology are now resulting into a more uniform terminology based on increasing consensus on the composition and origin of the various fascias and muscular structures bordering the prostate. This improved knowledge has led to more detailed pathological staging criteria for prostate cancers. Consensus meetings of the International Society of Urologic Pathology held during the past few years have further led to a more standardized approach to grading, staging, and determination of margin status in prostatectomy specimens, while resolving several staging-related issues of cancers extending into the bladder neck, the apex, and at the anterior boundary. Some molecular-pathologic evidence suggests that prostate cancers of the peripheral and transition zone are different, but for pathologists an accurate zonal assignation of a prostate cancer can be challenging. As a consequence of the advancement of imaging in prostate cancer management, including active surveillance and the application of focal therapy for low-risk prostate cancer patients, more attention is currently being paid to the clinicopathologic features of prostate cancers located in the anterior region of the prostate. Finally, awareness of the potential for overdiagnosis and overtreatment of prostate cancer continues to drive the search for improved pathological, molecular-genetic, and imaging parameters for diagnostic and prognostic purpose. In this respect, recognition of the histological heterogeneity of prostate cancer and its stromal composition, even within one Gleason grade might benefit the development of imaging tools distinguishing aggressive from favorable prostate cancer. Clearly, the possibility to accurately distinguish clinically low-risk from high-risk prostate cancers continues to be an important field of research in the years to come.

References

Al-Ahmadie HA, Tickoo SK, Olgac S et al (2008) Anterior-predominant prostatic tumors: zone of origin and pathologic outcomes at radical prostatectomy. Am J Surg Pathol 32:229–235

Andreoiu M, Cheng L (2010) Multifocal prostate cancer: biologic, prognostic, and therapeutic implications. Hum Pathol 41:781–793

Andriole GL, Bostwick DG, Brawley OW, REDUCE Study Group et al (2010) Effect of dutasteride on the risk of prostate cancer. N Engl J Med 362:1192–1202

Augustin H, Hammerer PG, Blonski J et al (2003) Zonal location of prostate cancer: significance for disease-free survival after radical prostatectomy? Urology 62:79–85

Ayala GE, Muezzinoglu B, Hammerich KH et al (2011) Determining prostate cancer-specific death through quantification of stromogenic carcinoma area in prostatectomy specimens. Am J Pathol 178(1):79–87

Aydin H, Tsuzuki T, Hernandez D et al (2004) Positive proximal (bladder neck) margin at radical prostatectomy confers greater risk of biochemical progression. Urology 64(3):551–555

Berney DM, Wheeler TM, Grignon DJ, ISUP Prostate Cancer Group et al (2011) International Society of Urological Pathology (ISUP) consensus conference on

handling and staging of radical prostatectomy specimens. Working group 4: seminal vesicles and lymph nodes. Mod Pathol 24:39–47

Billis A, Meirelles L, Freitas LL (2010) Mergence of partial and complete atrophy in prostate needle biopsies: a morphologic and immunohistochemical study. Virchows Arch 456:689–694

Bostwick DG, Liu L, Brawer MK et al (2004) High-grade prostatic intraepithelial neoplasia. Rev Urol 6: 171–179

Bott SR, Young MP, Kellett MJ et al (2002) Contributors to the UCL Hospitals' trust radical prostatectomy database. Anterior prostate cancer: is it more difficult to diagnose? BJU Int 89:886–889

Bouyé S, Potiron E, Puech P et al (2009) Transition zone and anterior stromal prostate cancers: zone of origin and intraprostatic patterns of spread at histopathology. Prostate 69:105–113

Brawn PN, Foster DM, Jay DW et al (1994) Characteristics of prostatic infarcts and their effect on serum prostate-specific antigen and prostatic acid phosphatase. Urology 44:71–75

Buschemeyer WC 3rd, Hamilton RJ, Aronson WJ et al (2008) Is a positive bladder neck margin truly a T4 lesion in the prostate specific antigen era? Results from the SEARCH database. J Urol 179:124–129

Cheng L, Darson MF, Bergstralh EJ et al (1999) Correlation of margin status and extraprostatic extension with progression of prostate carcinoma. Cancer 86:1775–1782

Cheng L, Koch MO, Juliar BE et al (2005) The combined percentage of Gleason patterns 4 and 5 is the best predictor of cancer progression after radical prostatectomy. J Clin Oncol 23(13):2911–2917

Chuang AY, Epstein JI (2008) Positive surgical margins in areas of capsular incision in otherwise organ-confined disease at radical prostatectomy: histologic features and pitfalls. Am J Surg Pathol 32:1201–1206

De Marzo AM, DeWeese TL, Platz EA et al (2004) Pathological and molecular mechanisms of prostate carcinogenesis: implications for diagnosis, detection, prevention, and treatment. J Cell Biochem 91(3): 459–477

Eggener SE, Scardino PT, Walsh PC et al (2011) Predicting 15-year prostate cancer specific mortality after radical prostatectomy. J Urol 185(3):869–875

Emerson RE, Koch MO, Daggy JK et al (2005) Closest distance between tumor and resection margin in radical prostatectomy specimens. Lack of prognostic significance. Am J Surg Pathol 29:225–229

Epstein JI (1990) Evaluation of radical prostatectomy capsular margins of resection: the significance of margins designated as negative, closely approaching, and positive. Am J Surg Pathol 14:626–632

Epstein JI (2009) Precursor lesions to prostatic adenocarcinoma. Virchows Arch 454:1–16

Epstein JI, Walsh PC, Carmicheal M et al (1994) Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. JAMA 271:368–374

Epstein JI, Algaba F, Allsbrook WC Jr et al (2004) Acinar adenocarcinoma in: WHO classification of tumours, pathology & genetics. Tumours of the urinary system and male genital organs. IARC Press, Lyon, pp 162–198

Epstein JI, Allsbrook WC Jr, Amin MB, ISUP Grading Committee (2005) The 2005 International Society of Urologic Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma. Am J Surg Pathol 29:1228–1242

Evans AJ, Humphrey PA, Belani J et al (2006) Large cell neuroendocrine carcinoma of prostate: a clinicopathologic summary of 7 cases of a rare manifestation of advanced prostate cancer. Am J Surg Pathol 30:684–693

Fine SW, Al-Ahmadie HA, Gopalan A et al (2007) Anatomy of the anterior prostate and extraprostatic space: a contemporary surgical pathology analysis. Adv Anat Pathol 14:401–407

Gosselaar C, Roobol MJ, Roemeling S et al (2008) The role of the digital rectal examination in subsequent screening visits in the European randomized study of screening for prostate cancer (ERSPC), Rotterdam. Eur Urol 54:581–588

Grignon DJ (2004) Unusual subtypes of prostate cancer. Mod Pathol 17(3):316–327

Guo CC, Epstein JI (2006) Intraductal carcinoma of the prostate on needle biopsy: histologic features and clinical significance. Mod Pathol 19:1528–1535

Hammerich KH, Ayala GE, Wheeler TM (2009) Anatomy of the prostate gland and surgical pathology of prostate cancer. Cambridge University, Cambridge, pp 1–10

Harnden P, Shelley MD, Coles B et al (2007) Should the Gleason grading system for prostate cancer be modified to account for high-grade tertiary components? A systematic review and meta-analysis. Lancet Oncol 8:411–419

Kovi J, Jackson MA, Heshmat MY (1985) Ductal spread in prostatic carcinoma. Cancer 56:1566–1573

Krijnen JL, Janssen PJ, Ruizeveld de Winter JA et al (1993) Do neuroendocrine cells in human prostate cancer express androgen receptor? Histochemistry 100:393–398

Langer DL, van der Kwast TH, Evans AJ et al (2008) Intermixed normal tissue within prostate cancer: effect on MR imaging measurements of apparent diffusion coefficient and T2 – sparse versus dense cancers. Radiology 249(3):900–908

Lawrentschuk N, Haider MA, Daljeet N et al (2010) 'Prostatic evasive anterior tumours': the role of magnetic resonance imaging. BJU Int 105:1231–1236

Lindsey I, Guy RJ, Warren BF (2000) Anatomy of Denonvilliers' fascia and pelvic nerves, impotence, and implications for the colorectal surgeon. Br J Surg 87:1288–1299

Magi-Galluzzi C, Evans AJ, Delahunt B, ISUP Prostate Cancer Group et al (2011) International Society of Urological Pathology (ISUP) consensus conference on handling and staging of radical prostatectomy specimens. Working group 3: extraprostatic extension, lymphovascular invasion and locally advanced disease. Mod Pathol 24(1):26–38

McNeal JE (1988) Normal histology of the prostate. Am J Surg Pathol 12:619–633
McNeal JE, Yemoto CE (1996) Spread of adenocarcinoma within prostatic ducts and acini: morphologic and clinical correlations. Am J Surg Pathol 20:802–814
Montironi R, Mazzucchelli R, Santinelli A et al (2005) Incidentally detected prostate cancer in cystoprostatectomies: pathological and morphometric comparison with clinically detected cancer in totally embedded specimens. Hum Pathol 36(6):646–654
Myers RP, Cheville JC, Pawlina W (2010) Making anatomic terminology of the prostate and contiguous structures clinically useful: historical review and suggestions for revision in the 21st century. Clin Anat 23:18–29
O'Brien BA, Cohen RJ, Wheeler TM et al (2011) A post-radical-prostatectomy nomogram incorporating new pathological variables and interaction terms for improved prognosis. BJU Int 107:389–395
Ohori M, Wheeler TM, Kattan MW et al (1995) Prognostic significance of positive surgical margins in radical prostatectomy specimens. J Urol 154:1818–1824
Pickup M, Van der Kwast TH (2007) My approach to intraductal lesions of the prostate gland. J Clin Pathol 60:856–865
Robinson BD, Epstein JI (2010) Intraductal carcinoma of the prostate without invasive carcinoma on needle biopsy: emphasis on radical prostatectomy findings. J Urol 184:1328–1333
Sobin LH, Gospodariwicz M, Wittekind C, International Union Against Cancer (UICC) (2009) TNM classification of malignant tumors, 7th edn. Wiley-Blackwell, Oxford, pp 243–248
Stamey TA, Freiha FS, McNeal JE et al (1993) Localized prostate cancer. Relationship of tumor volume to clinical significance for treatment of prostate cancer. Cancer 71(3 Suppl):933–938
Stamey TA, McNeal JE, Yemoto CM et al (1999) Biological determinants of cancer progression in men with prostate cancer. JAMA 281:1395–1400
Stephenson AJ, Wood DP, Kattan MW et al (2009) Location, extent and number of positive surgical margins do not improve accuracy of predicting prostate cancer recurrence after radical prostatectomy. J Urol 182:357–363
Stolzenburg JU, Schwalenberg T, Horn LC et al (2007) Anatomical landmarks of radical prostatectomy. Eur Urol 51(3):629–639
Tan PH, Cheng L, Srigley JR, ISUP Prostate Cancer Group et al (2011) International Society of Urological Pathology (ISUP) consensus conference on handling and staging of radical prostatectomy specimens. Working group 5: surgical margins. Mod Pathol 24:48–57
Têtu B, Srigley JR, Boivin JC, Dupont A et al (1991) Effect of combination endocrine therapy (LHRH agonist and flutamide) on normal prostate and prostatic adenocarcinoma. A histopathologic and immunohistochemical study. Am J Surg Pathol 15:111–120
Van der Heul-Nieuwenhuijsen L, Hendriksen PJ, van der Kwast TH et al (2006) Gene expression profiling of the human prostate zones. BJU Int 98:886–897
Van der Kwast TH, Amin MB, Billis A, ISUP Prostate Cancer Group et al (2011) International Society of Urological Pathology (ISUP) consensus conference on handling and staging of radical prostatectomy specimens. Working group 2: T2 substaging and prostate cancer volume. Mod Pathol 24:16–25
Villers A, McNeal JE, Freiha FS et al (1993) Invasion of Denonvilliers' fascia in radical prostatectomy specimens. J Urol 149:793–798
Vis AN, Roemeling S, Kranse R et al (2007) Should we replace the Gleason score with the amount of high-grade prostate cancer? Eur Urol 51:931–939
Walz J, Burnett AL, Costello AJ et al (2010) A critical analysis of the current knowledge of surgical anatomy related to optimization of cancer control and preservation of continence and erection in candidates for radical prostatectomy. Eur Urol 57(2):179–192
Williamson SR, Zhang S, Yao JL et al (2011) ERG-TMPRSS2 rearrangement is shared by concurrent prostatic adenocarcinoma and prostatic small cell carcinoma and absent in small cell carcinoma of the urinary bladder: evidence supporting monoclonal origin. Mod Pathol 24(8):1120–1127
Wise AM, Stamey TA, McNeal JE et al (2002) Morphologic and clinical significance of multifocal prostate cancers in radical prostatectomy specimens. Urology 60: 264–269
Wolters T, Roobol MJ, van Leeuwen PJ et al (2010) Should pathologists routinely report prostate tumour volume? The prognostic value of tumour volume in prostate cancer. Eur Urol 57:821–829
Wolters T, Roobol MJ, van Leeuwen PJ et al (2011) A critical analysis of the tumor volume threshold for clinically insignificant prostate cancer using a data set of a randomized screening trial. J Urol 185(1): 121–125
Yang XJ, Cheng L, Helpap B et al (2004) Ductal adenocarcinoma in: WHO classification of tumours, pathology & genetics. In: Tumours of the urinary system and male genital organs. IARC Press, Lyon, pp 199–201