11 Prostate

Most biopsies are performed for an elevated prostate-specific antigen (PSA) level, a palpable nodule, or a history of an abnormal biopsy. In the prostate, you are generally looking only for adenocarcinoma; there are very few nonneoplastic conditions to look for.

A typical sextant biopsy is six cores from left apex, mid, and base and right apex, mid, and base. Increasingly, urology centers are sampling additional areas, 12 or more. Laboratories differ in how many cores are placed on a single slide; some laboratories may have only two slides, left and right, with a handful of cores on each slide. It is important to preserve as much detail as the urologist or laboratory gives you and to localize the cancer as much as possible.

Approach to the Core Biopsy

On 4× to 10×, scan the length of the core looking for glands that stand out and look different.

- Low-power features of prostate cancer (Figure 11.1)
  - Small individual glands infiltrating among larger benign glands (for intermediate-grade cancer, or Gleason pattern 3; see more on Gleason grades, discussed later)
  - Crowded glands (for intermediate-grade cancer)
  - An unusually cellular infiltrate (individual cells of high-grade cancer, or Gleason pattern 5)
  - Cribriform areas (high-grade cancer)
  - Sheets of cells (high-grade cancer)
  - A different color or texture to the glands (cancer may appear denser or more bluish)
  - Blue mucin, crystalloids, or dense pink secretions in the lumen
  - Absence of desmoplastic response
- Low-power features of benign glands (Figure 11.2)
  - Irregularly shaped glands with papillary infoldings (a "frilly" look)
  - Glands with a modest amount of intervening stroma
  - Corpora amylacea

At high power (20×–40×), examine the cytology of the suspicious areas. Look for features seen in carcinoma:

- Large, often cherry-red nucleoli (Figure 11.3)
- Straight, crisp luminal borders to the glands
- Enlarged and/or hyperchromatic nuclei (however, pleomorphism is minimal)
- Lack of basal cell layer (can be confirmed by immunostains)
- Mitoses (uncommon)

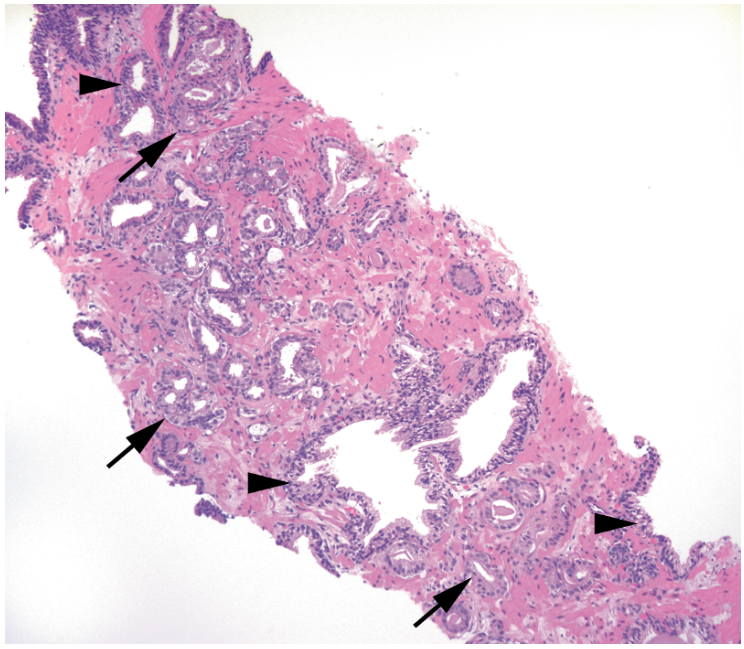

Figure 11.1. Low-power features of carcinoma. Adenocarcinoma (arrows) is seen infiltrating throughout benign glands (arrowheads) in this core biopsy specimen. The malignant glands are often back to back and have relatively denser cytoplasm, no basal layer, and straight luminal borders.

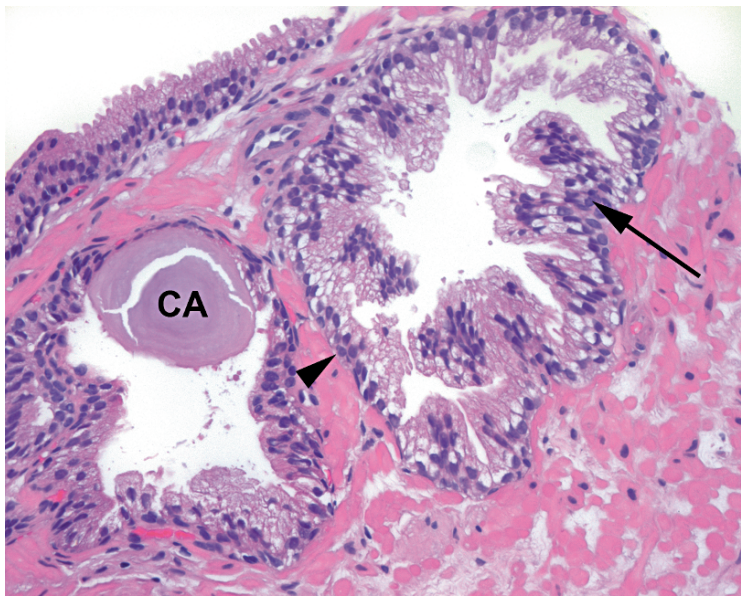

Figure 11.2. Benign prostate glands. These glands have a distinct basal cell layer underlying the epithelial cells (arrowhead) and papillary fronds in the lumen (arrow). Corpora amylacea (CA) are concentrically laminated concretions associated with benign glands.

Although none of these findings is completely sensitive and specific for cancer, having more malignant than benign features is a pretty good indication. There are three features that, although uncommon, are only seen in cancer:

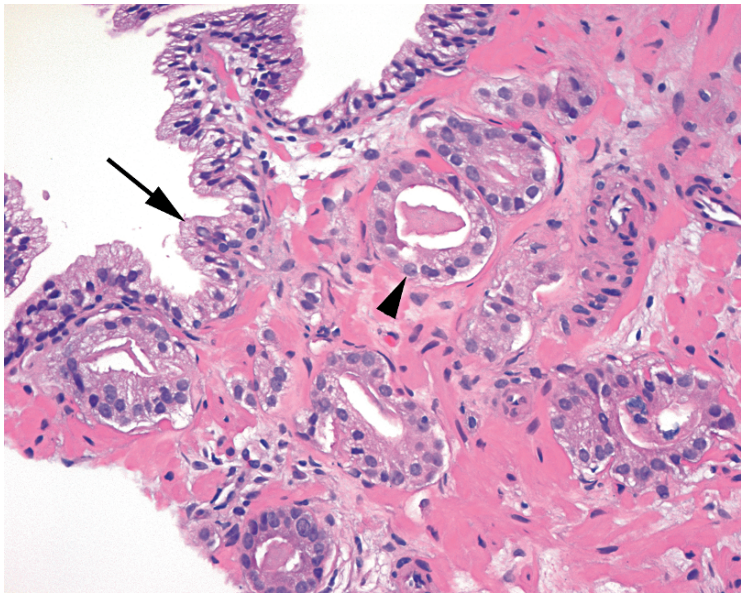

Figure 11.3. High-power features of carcinoma. Malignant glands show distinct nucleoli (arrowhead), sharp luminal borders, and an absence of basal cells. Benign glands are seen adjacent to the cancer (arrow).

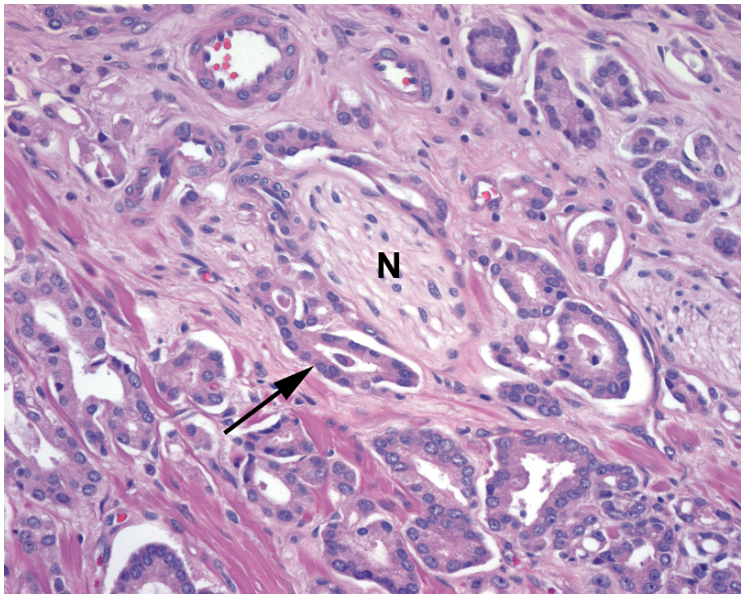

Figure 11.4. Perineural invasion. A nerve (N) is identified by the undulating axons and nerve sheath nuclei. Malignant glands are seen nearly surrounding the nerve (arrow).

1. Perineural invasion: The nerve appears as a discrete oval profile with wavy parallel stripes, almost like a fingerprint, and the malignant gland must be within the nerve sheath to count as perineural invasion (Figure 11.4). Often the gland will fill up the nerve sheath circumferentially, so the nerve appears to be floating in a gland.
2. Mucinous fibroplasia: Hyalinized whorls of organized dense secretions are present in the lumen; sometimes the surrounding gland epithelium may be compressed and indistinct.
3. Glomeruloid forms: Proliferative tangles of cells project into the larger gland lumen, resembling a glomerulus.

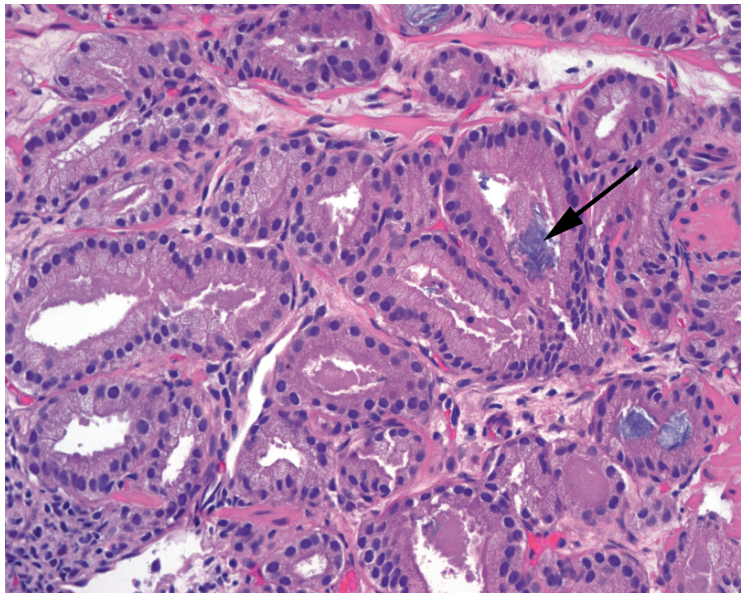

Figure 11.5. Gleason pattern 3. Individual, well-formed malignant glands make up pattern 3 cancer. Blue mucin, often associated with carcinoma, is present (arrow).

Gleason Grading

Once you have identified adenocarcinoma, you must give it a histologic grade. Prostatic adenocarcinoma is graded by the Gleason system, which is based on architectural pattern. Cytology does not affect grade. The patterns (and there may be many within a single tumor) are assigned a number from 1 to 5, with 5 being the least differentiated. After all tissue is examined, the first and second most common patterns are added together to give the Gleason score (a possible 2–10). A pure tumor of pattern 3 would be a 3 + 3 = 6; a mixture of 3 and 4 could be signed out as 4 + 3 = 7 or 3 + 4 = 7, depending on the amount of each.
You may want to take the Johns Hopkins online tutorial for prostate grading, available at http://pathology2.jhu.edu/gleason/. Other good grading websites can be found at www.isuporg.org. In summary, the pattern grades are as follows:

1. rarely used; a circumscribed nodule of uniform crowded glands
2. a circumscribed nodule of well-defined glands with minimal infiltration at the periphery; less uniform than pattern 1.
3. highly infiltrative (creeping between benign glands), with discrete and individual gland profiles such that you can mentally draw a circle around each gland (Figure 11.5).
4. fused and ill-defined glands, sheets of cribriform glands, poorly formed lumens (Figure 11.6).
5. a complete absence of glandular differentiation, solid sheets and cords of cells, single cells (Figure 11.7)

Gleason *scores* of 2–4 (i.e., a combination of patterns 1 and 2) are not diagnosed on needle biopsy, as they can only be identified in the context of surrounding tissue.

Features That Should Be Mentioned in Your Diagnosis

The following features should be mentioned in your diagnosis:

- Number of involved cores: A biopsy diagnosis should include a mention of how many cores are involved (e.g., *1 of 1 core*, or *2 of 4 cores*).

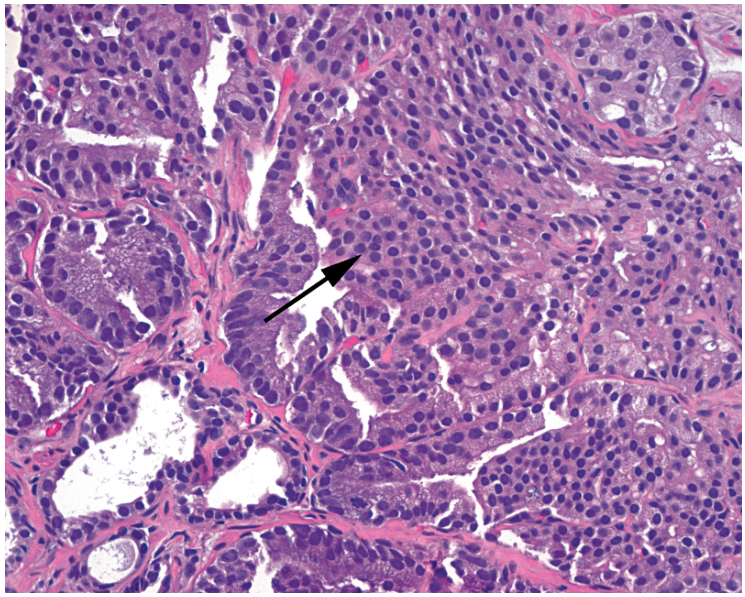

FIGURE 11.6. Gleason pattern 4. The area of cribriform growth (arrow) and adjacent fused glands is typical of pattern 4.

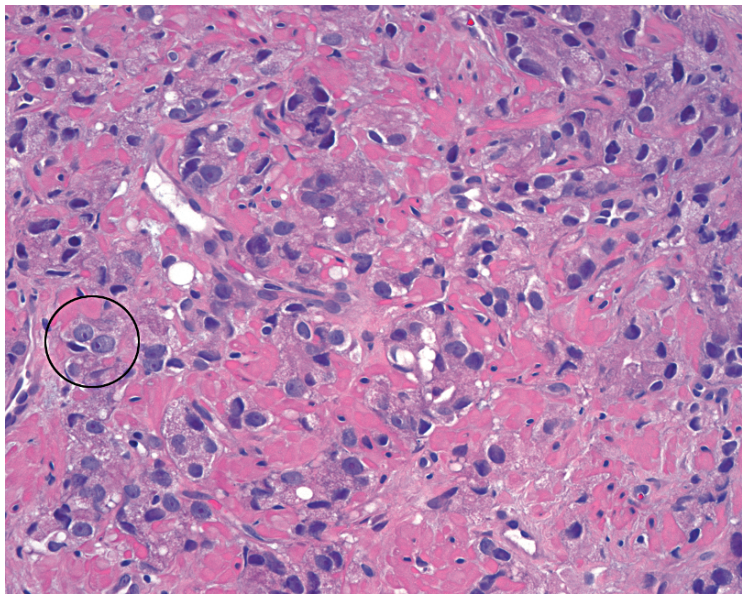

FIGURE 11.7. Gleason pattern 5. Individual malignant cells, without evidence of gland formation, are typical of pattern 5. The individual cells still cytologically resemble well-differentiated carcinoma, with round nuclei and prominent nucleoli (circle).

- Percent involvement: Note the approximate percentage involvement on each core (e.g., *involving 2 of 4 cores [30%, 60%]*). Small foci of cancer (<5% of a core) can be described as *small foci*.
- Perineural invasion: Once cancer is identified, look closely for foci of perineural invasion. The presence of perineural invasion in a biopsy specimen has adverse prognostic significance.
- Extraprostatic extension: Rarely, a core biopsy will go through the capsule of the prostate and into the fat beyond. An extremely lucky shot may show malignant glands trickling into the fat, which is diagnostic of extraprostatic extension. This also has adverse prognostic significance.

Prostatic Intraepithelial Neoplasia

Prostatic intraepithelial neoplasia (PIN) occupies a slightly uncertain place in pathology. It is considered to be a precursor to cancer and to demonstrate a generally increased risk of cancer, but, unlike precursor lesions such as high-grade squamous intraepithelial lesions (cervix) or ductal carcinoma in situ (breast), it does not warrant an immediate rebiopsy or excision. You can think of it as dysplasia in the prostate gland, but the natural history of the lesion is unclear. In any case, the lack of reproducibility and questionable significance of low-grade PIN are such that we do not mention it on biopsy. High-grade PIN, however, should be noted. Features of high-grade *PIN* include the following:

- Glands are large with prominent papillary or micropapillary luminal surfaces, similar to benign architecture. Cribriform PIN can be seen, but back-to-back glands are not PIN.
- Glands appear darker and more blue than surrounding glands (Figure 11.8).
- Nuclei are enlarged, elongated, and hyperchromatic, and by definition nucleoli are visible at 20×.
- The basal cell layer is usually still present, yet often patchy; immunostains show this nicely.

Mimickers of Prostate Cancer

There are some benign entities that may catch your eye and stand out in a biopsy specimen but that are definitely not carcinoma.

Adenosis

Adenosis literally means a proliferation of glands. Adenosis is a hyperplastic lesion, not a neoplastic one. It consists of a *lobular group* of crowded glands, which may include small suspicious-looking glands among them. The morphology of the small glands, however, should overlap with the intermixed larger, benign-looking glands; there should be a spectrum so that you cannot point to definite malignant versus benign glands. Adenosis may have visible small

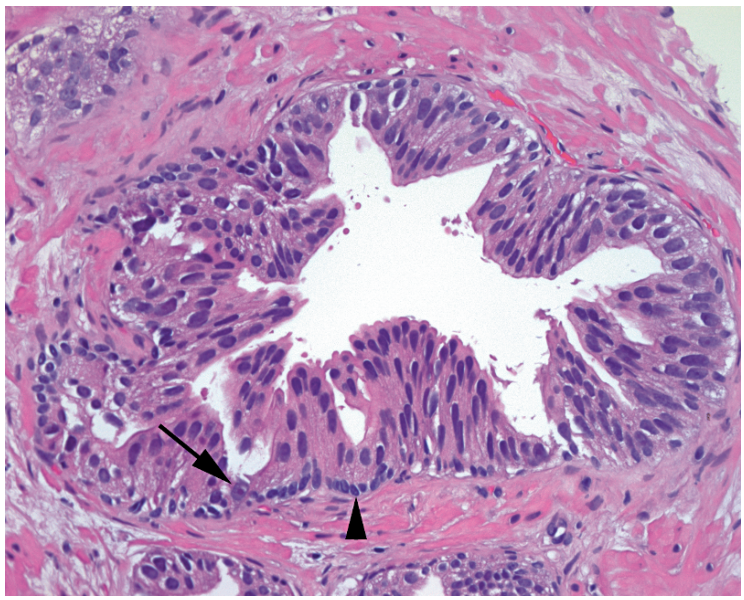

Figure 11.8. High-grade prostatic intraepithelial neoplasia. Although the papillary infoldings resemble benign prostate, the nuclei are larger and darker and show occasional prominent nucleoli (arrow). Basal cells are still present (arrowhead).

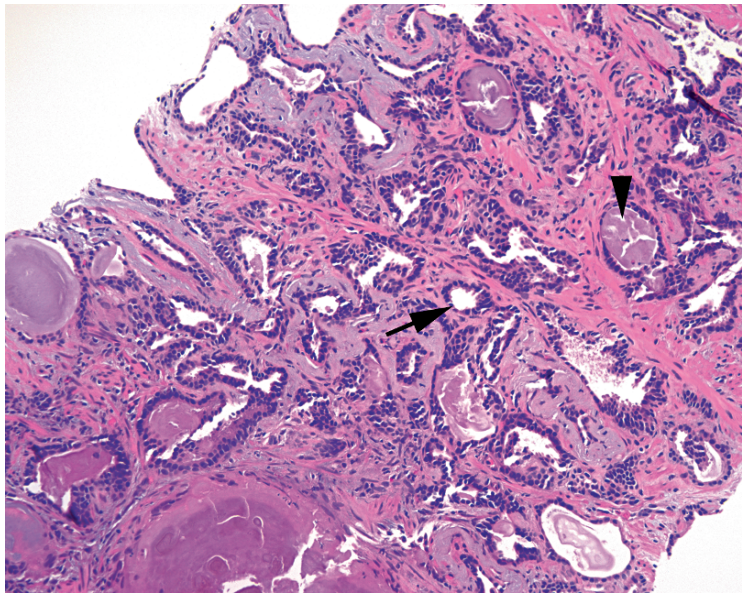

Figure 11.9. Atrophy. These glands appear hyperchromatic and infiltrative. However, the low cuboidal cells with attenuated cytoplasm (arrow) and angular gland profiles are typical of benign atrophy. Corpora amylacea are present (arrowhead).

nucleoli (how unfortunate) but by definition has a basal layer (visible by immunostains if not by H&E).

Atrophy

Atrophy is the shrinkage of the cells forming the glands. The cytoplasm shrivels down, leaving essentially rows of nuclei outlining the lumens (Figure 11.9). At low power these atrophic glands can look small and irregular, which may be suspicious. However, the lumens have an angular, almost staghorn look to them. Small- to medium-sized nucleoli may be seen, but the lack of cytoplasm should be a red flag against diagnosing cancer. Immunostains highlight a basal cell layer.

Basal Cell Hyperplasia

The basal cells that underlie the glandular cells are not usually well visualized. When they are noticeable, you can see them as sort of denim-blue, oval, regular nuclei surrounding the more purple glandular nuclei (Figure 11.10). The tricky part is that they may have nucleoli. In basal cell hyperplasia, the basal layers may proliferate and create several layers of worrisome-looking cells in the glands. The key is in recognizing the dual population; sometimes you can still see the glandular cells floating on top of the basal hyperplasia. Stains help.

Cowper's Glands

Cowper's glands are histologically normal glands (distal to the prostate, secreting directly into the urethra, and normally not sampled on needle biopsy) that consist of mucous-filled secretory glands surrounding a coil of ducts. They are lobular in architecture and have small bland nuclei. Their abundant mucin will stain with periodic-acid Schiff, and they are usually negative for the prostate markers prostate-specific antigen (PSA) prostate-specific acid phosphatase (PSAP).

Radiation Changes

Radiation atypia has a characteristic look that is difficult to describe in words. The nuclei are *too* pleomorphic to be cancer, especially when compared with the relatively uniform nuclei

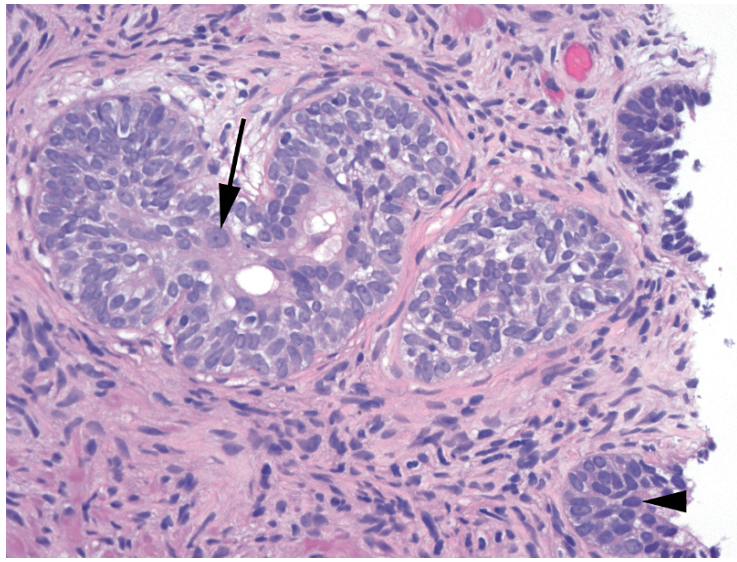

Figure 11.10. Basal cell hyperplasia. This proliferation of cells, some with prominent nucleoli (arrow), is actually an expanded basal cell layer. Comparison with benign epithelium (arrowhead) shows the relatively pale and greyish nuclei of the basal cells.

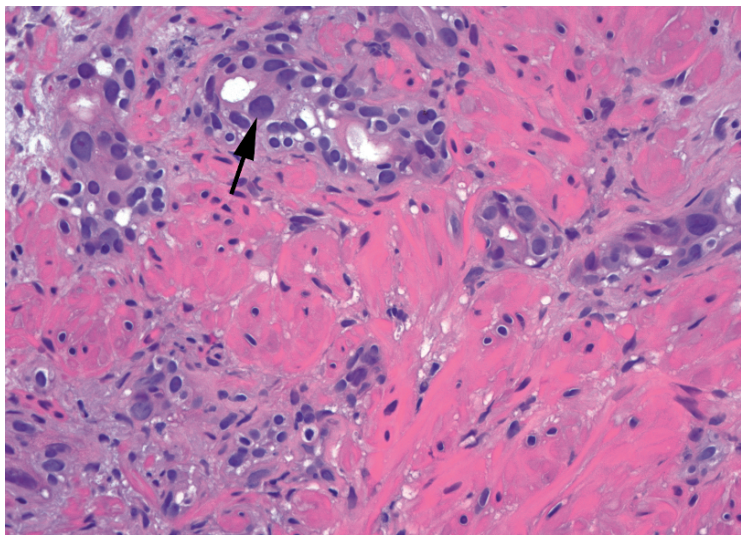

Figure 11.11. Radiation atypia in benign prostate. There is scattered and random nuclear pleomorphism (arrow). Enlarged nuclei classically have dense, uniform, smudgy chromatin.

of prostate cancer. Radiated benign glands show atrophic cytoplasm and wildly pleomorphic nuclei mixed in with normal nuclei (Figure 11.11). The nuclei may be very large, with angular shapes, and tend to have a dense smudgy chromatin without nucleoli. Identifying residual cancer in the radiated prostate is a diagnosis made largely on architecture (many individual cells with ample vacuolated cytoplasm and nuclei that ironically are often not as pleomorphic as the benign radiated nuclei).

Seminal Vesicle

The nuclei of the seminal vesicles have very pleomorphic nuclei, not unlike radiation atypia. They will definitely stand out in a needle biopsy specimen and can be very concerning based on cytology. However, remember that prostate cancer is usually not pleomorphic, and look for the telltale golden globs of lipofuscin to identify it as seminal vesicle (Figure 11.12).

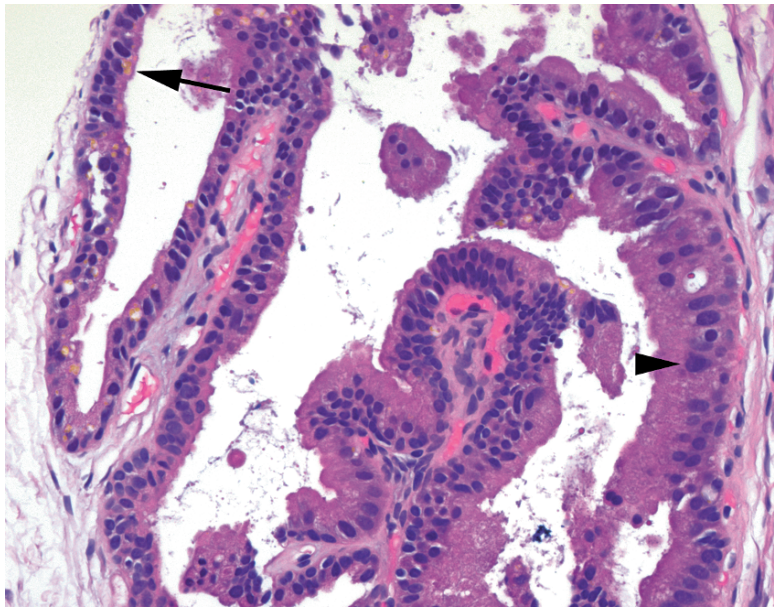

Figure 11.12. Seminal vesicle in a biopsy specimen. There are scattered large, hyperchromatic, and crowded nuclei in this gland (arrowhead). However, golden pigment is visible in the cytoplasm (arrow), identifying this as seminal vesicle.

Sclerosing Adenosis

Sclerosing adenosis is seen best in transurethral resection specimens. It is a hyperplastic and proliferative lesion that is complicated by a hypercellular stroma. The appearance is that of crowded glands and individual cells (which may have prominent nucleoli) in a background of cellular stroma. Remember that prostate cancer *does not* induce a stromal reaction.

Atypical Glands and Stains

It is not uncommon, in a needle core biopsy specimen, to stumble across one or two isolated glands that make you very nervous. However, unless several features of carcinoma are evident, most pathologists will be reluctant to make the diagnosis of cancer in that setting. One option is to sign it out as a focus of atypical glands. In the absence of definitive cancer, it will usually generate a repeat biopsy.

Immunostains may help in the diagnosis of these tiny lesions or with larger groups of glands that have some but not all of the features of cancer. Stains for the basal layer (CK903 or high-molecular-weight cytokeratin and p63) should highlight the basal cells in all benign glands and show loss of staining in malignant glands. Racemase is a newer marker that preferentially stains the cytoplasm of cancer. However, there are false-positive and false-negative results with all three of these antibodies, and so each case is interpreted in the context of the H&E appearance (which is the best approach for all immunostains).

Approach to the Radical Prostatectomy Specimen

For the radical prostatectomy specimen, the prostate is inked and bread loafed from apex (nearest the penile urethra) to base (nearest the bladder neck). Each slice is cut into four quadrants to fit them into cassettes. The margins are taken first:

1. Right and left vas deferens: These represent the true surgical margins of the vas deferens. Positive vas deferens margins are very rare, and some pathologists do not submit them.
2. Apical, or distal, margin: This is where the prostate meets the penile urethra. It is cut off as a thick tangential shave and then turned 90°, sliced, and submitted as a series of perpendicular sections that are parallel to the urethra. The presence of malignant glands is acceptable, as long as they do not touch the inked apical surface.
3. Bladder neck margin: This is where the prostate meets the bladder; it is a soft tissue margin, not a urethral margin. The urethra itself retracts back into the prostate at surgery and may not be seen on the slide. This is usually a shave margin, in which the presence of any malignant glands is considered a positive margin. It can also be treated like the apical margin, however, and sectioned perpendicularly.

After evaluating the margins, systematically examine each section of the prostate. Each full slice of prostate is halved into left and right sides. If the entire hemisection cannot fit into one block (usually it cannot), it is subdivided into anterior and posterior quadrants. Orienting the isolated quadrant can be tricky. For posterior sections, the true posterior surface should be flatter than the lateral surface. The neurovascular bundles, which sometimes come out with the prostate, are located at the posterolateral corners. For anterior sections, the anterior tip should have many smooth muscle bundles and a very poorly defined capsule. The verumontanum of the urethra (the bump on the posterior urethra) points anteriorly (Figure 11.13).

Examination of the edge of the prostate is prognostically important. There is no true organ capsule but rather the outer limit or edge of the prostate, which is best recognized posteriorly and posterolaterally as packed muscle bundles of the prostate. Extension of the cancer beyond the edge indicates extraprostatic extension (EPE) and increases the stage of the tumor. Capsular incision, where the surgeon has cut across the organ and left some prostate in the patient, becomes very important if there is cancer in the area. Malignant glands near big vessels or among skeletal muscle are not necessarily EPE, but cancer in fat is "out" by definition (Figure 11.14), as there is no intraprostatic fat. However, if you wait to diagnose EPE until seeing tumor in fat, you will miss some EPE. As cancer extends beyond the border of the prostate it is often associated with a fibrotic response to the tumor, wiping out the fat. This type of EPE is better appreciated at low power by following the contour of the edge of the prostate. Anteriorly, the muscle bundles are loose and disorganized, so it is difficult to recognize EPE except by seeing tumor in or beyond the plane of adjacent fat.

Although calling it "out" changes the tumor stage, it does not necessarily mean a positive margin. To call a positive margin, you must have glands not just really, really close to ink but actually transected by ink. The threshold is very high. In a positive margin, you must also

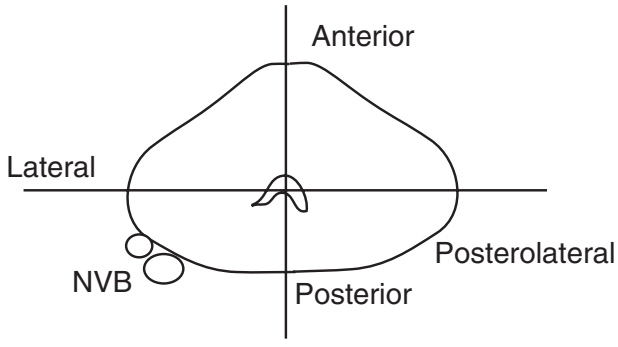

Figure 11.13. Low-power view of radical prostatectomy sections. Each cross section of prostate is cut into quadrants to fit into cassettes. The neurovascular bundles (NVB) are found at the posterolateral border of the prostate. The verumontanum points anteriorly.

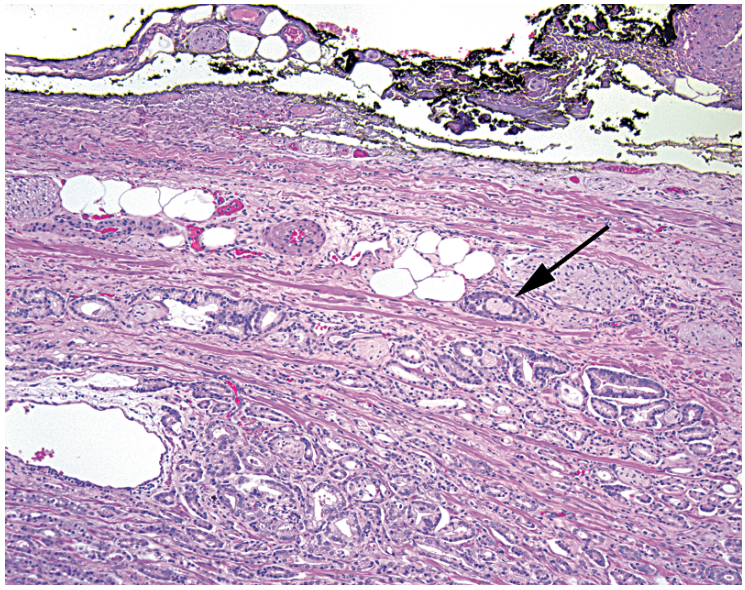

Figure 11.14. Extraprostatic extension. Malignant glands are seen wrapping around a nerve (arrow) adjacent to extraprostatic fat, diagnostic of focal extraprostatic extension. The margin, seen as the ink at the top of the photograph, is negative.

decide "why" it is positive—by noting if it occurs in an area of capsular incision or in an area of EPE. A positive margin is almost always going to be considered EPE in the anterior prostate, because the capsule is so poorly defined.

Perineural invasion is a big deal in a biopsy specimen but is taken for granted in a radical. It is not worth mentioning in the diagnosis. Grading in a radical is the same as grading in a needle core. You only have to grade the one or two biggest nodules (not the little multifocal ones), and each big nodule is given its own grade.

The seminal vesicles are examined by sampling the seminal vesicle at the point where it meets the prostate. Seminal vesicle invasion, if present, is seen on this section. Microscopically, you need to see tumor in the parenchyma of the seminal vesicle, not just next to it.

Other Prostate Neoplasms

Ductal adenocarcinoma is a variant type of adenocarcinoma that is characterized by tall, stratified columnar cells making papillary or cribriform structures (Figure 11.15). They may grow into the urethra as exophytic masses, or they may arise from more peripheral ducts in the prostate. It may be found in conjunction with conventional adenocarcinoma. It is not assigned a Gleason grade but behaves like a pattern 4 lesion.

Other types of carcinoma include mucinous carcinoma, squamous cell carcinoma, urothelial (transitional cell) carcinoma, sarcomatoid carcinoma, basal cell carcinoma, and small cell carcinoma. The more difficult-to-recognize variants of usual prostate cancer are pseudohyperplastic carcinoma (a sneaky variant that mimics the papillary architecture of benign hyperplasia), atrophic cancer (mimicking benign atrophy), and foamy gland cancer (with abundant xanthomatous appearing cytoplasm).

Spindle cell lesions may arise in the prostate. Stromal lesions arising from the unique stroma of the prostate range from the benign stromal nodules, to stromal tumors of uncertain malignant potential, to stromal sarcomas. The most common prostatic sarcoma in adults is leiomyosarcoma. Rhabdomyosarcomas occur mainly in children.

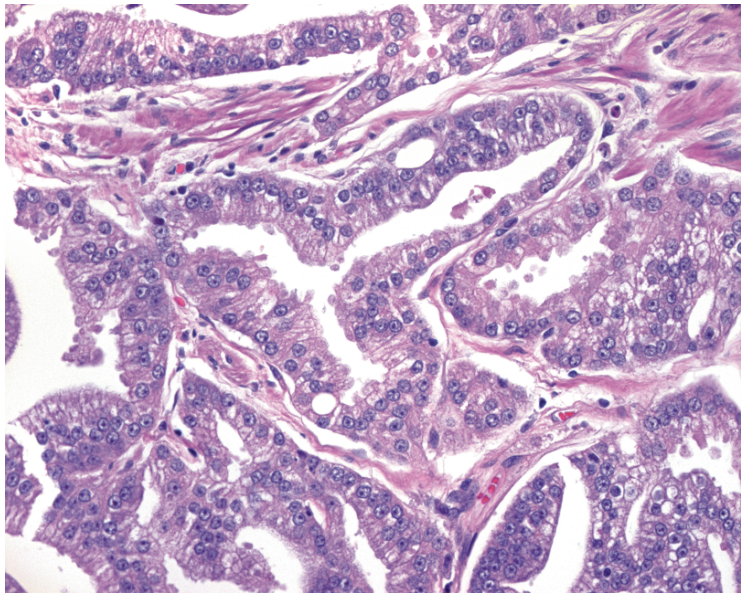

Figure 11.15. Ductal adenocarcinoma. In this variant, the tumor cells have a tall columnar morphology. The nuclei still resemble conventional prostate adenocarcinoma.