Interpretation of prostate biopsy

Author: Ximing J Yang, MD, PhD
Section Editors: Nicholas Vogelzang, MD, W Robert Lee, MD, MS, MEd, Jerome P Richie, MD, FACS
Deputy Editor: Diane MF Savarese, MD

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INTRODUCTION

Prostate cancer is the second most common cancer in men worldwide, according to data from the World Health Organization GLOBOCAN database. The increasing frequency of prostate cancer over the last decade is due in part to widespread screening with serum prostate-specific antigen (figure 1). However, the incidence of the disease was increasing even before the introduction of this test [1-3]. The reasons for this increase are not known; both genetic and environmental factors have been implicated. (See "Screening for prostate cancer", section on 'Epidemiology and natural history' and "Risk factors for prostate cancer".)

A histologic diagnosis is required prior to instituting therapy for any stage of prostate cancer. Needle core prostate biopsy under ultrasound guidance is the most common method of obtaining diagnostic tissue. However, with the increasing use of multiparametric magnetic resonance imaging prior to biopsy, targeted fusion biopsies are becoming increasingly common. Other potential sources of diagnostic tissue include material from transurethral resections of the prostate, prostatectomy or cystoprostatectomy specimens, or biopsies from metastatic sites (most often lymph nodes and/or bone).

This topic review will discuss the pathology of prostate cancer and the interpretation of the prostate biopsy. Specific issues related to clinical presentation, diagnosis, biopsy, staging, and treatment of prostate cancer are discussed separately:

- (See "Clinical presentation and diagnosis of prostate cancer".)
- (See "Prostate biopsy".)
- (See "Localized prostate cancer: Risk stratification and choice of initial treatment".)

BIOPSY TECHNIQUE

Core needle biopsy of the prostate is essential to determine whether or not cancer is present in men with an elevated serum prostate-specific antigen level and/or an abnormal digital rectal examination. The standard is to take multiple core biopsies, usually under transrectal ultrasound guidance. Primary diagnosis of prostate cancer using fine-needle aspiration is not acceptable in the United States, although it was widely used in other countries in the past. The technique for prostate biopsy and the diagnosis of prostate cancer are discussed separately. (See "Prostate biopsy" and "Clinical presentation and diagnosis of prostate cancer".)

Issues related to sampling error — Using the standard 12-core biopsy, less than 1 percent of the prostate gland is sampled. This limited sampling explains why a random 12-core biopsy can miss tumor in at least 20 percent of cases and why the Gleason grade may be underestimated in another 20 to 30 percent of cases. Saturation biopsy, using 24 or more cores, has been used to increase the likelihood of identifying areas of tumor [4]. However, this technique may be associated with an increased risk of complications and increased detection of small foci of low-grade carcinoma, which may be clinically insignificant. (See "Prostate biopsy", section on 'Sampling methods'.)

Incorporation of prebiopsy magnetic resonance imaging (MRI) into the diagnostic pathway for a clinically suspected prostate cancer improves the detection of clinically significant disease, reduces adverse effects from biopsy, and can potentially prevent unnecessary biopsies in some individuals. Higher-grade, clinically significant prostatic adenocarcinoma tends to have higher glandular density and a prominent desmoplastic stromal reaction, which can be better detected by MRI [5]. (See "Prostate biopsy", section on 'MRI'.)

However imaging studies including MRI are not diagnostic tests for prostate cancer and they cannot be used to replace prostate needle core biopsy for establishing the diagnosis of a prostate cancer.

Furthermore, MRI-targeted biopsies alone have not replaced the need for standard systematic biopsies because they can miss a significant number of high-grade, clinically significant cancers (Gleason score 7 or above), and there are three major benign conditions, which can be found in negative targeted biopsies that were detected as suspicious lesions on MRI (inflammation, stromal fibrosis, and conditions causing benign increased glandular density such as, benign prostatic hyperplasia). Combining targeted and systematic biopsies offers the best chance of detecting the clinically significant cancer. (See "The role of magnetic resonance imaging in

prostate cancer", section on 'Should males with positive MRI scans only undergo targeted biopsy?' and "Prostate biopsy", section on 'MRI'.)

HISTOLOGIC FEATURES

Adenocarcinoma accounts for more than 95 percent of malignancies of the prostate. Other types of cancers including neoplasms with neuroendocrine differentiation, urothelial (transitional cell) carcinoma, carcinosarcoma, basal cell carcinoma, lymphomas, or stromal sarcoma do occur within the prostate [6]. The following sections will focus on the diagnostic features of prostatic adenocarcinomas and neuroendocrine neoplasms.

Precancerous lesions of the prostate, including prostatic intraepithelial neoplasia (PIN), are discussed separately. (See "Precancerous lesions of the prostate: Pathology and clinical implications".)

Adenocarcinoma — The diagnosis of prostatic adenocarcinoma, particularly on limited material from needle core biopsy, is based on a constellation of architectural and cytologic features [6], and no single feature is sensitive and specific enough to establish diagnosis of prostatic adenocarcinoma in all cases.

Prostatic adenocarcinoma includes acinar and ductal types (picture 1A-B). Acinar adenocarcinoma is much more common than the ductal type [7]. Therefore, most descriptions on prostatic adenocarcinoma refer to acinar type if not specified. Prostatic adenocarcinoma can be diagnosed histologically by the presence of small infiltrating glands with prominent nucleoli. Architecturally, acinar adenocarcinoma cells form glands that are typically smaller than benign glands (acini or ducts (picture 1A)), while ductal adenocarcinoma cells usually form large glands with papillary configurations (picture 1B).

The adenocarcinoma cells, both acinar and ductal types, tend to grow in an infiltrative and haphazard manner (picture 2). In less differentiated tumors, the glandular pattern is irregular, less organized, fused, or even absent (picture 3), and the tumor cells tend to grow in as cords, nests, or sheets, more often in cribriform patterns (picture 4).

Cytologically, the cytoplasm of tumor cells is often purple and darker than the pale cytoplasm of the benign epithelium on hematoxylin and eosin (H&E)-stained sections. Tumor cells often display nuclear enlargement, irregularity, and hyperchromasia, and large nucleoli can be seen in the majority of cases (picture 5). Intraluminal crystalloids, amorphous secretion, or blue-tinged mucin are frequently present in malignant glands but are uncommonly found in benign glands (picture 6) [6]. The common morphologic features associated with the diagnosis of

malignancy as reported in one series of 250 needle biopsies performed at a single institution are listed in the following table (table 1) [8].

Immunohistochemistry — Immunohistochemical staining (IHC) may complement histologic examination of H&E-stained tissue sections to confirm a diagnosis of prostate cancer. We often use an IHC "cocktail," which includes alpha-methylacyl-CoA racemase (AMACR; positive in prostate adenocarcinoma), p63, and high molecular weight cytokeratin (34bE12) antibodies (both negative in prostate adenocarcinoma), when diagnostic uncertainty is encountered at the time of a prostate biopsy.

IHC for 34bE12 can identify basal cells, which are present in benign prostatic glands but typically absent in prostatic adenocarcinomas [9,10]. This immunostain should be used with caution because some cancer cells are positive and some benign prostatic glands display only weak staining [11].

Another molecule, AMACR, also known as P504S, was identified as a molecular marker for prostatic adenocarcinoma by complementary DNA microarray technology [12-15]. Expression of AMACR is a useful marker for tissue diagnosis of prostate cancer in several studies reported by our group (picture 7) [16-18] and others [14,15,19].

More recently, p63, a nuclear protein present in prostatic basal cells and absent in prostatic adenocarcinomas, has also been shown to be a more reliable marker than 34bE12 because of its prominent nuclear staining [20].

IHC using prostate-specific antigen (PSA) has a limited role in pathologic diagnosis of prostate cancer on needle biopsy because both adenocarcinomas and benign prostatic epithelium are reactive. On the other hand, PSA IHC may be applied in biopsy material from other organs to confirm the prostatic origin of epithelial cells rather than determining whether they are benign or malignant. PSA-positive cells derived from lymph nodes, bone, or the prostate bed following prostatectomy are more likely to represent malignant cells than are those taken from a core biopsy of an intact prostate.

NK3 homeobox 1 (NKX3.1) is a validated prostate-specific marker that has better sensitivity and specificity than PSA [21,22]. In the vast majority of high-grade prostatic adenocarcinomas, the distinct nuclear staining in tumor cells is present (picture 8). NKX3.1 has been primarily used to determine prostatic origin in a possible metastatic prostate cancer. But on prostate needle core biopsies, its utility is limited because, like PSA, it also labels benign prostatic epithelium.

Other prostate-specific markers can be used for diagnostic IHC, including prostate-specific membrane antigen, prostatic-specific acid phosphatase, and Prostein (P501S) [23-25]. They can

all be used as a panel of markers to determine a prostatic primary for an individual with a metastatic epithelial tumor, in which a prostatic origin is possible. But, like PSA and NKX3.1, these markers are not cancer specific since they are all present in benign prostatic epithelium.

ERG/TMPRSS2 fusion protein — The erythroblast transformation-specific (ETS) related gene (*ERG*) is a member of the ETS family of transcription factor genes. A fusion gene between *ERG* and the transmembrane protease, serine 2 (*TMPRSS*) gene has been found in prostatic adenocarcinoma. ERG protein immunostaining has been used to detect the ERG/TMPRSS2 fusion protein, a product of the fusion gene [26]. In North America, ERG nuclear staining is detected in approximately 50 percent of prostatic adenocarcinoma cases. However, compared with white populations, rates of *ERG/TMPRSS2* gene fusions in prostate cancer are much lower for populations of Black or Asian descent [27-29]. The low sensitivity of ERG immunoreactivity may limit its clinical utility in diagnosis of prostate cancer on needle core biopsies [30]. However, this fusion gene product is fairly specific for prostate cancer [31], and it does have potential diagnostic value in determination of prostatic origin of a metastatic focus, and possibly to differentiate a small cell neuroendocrine carcinoma that arose in the prostate from one arising elsewhere (eg, the lung). (See 'Small cell (neuroendocrine) carcinoma' below.)

Although there are some studies suggesting a role for the *ERG/TMPRSS* fusion gene in prostate cancer progression, more recent reports have not confirmed this finding [32], and ERG expression by itself has not been routinely used in clinical practice for predicting prognosis of prostate cancer. Data on the prognostic influence of combined expression of ERG and loss of phosphatase and tensin homolog are discussed elsewhere. (See "Molecular prognostic tests for prostate cancer", section on 'Phosphatase and tensin homolog loss'.)

Neuroendocrine neoplasms — Neoplasms with neuroendocrine differentiation arising within the prostate include prostatic adenocarcinoma with neuroendocrine differentiation, well-differentiated neuroendocrine tumors, small cell neuroendocrine carcinoma, and large cell neuroendocrine carcinoma [33,34]. The clinical and prognostic implications of neuroendocrine differentiation are discussed elsewhere. (See "Localized prostate cancer: Risk stratification and choice of initial treatment", section on 'High-grade, low-PSA prostate cancer'.)

Adenocarcinoma with focal neuroendocrine differentiation — Many prostatic adenocarcinomas show areas of focal neuroendocrine differentiation using IHC for neuroendocrine markers such as chromogranin, synaptophysin, neuron-specific enolase, or CD56. Typically, the tumor cells that are positive for neuroendocrine markers account only for a small percentage of the total. Neuroendocrine differentiation is not a part of Gleason grading.

Focal neuroendocrine differentiation can be observed in several types of prostatic tumors, which may have different biologic and biochemical features [35-39]:

- Focal neuroendocrine differentiation may be seen in 47 to 100 percent of cases of typical de novo prostatic adenocarcinomas [37,38], particularly high-grade tumors. The presence of isolated adenocarcinoma cells with large eosinophilic cytoplasmic granules also suggests the presence of neuroendocrine differentiation (also known as Paneth cell differentiation).

  Increasingly, IHC is being performed to assess for neuroendocrine markers to search for the presence and document the percentage of neuroendocrine cells in high-grade prostatic adenocarcinoma before any treatment. However, with the exception of treatment-related neuroendocrine prostate cancers, described below, the contribution of focal neuroendocrine differentiation to clinical behavior in de novo prostate adenocarcinoma is uncertain [40-42]. Specifically, focal neuroendocrine differentiation is usually not associated with aggressive clinical behavior, and there is insufficient evidence at this time to support treating these tumors with focal neuroendocrine differentiation differently than typical high-grade prostatic adenocarcinoma. However, pure neuroendocrine carcinomas including small cell carcinoma and large cell neuroendocrine cells are treated differently than conventional prostatic adenocarcinoma. (See 'Small cell (neuroendocrine) carcinoma' below and 'Large cell (neuroendocrine) carcinoma' below.)

- Neuroendocrine differentiation may also emerge in men who have previously had androgen deprivation therapy (ADT) for advanced castration-sensitive prostate adenocarcinoma. These tumors, sometimes called treatment-related neuroendocrine prostate cancers or aggressive-variant prostate cancers, are increasingly recognized in the castration-resistant phases of disease progression. (See "Chemotherapy in advanced castration-resistant prostate cancer", section on 'Aggressive prostate cancer variants'.)

  The underlying biology evolves due to the selective pressure of ADT, especially with potent androgen receptor pathway inhibitors. It is possible that a small population of tumor cells with neuroendocrine features present in the untreated prostatic adenocarcinoma were resistant to ADT and became a dominant population after ADT. These tumors can be androgen receptor negative, have a varying degree of histologic features of neuroendocrine cells (such as fine "salt-pepper" chromatin), can express markers of neuroendocrine differentiation (eg, chromogranin, synaptophysin), and may be low in PSA production [43]. The presence of these neuroendocrine tumor cells can be associated with an aggressive clinical course with atypical clinical manifestations, and a relative resistance to androgen signaling inhibitors, but possible sensitivity to taxane/platinum combinations.

(See "Chemotherapy in advanced castration-resistant prostate cancer", section on 'Treatment'.)

Well-differentiated neuroendocrine tumor — Primary well-differentiated neuroendocrine tumors, previously termed carcinoid tumors, are extremely rare in the prostate as a primary [44]. Morphologically similar to the counterpart in the gastrointestinal tract, this tumor is usually positive for neuroendocrine markers and negative for PSA. A well-differentiated neuroendocrine tumor of the prostate also may present with locally advanced disease or even metastasis, but it still has a favorable prognosis [44,45]. (See "Clinical characteristics of well-differentiated neuroendocrine (carcinoid) tumors arising in the gastrointestinal and genitourinary tracts".)

Small cell (neuroendocrine) carcinoma — Small cell (neuroendocrine) carcinoma, a rare primary tumor of the prostate, is an aggressive and fatal disease [46]. Its pathologic diagnosis requires the presence of small, undifferentiated (oat cell) carcinoma cells demonstrating scan cytoplasm, "salt pepper" chromatin, high mitotic, and apoptotic activities. These features are almost identical to pulmonary small cell carcinoma.

Typically, small cell carcinoma of the prostate will show positivity for one or multiple neuroendocrine markers (chromogranin, synaptophysin, neuron-specific enolase, and CD56). The prostatic specific markers such as PSA, PSAP, PSMA, and NKX3.1 may be lost partially or completely in prostatic small cell carcinoma. Approximately 50 percent of small cell carcinomas of the prostate coexist with typical adenocarcinomas indicating a dedifferentiation process. In addition, only approximately 50 percent of prostatic small cell carcinomas show TTF1 positivity, this rate is much lower than that of the pulmonary counterpart. Therefore, the coexistence with high-grade prostatic adenocarcinoma, partial expression of prostatic markers including positive ERG [47,48] and/or negative TTF1 [49,50] staining in small cell carcinoma are features suggestive of a primary prostatic small cell carcinoma. (See "Extrapulmonary small cell cancer", section on 'Prostate ESCC'.)

Pure small cell carcinomas of the prostate are typically resistant to ADT that is typically the first-line treatment for prostatic adenocarcinoma [51], and they are usually approached with platinum-containing chemotherapy similar to pulmonary small cell carcinomas. Because of this important therapeutic distinction, care should be taken to distinguish this entity from prostatic adenocarcinoma with focal neuroendocrine differentiation. (See "Overview of systemic treatment for advanced, recurrent and metastatic castration-sensitive prostate cancer and local treatment for patients with metastatic disease", section on 'Androgen deprivation therapy' and "Chemotherapy in advanced castration-resistant prostate cancer", section on 'Aggressive prostate cancer variants'.)

Large cell (neuroendocrine) carcinoma — Large cell neuroendocrine carcinoma is an entity that was newly incorporated into the World Health Organization classification of prostate tumors in 2016 [33,34]. The tumor is composed of cells with prominent neuroendocrine features, including salt-pepper chromatin, high mitotic rate, and neuroendocrine differentiation supported by strong positivity for neuroendocrine markers immunohistochemically (picture 9). In addition, the tumor cells are larger than the cells seen in small cell carcinoma. The tumors do not show glandular differentiation as adenocarcinoma but often form large nests with peripheral palisading and necrosis. This tumor may be associated small cell carcinoma or high-grade adenocarcinoma.

Large cell neuroendocrine carcinoma is rare and highly aggressive, particularly the pure form, and is similar to small cell carcinoma in behavior [52]. However, the clinical experience of optimal management is limited because of its rarity.

Intraductal carcinoma of the prostate — Intraductal carcinoma of the prostate (IDCP) is a fairly recently defined entity [53,54]. Although not graded using the Gleason grading system [55], IDCP is an indicator of the presence of high-grade invasive prostatic adenocarcinoma, and it is often associated with high-stage, high-volume invasive disease with a poor prognosis. In general, the presence of IDCP generally warrants definitive aggressive therapy because of its association with high-grade invasive cancer. However, a small subset (5 to 10 percent) of patients who have IDCP alone on biopsy may not have high-grade invasive disease at the time of prostatectomy after the histologic specimen is examined thoroughly.

IDCP is defined by the presence of malignant epithelial cells filling large prostatic acinar ducts, with preservation of basal cells forming either (1) solid or dense cribriform patterns or (2) a loose cribriform or micropapillary pattern with either marked nuclear atypia (nuclear size six times normal or larger) or nonfocal comedonecrosis. The controversy lies with the difficulty in distinguishing "neoplastic cells" in high-grade PIN from "malignant cells" in IDCP, and the reproducibility in recognizing "loose cribriform patterns" where IDCP and high-grade PIN may overlap. (See "Precancerous lesions of the prostate: Pathology and clinical implications", section on 'Prostatic intraepithelial neoplasia'.)

Histologically, the neoplastic cells in IDCP are growing within pre-existing ducts in a noninvasive pattern, similar to high-grade PIN (picture 10). However, IDCP is associated with a coexisting invasive adenocarcinoma in 90 to 100 percent of cases, unlike high-grade PIN, which is associated with a lower risk for invasive carcinoma.

Thus, although morphologically almost identical, IDCP may represent one of two distinct entities:

- Adjacent advanced invasive prostate cancer, representing "colonization" of high-grade invasive adenocarcinoma into benign prostatic ducts; this accounts for the vast majority of IDCP cases.

- In situ carcinoma when associated with minimal low-grade or noninvasive carcinoma; this accounts for a small subset of IDPC cases.

The molecular basis of IDCP is uncertain. The few studies reporting the molecular changes seen with IDCP likely are not limited to IDCP with adjacent invasive high-grade carcinoma because of the difficulty in dissecting IDCP alone. Although some experts disagree, there is a general consensus that when present, IDCP should not be graded using the Gleason score or grade groups at this time [56,57] (see 'Gleason grading system' below).

IDCP by itself is not an aggressive invasive disease, but it could be the product and indicator of highly invasive prostate cancer. As a result, it is an independent predictor for poor prognosis in the vast majority of cases in which it is found. It is more commonly associated with high-grade, mostly acinar-type prostatic adenocarcinoma, and occasionally ductal adenocarcinoma. IDCP is often associated with biologically and clinically aggressive disease with a high risk for advanced tumor stage, high tumor volume, and poor outcomes [56,58-62]:

- In a study of 21 radical prostatectomies in patients who originally had IDCP on biopsy, the average Gleason score was 7.9 [56]. Pathologic staging in these cases found that 11 (51 percent) had prostatic cancer with extraprostatic extension (pT3), eight (38 percent) had cancer that was confined to the prostate (pT2), and two (10 percent) showed only intraductal carcinoma without invasive cancer.

- In a systematic review of 31 studies totaling 179,721 patients with localized and advanced prostate cancer, intraductal disease was associated with lower biochemical recurrence-free survival (pooled hazard ratio [HR] 2.09, 95% CI 1.75-2.50) and cancer-specific survival (pooled HR 2.93, 95% CI 2.25-3.81) in men with localized disease [62]. Among men with advanced prostate cancer, overall survival was lower in those with versus without intraductal disease (pooled HR 1.75, 95% CI 1.43-2.14). The presence of intraductal carcinoma was an adverse feature in both prostate biopsies and prostatectomy specimens.

Definitive therapy (prostatectomy, radiation therapy) is recommended in patients with an established diagnosis of IDCP on needle biopsy, even in the absence of pathologically documented invasive prostate cancer on needle biopsy, because of the risk of high-grade, high-stage prostatic adenocarcinoma. (See "Initial approach to low- and very low-risk clinically

localized prostate cancer" and "Initial management of regionally localized intermediate-, high-, and very high-risk prostate cancer and those with clinical lymph node involvement".)

The presence of intraductal histology is also associated with a higher risk of biochemical recurrence, metastasis, and mortality following treatment of localized prostate cancer [58,61], and it is enriched for oncologic driver mutations. In particular, men with germline breast cancer susceptibility gene mutations may have a higher incidence of IDCP. (See "Genetic risk factors for prostate cancer", section on 'Aggressive prostate cancer'.)

Urothelial (transitional cell) carcinoma — Urothelial carcinoma involving the prostate is relatively common. However, most of these tumors result from direct extension into prostatic urethra or prostatic ducts from urothelial carcinoma of the urinary bladder; prostate involvement may be identified in 12 to 48 percent of patients who undergo radical cystectomy for a urothelial bladder cancer [63]. (See "Clinical presentation, diagnosis, and staging of bladder cancer".)

Primary urothelial carcinoma of the prostate without bladder involvement is rare. In the older literature, primary urothelial carcinoma of the prostate was estimated to account for 1 to 4 percent of prostatic malignancies [63]. However, these figures were obtained before the radical prostatectomy era, and therefore, the actual incidence may be even lower.

Urothelial carcinoma is not infrequent in prostate needle core biopsy because needle biopsy sample areas are mostly in the prostatic peripheral zone (figure 1). Because of the differences in clinical management, it is important to recognize urothelial carcinoma, which displays morphologic and IHC characteristics different from prostatic adenocarcinoma.

Distinguishing primary prostatic urothelial carcinoma from secondary involvement of the prostate by bladder cancer is very difficult on biopsy specimens. Therefore, clinical investigation of the bladder and urinary tract is necessary if urothelial carcinoma is initially detected in the prostate. The presence of prostatic stromal invasion of urothelial carcinoma, which is associated with worse prognosis, should be evaluated in the case of prostatic urothelial carcinoma, in addition to the grade and location of the tumor.

KEY COMPONENTS OF THE PATHOLOGY REPORT

When cancer is present — The histologic diagnosis of prostate cancer on a biopsy specimen must be made without any uncertainty. Any equivocal diagnostic term, such as "possible," "likely," "suspicious," or "atypical," should not be accepted as a definitive diagnosis of

malignancy. Therapy should not be initiated for a patient based upon an equivocal or uncertain diagnosis. (See 'Cases with diagnostic uncertainty' below.)

When prostatic adenocarcinoma is present on needle biopsy, it is not sufficient to simply confirm its presence. The following important features should be included in the pathology report.

Gleason grading system — The Gleason grade is based solely on the architectural features of prostate cancer cells, and correlates closely with clinical behavior. A higher score indicates a greater likelihood of having non-organ-confined disease, as well as a worse outcome after treatment of localized disease [64,65]. Based on the growth pattern and degree of differentiation, tumors are graded from 1 to 5, with grade 1 being the most and grade 5 the least differentiated [66].

Gleason score — The Gleason score is derived by adding together the numerical values for the two most prevalent differentiation patterns (a primary grade and a secondary grade). As an example, if a biopsy consists of predominantly grade 3 and secondarily grade 4 disease, the combined score is "3+4" or 7. As more experience has been gained with Gleason grading, pathologists generally will not diagnose prostate cancer with composite Gleason scores of 2 to 5 on needle biopsy; thus, the range of composite Gleason scores on prostate biopsies for clinical practice range Gleason 6 to 10.

The Gleason score has been the preferred system for grading tumors and was incorporated as a key prognostic factor in the 2010 tumor, node, metastasis (TNM) staging system for prostate cancer. In the eighth (2017) edition of the TNM staging system, the Gleason score information has been incorporated into the new histologic grade group, which is used in assigning patients to prognostic stage groups (table 2 and table 3). (See "Localized prostate cancer: Risk stratification and choice of initial treatment".)

The grade group system — The 2014 International Society of Urological Pathology (ISUP) consensus conference adopted a new five-tier grading system based on the modified Gleason scores (table 4) [67]. This new grading (ISUP grade group) system was adopted in the 2016 World Health Organization classification of genitourinary tumors [33].

The new grade group system is not designed to replace the Gleason grading system; instead, it is based on the Gleason score and provides more accurate risk stratification than the composite Gleason score [68]. Tumors are separated into five categories based on the primary and secondary Gleason pattern. The grade group system was validated in an analysis of over 20,000 patients undergoing radical prostatectomy at five academic centers between 2005 and 2014

[69,70]. In the validation study, there was an increasing risk of prostate cancer mortality with increasing overall grade group [69]:

- Grade group 1: Gleason score ≤6
- Grade group 2: Gleason score 3+4 = 7 (hazard ratio [HR] for death 2.8 relative to grade group 1)
- Grade group 3: Gleason score 4+3 = 7 (HR 6.0 relative to grade group 1)
- Grade group 4: Gleason score = 8 (including 4+4 = 8, 3+5 = 8, or 5+3 = 8; HR 7.1 relative to grade group 1)
- Grade group 5: Gleason scores 9 to 10 (4+5, 5+4, or 5+5; HR 12.7 relative to grade group 1)

In another report, five-year recurrence-free survival rates were 95, 83, 65, 63, and 35 percent, respectively, for grade group 1, 2, 3, 4, and 5 [71].

We recommend the inclusion of the grade group after the Gleason score in the pathology report as the current practice. As an example, "prostatic adenocarcinoma, Gleason score 3+4 (grade group 2, with 30 percent Gleason 4 tumor)." It is important, however, that the pathology report includes the percent of the higher Gleason score component, especially for grade groups 2 and 3 [72]. In the United States, we typically report an individual diagnosis Gleason score (grade group) for each part/container of prostate biopsy specimens, which may be related to billing issues. Therefore, one single case may have multiple Gleason scores from the different parts that were sampled. In other countries, the pathologists may provide a global Gleason score (grade group) for the whole biopsy specimen in addition to the diagnoses for each individual part. This is generally more consistent with the final grading from radical prostatectomies; however, it is not required based on the current consensus [55,72,73].

There is no consensus whether the clinical management decision should be based on the highest score (grade group) of one part or on the overall (global) Gleason score (grade group) in a prostate biopsy. However, if Gleason 5 tumor component is present in biopsy such as in 3+5, 4+5, the highest score should be considered primarily. For Gleason score 4+3, 4+4, or 3+4, the decision should be mostly decided on the individual basis considering the focus of these higher grades with 4 tumor component could be very small.

A diagnosis of prostate cancer with a single-digit Gleason grade should be avoided. For example, a diagnosis of "prostatic adenocarcinoma, Gleason grade 4" is confusing. It could mean a tumor with Gleason score "2+2" or 4, which is a low-grade tumor with limited aggressive behavior, or it could mean a tumor with Gleason score "4+4" or 8, which is very aggressive. A

Gleason score or grade group should be reported even for a single small focus of cancer on needle biopsy [74].

Does a grade group 1 lesion represent prostate cancer? — Autopsy studies initially noted that there was a disproportionate number of prostate cancers that never caused any symptoms, and subsequent randomized trials confirmed that a great proportion of cancers diagnosed through prostate-specific antigen (PSA) screening were "clinically insignificant" (ie, very low risk) [75,76]. (See "Screening for prostate cancer", section on 'Benefits and harms of screening'.)

The identification of those men who have clinically insignificant prostate cancer has been the center of prostate cancer research for decades. Although debated [77], current definitions of insignificant cancer based on pathologic findings at needle biopsy include grade group 1 cancer, <3 cores with cancer, and ≤50 percent of core involved by cancer. These patients can choose to be followed on an active surveillance program, although significant percentages of cases will progress to higher-grade and higher-volume tumor if not treated; the latent period of progression is uncertain. Because of this, close follow-up with serum PSA, repeat biopsy, and/or magnetic resonance imaging is necessary to detect early progression. (See "Localized prostate cancer: Risk stratification and choice of initial treatment" and "Active surveillance for males with clinically localized prostate cancer".)

Grade group 1 prostatic adenocarcinoma of a small volume can thus be considered an early phase of prostate cancer, which can be clinically insignificant. This has led some to question whether prostatic adenocarcinoma grade group 1 should even be considered prostate cancer [71,78,79].

Key issues that clarify this confusion include:

- Gleason grading of prostate cancer is based on the architectural features, not cytologic features, of the tumor cells. In other words, Gleason grade 6, Gleason grade 7, and Gleason grade 8 are all composed of malignant cells with similar cytologic features but with different architectural patterns.

- The histologic features of Gleason grade 6 adenocarcinoma include uncontrolled cellular proliferation, invasiveness, and the lack of basal cells. All of these are the characteristics of a malignant neoplasm.

- Almost all the cases of very low-volume prostate cancer demonstrate Gleason 6 (or lower), which suggests that they are the early phase of prostate cancer.

- Only a very small subset of Gleason 6 adenocarcinomas is associated with subsequent development of metastatic disease, and these may represent sampling error in the original needle biopsy. A prostate with biopsy-proven Gleason 6 tumor may harbor occult higher-grade tumors, and these undetected higher-grade tumors can metastasize.

- Even in the absence of an undetected higher-grade tumor, with current techniques, the Gleason 6 adenocarcinomas that will versus will not develop recurrent disease cannot be predicted with confidence. Contemporary studies of men with Gleason 6 disease strongly suggest that pure Gleason 6 tumors after radical prostatectomy almost never develop metastases [80,81]. In rare cases, however, the Gleason 6 tumors may extend outside the prostate (ie, pathologic stage III), which increases the risk for recurrence. In a study of 7817 patients undergoing radical prostatectomy, only 7 of 2502 patients (0.3 percent) with Gleason 6 tumors had extraprostatic extension (T3a), and none of the 2502 patients with Gleason 6 tumors had seminal vesicle invasion (T3b) [81].

- In the absence of treatment, individuals with Gleason 6 adenocarcinoma may be found to have Gleason 7 or higher-grade, or clinically significant cancer with a higher risk of metastases [82,83]. Although most of these cases can be attributed to initial sampling error, others may represent true disease progression. (See "Active surveillance for males with clinically localized prostate cancer".)

Gleason 3+4 versus 4+3 — Gleason 3+4 and 4+3 were formally grouped as Gleason score 7; however, these groups differ substantially in prognosis and have been divided into grade group 2 and grade group 3, respectively. Men with Gleason 4+3 tumors (where grade 4 is more prevalent than grade 3) have a less favorable outcome than do those with Gleason 3+4 disease, where grade 3 is more prevalent [84-89]. As an example, a multivariate analysis of a single-institution series of 1333 men with Gleason 7 prostate cancer found a significantly increased risk of seminal vesicle invasion in those with Gleason 4+3 disease (20 versus 9 percent, odds ratio 2.26) [89]. This observation appears to be more reliable when applied to a prostatectomy specimen rather than one from a biopsy [90,91]. The new group grading system, as discussed above, separates Gleason score 7 into grade group 2 (Gleason 3+4) and grade group 3 (Gleason 4+3) to address the different risks associated with each group.

Gleason 8, grade group 4 — Gleason score 8, grade group 4 includes patients with Gleason score 4+4 disease as well as those with Gleason score 3+5 or 5+3 prostate cancer. In a contemporary cohort study, the presence of a component of Gleason grade 5 (either 3+5 or 5+3) was associated with an increased risk of prostate cancer mortality (adjusted HR 2.77, 95% CI 1.13-6.80) compared with Gleason score 4+4 disease [92]. However, more studies with larger cohorts are necessary to validate this finding. However, more studies with larger cohorts are

necessary to validate this finding. In our experience, most of these cases should be graded Gleason 4+5 or 5+4 (grade group 5) if sufficient tissue sampling can be done.

Tertiary Gleason scores — In some cases, a tumor may contain a small component (<5 percent) of higher-grade tumor in addition to the two predominant patterns; the grade of this minor component is referred to as the tertiary Gleason grade. Traditionally, the tertiary Gleason grade has been noncontributory to the overall Gleason score in biopsy specimens. However, in 2005, the ISUP consensus conference recommended that men with biopsy Gleason score 3+4 or 4+3 prostate cancer and a tertiary pattern 5 should have their cancers classified as Gleason score 8 or 9, respectively [93]. These men have a higher pathologic tumor stage and an increased risk of biochemical and clinical recurrence compared with men who have Gleason score 7 disease without a tertiary grade 5 component [88,94-96]. The 2019 consensus conference on grading of prostatic carcinoma recommended reporting separate tertiary Gleason pattern 4 or 5 only when less than 5 percent of tumor volume in radical prostatectomy specimens. If more than 5 percent, these patterns should be included in the Gleason score [55].

For radical prostatectomy specimens, the tertiary pattern should be reported in addition to the Gleason score (eg, "Gleason 4+3 = 7 [grade group 3] with tertiary 5 pattern").

The percentage of a tumor consisting of high-grade prostate cancer (ie, combined Gleason pattern 4 or 5) may provide additional prognostic information [97]. In a series of 504 consecutive patients undergoing prostatectomy, an increasing percentage of high-grade tumor was associated with a statistically significant poorer cancer-specific survival.

Clinical relevance of Gleason score and grade groups — The numerical Gleason score and grade group are of clinical relevance, and they are a component of the American Joint Committee on Cancer staging system (table 3), and the risk stratification schema of the National Comprehensive Cancer Network that is used to select initial treatment for localized disease (table 5), as well as most nomograms and tables that estimate prognosis based on pretreatment variables (see "Localized prostate cancer: Risk stratification and choice of initial treatment"). Several studies suggest that contemporary Gleason grade readings may be significantly higher than they were 10 years ago [98-100]. The effect of this subtle upgrading of Gleason scores over time could be an apparent improvement in outcome for all categories of men with clinically localized prostate cancer (the so-called Will Rogers phenomenon). This issue has the potential to impact the interpretation of studies that suggest improvements in outcome from treatment over time.

However, there can be substantial interobserver variability in the Gleason grading of a biopsy specimen, particularly for pathologists with less experience interpreting prostate biopsies. In a

study in which the interpretations from 29 pathologists were compared with that of an expert in prostate cancer pathology on an average of 278 samples, only 68 percent of samples were correctly classified as Gleason score <7, 7, or >7 [101]. Therefore, additional training may be necessary for those pathologists who are unfamiliar with the Gleason grading system.

Furthermore, there can also be discrepancies between the Gleason score as determined on the prostate biopsy, and the Gleason score that is determined on the final histologic examination of radical prostatectomy specimens. These discrepancies, usually minor, primarily result from the sampling issues on biopsies. With current combined standard biopsy and targeted biopsy and advanced training, the degree of discrepancies is decreasing. This issue is discussed separately. (See "Prostate biopsy", section on 'Sampling methods'.)

Modifications to the Gleason grading system — Several minor modifications to the Gleason grading system were proposed during the 2014 ISUP prostate cancer grading consensus conference. These changes include recognition of certain histologic patterns (eg, cribriform, glomeruloid, or mucinous (picture 11 and picture 12 and picture 13)) and are summarized in the table (table 6).

As an example, invasive cribriform patterns in prostatic adenocarcinoma, either Gleason 4 or Gleason 5 (comedo type), have been recognized as a morphologic biomarker for poor prognosis of prostate cancer [102]. It has even been suggested that the large expansile cribriform patterns (now defined as Gleason pattern 4) in prostatic adenocarcinoma should be distinguished from other Gleason pattern 4 lesions and possibly categorized as Gleason pattern 5. However, there is no consensus currently on how to define these cribriform lesions histologically and how to report them in the pathology report in prostate specimens. More studies are being conducted to further characterize the biologic and biochemical features and clinical implications of these lesions [103,104].

Side and location of the tumor — Because a partial prostatectomy is not practical, some pathologists do not record which side of the prostate harbors the tumor in core biopsies. However, documentation of tumor side and location is critical for urologists planning to perform focal therapy or a nerve-sparing radical prostatectomy [105]. Based on this information, one or both neurovascular bundles may be spared, with a potentially significant impact on postprostatectomy potency rates. (See "Radical prostatectomy for localized prostate cancer", section on 'Nerve-sparing approach'.)

Estimated tumor volume — An estimate of tumor volume (often generically termed the "percentage or the length of positive biopsies") can add clinically significant information to other factors, such as the biopsy Gleason score, in risk stratification, and in predicting outcome

following therapy for early stage prostate cancer [106-110]. (See "Localized prostate cancer: Risk stratification and choice of initial treatment", section on 'Percentage of positive biopsies'.)

There is no major difference between providing the percentage or length (in mm) of positive cores in determination of the tumor extent; since the core length is typically 10 to 15 mm, the length and percentage can be calculated and exchanged roughly if necessary.

Both the number of involved cores and extent of tumor within each core should be included in the pathology report. Tumor involvement within a core can be estimated by measuring either the percentage or the length by millimeter of tumor involvement [106,107].

Perineural invasion — The presence of perineural invasion (PNI) in a prostate biopsy should be reported since it represents information that may be used by the clinician in planning therapy (picture 14) [111,112]. PNI in a core biopsy is an important predictor of pathologic stage, with most [106,111,113-117], but not all [118], studies finding a correlation between PNI on biopsy and extraprostatic extension at the time of prostatectomy. The presence of PNI on pretreatment core biopsy is also associated with a significantly higher likelihood of disease recurrence after radiation therapy [117,119].

Finding PNI in a prostatectomy specimen is very common. Although this finding has limited independent predictive value for clinical outcomes, PNI found in a prostatectomy specimen is correlated with a higher volume of prostate cancer in our own experience.

Extraprostatic extension — Although extraprostatic extension is usually documented only at the time of radical prostatectomy, direct extension of tumor cells beyond the confines of the prostatic capsule into periprostatic adipose tissue can occasionally be observed in needle biopsy specimens (picture 15). As an example, in one series of 150 malignant needle biopsy specimens, invasion of fat was only detected in one case (table 1) [8].

The presence of extraprostatic extension is clinically significant because it changes the tumor stage to a clinical T3 lesion, which constitutes locally advanced disease (table 2 and table 3), which may have implications for initial treatment (table 5). (See "Initial management of regionally localized intermediate-, high-, and very high-risk prostate cancer and those with clinical lymph node involvement".)

Involvement of skeletal muscle, ganglions, or individual nerves by tumor cells should not be considered to represent extraprostatic extension because these structures can also be observed within the normal prostate gland.

Seminal vesicles, and their continuation within the prostate (the ejaculatory duct), can sometimes be seen on needle biopsy specimens. The epithelial cells of the seminal vesicles are characterized by the presence of hyperchromatic and pleomorphic nuclei with intracellular golden-brown lipofuscin pigment. A diagnosis of tumor involvement of the seminal vesicles must be made cautiously, unless the biopsy is specifically indicated as from the seminal vesicle. Although targeted biopsy of the seminal vesicle is not a routine component of tumor staging, it is occasionally performed.

Presence of a special subtype of cancer — Occasionally, the presence of special subtypes of malignant tumor cells may be observed coexisting with conventional prostatic adenocarcinoma. The reason to include these tumor components in the diagnostic report is that they are all associated with a poor prognosis, which may require special management [6].

These subtypes or components may include but are not limited to the following:

- Ductal adenocarcinoma, characterized by the presence of tall columnar tumor cells (picture 1B). This tumor type can be present centrally around prostatic urethra, but more frequently as associated with high-grade invasive acinar adenocarcinoma in the peripheral zones. Tumor cells form single or pseudostratified layers, with papillary, large gland, or cribriform configuration, and resemble endometrioid carcinoma or colonic adenocarcinoma. Ductal adenocarcinoma, which differs from intraductal carcinoma that is noninvasive, is a mostly high-grade invasive cancer, and should be graded as Gleason 4 pattern [120-122].

- Small cell carcinoma, characterized by the presence of small cell neuroendocrine components, which should be confirmed using immunohistochemistry (IHC) markers of neuroendocrine differentiation. (See 'Small cell (neuroendocrine) carcinoma' above.)

- A sarcomatoid component along with the carcinoma (carcinosarcoma or sarcomatoid carcinoma), which is characterized by the presence of high-grade spindle tumor cells in addition to typical carcinomatous components.

When cancer is absent — Even if invasive cancer cannot be determined with certainty on the diagnostic prostate biopsy, several benign features warrant mention in the pathology report.

Prostatic intraepithelial neoplasia — The presence of high-grade prostatic intraepithelial neoplasia (PIN) in the needle biopsy specimen is clinically significant and should be included in the report, although it does not represent an invasive cancer.

High-grade PIN is believed to be a precursor to prostatic adenocarcinoma. The presence of high-grade PIN traditionally mandates a follow-up core biopsy to rule out the presence of a coexisting cancer. However, contemporary studies have shown that the risk of finding cancer in a patient with isolated high-grade PIN was only slightly higher than that in a patient with a benign prostate biopsy. By contrast, the presence of low-grade PIN is not usually reported because of its lack of clinical significance and possible confusion with high-grade PIN. (See "Precancerous lesions of the prostate: Pathology and clinical implications".)

Inflammation — Inflammation, particularly if it is acute, can contribute to an elevated serum PSA; therefore, its presence should be specified in the pathology report [123,124]. In core biopsy specimens of prostate tissue, a severe inflammatory reaction can mask the diagnostic histologic features of an adenocarcinoma; therefore, extreme care should be taken to exclude the presence of a cancer. Nonspecific granulomatous prostatitis, which is characterized by infiltrates of histiocytes and other inflammatory cells, along with destruction of the prostate glandular structures, can be misdiagnosed as high-grade prostate cancer [125].

Infarction — If an infarct is present in biopsy tissue, it should be included in the diagnosis because it could be responsible for an elevated PSA level, presumably as a result of tissue necrosis releasing massive amounts of PSA into the serum. Prostatic infarcts are uncommon, and in the past have only been reported on transurethral resection of the prostate material. However, infarcts may be identified in a small number of prostate core needle biopsies (eg, 2 cases in 2959 biopsies in one series [126]). Histologically, a relatively fresh prostatic infarct is characterized by defined areas of coagulative necrosis, with or without hemorrhage; intermediate-aged infarcts have reactive stroma and epithelium without necrosis, and older infarcts are characterized by replacement of the stroma by dense fibrosis and reparative changes (eg, squamous metaplasia at the infarct edges) [126].

Benign prostatic hyperplasia — Another common condition that can contribute to an elevated serum PSA is benign prostatic hyperplasia (BPH) [127]. (See "Clinical manifestations and diagnostic evaluation of benign prostatic hyperplasia".)

The "diagnosis" of BPH on a core needle biopsy specimen should be avoided since it may give a false impression that it is the cause of serum PSA elevation. Some pathologists routinely diagnose BPH in every prostate needle biopsy specimen without sufficient histologic evidence. However, BPH cannot be reliably diagnosed in such specimens because histologic diagnosis requires the presence of hyperplastic nodules, which cannot be assessed on needle core tissue [128].

Cases with diagnostic uncertainty — With advances in knowledge and development of diagnostic markers for prostate cancer, the number of prostate biopsy cases with diagnostic uncertainty have been greatly reduced. However, a definitive diagnosis of cancer can still be difficult in some situations, even for the most experienced pathologists. One of the most common problems encountered is the very small size of the suspicious lesion. Furthermore, the histologic features of prostatic adenocarcinoma are complex and may be subtle. An error in any step of tissue processing, including tissue fixation, dehydration, embedding, and even staining, may interfere with a proper diagnosis.

In the situation where the pathologist is suspicious but not totally convinced about a diagnosis of prostate cancer, the term "atypical glands suspicious for, but not diagnostic of, prostatic adenocarcinoma" is often applied. Other pathologists may prefer the diagnostic term "atypical small acinar proliferation (ASAP) suspicious for prostatic adenocarcinoma" [129]. This situation of suspicious cases, approximately representing 5 percent of prostate needle core biopsies [130], is not a pathologic entity, but a diagnostic term.

The following options are available for cases with diagnostic uncertainty:

- Examine multiple deeper tissue sections, which may show sufficient evidence to permit a definitive diagnosis of cancer.
- Perform IHC for 34bE12 or p63 (negative for prostatic adenocarcinoma) and AMACR (positive for prostatic adenocarcinoma). However, IHC stains may be false positive or false negative, and the diagnosis of prostatic adenocarcinoma should always be primarily based on the histologic features from hematoxylin and eosin-stained slides, rather than IHC stains alone. (See 'Immunohistochemistry' above.)
- Rebiopsy of the prostate, if clinically indicated. Approximately one-half of men with atypical or suspicious foci will have cancer identified on repeat biopsy [131-134].
- Clinically follow the patient as in active surveillance program, if high grade prostate cancer can be safely excluded. Most of the suspicious cases turn out to be Gleason 6 tumors (grade group 1).

Application of artificial intelligence in detection of prostate cancer — The use of computer-based analysis of histologic features of prostate cancer is not new [135]. However, with advances in whole-slide imaging capability and advanced computing technologies, an increasing number of studies of artificial intelligence (AI) in prostate cancer pathology are being undertaken [135-139].

One group of investigators has reported their findings using an AI software system (Paige Prostate) for detecting prostate cancer [137]. In this study of 1876 whole slide images of prostate core biopsy specimens, the use of the AI software showed high sensitivity (97.7 percent) and high specificity (99.3 percent) in detecting prostate cancer. Notably, Paige Prostate may be more beneficial to nonspecialist pathologists because they were as accurate in making a diagnosis when using Paige as prostate cancer specialists who were not using Paige.

Largely based on this study, in September 2021, the United States (US) Food and Drug Administration (FDA) approved the Paige Prostate system, to assist pathologists in making better and more accurate histologic diagnosis of prostate cancer [140].

Although there are still questions about current AI systems and whether it can distinguish 1) treated prostate cancer, which displays many other histologic changes; 2) many benign mimickers of prostate cancer; and 3) so called "atypical" lesions in the prostate core biopsy. More studies are necessary clarify these issues.

Therefore, in our view, the Paige or other AI systems cannot be used to replace diagnosis by pathologists at this point, but rather enhance the efficiency and accurate of pathology diagnosis of prostate cancer.

There are several AI systems for detection prostate cancer on tissue sections from companies in the United States and elsewhere [141]. None have been routinely used in clinical practice in the United States or worldwide, and the Paige system is the first and only one that has received FDA approval in the United States. It is anticipated that more AI systems will be approved in the coming years for assistance of diagnosis and predication of prognosis of prostate cancer.

Effect of treatment on biopsy specimens — Several factors can have a significant effect on the histologic appearance of a prostate biopsy specimen (table 7).

Hormone therapies

Androgen ablation — Androgenic influences are important for both the growth and malignant transformation of prostatic tissue. The testes account for 90 to 95 percent of total circulating testosterone, while the adrenal glands produce the remainder. In the prostate, testosterone is converted into dihydrotestosterone (DHT) by the enzyme 5-alpha reductase. DHT is the primary androgen that stimulates the growth of both benign and malignant prostate tissues.

Palliation of metastatic disease can be achieved by androgen deprivation therapy (ADT), which can be accomplished surgically (orchiectomy) or medically by administration of gonadotropin-

releasing hormone (GnRH) agonists, GnRH antagonists, or androgen receptor blockers (antiandrogens). Although usually reserved for the treatment of advanced or metastatic prostate cancer, ADT may be used in men with less advanced disease (ie, clinically organ-confined or locally advanced) as an adjunct to radiation therapy (RT) or surgery. (See "Initial systemic therapy for advanced, recurrent, and metastatic noncastrate (castration-sensitive) prostate cancer".)

A short course of systemic ADT may be administered after the diagnosis of prostate cancer but before local therapy such as radical prostatectomy. Although this therapy is not widely accepted in the United States as a standard therapy, it is being used more commonly for special circumstances, especially during the COVID-19 pandemic as a means of postponing radical prostatectomy. (See "COVID-19: Considerations in patients with cancer" and "Initial management of regionally localized intermediate-, high-, and very high-risk prostate cancer and those with clinical lymph node involvement", section on 'Neoadjuvant ADT approaches'.)

Neoadjuvant ADT affects the appearance of the prostate cancer at the time of subsequent surgery. Histologically, following a short course of neoadjuvant ADT, prostatic adenocarcinoma cells undergo the same degenerative changes including atrophy and cytoplasmic vacuolation as are seen in men undergoing continuous ADT for advanced prostate cancer (picture 5). Generally speaking, however, these histologic changes are milder compared with those seen in men undergoing prolonged periods of ADT.

Regardless of the duration of ADT, the histologic changes in the prostate gland in prostatectomy specimens are indistinguishable. The effects can be shown both in normal secretory epithelium and in adenocarcinoma cells, the vast majority of which maintain the secretory epithelial phenotype (table 7) [142,143]. Regression and degenerative changes, such as pyknotic nuclei, clear cytoplasm, or vacuolated cytoplasm, are evident, while the features of cytologic atypia (eg, nuclear enlargement and prominent nucleoli) that are typically present in adenocarcinoma cells are diminished or absent. These changes can cause difficulty in assessment of prostate biopsies and may result in underestimation of the extent of disease if hormone therapy was administered prior to a biopsy or prostatectomy. Furthermore, because of the severe histologic changes in tumor cells caused by prior hormonal therapy, the assignment of a Gleason score may not be reliable in this situation and is often withheld. However, it is a challenge for histologic assessment of treated prostate cancer and predication of its biologic behavior. The issue of grading treated prostate cancer should be revisited with more contemporary studies.

Despite this, the infiltrating pattern of a prostatic adenocarcinoma is mostly retained and can be recognized. In particular, identification of scattered individual malignant epithelial cells in the stroma is diagnostic evidence of prostatic adenocarcinoma (picture 16). Immunostaining for

keratins or for prostate-specific antigen (PSA) may be helpful in identifying the individual tumor cells in this situation to confirm the diagnosis [144].

Other nonspecific histologic changes, including basal cell hyperplasia, transitional cell and squamous cell metaplasia in benign epithelium, and chronic inflammation, may also be present. These nonspecific histologic changes in benign prostatic epithelial cells often provide the pathologist with a clue as to the use of prior hormonal therapy.

As noted above, advanced prostate adenocarcinomas can evolve, under the pressure of androgen deprivation therapy, to develop neuroendocrine differentiation (so-called treatment-related neuroendocrine prostate cancer or aggressive-variant prostate cancer). (See 'Adenocarcinoma with focal neuroendocrine differentiation' above.)

5-alpha reductase inhibitors — The 5-alpha reductase inhibitors, finasteride and dutasteride, which are widely used in the treatment of benign prostatic hyperplasia, are considered to be weak antiandrogens. (See "Medical treatment of benign prostatic hyperplasia", section on '5-alpha reductase inhibitors'.)

Both finasteride and dutasteride appear to have a limited effect on the histologic appearance of prostatic adenocarcinomas in biopsy specimens in contrast to the steroidal antiandrogens (table 7) [145-149]. Therefore, the histologic diagnosis of prostate cancer on biopsy specimens from men receiving finasteride or dutasteride is not difficult.

However, it has been suggested that 5-alpha reductase inhibitors have the potential to alter the Gleason score of prostate cancers [150]. This hypothesis was proposed largely to explain the findings of the Prostate Cancer Prevention Trial, in which men treated with finasteride had fewer prostate cancers overall but significantly more tumors of Gleason score 7 to 10 than the control group [151]. However, this observation was not confirmed in two other trials, and the relationship between 5-alpha reductase inhibitors and Gleason score in incident prostate cancer remains unsettled. (See "Chemoprevention strategies in prostate cancer", section on '5-Alpha reductase inhibitors'.)

Administration of a 5-alpha reductase inhibitor may complicate the diagnosis of a prostate cancer because these agents produce a nearly 50 percent decrease in serum PSA concentrations during the first three months of therapy, which persists as long as the drug is continued. (See "Measurement of prostate-specific antigen", section on 'Medications'.)

Radiation therapy — Radiation therapy (RT) including both external beam and brachytherapy will cause significant cytologic damage to prostate cancer cells as well as benign prostatic stromal and epithelial cells. The majority of series describing the histologic appearance of the

irradiated prostate glands were derived from patients receiving external beam RT [152,153]. Histologic changes following brachytherapy are similar but may be more pronounced [153,154]. (See "Brachytherapy for low-risk or favorable intermediate-risk, clinically localized prostate cancer".)

Postradiation biopsy is not routine following RT but may be indicated only if the PSA is rising, recurrent disease is suspected, and salvage surgery or brachytherapy is being considered. (See "Rising serum PSA after radiation therapy for localized prostate cancer: Salvage local therapy", section on 'General approach'.)

Several weeks after RT, prostatic cells undergo severe degenerative changes, including nuclear shrinkage and cytoplasmic damage. Occasionally, small foci of necrosis will be evident, both in benign and malignant glands. Acute inflammatory cells, such as neutrophils, macrophages, and later lymphocytes, accumulate. Gradually, the infiltration of reactive cells subsides, and fibrosis develops in areas of tissue damage. Prostate biopsy is rarely done in the acute phase within six months after radiation because it does not provide significant clinical information.

In response to RT, benign epithelial and stromal cells develop cytologic atypia, with the epithelial cells showing prominent nuclear irregularity, hyperchromasia, and polymorphic changes (table 7). Because of the presence of smudged nuclei, prominent nucleoli are not commonly seen. Irradiated benign epithelial cells often show a slightly spindled appearance, termed "streaming" histology. Despite marked nuclear atypia, benign glands still retain their lobular noninfiltrating patterns (picture 17). Irradiated tumor cells may display clear cytoplasm and other degenerative changes, or they may show no apparent histologic changes from the radiation (picture 18).

Nonspecific histologic changes, such as chronic inflammation, basal cell proliferation, or stromal fibrosis, may also be present to varying degrees. Postradiation changes in the benign glands may persist for many years following prostatic RT, causing difficulty interpreting prostate biopsies in irradiated men [154]. In diagnostically difficult cases, immunostaining specific for basal cells (p63 and high molecular weight keratins) may be helpful, often showing positive staining in the benign atypical cells but not in malignant cells.

Whether the Gleason grade of recurrent adenocarcinoma following a course of RT accurately reflects tumor aggressiveness or clinical behavior is uncertain [155]. In general, current recommendation is to report the Gleason score and grade group in cases with no obvious histologic evidence of treatment effect on the prostatic adenocarcinoma cells. How to grade and report the cases of prostatic adenocarcinoma with obvious treatment effects is still in debate. Further studies are necessary to evaluate this issue.

In contrast to the benign glands, the characteristic haphazard infiltrating architectural pattern and cytologic features of malignant prostate glands are often retained (table 7) [6].

The presence of malignant cells six months following RT to the prostate should not be interpreted as treatment failure. The long doubling time of many prostate tumors, coupled with radiobiologic data indicating that cell death following RT is a postmitotic event, suggests that the time course of disappearance of viable cancer from the prostate is prolonged. As a result, false-positive biopsies may be due to delayed tumor regression, and indeterminate biopsies (usually showing radiation effect in viable tumor cells) are of uncertain significance. In one series, for example, 30 percent of indeterminate biopsies showed eventual clearance of tumor at a mean time of 30 months following RT [156]. A higher number of indeterminate biopsies may convert to negative in men undergoing brachytherapy [157].

A biopsy that demonstrates the presence of tumor cells beyond 18 to 24 months is more likely to indicate active disease (either persistence or a local recurrence) [155,157,158]; however, even this is not absolute. In at least one series, 22 of 46 men who underwent routine prostate biopsy after combined external beam RT and brachytherapy had evidence of residual tumor cells; however, 16 had no evidence of an elevated serum PSA (biochemical failure) [155].

SUMMARY

- Core needle biopsy of the prostate is essential to determine whether or not cancer is present in men with an elevated serum prostate-specific antigen level and/or an abnormal digital rectal examination. The standard is to take multiple core biopsies under transrectal ultrasound guidance. Primary diagnosis of prostate cancer using fine-needle aspiration is not acceptable in the United States, although it was widely used in other countries in the past. (See 'Biopsy technique' above.)

- More than 95 percent of malignancies arising in the prostate are adenocarcinomas. The remaining types include neoplasms with neuroendocrine differentiation, urothelial carcinoma, basal cell carcinoma, lymphoma, and sarcoma. (See 'Histologic features' above.)

- When prostatic adenocarcinoma is present in the biopsy, histologic grading is accomplished using the Gleason score, which is based on the architectural features of the prostate cancer cells. The Gleason grades for the two most prevalent differentiation patterns have been used to create the Gleason score, and this is now being used in the newly adopted grade group system (table 4). This information correlates closely with

clinical behavior, and a grade group system has been incorporated into the 2017 Tumor, Node, Metastasis prognostic group staging system for prostate cancer (table 2 and table 3). (See 'Gleason grading system' above and "Initial staging and evaluation of men with newly diagnosed prostate cancer", section on 'Staging system'.)

There is no consensus whether the clinical management decision should be based on the highest score (grade group) of one part or on the overall (global) Gleason score (grade group) in a prostate biopsy. However, if a Gleason 5 tumor component is present in the biopsy specimen such as in 3+5 and 4+5, the highest score should be considered primarily. For Gleason score 4+3, 4+4, or 3+4, the decision should be mostly decided on the individual basis considering the foci of these higher grade tumors with Gleason 4 component could be very small. (See 'Gleason score' above.)

- Besides histologic type, additional information that may be derived from the prostate biopsy includes the number of positive cores, the percentage (or length) of cancer in the positive core, the presence of perineural invasion or extraprostatic extension, and the presence of histologic types other than conventional adenocarcinoma. (See 'When cancer is present' above.)

- Even if invasive cancer cannot be determined with certainty on the diagnostic prostate biopsy, several benign features, including prostatic intraepithelial neoplasia and benign prostatic hyperplasia, warrant mention in the pathology report. (See 'When cancer is absent' above.)

- A definitive pathologic diagnosis of prostate cancer is usually needed for clinical management, but definitive diagnosis is not always possible. The accuracy of pathologic diagnosis of prostate cancer can be improved by assessing deeper sections and by using immunohistochemistry (IHC) markers; correct interpretation of the IHC results is critical for success. (See 'Cases with diagnostic uncertainty' above.)

  Artificial intelligence-based software systems are a promising tool to aid pathologists in making an accurate diagnosis of prostate cancer, but they cannot replace review of histologic material by a trained pathologist. (See 'Application of artificial intelligence in detection of prostate cancer' above.)

- Several factors can have a significant effect on this histologic appearance of a prostate biopsy specimen, especially cancer treatment (table 7). (See 'Effect of treatment on biopsy specimens' above.)

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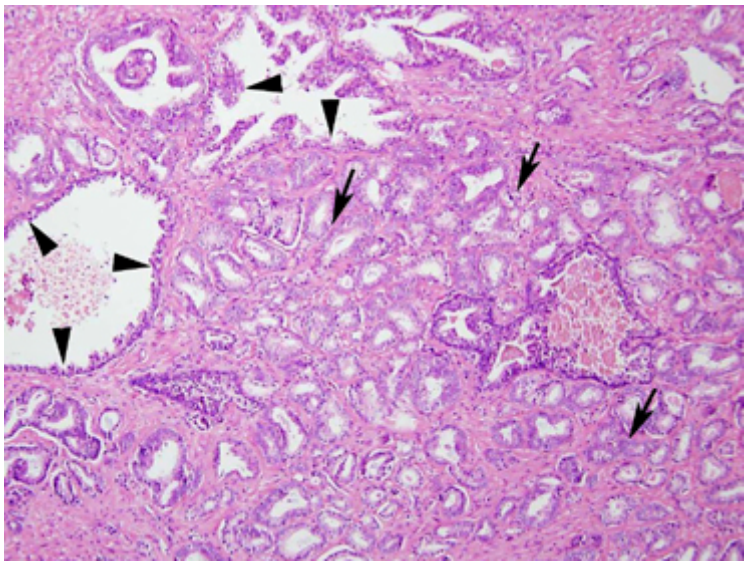
Topic 6924 Version 40.0

GRAPHICS

Prostate adenocarcinoma, acinar type

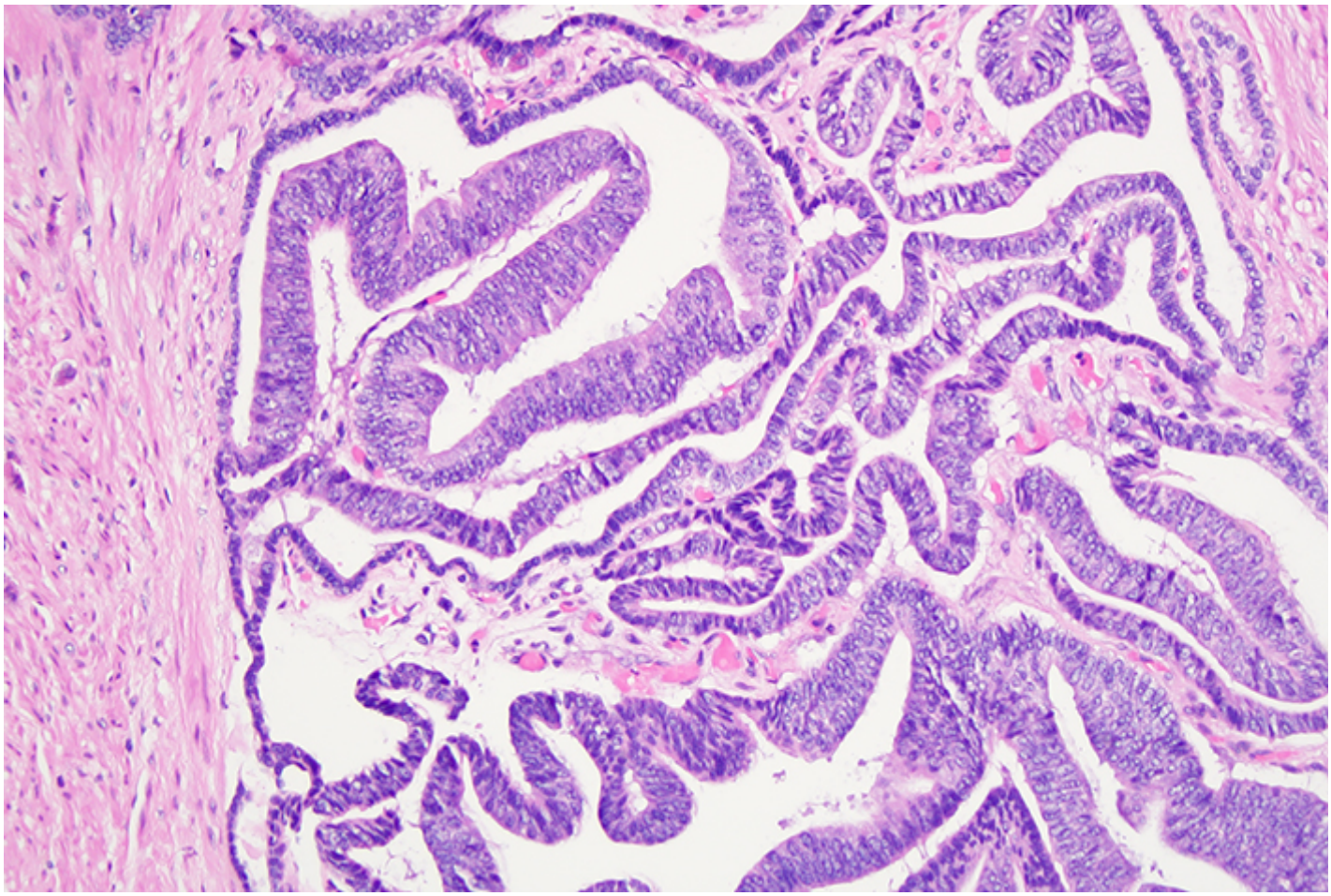


Low-power photomicrograph of an hematoxylin- and eosin-stained sample of prostate adenocarcinoma of the acinar type, demonstrating that the malignant glandular structures of the adenocarcinoma (arrows) are composed of cuboidal cells that are smaller in size to the benign glandular structures (arrowheads).

Courtesy of Ximing Yang, MD.

Graphic 76155 Version 3.0

Prostatic adenocarcinoma, ductal type



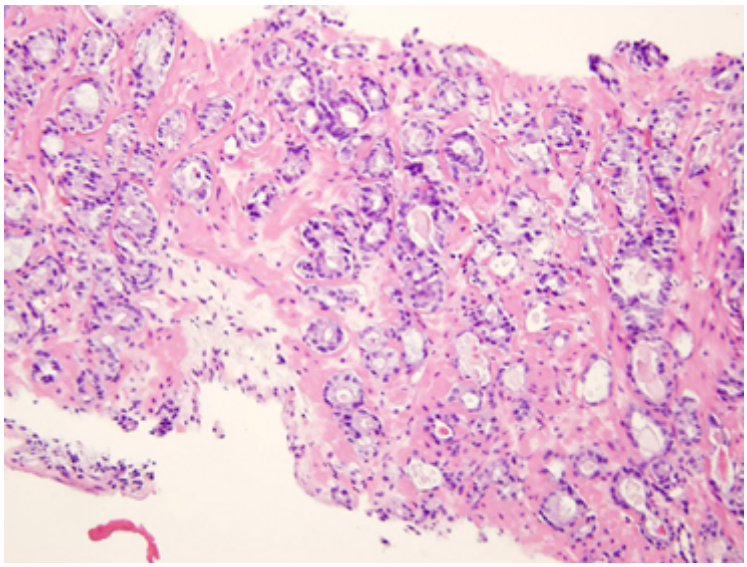
Low-power photomicrograph of an H&E-stained section of ductal-type prostatic adenocarcinoma. In contras
prostatic carcinoma of the acinar type, ductal tumors are composed of pseudostratified tall columnar cells, c
forming large glandular structures with papillary configurations.

H&E: hematoxylin and eosin.

Courtesy of Ximing Yang, MD.

Graphic 130804 Version 1.0

Prostate cancer, Gleason pattern 3

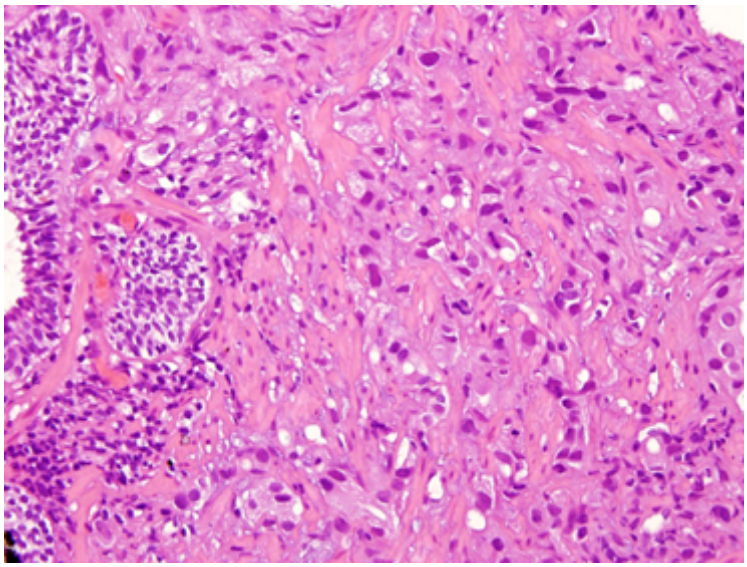


Low-power photomicrograph of an hematoxylin- and eosin-stained core biopsy of the prostate. The entire biopsy is involved with prostate adenocarcinoma, Gleason pattern 3, characterized by haphazardly infiltrating, well-formed malignant glands.

Courtesy of Ximing Yang, MD.

Graphic 66109 Version 3.0

Prostate cancer, Gleason pattern 4

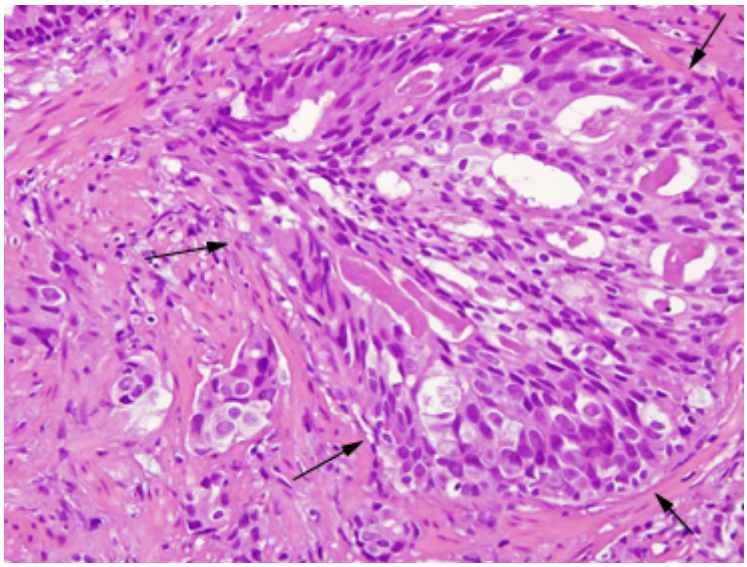


High-power photomicrograph of an hematoxylin- and eosin-stained section of the prostate gland containing prostate adenocarcinoma. This high-grade Gleason pattern 4 cancer is characterized by haphazardly infiltrating, poorly formed glands.

Courtesy of Ximing Yang, MD.

Graphic 63504 Version 3.0

Cribriform prostate adenocarcinoma

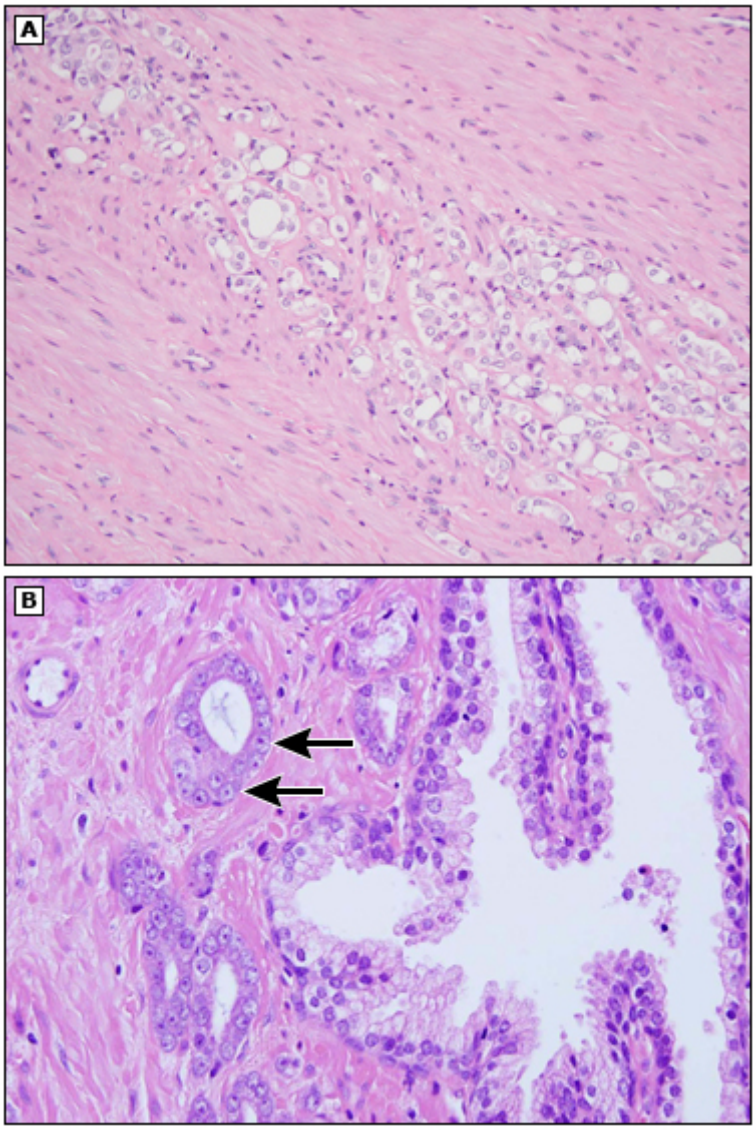


High-power photomicrograph of an hematoxylin- and eosin-stained section of the prostate gland. The majority of this tissue section is taken up by a prostate adenocarcinoma (arrows) with a cribriform pattern, corresponding to a Gleason pattern 4 lesion.

Courtesy of Ximing Yang, MD.

Graphic 52604 Version 2.0

Prostate cancer and prominent nucleoli



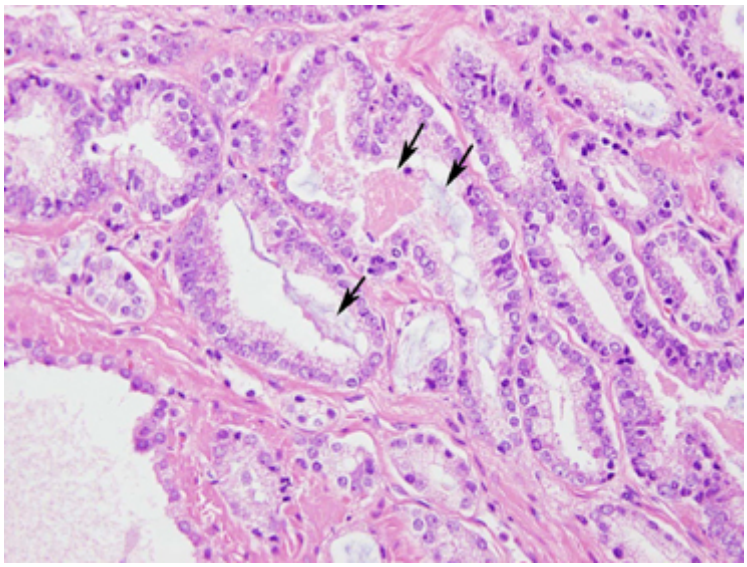
High-power micrograph of a H&E-stained tissue section of a prostate gland adenocarcinoma following a short course of neoadjuvant hormone therapy (depot leuprolide acetate [panel A]); high-power photomicrograph of an H&E-stained prostate adenocarcinoma not previously treated with hormone therapy (panel B). The treated tumor cells have atrophic changes and cytoplasmic vacuolations, and the infiltrating patterns of the cells are retained, but the degree of nuclear atypia of the tumor cells, including the presence of prominent nucleoli, is reduced compared with untreated prostate cancer (panel B), in which the tumor cells have prominent nucleoli and amphophilic cytoplasm (arrows).

H&E: hematoxylin and eosin.

Courtesy of Ximing Yang, MD.

Graphic 77354 Version 3.0

Prostate adenocarcinoma



This low-power photomicrograph of an hematoxylin- and eosin-stained section of the prostate gland demonstrates the characteristic blue-tinged mucin and amorphic secretion in the malignant glands (arrows).

Courtesy of Ximing Yang, MD.

Graphic 52171 Version 2.0

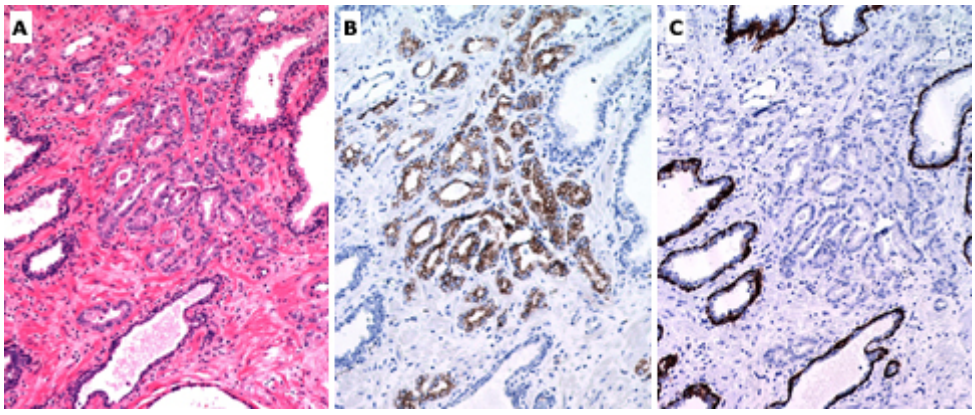
Morphologic features associated with malignancy on needle biopsy of the prostate

Morphologic feature	Malignant lesions, percent (n = 100)	Benign lesions, percent (n = 150)
Prominent nucleoli	94	25
Marginated nucleoli	88	7
Multiple nucleoli	64	0
Blue-tinged mucinous secretions	52	0
Intraluminal crystalloids	41	1
Intraluminal amorphous eosinophilic material	87	2
Collagenous micronodules	2	0
Glomerulations	15	0
Perineural invasion	22	0
Retraction clefting	39	7
Invasion of fat	0.7	0

Modified from Varma M, Lee MW, Tamboli P, et al. Morphologic criteria for the diagnosis of prostatic adenocarcinoma in needle biopsy specimens. A study of 250 consecutive cases in a routine surgical pathology practice. Arch Pathol Lab Med 2002; 126:554.

Graphic 59862 Version 2.0

Prostate tissue immunohistochemistry

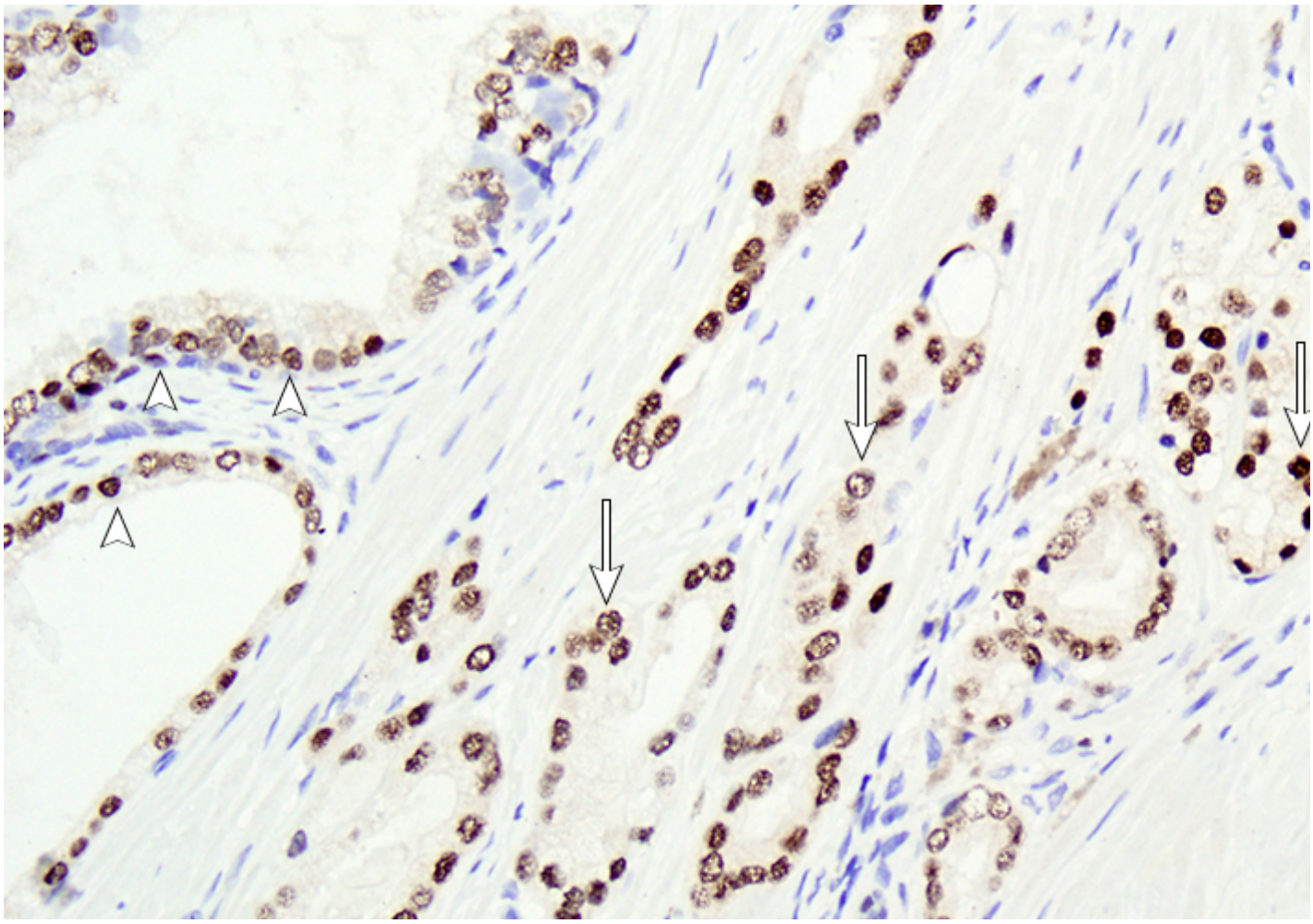


Low-power photomicrographs of serial tissue sections of the prostate gland, stained with hematoxylin and eosin (panel A), alpha-methylacyl-CoA racemase (AMACR/P504S) (panel B), and 34bE12 (panel C). The prostate adenocarcinoma stains positively for AMACR (brown stain) and negatively for 34bE12. In contrast, the peripheral benign glands adjacent to the cancer stain negatively for AMACR but positively for 34bE12.

Courtesy of Ximing Yang, MD.

Graphic 77883 Version 2.0

Prostate adenocarcinoma with positive immunohistochemical staining for NKX

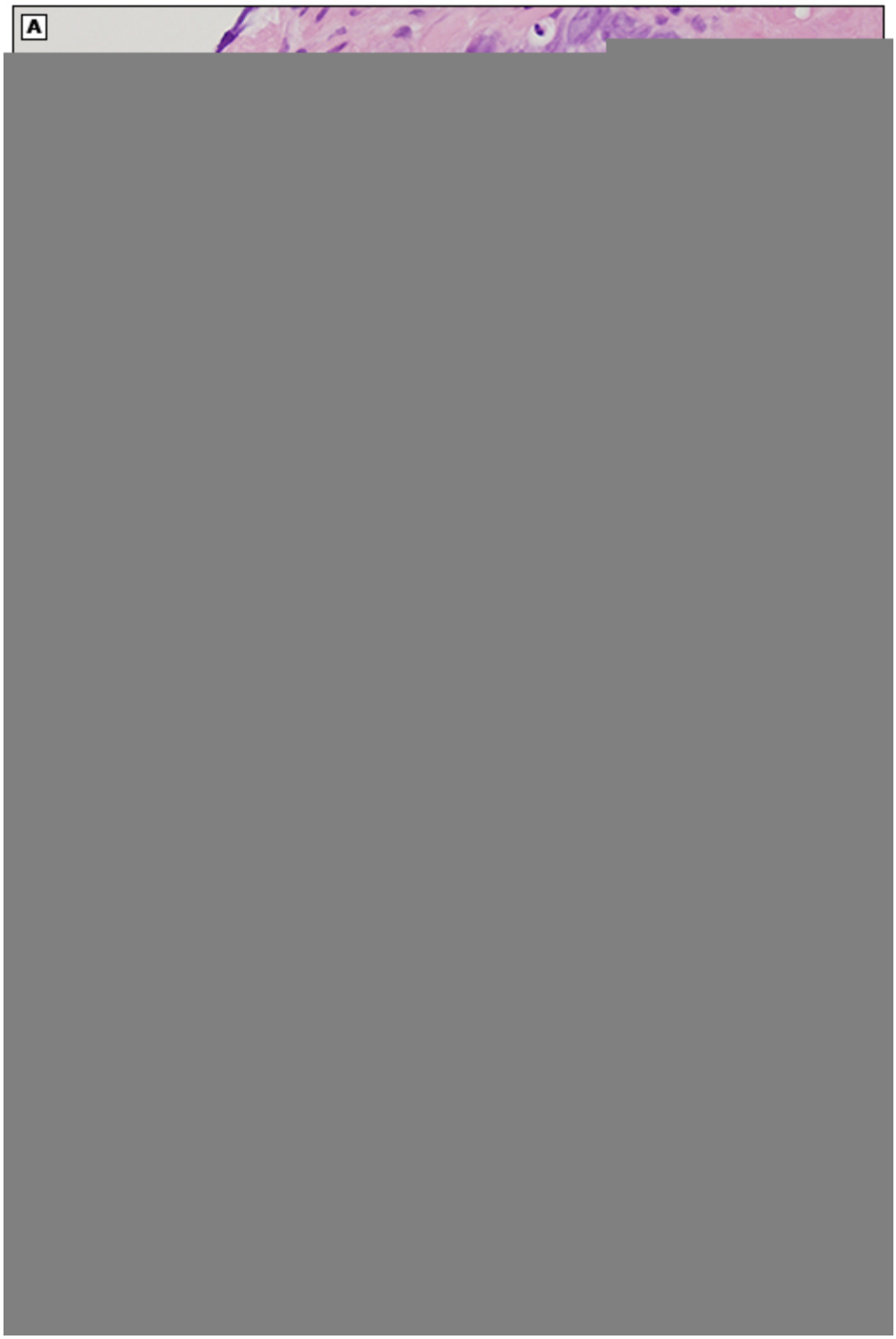


Prostatic adenocarcinoma cells (arrows) show strong nuclear staining for NKX3.1. In the large benign prosta glands (arrowheads), secretory cells also show strong nuclear staining for NKX3.1 and some benign basal ce also show weaker nuclear staining.

Courtesy of Ximing Yang, MD.

Graphic 130805 Version 1.0

Large cell neuroendocrine carcinoma of the prostate



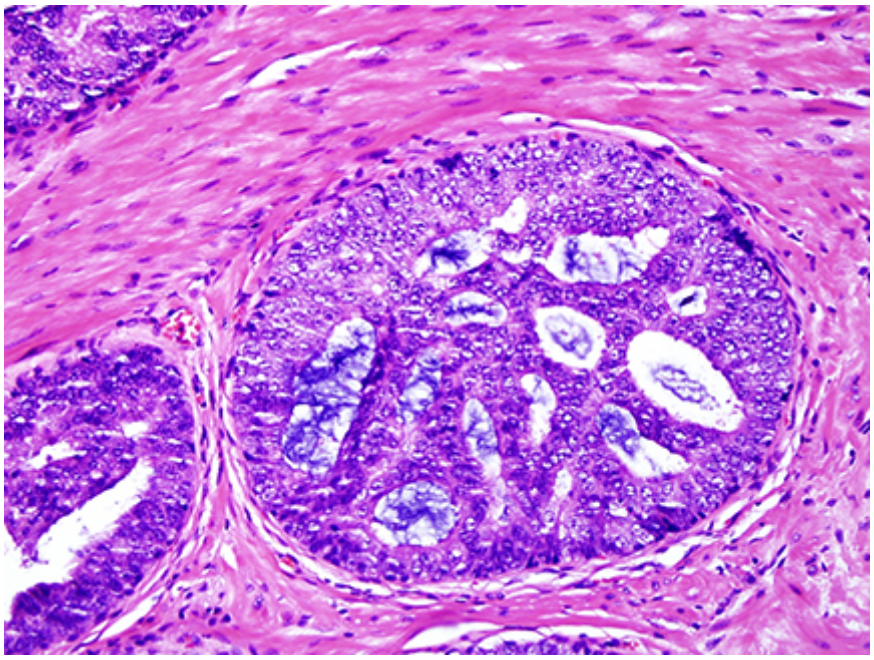
(A) Large cell (neuroendocrine) carcinoma is characterized by the large tumor cells with salt-pepper chromatin, forming a large nest with peripheral palisading. (B) Another case of large cell (neuroendocrine) carcinoma of the prostate metastatic to an axillary lymph node, showing similar neuroendocrine features, numerous mitotic figures, and apoptotic bodies.

Both cases are positive for neuroendocrine markers by immunohistochemistry (not shown).

Courtesy of Ximing Yang, MD.

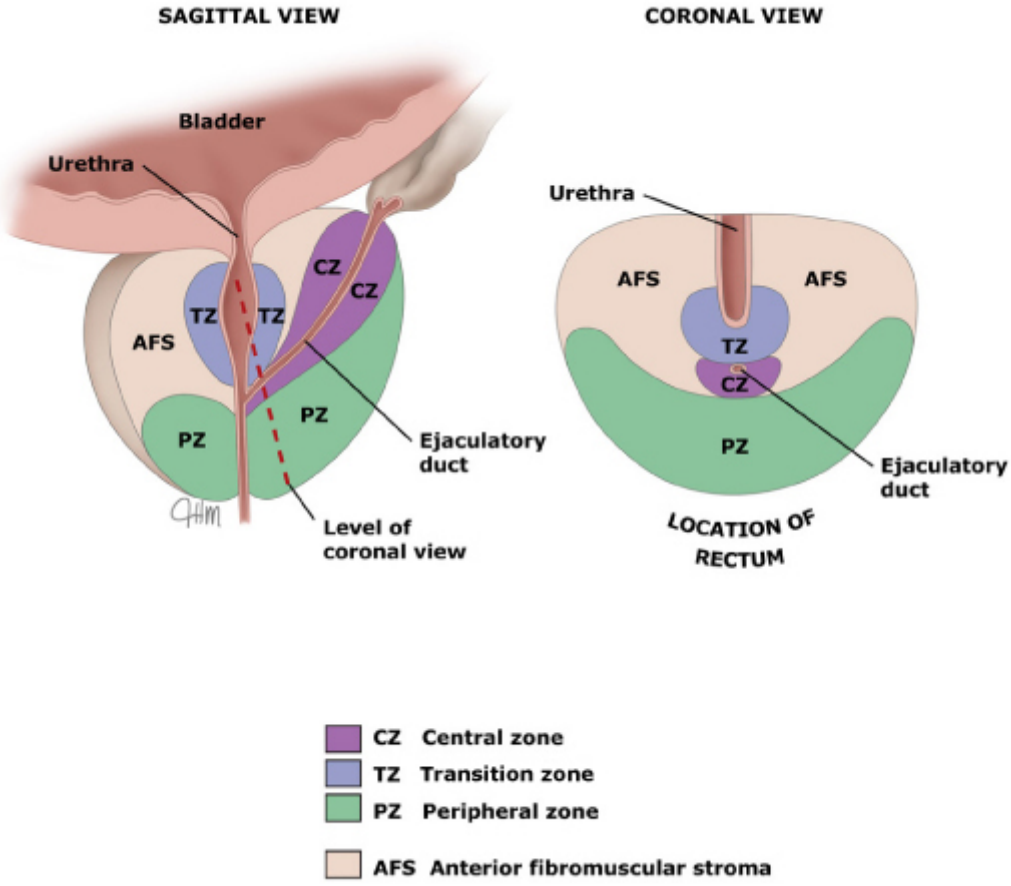
Graphic 110161 Version 1.0

Intraductal carcinoma of the prostate



Graphic 62418 Version 1.0

Zones of the prostate gland



The bulk of the prostate gland is contained within the peripheral zone. The transition zone is the site of benign prostatic hypertrophy. The majority of prostate cancers originate in the peripheral zone, whereas only 5 and 10% originate from the central and transition zones, respectively.

Graphic 57801 Version 3.0

Prostate cancer TNM staging AJCC UICC 8th edition

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

NOTE: There is no pathological T1 classification.
NOTE: Positive surgical margin should be indicated by an R1 descriptor, indicating residual microscopic disease.

Regional lymph nodes (N)

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

Distant metastasis (M)

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

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

Prostate-specific antigen (PSA)

PSA values are used to assign this category.

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

Histologic grade group (G)

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

Grade Group	Gleason score	Gleason pattern
1	≤6	≤3+3
2	7	3+4
3	7	4+3
4	8	4+4, 3+5, or 5+3

5	9 or 10	4+5, 5+4, or 5+5

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

Graphic 110728 Version 10.0

Prostate cancer TNM prognostic stage groups AJCC UICC 8th edition

When T is...	And N is...	And M is...	And PSA is...	And Grade Group is...	Then the stage group is...
cT1a-c, cT2a	N0	M0	<10	1	I
pT2	N0	M0	<10	1	I
cT1a-c, cT2a, pT2	N0	M0	≥10 <20	1	IIA
cT2b-c	N0	M0	<20	1	IIA
T1-2	N0	M0	<20	2	IIB
T1-2	N0	M0	<20	3	IIC
T1-2	N0	M0	<20	4	IIC
T1-2	N0	M0	≥20	1-4	IIIA
T3-4	N0	M0	Any	1-4	IIIB
Any T	N0	M0	Any	5	IIIC
Any T	N1	M0	Any	Any	IVA
Any T	Any N	M1	Any	Any	IVB

NOTE: When either PSA or Grade Group is not available, grouping should be determined by T category and/or either PSA or Grade Group as available.

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control; PSA: prostate-specific antigen.

Graphic 110729 Version 10.0

ISUP grade group classification system

Grade group	Gleason score and pattern
1	Grade 6 (3+3)
2	Grade 7 (3+4)
3	Grade 7 (4+3)
4	Grade 8 (4+4, 3+5, or 5+3)
5	Grade 9 or 10 (4+5, 5+4, or 5+5)

ISUP: International Society of Urological Pathology.

Adapted from: Epstein JI, Egevad L, Amin MB, et al. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New Grading System. Am J Surg Pathol 2016; 40:244.

Graphic 107132 Version 2.0

Risk stratification schema for localized prostate cancer, according to the National Comprehensive Cancer Network (NCCN)

Risk group	Clinical/pathologic features
Very low	▪ T1c AND ▪ Grade group 1 AND ▪ PSA <10 ng/mL AND ▪ Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core AND ▪ PSA density <0.15 ng/mL/g
Low	▪ T1 to T2a AND ▪ Grade group 1 AND ▪ PSA <10 ng/mL AND ▪ Does not qualify for very low risk
Favorable intermediate	▪ No high or very high risk features ▪ No more than one intermediate risk factor: • T2b to T2c OR • Grade group 2 or 3 • PSA 10 to 20 ng/mL AND ▪ Grade group 1 or 2 AND ▪ Percentage of positive biopsy cores <50%
Unfavorable intermediate	▪ No high or very high risk features ▪ Two or three of the intermediate risk factors: • T2b to T2c • Grade group 2 or 3 • PSA 10 to 20 ng/mL AND/OR ▪ Grade group 3 AND/OR ▪ ≥50% of positive biopsy cores
High	▪ No very high risk features AND ▪ T3a OR ▪ Grade group 4 or 5 OR ▪ PSA >20 ng/mL

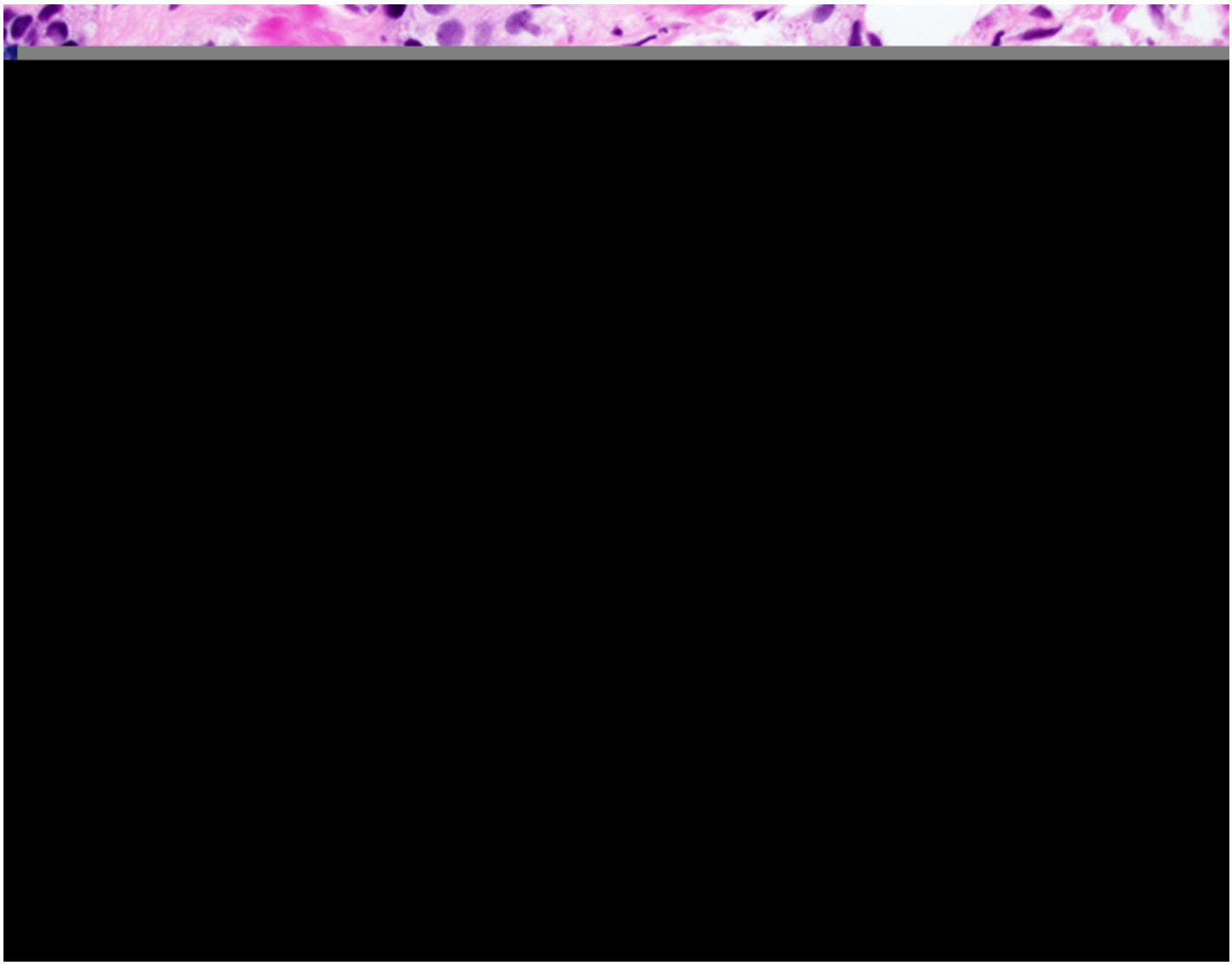
Very high	■ T3b to T4 OR ■ Primary Gleason pattern 5 OR ■ Two or three high-risk features OR ■ >4 cores with Grade group 4 or 5

PSA: prostate-specific antigen.

Adapted from: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Prostate Cancer. Version 4.2018.

Graphic 118962 Version 4.0

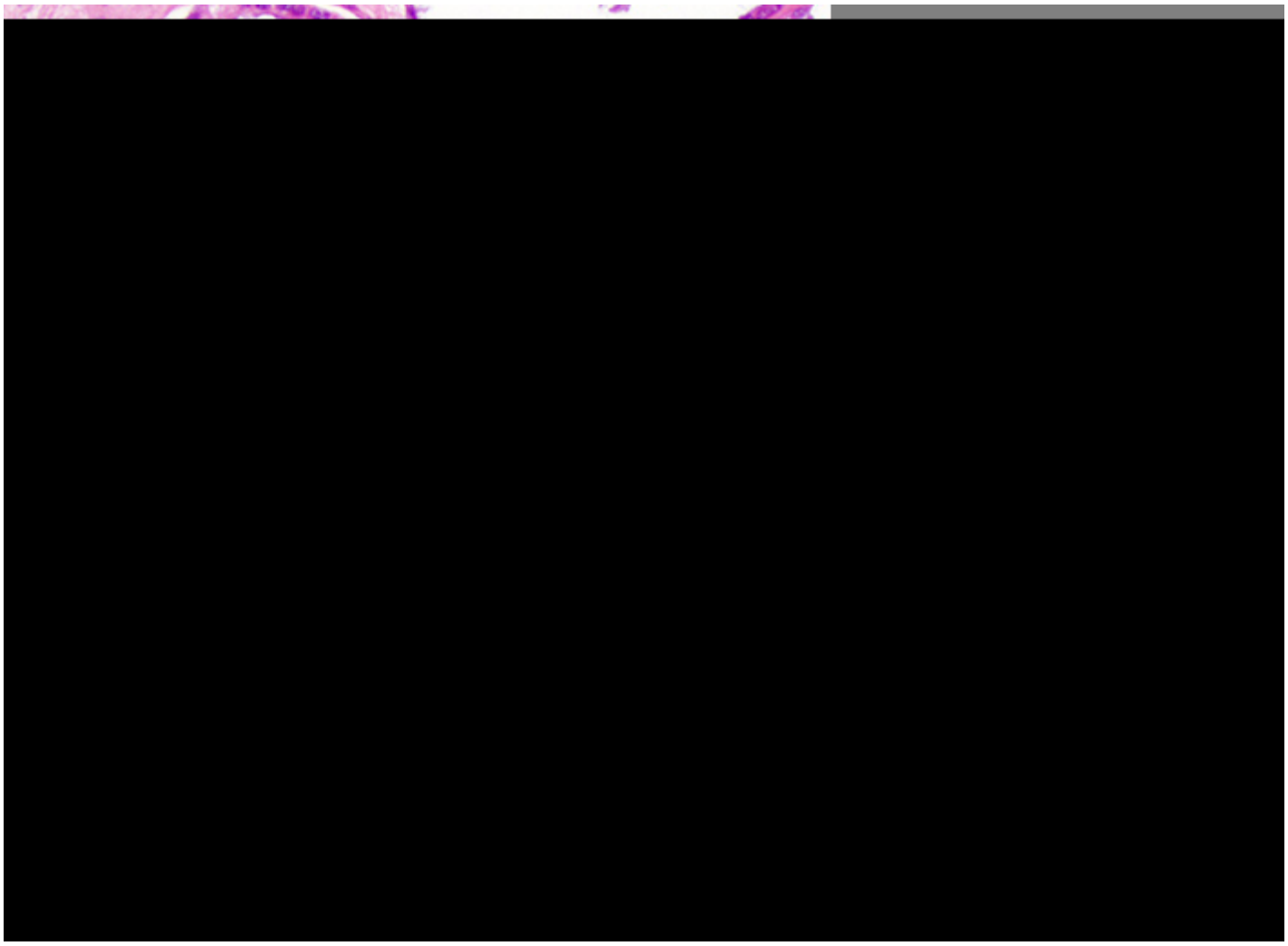
Cribriform pattern



Cribriform pattern of prostatic adenocarcinoma should be assigned Gleason pattern 4.

Graphic 107283 Version 1.0

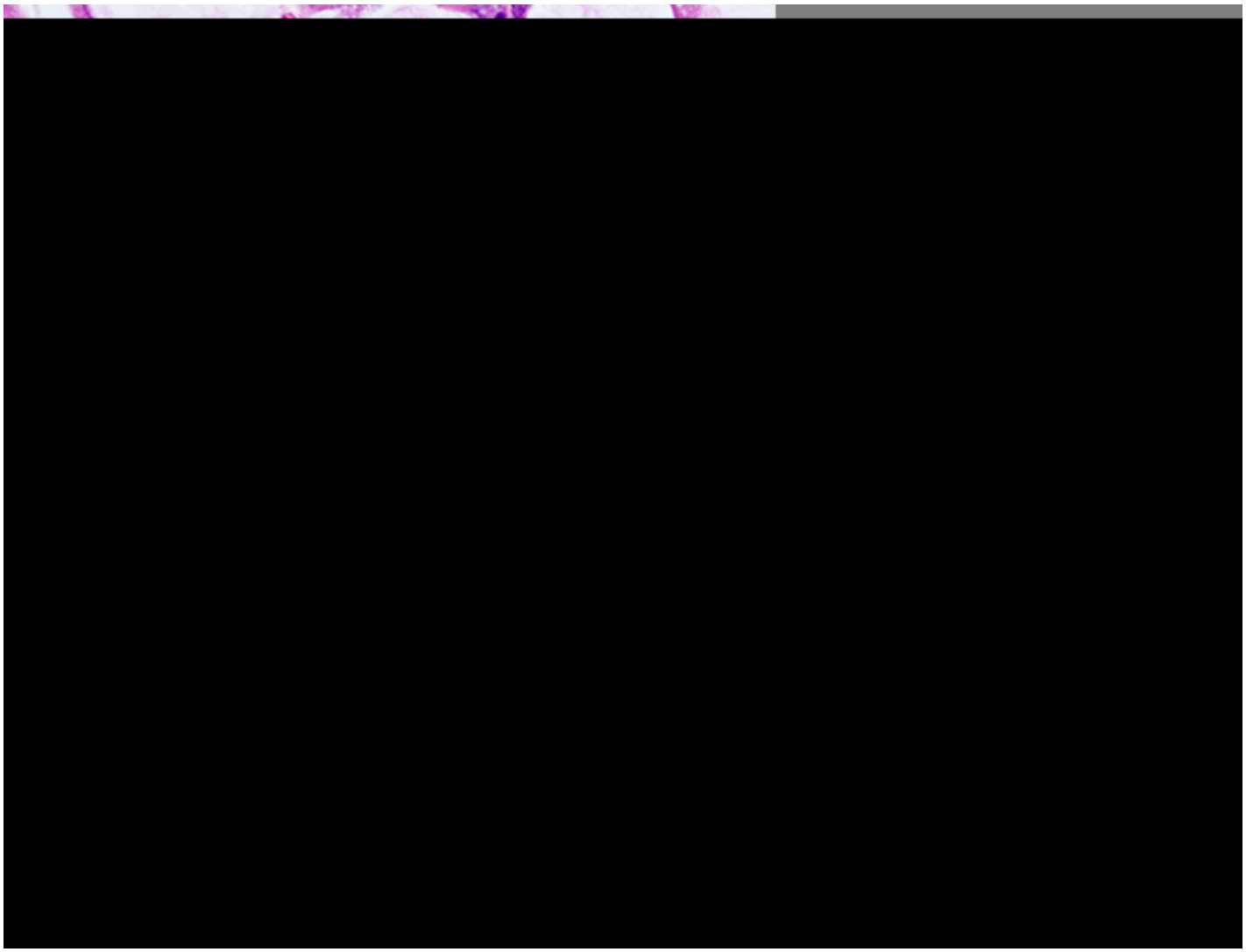
Glomeruloid pattern



Several glomeruloid glands in prostatic adenocarcinoma, characterized by the presence of a cluster of tumor cells within a malignant gland, should be assigned Gleason pattern 4.

Graphic 107284 Version 1.0

Mucinous pattern



Grading of mucinous prostatic adenocarcinoma should be based on its underlying growth pattern. In this case, it is Gleason pattern 4 because of the fused glands. In other cases, mucinous carcinoma can be Gleason pattern 3 or 5.

Graphic 107285 Version 1.0

Updated Gleason grading from the ISUP Consensus Conference

Major conclusion

1. Cribriform glands should be assigned a Gleason pattern 4, regardless of morphology.
2. Glomeruloid glands should be assigned a Gleason pattern 4, regardless of morphology.
3. Grading of mucinous carcinoma of the prostate should be based on its underlying growth pattern.
4. Intraductal carcinoma of the prostate without invasive carcinoma should be not assigned a Gleason grade, and a comment as to its invariable association with aggressive invasive prostatic adenocarcinoma should be made.

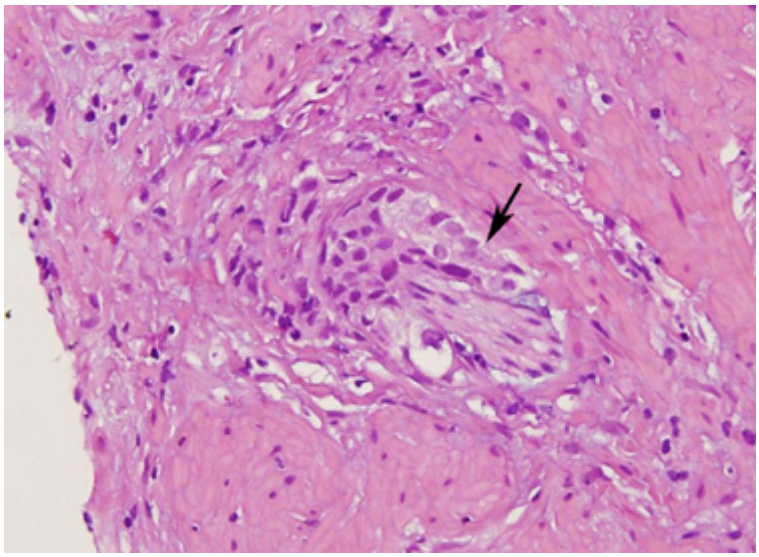
Morphologies within Gleason patterns

1. Gleason pattern 4 includes cribriform, fused, and poorly formed glands.
2. The term "hypernephromatoid" cancer should not be used.
3. For a diagnosis of Gleason pattern 4, it needs to be seen at 10 times lens magnification.
4. Occasional poorly formed or fused glands between well-formed glands are insufficient for a diagnosis of Gleason pattern 4.
5. In the case of borderline morphology between Gleason pattern 3 and pattern 4 with crush artifacts, the lower grade should be favored.
6. Branched glands are allowed in Gleason pattern 3.
7. Small solid cylinders represent Gleason pattern 5.
8. Solid medium or large nests with rosette-like space should be considered Gleason pattern 5.
9. Presence of unequivocal comedo necrosis, even if focal is indicative of Gleason pattern 5.

Adapted from: Epstein JI, Egevad L, Amin MB, et al. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New Grading System. Am J Surg Pathol 2016; 40:244.

Graphic 107288 Version 1.0

Prostate cancer with perineural invasion



Low-power photomicrograph of an hematoxylin- and eosin-stained section of a prostate core needle biopsy. One of the diagnostic features of prostate adenocarcinoma is perineural invasion (arrow).

Courtesy of Ximing Yang, MD.

Graphic 69000 Version 2.0

Prostate adenocarcinoma with extraprostatic extension

Low-power photomicrograph of an hematoxylin- and eosin-stained section from a prostate core needle biopsy. Evidence of extraprostatic extension of the tumor is suggested by the presence of tumor cells infiltrating fat (arrows).

Courtesy of Ximing Yang, MD.

Graphic 80254 Version 2.0

Posttherapy histologic features of the prostate gland

Treatment type	Changes in prostate cancer cells	Changes in benign epithelium
Androgen ablation	Severe atrophic changes Clear or vacuolated cytoplasm Decreased nuclear atypia (Retained infiltrating pattern)	Severe atrophy Basal cell hyperplasia
Estrogen	Atrophic changes Squamous metaplasia	Squamous metaplasia
Finasteride and dutasteride	Minimal changes	Mild atrophy
Radiation therapy	Degenerative changes (Retained infiltrating pattern)	Marked nuclear atypia

Graphic 50546 Version 1.0

Prostatic adenocarcinoma after androgen ablation

Low-power photomicrograph of an hematoxylin- and eosin-stained tissue section of a prostate gland following androgen deprivation therapy. The scattered tumor cells have undergone cytoplasmic vacuolization and other degenerative changes (arrows). In a benign gland (arrowheads), the secretory epithelium also shows atrophic changes while basal cells are prominent.

Courtesy of Ximing Yang, MD.

Graphic 69529 Version 2.0

Post-radiation atypia in benign prostatic epithelium

Benign epithelial cells in an irradiated prostate gland show degenerative atypia and a "streaming" appearance (arrowheads).

Courtesy of Ximing Yang, MD.

Graphic 66055 Version 1.0

Radiation therapy effects on prostate adenocarcinoma

The variability in the histologic appearance of prostate cancer following radiation therapy is illustrated by these high-power photomicrographs of two hematoxylin- and eosin-stained tissue sections from the same patient. Top panel: This area of the biopsy is characterized by marked histologic change, with the tumor cells demonstrating significant degenerative changes and atrophy. The cytologic atypia can hardly even be recognized (arrowheads). Bottom panel: In contrast, tumor cells from a different area of the same specimen from the same irradiated patient shown in the above panel demonstrate the characteristic cytologic atypia of prostate cancer (arrows) without significant atrophic changes.

Courtesy of Ximing Yang, MD.

Graphic 64711 Version 2.0

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