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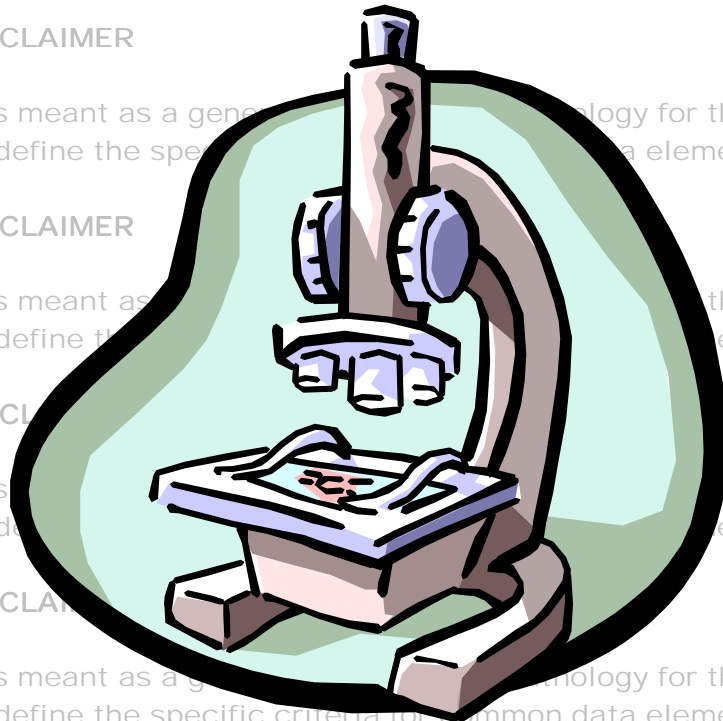
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Cooperative Prostate Cancer Tissue Resource (CPCTR) Histomanual

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Introduction

This manual details the pathologic definitions needed to complete the CPCTR Pathology Common Data Elements (CDEs). The descriptions and definitions are based on the AFIP Fascicle 28, Third series: Tumors of the Prostate, Seminal Vesicles, Male Urethra, and Penis. Resource pathologists should use this manual as a guide for the assignment of Histology and Matrix CDEs for the CPCTR. Use of this manual as a guideline will ensure a standardized approach to assignment of the pathologic CDEs, and to the choice of paraffin blocks (matrix blocks) selected from submitted cases.

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1. HISTOLOGIC TYPE OF CANCER

A. ACINAR CARCINOMA, NOS

Acinar carcinoma is used for "conventional" adenocarcinoma, which accounts for more than 90-95% of prostatic carcinoma. Prostatic adenocarcinoma is identified based on the following features:

- Architecture features

The architecture of prostatic acinar adenocarcinoma is best assessed at low power. The adenocarcinoma is most often composed of small, closely-packed, relatively uniform glands with a simplified architecture, that differ in appearance from the surrounding glands. The small glands often have amphophilic cytoplasm. In some cases the unique pattern of glomeruloid structures assists the diagnosis. The neoplastic glands may infiltrate in between and around clearly benign glands, or form confluent groups of individual glands. Other higher grade features include cords and fused groups of ill-defined glands, sheets of cells, or single cells. Other architectural features associated with prostatic adenocarcinoma include perineural invasion, identified by the involvement of nerve fibers by malignant tumor cells, or lymphatic invasion, with malignant cells in spaces clearly lined by endothelium.

- Cytologic features

Features helpful in identifying prostatic adenocarcinoma include nucleomegaly, and hyperchromasia, even though in general the tumor cells demonstrate less nuclear variation than is seen in other types of tumors. The "gold standard" feature most often used in the cytologic diagnosis of prostatic adenocarcinoma is the presence of prominent, often multiple or eccentric enlarged nucleoli. Mitotic figures are extremely uncommon in the prostatic epithelium, and thus their presence should lead to a careful examination for other features of malignancy. Cytoplasmic cytologic features include the presence of ample amphophilic cytoplasm or excessive pale cytoplasm. A very helpful feature is cytologic chromasia that is different from adjacent clearly benign glands. Glandular luminal contents such as wispy blue mucin, pink granular material and in places well-formed crystalloids are helpful

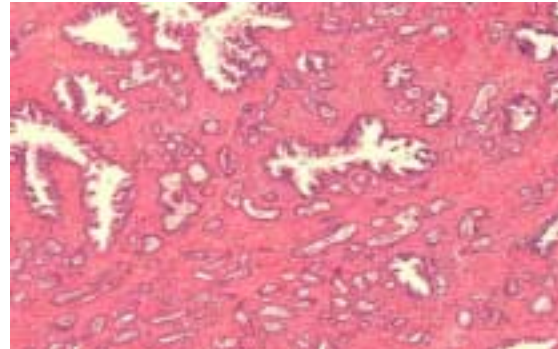


FIG. 1. Small neoplastic glands (right) with increased cytoplasmic tincture

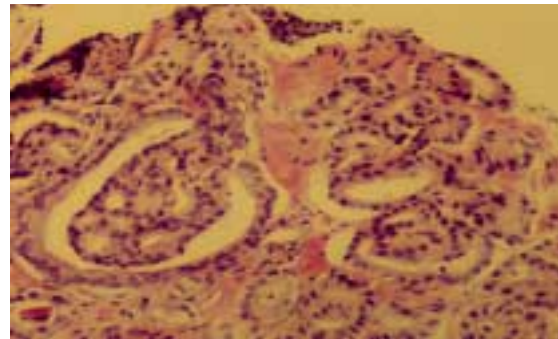


FIG. 2. Glomeruloid architecture in a prostatic adenocarcinoma

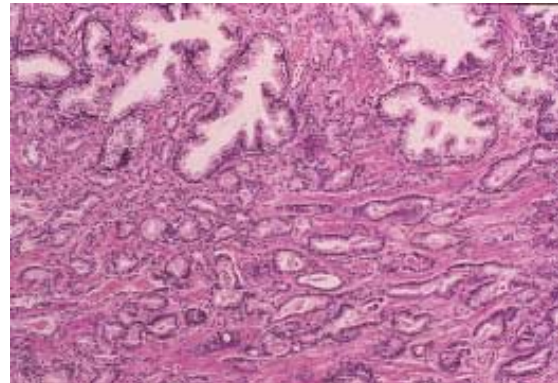
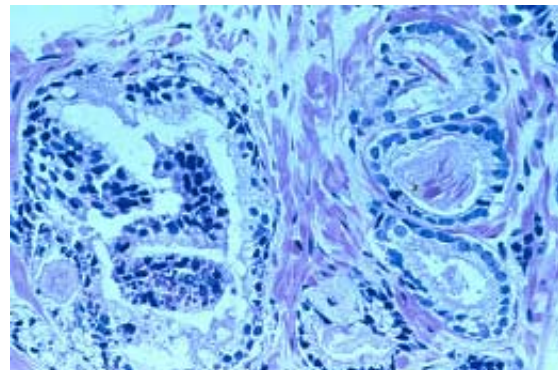


FIG. 3. Infiltrating simple glands in and around residual benign glands



in raising the suspicion of carcinoma, but in an of themselves are not diagnostic.

- Immunohistochemical features

An immunohistochemical aid to the diagnosis of prostatic adenocarcinoma is provided by the loss of a basal cell layer by immunohistochemistry for high molecular weight cytokeratin (CK-903 antibody).

Other types of carcinoma include variants of prostatic adenocarcinoma, other primary carcinomas and secondary carcinomas. These include:

B. DUCTAL CARCINOMA

These tumors account for 1% of prostatic adenocarcinoma. Up to 50% are associated with a component of conventional prostatic adenocarcinoma that usually comprises a minor portion of the tumor. Microscopic: The key histologic features are enlarged cells with increased nuclear and cytoplasmic size when compared to adjacent normal glands. There is an elongation of the cells with a columnar appearance and an associated increased nuclear size and anaplasia and mitoses are common. These features give the cells and tumor an "endometrioid" or "colonic" appearance. At low power the tumor is characterized by two patterns, A and B.

FIG. 4. Luminal crystallioids (right side glands)

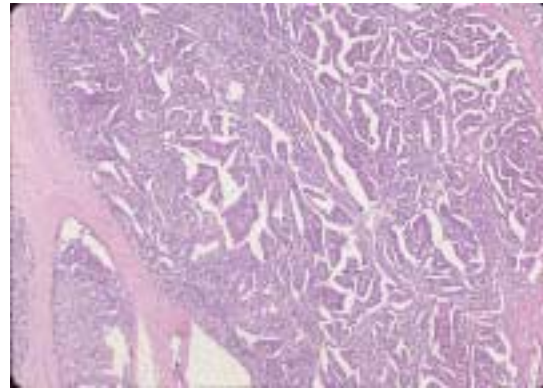


FIG. 5. Ductal carcinoma

A: complex often intraluminal tubulopapillary structures lined by stratified to tall columnar epithelium with irregular chromatin and prominent nucleoli, and

B: Complex cribriform arrangements that can have comedo necrosis. The two patterns may coexist or merge. These patterns may be associated with conventional acinar carcinoma (NOS).

NOTE: The CPCTR has chosen to use the overall case diagnosis of "Large Duct Carcinoma" ONLY for cases comprised solely of large duct tumor. For cases with both large duct and acinar components the overall case should be referred to as "Acinar Carcinoma with ductal features". Individual blocks should be coded according to the patterns of tumor present in the associated block.

C. MUCINOUS CARCINOMA

This tumor is distinctly uncommon, with approximately fifty cases reported in the literature. These tumors may have three distinct patterns:

1) Individual neoplastic glands with luminal distension by mucin, 2) Cribriform neoplastic glands with distortion/distension by mucin, and, 3) pools of extracellular mucin with tumor cells "floating" in these pools (colloid carcinoma appearance). Abundant extracellular mucin must be present for this diagnosis (> 25% of tumor) with associated anastomosing neoplastic acini. Bland cytology is usually present with only occasional prominent nucleoli identified. The mucin is positive by mucicarmine, Alcian blue, and PAS stains.

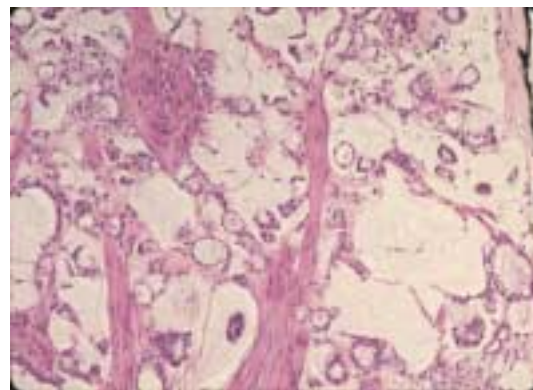


FIG. 6. Mucinous carcinoma

D. SIGNET RING CELL CARCINOMA

Less than twenty cases of this rare tumor have been reported in the prostate. This tumor is composed of cells with classical signet ring cell morphology, often in clusters or singly, and widely infiltrative. Often associated with conventional high-grade acinar carcinomas (NOS). Clear cytoplasmic vacuoles displace the nucleus. Note: most tumors are weakly positive for intracytoplasmic mucin by PAS, and negative for mucin by mucicarmine, and Alcian blue stains.

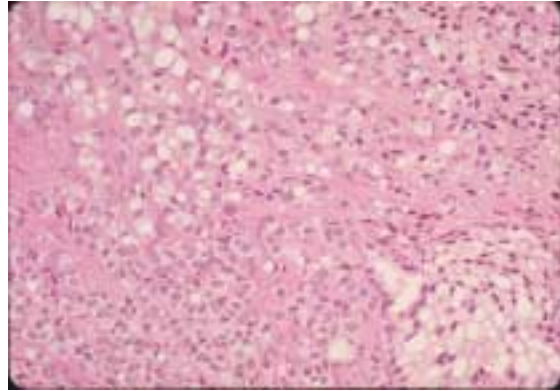


FIG. 7. Signet ring cell carcinoma with residual areas of high grade prostatic acinar adenocarcinoma.

E. BASAL CELL CARCINOMA

The histologic features of this rare tumor are part of a continuum with adenoid basal cell tumor and basal cell adenoma, and can be similar to adenoid cystic carcinoma present at other sites. They often present in infiltrating nests, cords, trabeculae, and sheets of cells with scant pale or acidophilic cytoplasm, round to angulated nuclei, and stippled chromatin. Mitotic activity is not striking. Peripheral palisading and cystic dilatation can be seen.

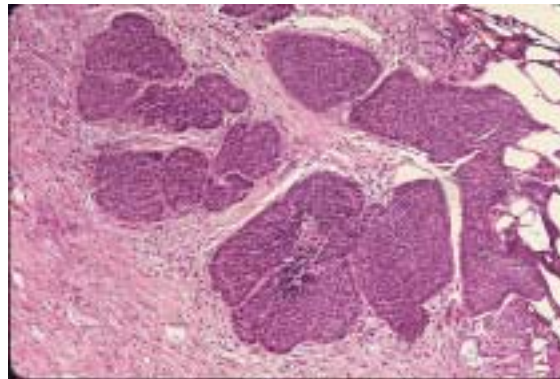


FIG. 8. Basal cell carcinoma

NOTE: If diagnosed should be referred to as an "adenoid basal cell tumor" and should be reviewed by the other members of the CPCTR due to the rarity of the diagnosis and the difficulty in separating this lesion from florid basal cell hyperplasia and basal cell adenoma.

F. TRANSITIONAL CELL CARCINOMA

Transitional cell carcinoma of prostate is histologically identical to the typical transitional cell carcinoma of the urinary bladder. The tumor cells invade as nests, cords, or individually. Focal squamous or glandular differentiation may be seen. Tumor cell nuclear variation, nuclear clefts, and pleomorphism are more prominent than in prostatic acinar tumors and is helpful in the distinction. Immunohistochemical studies reveal tumor cell negativity for PSA and PAP, a contrast from prostatic adenocarcinoma.

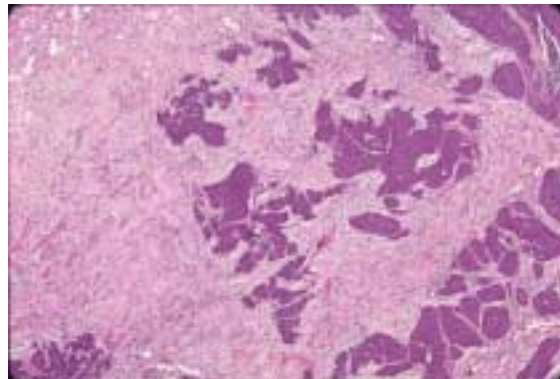


FIG. 9. Basal Cell Carcinoma

G. UNDIFFERENTIATED NON-SMALL CELL CARCINOMA

This uncommon diagnostic category represents a high grade carcinoma which does not qualify as small cell or neuroendocrine type. These tumors have often also greatly decreased or lost PSA and PAP positivity and may retain only a fraction of their cytokeratin positivity.

H. SARCOMATOID CARCINOMA

Characterized mainly by the presence of markedly atypical spindle cells with large pleomorphic hyperchromatic nuclei, brisk mitotic activity, and atypical mitoses. Often mistaken for a sarcoma, these tumors may have heterologous elements of bone, cartilage, and muscle. A concurrent acinar tumor may or may not be identified, having been destroyed by the high grade sarcomatoid component.

I. LARGE CELL NEUROENDOCRINE CARCINOMA (also referred to as adenocarcinoma with neuroendocrine cells)

The tumor is of typical acinar morphology with prominent neuroendocrine cells that have a "paneth cell"-like histology. This neuroendocrine change must be present in the tumor cells in greater percentages than in the adjacent normal prostatic glands

J. SMALL CELL CARCINOMA

This tumor is in essence a variant of Gleason pattern 5 prostatic adenocarcinoma that has decreased or lost PSA and PAP positivity and gained neuroendocrine positivity. When present in the prostate this tumor is seen as diffuse sheets, clusters or cords of intermediate sized cells with minimal cytoplasm, salt and pepper chromatin, and brisk mitotic activity. Nuclear molding and inconspicuous nucleoli are common. May be adjacent to a conventional acinar carcinoma. Immunohistochemistry will have positive reactions to typical neuroendocrine markers including chromogranin A, synaptophysin, and NSE.

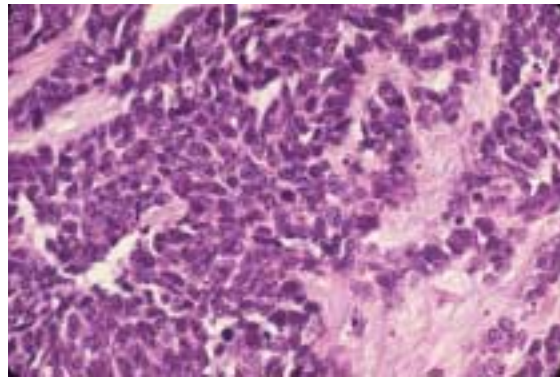


FIG. 10. Small cell anaplastic carcinoma

K. SQUAMOUS CELL OR ADENOSQUAMOUS CARCINOMA

A very rare tumor, with less than fifty cases described, most of which are pure squamous cell carcinomas. Only ten cases are mixed adenosquamous carcinomas. They usually are moderately differentiated with nests and sheets of cells with unequivocal keratin formation including keratin pearls, intracellular keratin, and intercellular bridges.

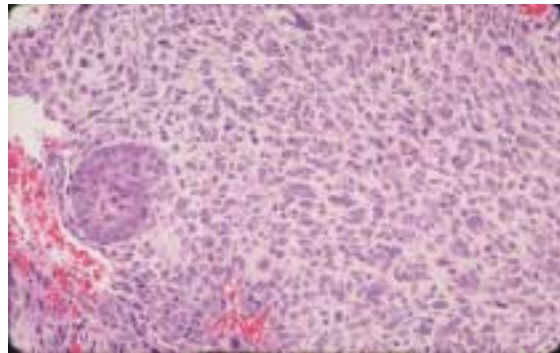


FIG. 11. Large cell lymphoma

L. MESENCHYMAL TUMORS

While rare, the most common types will include leiomyosarcoma, carcinosarcoma, rhabdomyosarcoma, and phylloides tumor. The final diagnosis should have immunohistochemical ancillary studies and it is recommended that the case be reviewed, at least within the CPCTR.

M. LYMPHOMA

Subtyping of the lymphoma is not necessary (although most likely has been done). An attempt should be made to separate primary lymphoma of the prostate from secondary involvement, although this is

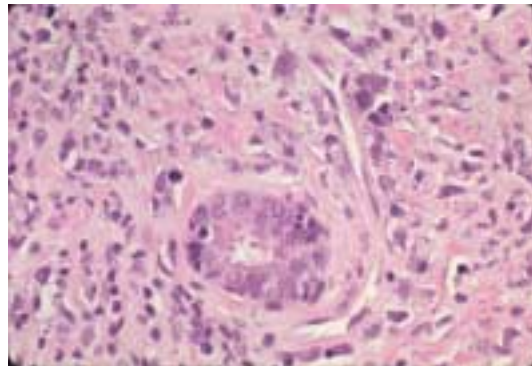


FIG. 12. Large cell lymphoma

not always possible. Evidence of tumor in the extraprostatic sites, including the iliac and obturator lymph node chain, at the time of or within one month after diagnosis excludes a primary tumor of the prostate.

N. OTHER TUMORS

The CPCTR considers "other" to be any tumor that does not fit into the above classification. Examples would include metastatic involvement by a tumor or direct extension by colorectal tumors. For greater detail on soft tissue tumors and metastatic tumors, members of the CPCTR are encouraged to utilize the AFIP Fascicle, which amplifies on the various types and variants.

2. GLEASON GRADING

The Gleason score is the sum of the primary (most predominant) and the secondary (second most predominant) Gleason grade. Where no secondary Gleason grade exists, the primary Gleason grade is doubled to arrive at a Gleason score. For example 70% grade 3, 20% grade 2, 10% grade 4 is scored as 3+2 =5/10). This only applies to prostatectomies and transurethral resections. In radical prostatectomy specimens in which more than 1 separate tumor is identified, the Gleason score of the most significant lesion should be recorded. For instance, if there is a large Gleason score 5 transitional zone cancer and a smaller Gleason score 7 peripheral zone cancer, the latter score should be used rather than the scores being averaged. The rules are different for Gleason grading of needle biopsies. In needle biopsy specimens in which more than 2 grades exist and the highest grade is neither the most predominant nor the secondary grade, the predominant and the highest grade should be added to arrive at a score (e.g. 70% grade 3, 20% grade 2, 10% grade 4 is scored as 3+4 =7/10).

GLEASON PATTERN 1

The tumor is composed of a well-circumscribed group of single separate individual glands with only minimal size variation, closely packed and without significant intervening stroma. There is a definite edge to the tumor nodule and a round pushing interface with the stroma. NOTE: since this grading requires a low power observation of the WHOLE tumor architecture, the diagnosis CANNOT be made on needle biopsy.

GLEASON PATTERN 2

Like Gleason pattern 1, the tumor is composed of a single group of separate individual glands closely packed and without appreciable intervening stroma. Unlike the pattern 1 tumors the border of the whole tumor nodule has mildly irregular "ragged" borders. There may be some variation in glandular size and shape. As compared to pattern 1, the glands are more loosely arranged and less uniform.

NOTE: This grading, like pattern 1, requires a low power observation of the WHOLE tumor architecture, and thus the diagnosis cannot be made on needle biopsy. In some cases where a needle biopsy presents a large portion of the "edge" of the tumor nodule this

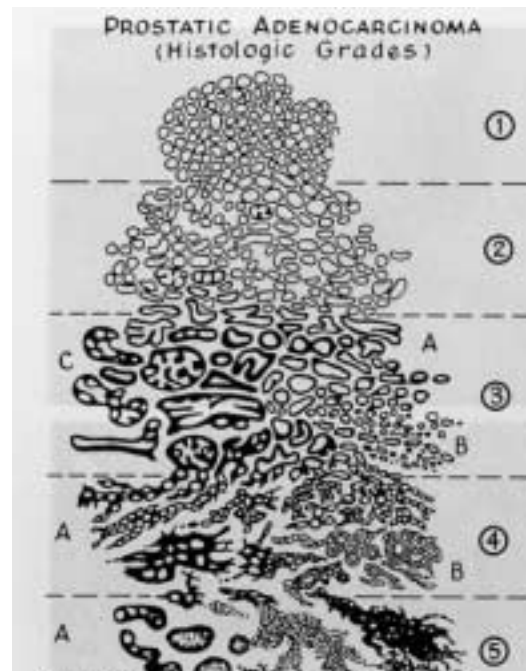


FIG. 13. Gleason Grading

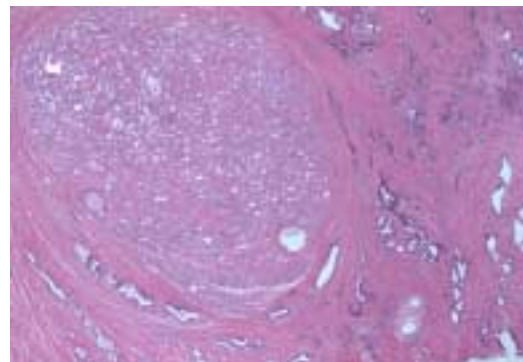


FIG. 14. Gleason pattern 2

grade could be considered, BUT THESE CASES ARE RARE.

CPCTR Comment: "How do I diagnose a 3+2/2+3 tumor?" In most cases these tumors are diagnosed based on the presence of a well-circumscribed nodule of closely packed individual glands with mild irregular borders (pattern 2), which along one border breaks into individual infiltrating glands (pattern3).

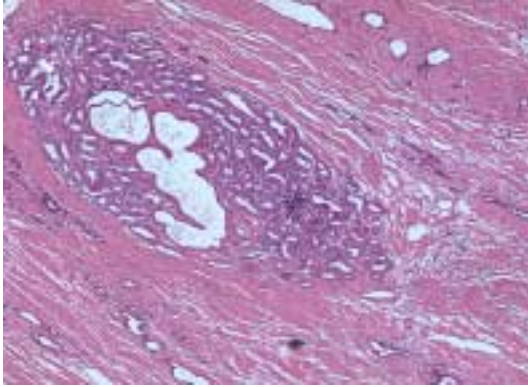


FIG. 15. Gleason pattern 2

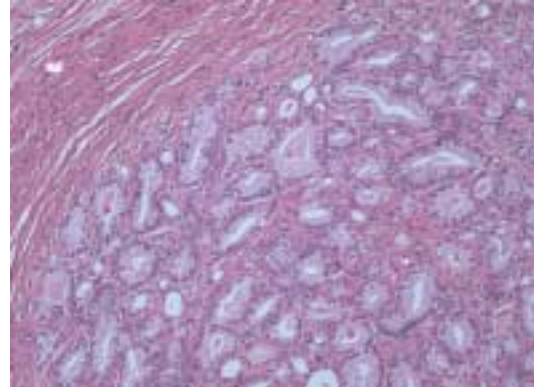


FIG. 16. Edge, Gleason pattern 2

GLEASON PATTERN 3

Gleason pattern 3a: A key feature is the separation of individual malignant glands by intervening stroma. The angulated and elongated glands are of typical size and are scattered, present in and around benign glands with tumor cells often having amphiphilic cytoplasm.

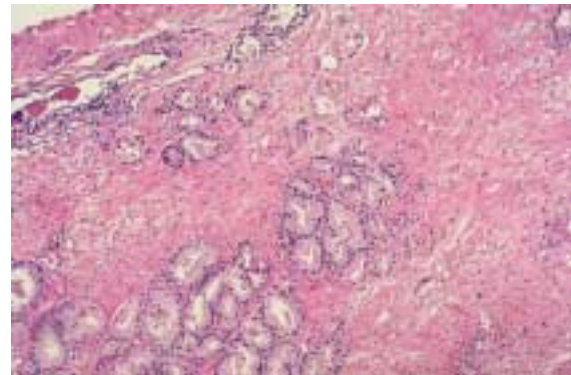


FIG. 17. Gleason pattern 3

Gleason pattern 3b: The glands still are separated by intervening stroma, but are smaller than the typical size (microacini) and are scattered, such that they can be present in and around benign glands.

Gleason pattern 3c: Irregular groups of glands, which individually may have cribriform, or papillary architecture but smooth glandular edges. Lumens are uniform and regular without evidence of comedo-type necrosis. The groups of glands are separated by intervening stroma.

GLEASON PATTERN 4

Gleason Pattern 4a: Irregular groups of raggedly infiltrating fused glands, prominent fusion of the epithelial elements with irregular or inconspicuous glandular lumens. The groups of fused glands have large irregular fused masses without smooth stromal borders. Gleason pattern 5b: Irregular groups (sheets) of cells with ragged group borders and diffuse infiltration. Glandular differentiation is inconspicuous. The other form is as individual single tumor cells. While these tumors still tend to have limited nuclear pleomorphism, there can be more anaplasia.

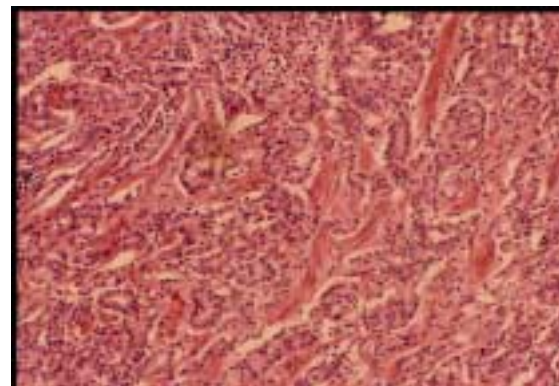


FIG. 18. Gleason pattern 4a

CPCTR Comment: "How do I separate sheets of tumor into pattern 4 and pattern 5?" A good rule is that if the sheets of tumor cells have interspersed identifiable lumina then it is pattern 4. The lack of identifiable lumens makes the specimen pattern 5. The key is to separate identifiable lumens from single cells necrosis and intracytoplasmic vacuoles.

3. PERCENTAGE OF GLEASON 4/5

Background: The percentage of Gleason 4/5 component has been found to be a reliable predictor of disease progression. Cancer grade expressed as percent Gleason grade 4/5 has been found to be highly predictive of disease progression. In a Cox proportional hazards model that included percent Gleason grade 4/5, the traditional Gleason score was not an independent predictor of treatment failure. This suggests an enhanced predictive potential of this component of Gleason pattern over the conventional Gleason scheme ([abstract](#)).

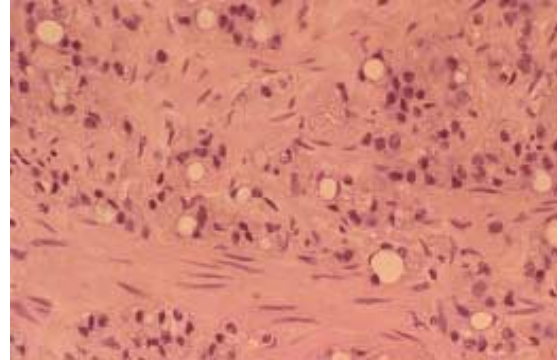


FIG. 19. Gleason pattern 5

Other investigators have suggested accounting for components of Gleason 4 and 5 particularly in the situation where they constitute less than 5% of the tumor or form a tertiary pattern. In these instances, accounting for this tertiary high grade component enhances predictive potential of any grading system ([abstract](#)). This is also reflected in the different behavior of Gleason 4+3 as compared to Gleason 3+4 carcinomas.

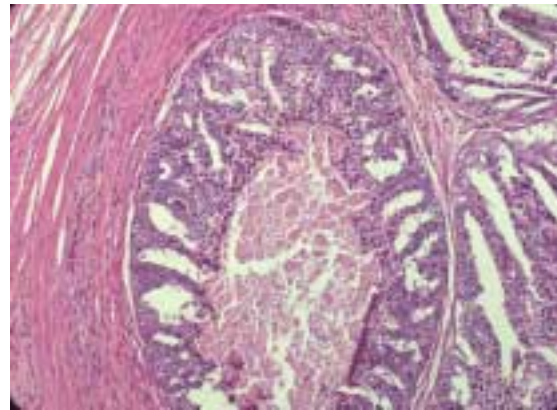


FIG. 20. Gleason pattern 5a

Method: The percentage of carcinoma occupied by Gleason 4 or 5 components should be estimated from review of all sections of prostate with adenocarcinoma. The Gleason pattern 4 or 5 may be "eyeballed" and does not require formal measurement. The value may be expressed as a percentage of the total tumor.

4. SIZE OF LARGEST NODULE OF INVASIVE CANCER

Background: The amount of tumor in radical prostatectomy specimens can be determined with several techniques. Maximum tumor diameter correlates well with total tumor volume and can readily be obtained in incompletely submitted specimens. Renshaw et al, have shown in a series of 431 patients that maximum tumor diameter was an independent risk factor for PSA failure ([abstract](#)).

Method: The slide containing the largest amount of tumor should be used to measure (in cms) the linear dimension of the adenocarcinoma. This measurement may be again reflected in the matrix slide allocation.

5. PERCENTAGE OF GLAND OCCUPIED BY TUMOR

Background: Carvahal et al, have shown (in a series of 595 patients) that a visual estimate of the percentage of carcinoma in prostatic tissue specimens from patients who undergo radical prostatectomy was a sig-

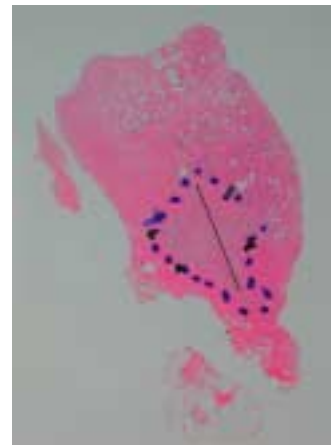


FIG 21. Largest Linear Dimension of carcinoma on a slide

nificant predictor of disease recurrence. Therefore they recommend a visual estimate as a practical, simple, and inexpensive method that provides important prognostic information after radical prostatectomy ([abstract](#)). Method: "Eyeball" of all available prostate tissue slides. This may be done by examining all slides laid out on the same surface, and visually estimating the tumor area (which has been circled on the slides).

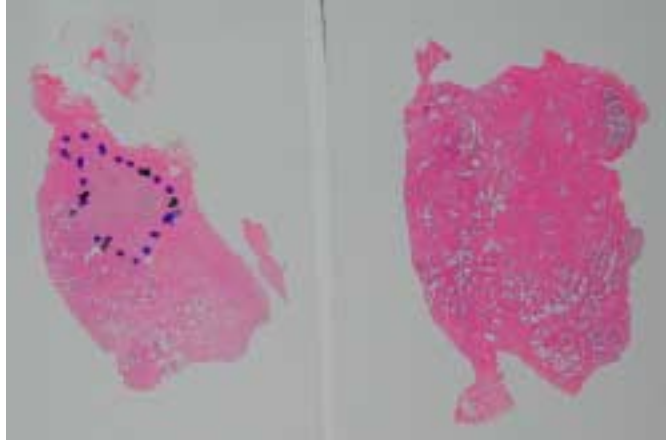


FIG 22. Percentage of gland assessed by "eyeballing" slides with area of carcinoma circled

Alternatively it can be done by evaluating the number of slides with tumor divided by the number of total prostate slides, with an additional factor for the percentage of each slide involved by tumor. For example, if 15 of 20 slides have tumor, the initial value is 75%. Then if the average involvement of each tumor slide is 20%, the final percentage is $75\% \times 20\% = 15\%$

6. EXTRAPROSTATIC EXTENSION / EXTRACAPSULAR INVASION

Tumor abutting on or admixed with fat constitutes extraprostatic extension. Extraprostatic involvement may also be reported when tumor involves perineural spaces in neurovascular bundles even in the absence of periprostatic fat involvement. In certain locations such as the interior prostate and bladder neck regions, there is a paucity of fat, and in these locations extraprostatic extension is determined when the tumor extends beyond the confines of the normal glandular prostate. Sometimes there is a distinct bulging tumor nodule that may be associated with a desmoplastic stromal reaction. Only a few glands outside-"focal" extension. More glands in the fat considered "established" extension.

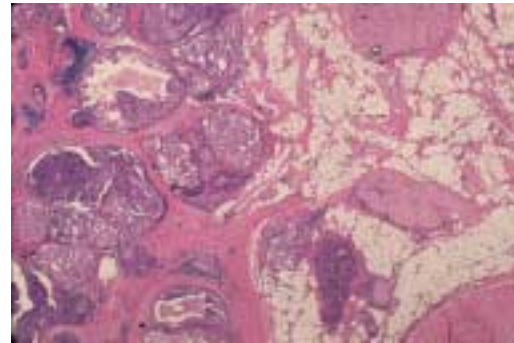


FIG. 23. Extraprostatic extension

7. SURGICAL MARGIN INVOLVEMENT

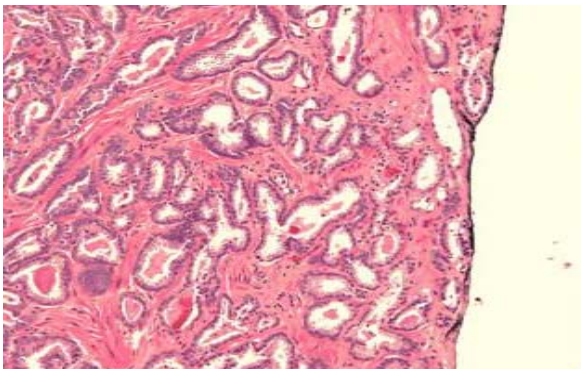


FIG. 24. Tumor involving the inked surgical margin

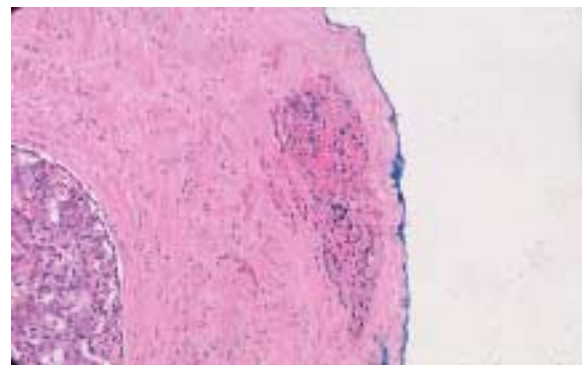


FIG. 25. Tumor close to but not involving the inked surgical margin

Surgical margins should be designated as negative if tumor is not present at the inked margin, even if it approaches close to the margin. Surgical margins are designated as positive if tumor cells extend to an inked margin. Positive surgical margins should not be interpreted as extraprostatic extension.

8. HIGH GRADE PROSTATIC INTRAEPITHELIAL NEOPLASIA (PIN)

PIN refers to the precancerous cellular proliferation within pre-existing prostatic ducts and acini. PIN is currently diagnosed in two grades low and high to replace the previous three grades system. It represents a continuum from low grade PIN to high PIN to cancer characterized by nuclei enlargement, nuclei overlap, basal layer disruption and increased nucleoli prominence.

High grade PIN is identified in within medium and large glands which retain normal shape and architecture, but show nuclear and cytoplasmic features associated with carcinoma. The identification of high grade PIN is performed at low magnification - based on "basophilic" or hyperchromatic glands due to nuclear crowding and enlargement. The four major patterns of PIN are tufting, micropapillary, flat, and cribriform.

High magnification shows crowding and heaping up of the secretory cell layer. Nuclei overlap, and cytoplasmic blebs may be present along the luminal surface. Nuclei are usually uniformly enlarged with an oval shape, however some can be hyperchromatic and shrunken, particularly toward the luminal surface. Nuclei contain nucleoli which may be single or multiple and are often eccentric or apposed to the nuclear membrane

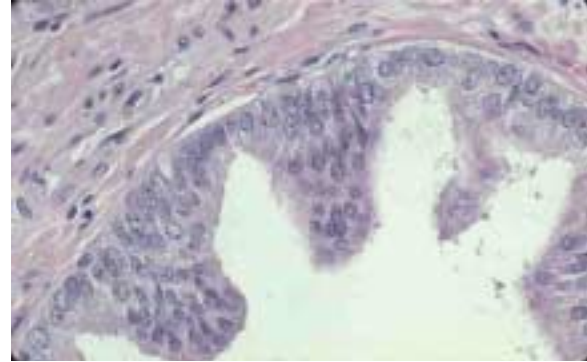


FIG. 26. Tufting pattern of PIN. The lining epithelial cells containing enlarged nuclei with vesicular chromatin and prominent nucleoli

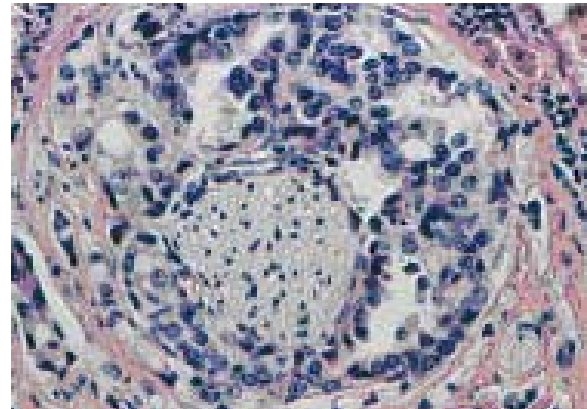


FIG. 27. Nerve encircled by adenocarcinoma

9. PERINEURAL INVASION

Nerves are surrounded by small acini with the cytologic features of neoplasia. Circumferential or intraneural invasion can be seen.

10. SEMINAL VESICLE INVASION

Requires invasion of the muscularis of the seminal vesicle, not just involvement of the adjacent connective tissue.

11. ANGIOLYMPHATIC INVASION

Angiolymphatic invasion is defined as the unequivocal presence of tumor cells within an endothelium-lined space. It occurs more commonly in high-grade neoplasms, but overall is still rare.

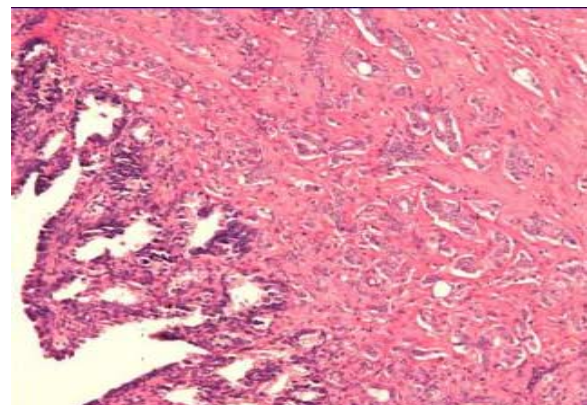


FIG. 28. Seminal vesicle invasion

When present it is often extensive, and extends to vessels outside of the substance of the prostate. Criteria of McNeal and Yemoto ([abstract](#)) are used by the CPCTR for histologic identification of vascular channels: Identification of endothelial nuclei resting against a uniformly smooth luminal surface is required for identifying a vascular channel. A single endothelial nucleus is acceptable in a small vessel where much of the channel lining is occluded by adherent tumor.

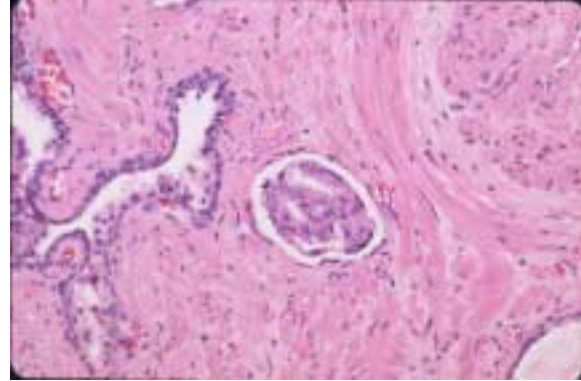


FIG. 29. Vascular invasion

Emboli may be completely free in the lumen of the vessel however less commonly a portion of the tumor embolus may be adherent to the wall. The free luminal border of the tumor mass in the lumen is usually smooth although it might show some irregularity of contour (serration). Care should be taken to exclude retraction artifact, tumor within prostatic ducts, and tumor within perineural spaces.

12. PATHOLOGIC STAGING

AJCC STAGING SYSTEM, PROSTATE, 1997

Primary Tumor, Pathologic (pT)

pT2*** Organ confined

pT2a Unilateral

pT2b Bilateral

pT3 Extraprostatic extension

pT3a Extraprostatic extension

pT3b Seminal vesicle invasion

+pT4 Invasion of bladder, rectum

***Note: There is no pathologic T1 classification.

Invasion of bladder indicates direct spread into the wall of the urinary bladder. The basal prostatic stroma blends imperceptibly into the bladder neck musculature, and in most instances involvement of the bladder neck margin in a radical prostatectomy does not indicate that the tumor is pT4.