

The pathology of unusual subtypes of prostate cancer

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Abstract: There are some current literatures describing the morphologic change of prostate carcinoma variants. Some subtypes do not respond to hormone deprivation therapy, for example adenosquamous and squamous cell carcinoma (SQCC), basaloid and adenoid cystic carcinoma (ACC), small cell carcinoma (SmCC), sarcomatoid carcinoma, urothelial carcinoma; some are defined in special Gleason grade, some develop different prognosis. So, it is very important to identify these rare subtypes to avoid misdiagnosis. In this review, we aim to describe the typical clinicopathological features of the rare variants of prostate cancer, including prostate acinar adenocarcinoma morphologic variants.

Keywords: Prostate carcinoma; subtype; ductal; neuroendocrine (NE); squamous; mucinous; foamy; pseudo hyperplastic

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The incidence of prostate cancer (PCa) is the first in malignant tumors among men in the United States, and the mortality rate is the second cause of cancer related deaths. The overwhelming majority of PCas are acinar adenocarcinomas (AC), which are mostly frequently encountered in our daily diagnostic work. Moreover, there are some unusual histological variants of prostate, because of their rarity, it is important for pathologists to recognize and make diagnosis accurately. In the 1973–2008 Surveillance, Epidemiology and End Results (SEER) program data, there were 790,937 acinar adenocarcinoma, and 806 cases of mucinous adenocarcinoma, 662 cases of ductal adenocarcinoma, 130 cases of signet ring cell carcinoma, 502 cases of neuroendocrine (NE) carcinoma, and 27 cases of adenosquamous carcinoma in US (1). Here, we mainly described the unusual histological variants of prostate adenocarcinoma, including atrophic, pseudo hyperplastic carcinomas, foamy gland, mucinous (colloid) carcinoma, signet ring cell carcinoma, basal cell and adenoid cystic carcinoma (ACC), squamous cell carcinoma (SQCC), ductal carcinoma, PCa with NE differentiation, and sarcomatoid carcinoma (*Table 1*).

Acinar adenocarcinoma morphologic variants

These variants may have the same response to the hormone deprivation therapy as usual acinar adenocarcinoma. But, there may be distinctive morphologic change different from acinar adenocarcinoma, imitating the atrophy glands, foamy cells or usual hyperplastic glands. Sometimes, it is difficult to be differentiated from benign lesions, and leading to the missed diagnosis. Furthermore, some variants have different Gleason grading score, and different prognosis.

Atrophic variant

Atrophy in adenocarcinoma is identified with glands lined by cells with scant cytoplasm, which can simulate the appearance of atrophy in the prostate. Useful features in diagnostic recognition include infiltrative growth pattern and cytology of malignancy, the presence of macro nucleoli, nucleomegaly, and the presence of adjacent, non-atrophic prostatic carcinoma with the usual moderate amount of cytoplasm (2). In contrast, benign atrophic glands typically have dense hyperchromatic nuclei and lobular growth.

Table 1 The pathological characters and hormonal reaction of the unusual variants of prostate cancer

Subtype	Morphologic characters	Immunostaining characters	Gleason score	Response to androgen deprivation therapy
Atrophic variant	<ul style="list-style-type: none"> Prostate cancer glands lined by cells with scant cytoplasm, resembling atrophy Infiltrative growth, cytology of malignancy Usually admixed with nonatrophic prostate carcinoma 	<ul style="list-style-type: none"> 34βE12 and p63 are completely negative in the glands of concern AMACR is overexpressed in 70% of cases 	<ul style="list-style-type: none"> The same as the usual acinar adenocarcinoma 	Responder
Pseudohyperplastic variant	<ul style="list-style-type: none"> Large-sized or dilated glands, with branching and papillary infolding Tall columnar cells with abundant pale to slight granular luminal cytoplasm Basally located nuclei along basement membrane Diagnostic malignant nuclear features retained 	<ul style="list-style-type: none"> 34βE12 and p63 are completely negative in the glands of concern AMACR is overexpressed in 70–83% of cases 	<ul style="list-style-type: none"> ISUP recommends grade of 3+3=6 	Responder
Foamy gland (xanthomatous) variant	<ul style="list-style-type: none"> Abundant foamy cytoplasm Malignant nuclear features not always present, as nuclei may be small and pyknotic Presence of infiltrative pattern 	<ul style="list-style-type: none"> The foamy cells are PSA + and CD68– AMACR + in 68% cases 	<ul style="list-style-type: none"> Discounting foamy cytoplasm and assigning grade based on architecture 	Responder
Mucinous (colloid) adenocarcinoma	<ul style="list-style-type: none"> ≥25% of resected tumor shows extracellular mucin Intraluminal mucinous material does not qualify, and extraprostatic origin must be excluded 	<ul style="list-style-type: none"> 34βE12 and p63 are completely negative in the glands of concern PSA and CK8/18 (+) 	<ul style="list-style-type: none"> Grade irregular cribriform glands floating in mucin as 4+4=8; no consensus if individual discrete glands in mucin 	Responder
Signet ring cell variant	<ul style="list-style-type: none"> ≥25% of resected tumor shows signet ring cell Tumor cells contain optically clear vacuoles displacing nuclei and are widely infiltrative 	<ul style="list-style-type: none"> 34βE12 and p63 are completely negative in the glands of concern PSA positive 	<ul style="list-style-type: none"> Not recommended 	Responder

Table 1 (continued)

Table 1 (continued)

Subtype	Morphologic characters		Immunostaining characters	Gleason score	Response to androgen deprivation therapy
Aberrant expression of P63 in PCa	<ul style="list-style-type: none">• A mixture of atrophic glands, poorly formed or solid, with glands having multilayered, spindled, and basaloid nuclei• Nucleoli were present and prominent• In a few cases, the neoplastic glands were more akin to usual-type atrophic adenocarcinoma and lined by columnar cells		<ul style="list-style-type: none">• Aberrant diffuse p63 expression• CK18, CK8, and androgen receptor, NKX3.1, AMACR and PSA are positive	The same as the usual acinar adenocarcinoma	Responder
Lymphoepithelioma-like variant	<ul style="list-style-type: none">• Characterized by syncytial growth amid dense lymphocytic background• No Epstein-Barr virus association		<ul style="list-style-type: none">• PSA and AMACR are positive	Not recommended	Non-responder
Prostate carcinoma with stratified epithelium (“PIN-like”)	<ul style="list-style-type: none">• Glands lined by ≥ 2 layers of malignant cells• May resemble flat or tufted high-grade PIN but lacks basal cells		<ul style="list-style-type: none">• 34βE12 and p63 are completely negative	Not recommended	Responder
Basal cell and adenoid cystic carcinoma	<ul style="list-style-type: none">• Basaloid tumor cells have scant cytoplasm, high N/C ratio, irregular or angulated nuclei with open chromatin• May exhibit nuclear and cytoplasmic micro vacuolation• Infiltration of adjacent parenchyma	<p>BCC pattern:</p> <ul style="list-style-type: none">• Variably sized solid nests, cords, or trabeculae, peripheral palisading of basaloid cells <p>ACC pattern:</p> <ul style="list-style-type: none">• prominent cribriform architecture• Eosinophilic, hyaline, basement membrane-like material	<ul style="list-style-type: none">• Basal cell markers (+), p63 or HMCK(34βE12)• Typically CK20 (–)/CK7(+) Exhibits luminal (+) staining in ACC pattern, inverse to HMCK (34βE12), which stains peripheral aspect• CK7 (–) in pure solid basal cell nests• Bcl-2 is strongly and diffusely (+)• High Ki-67 nuclear staining (>20%)	Gleason system should not be used	Non-responder

Table 1 (continued)

Table 1 (continued)

Subtype	Morphologic characters	Immunostaining characters	Gleason score	Response to androgen deprivation therapy
Carcinomas with squamous differentiation	<ul style="list-style-type: none"> Glandular component are similar to acinar adenocarcinoma Squamous and glandular components intermingled 	<ul style="list-style-type: none"> The squamous cells are negative for PSA and PSAP 	Not recommended for the squamous component	Non-responder
Urothelial carcinoma of prostate	<ul style="list-style-type: none"> Diagnostic criteria identical to those of bladder UroCa 	<ul style="list-style-type: none"> PSA and PSAP (–) GATA3, CK7, CK20, p63, and thrombomodulin (+) 	Not recommended	Non-responder
Ductal adenocarcinoma	<ul style="list-style-type: none"> Large glandular and papillary architecture lined by tall columnar cells, often with pseudostratified growth Papillary, cribriform, individual glands, or solid Tall columnar cells in pseudostratified growth pattern Cytoplasm usually amphophilic and nucleus obligated with variably prominent nucleolus Can show intraductal growth pattern 	<ul style="list-style-type: none"> Positive for AMACR in 77% of cases Majority has no detectable basal cells 	<ul style="list-style-type: none"> ISUP 2005 consensus recommends grading as Gleason pattern 4; if necrosis present, pattern 5 	Responder
Sarcomatoid carcinoma	<ul style="list-style-type: none"> Carcinoma admixed with sarcomatoid spindle cell component Carcinoma admixed with sarcomatous component containing heterologous elements Monophasic spindle cell tumor with evidence of epithelial differentiation 	<ul style="list-style-type: none"> Carcinoma typically PSA (+) Spindle cells at least focally (+) for at least 1 epithelial marker 	Not recommended	Non-responder
Small cell carcinoma	<ul style="list-style-type: none"> Histologically similar to SCC of lungs—Small blue cell tumor with scant cytoplasm, high N/C ratio, “salt and pepper” chromatin, nuclear molding, single cell necrosis or geographic necrosis, and smearing artifacts—Half of SCC cases have acinar carcinoma components 	<ul style="list-style-type: none"> Synaptophysin 84–89% (+) Chromogranin 61–75%(+) CD56 83–92%(+) <ul style="list-style-type: none"> <20% are PSA, PSMA (+) 50% of SCC are TTF-1 (+) 	Not recommended	Non-responder

Table 1 (continued)

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Subtype	Morphologic characters	Immunostaining characters	Gleason score	Response to androgen deprivation therapy
Pleomorphic giant cell carcinoma	<ul style="list-style-type: none"> • Large bizarre tumor cells with prominent nucleoli • Multiple coexistent histologic components 	<ul style="list-style-type: none"> • The bizarre giant cells are positive for cytokeratins • PSA may be negative or different degree positivity. 	Not recommended	Non-responder

AMACR, a-methylacyl-coenzyme A racemase; PSA, prostate-specific antigen; PCa, prostate cancer; CK, cytokeratin.

High molecular weight cytokeratins (CKs) (34 β E12) and p63 are completely negative in the glands of concern, and a-methylacyl-coenzyme A racemase (AMACR) is overexpressed in 70% of cases (3). It should be emphasis that focal basal cell loss and AMACR overexpression should be interpreted with caution, as this pattern can be seen in benign atrophic glands (4). Atrophic variant does not affect the Gleason grade or pathological stage (5), so it does not appear to have a different prognosis from usual acinar adenocarcinoma.

Pseudohyperplastic variant

Pseudohyperplastic adenocarcinoma is a variant characterized by large-sized or dilated glands, with branching and papillary infolding, tall columnar cells with abundant pale to slight granular luminal cytoplasm, which resemble the appearance of epithelial hyperplasia in the prostate (2,6,7). However, the abnormal architecture can be seen in majority of pseudohyperplastic carcinoma cases (2,8,9), such as infiltrative growth configuration, intraluminal crystalloids, perineural invasion, and intraluminal wispy blue mucin. In contrast to benign hyperplastic glands, diagnostic malignant nuclear features retained, including macro nucleoli, and complete absence of basal cells are present in every case.

It should be with great caution when the diagnosis of pseudohyperplastic prostatic adenocarcinoma made in needle core cases. It is recommended to perform immunohistochemical stains for basal cells (34 β E12 and/or p63) and AMACR in all suspect cases. It was reported that 70–83% of pseudohyperplastic prostatic adenocarcinoma

cases are positive for AMACR by immunostaining (7) (Figure 1A).

ISUP recommends grade of 3+3=6 for pseudohyperplastic carcinoma. It was also recommended grade group of 1 accepted by the World Health Organization (10). The prognosis for patients with pseudohyperplastic prostatic adenocarcinoma is not certain, so clinical follow-up studies will be necessary to define the true prognostic impact of a pseudohyperplastic component.

Foamy gland (xanthomatous) variant

Foamy gland variant is characterized by abundant foamy cytoplasm. Malignant nuclear features not always present, as nuclei may be small and pyknotic (11,12). There is an architectural infiltrative pattern. Peripheral nerve invasion was more common in foamy gland carcinoma compared to acinar type adenocarcinoma (13). Foamy gland carcinoma may be deceptively benign appearing and missed on needle biopsy. Immunohistochemical stains are required in some cases for diagnosis, with prostate-specific antigen (PSA) and CD68 antibodies demonstrate the foamy cell are derived from prostate gland, and with 34 β E12 and/or p63 antibodies demonstrate the absence of a basal cell layer in all cases of invasive foamy gland carcinoma. AMACR expression can be detected by immunohistochemistry in 68% foamy gland carcinomas (7), these stainings are useful to differential from xanthoma (4,13). ERG immunohistochemistry could be considered in a second round of immunostaining of select difficult cases of foamy gland carcinoma with low AMACR expression (14) (Figure 1B). ISUP recommends discounting foamy

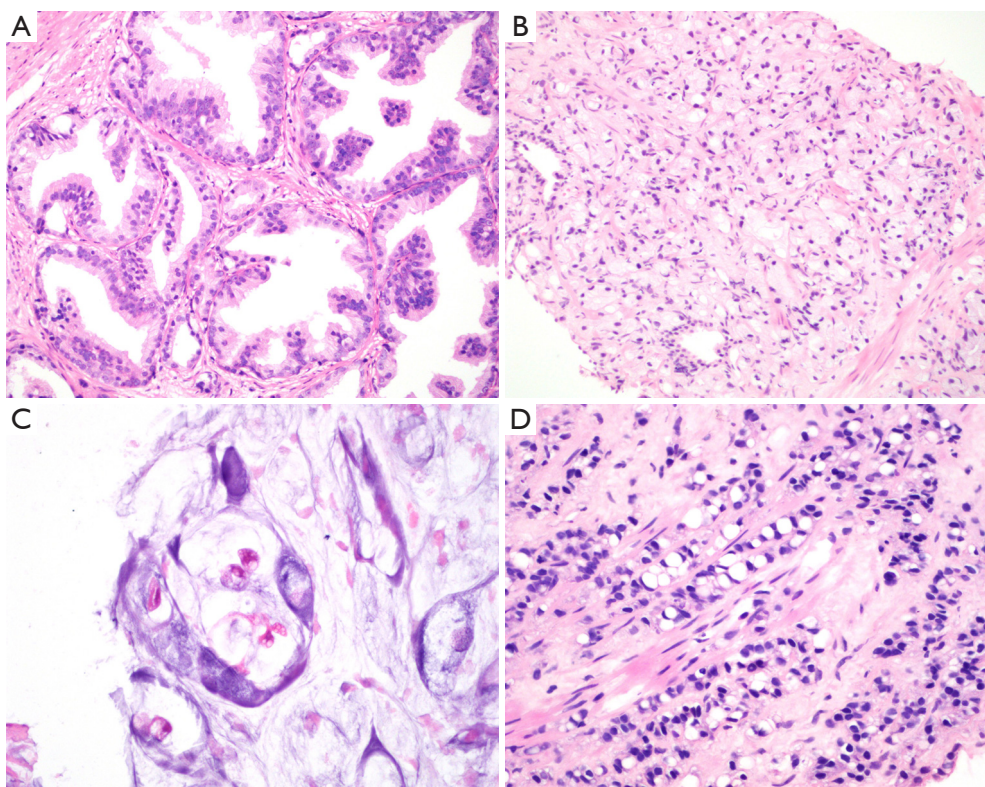


Figure 1 Pseudohyperplastic variant, foamy gland variant, mucinous (colloid) adenocarcinoma and signet ring cell variant of prostate cancer. (A) Pseudohyperplastic variant: large-sized or dilated glands, with branching and papillary infolding; diagnostic malignant nuclear features (200×); (B) foamy gland (xanthomatous) variant: PCa with abundant foamy cytoplasm, infiltrative pattern and malignant nuclear features (100×); (C) mucinous (colloid) adenocarcinoma: tumor shows extracellular mucin lake (400×); (D) signet ring cell variant: tumor cells show signet ring cell, contain optically clear vacuoles displacing nuclei and are widely infiltrative (200×).

cytoplasm and assigning grade based on architecture, most are 3+3=6 tumors.

Clinically, patients with foamy gland carcinoma are of age ranging 50–78 years (15). Foamy gland carcinomas are of similar age, pathological stage, Gleason score as conventional acinar type adenocarcinoma, and may exhibit extraprostatic extension with foamy gland features (13,16).

Mucinous (colloid) adenocarcinoma

Mucinous adenocarcinoma of the prostate is defined as adenocarcinoma with at least 25% of resected tumor shows extracellular mucin, with exclusion of a non-prostatic origin (*Figure 1C*). Intraluminal mucinous material does not qualify. This carcinoma is one of the rare prostatic carcinoma variants, with an incidence of 0.3% of all prostatic carcinomas (17-19). If mucinous lakes are detected in needle biopsy, the recommended diagnosis

is “adenocarcinoma with mucinous features”. If <25% of the tumor in radical prostatectomy sections is mucinous, one can make diagnosis of adenocarcinoma with focal mucin. With strict diagnostic criteria, it is suggested to have similar features and behavior with conventional PCa (17,18). PSA and CK8/18 antibodies demonstrate the mucinous cell are derived from prostate gland, other than metastasizing.

ISUP recommend to grade irregular cribriform glands floating in mucin as 4+4=8; no consensus if individual discrete glands in mucin. Two recent reports indicated that mucinous adenocarcinoma treated by radical prostatectomy might even be less aggressive than usual acinar adenocarcinoma (17,18).

Signet ring cell variant

Signet ring carcinoma is not an exactly defined rare

prostate adenocarcinoma type, with the required percentage of the tumor to be signet ring cells ranging from 25% to 50% in the literature. True signet ring cell carcinomas should have intracytoplasmic mucin, optically clear vacuoles displacing nuclei and are widely infiltrative (20-23) (*Figure 1D*). Moreover, it should be identified with vacuolated adenocarcinoma of the prostate. Most cases are signet ring cell-like adenocarcinoma (20). There may be mucin-producing PCa, named “mucinous carcinoma with signet ring cells”. It is not clear if nonmucinous (mucicarmine negative) signet ring PCa is distinct clinically.

The true incidence of prostate signet ring carcinoma is not known. The prognosis for patients with signet ring carcinoma is poorer than conventional prostate carcinoma, and less response to the hormonal treatment.

Aberrant expression of P63 in PCa

Prostatic carcinoma with aberrant diffuse p63 expression is a recently described rare unusual variant of PCa. It is important to avoid making misdiagnosis as benign acinar proliferation. The differential diagnosis includes basal cell hyperplasia and basal cell carcinoma (24). The mean age of the patients was 65 years (range, 50–81 years old) (25). The morphologic change is consist of a mixture of atrophic glands, some poorly formed or solid, with glands having multilayered, spindled, and basaloid nuclei. Nucleoli were present and prominent in the majority of the neoplastic glands (26). In a few cases, the neoplastic glands had no distinctive morphology and were more akin to usual-type atrophic adenocarcinoma without nuclear palisading or basaloid morphology or showed neoplastic glands lined by columnar cells. In 19/21 cases, 100% of the cancer nuclei stained intensely for p63, with 70% staining in the remaining 2 cases (25). Despite p63 positivity, these tumors uniformly expressed luminal-type cytokeratin proteins such as CK18 (13/13), CK8 (8/8), and markers of androgen axis signaling commonly seen in luminal cells, including androgen receptor (10/11), NKX3.1 (8/8), and prostatein (12/13) (27). In 13/13 cases studied, tumor was positive for AMACR and in 12/12 cases (100%) were positive for PSA. Mean ki-67 expression was 6.25% (range, 5% to 10%) in 7 cases (25). In contrast to usual prostatic AC, p63-PCa shows a mixed luminal/basal immunophenotype, uniformly lack *ERG* gene rearrangement, and frequently express *GSTP1* (27). Gleason grading of this rare variant of PCa is controversial at present. About 80% cases are graded as

Gleason 3+X, while about 20% cases as Gleason 4+X and 5+X (26).

PCa with stratified epithelium (“PIN-like”)

Prostate intraepithelialneoplasia (PIN)-like adenocarcinoma is described as glands lined by more than 2 layers of malignant cells that resembling PIN in gland architecture (28,29). It may resemble flat or tufted high-grade PIN but lacks basal cells by immunohistochemical stain for 34βE12 and p63. AMACR staining can be a positive. Some may have high columnar cells like ductal AC. The reported clinical follow-up is at only 5 months (29) and so its prognosis is not definite.

Other rarer variants

These rare variants have quite different clinical and pathological characteristics with acinar adenocarcinoma, they may represent the “true” subtypes, since many of them do not respond to hormone deprivation treatment, it is very important to recognize these variants.

Lymphoepithelioma-like variant

Lymphoepithelioma-like variant are very rare, poorly differentiated. Histologically, they resemble lymphoepithelioma in other organs, characterized by syncytial growth amid dense lymphocytic background, but do not appear to be related to Epstein-Barr virus infection. The carcinoma cells are positive for PSA and AMACR. The prognosis is poor. It is reported that patients died of the cancer at 8–26 months after diagnosis (30).

Basal cell and ACC

Basal cell lesions in the prostate gland span a wide range from obviously benign basal cell hyperplasia through varying ranges of atypia to lesions. A precise definition of malignant features include elusive, haphazard infiltrative growth, perineural invasion, extraprostatic extension—with the bladder neck as a preferred site, the presence of necrosis are widely accepted features (31-33). Clinically, it mainly occurred in older men, most commonly presents with obstructive urinary symptoms; it has reported that PSA is elevated in some cases (34). Local recurrence, metastasis, and death from disease reported in approximately 30% of cases. Given limited case numbers with clinical outcome

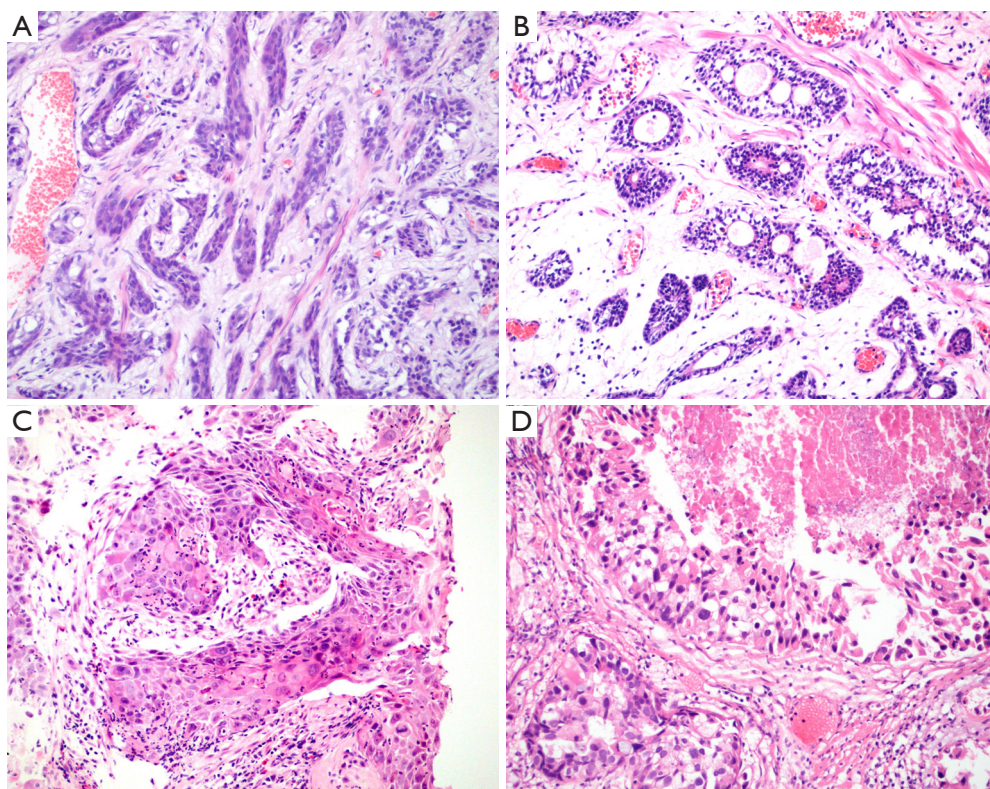


Figure 2 Basaloid tumor, carcinoma with squamous differentiation and urothelial carcinoma of prostate. (A) Basal cell carcinoma (BCC pattern): variably sized solid nests, cords, or trabeculae with peripheral palisading of basaloid cells (200×); (B) adenoid cystic carcinoma (ACC pattern): tumor grows in nests with prominent cribriform architecture (200×); (C) carcinomas with squamous differentiation: tumor grows in nests with cytologic atypia, infiltration pattern (200×); (D) urothelial carcinoma of prostate: the morphologic change is identical to those of bladder UroCa with extensive necrosis (200×).

data, the varying ranges of atypical lesions can be viewed as a low malignant potential neoplasm.

Basaloid tumor cells have scant cytoplasm, high nuclear to cytoplasmic ratio, and irregular or angulated nuclei with open chromatin. Most experts recognize malignant “basaloid” neoplasms as either basal cell or ACC (31,33). Basal cell carcinoma (BCC) pattern, composed of variably sized solid nests, cords, or trabeculae with peripheral palisading of basaloid cells, may be associated with extensive central necrosis. Basal cell carcinoma of the prostate is an aggressive tumor with frequent loss of PTEN expression and overexpression of EGFR (35) (*Figure 2A*). ACC pattern, in which tumor grows in nests with prominent cribriform architecture, and eosinophilic, hyaline, basement membrane-like material may be present. Basophilic mucinous secretions may be presented in lumina (*Figure 2B*). Histologically, basaloid carcinomas of the prostate were considered to

originate from basal/reserve cells, not the same as the usual PCa (31,33). Recently, it was considered that true ACCs often harbor MYB translocations resulting in the MYB-NFIB fusion protein (36). The Gleason system should not be applied to these tumors.

The main differential diagnoses are primary benign or atypical basal cell hyperplasia. In resolving challenging cases, it is important to recognize the nuclear atypia (33). Some adenoid cystic-like proliferations may be multifocal, exhibit focal cribriform architecture, but they typically show well-defined lobulated growth patterns, lacking the confluent, expansile cribriform architecture or widely irregular infiltrative patterns of basaloid carcinomas (37). In addition to assessment of architectural features such as infiltrative growth, perineural invasion, extraprostatic extension and cytologic features, IHC for p63, HMCK (34βE12), CK7, CK20, Bcl-2 and Ki67 may be helpful

to distinguish basal cell hyperplasia (BCH) from basaloid carcinoma. Basal cell markers, p63 or HMCK (34 β E12) may stain multiple layers of cells, only peripheral aspect of tumor clusters, or in only few scattered tumor cells. CK7 exhibits luminal positive staining in ACC pattern, inverse to HMCK (34 β E12), which stains peripheral aspect, while CK7 is negative in pure solid basal cell nests. Unlike usual PCa and BCH, in which Bcl-2 staining is absent or is focal/weak, basaloid carcinomas often demonstrate diffuse Bcl-2 positivity. The proliferative rate for basaloid carcinomas is always >20%, significantly higher than that of BCH (38).

Carcinomas with squamous differentiation

The prostatic pure SQCC is similar to SQCC of other anatomic sites, which showed well to poorly differentiating with variable cytologic atypia (*Figure 2C*). Glandular component of prostatic adenosquamous cell carcinoma (ASC) is similar to acinar adenocarcinoma. Squamous and glandular components intermingled. If there is no history of hormonal therapy, the glandular component of adenosquamous carcinomas can be Gleason graded. But the squamous component can show variable differentiation and not be graded using the Gleason system. The malignant squamous cells are most often negative for PSA and PSAP immunostains. The mean survival for prostatic SQCC is not long, about 6–24 months (39).

Urothelial carcinoma of prostate

Urothelial Carcinoma of Prostate (UroCa) involving prostate arise from prostatic urethra, periurethral glands, and proximal prostatic ducts. Prostate involvement by invasive bladder UroCa is relatively more common. Most primary prostatic UroCa presents with obstructive urinary symptoms. Diagnostic criteria are identical to those of bladder UroCa. Cytologically, urothelial carcinoma in the prostate has a high nuclear grade, with substantial nucleomegaly, nuclear pleomorphism, and nuclear hyperchromasia. The cytoplasm often has an eosinophilic 'squamoid' appearance (*Figure 2D*). Carcinoma *in situ* of UroCa can spread from prostatic urethra, involves ducts and acini, or grows along ejaculatory duct to seminal vesicle, stromal invasion may arise anywhere along this spread. Prostatic stromal invasion by urothelial carcinoma is typical fied by irregular solid nests and cords that extend beyond the rounded, smooth outer profile of the urothelial carcinoma *in situ*, with a fibroinflammatory

stromal response (30).

The immunohistochemistry stain is useful to differentiate the urothelial carcinoma from poorly differentiated prostatic adenocarcinoma. PSA and PSAP staining is negative for the urothelial carcinoma, CK7, CK20, high molecular weight CKs bound by 34 β E12 (CK903), p63, and thrombomodulin are frequently positive (30). GATA3 is positive in the UroCa and negative in the prostatic adenocarcinoma, it is a good marker to identify the urothelial origin (4,40).

Clinically, Serum PSA level of UroCa typically is not elevated. Grading and pathological staging have been inconsistently performed. The outcome for patients diagnosed with primary urothelial carcinoma of the prostate has been dismal in the past, with an average survival of 17–29 months (41).

Ductal adenocarcinoma

Prostatic ductal adenocarcinoma (PDA) is characterized as adenocarcinoma of prostatic epithelial cell origin with large glandular and papillary architecture lined by tall columnar cells, often with pseudostratified growth. Histologically, main architectural patterns include papillary, cribriform, individual glands and solid. Cytoplasm usually amphophilic and nucleus obligated with variably prominent nucleolus. It can grow intraluminally into preexisting ducts retaining "native" basal cell layer. Cytologically, in ductal adenocarcinoma, nucleus typically elongated, variably usually prominent nucleolus, occasional to frequent mitoses present. It has greater degree of chromatin irregularities compared to usual acinar prostate adenocarcinoma (*Figure 3A,B*).

Clinically, mixed ductal and acinar adenocarcinoma was reported in 5–6.3% of PCas (42). It is considered that PDA and the synchronous usual-type acinar adenocarcinoma are clonally related in some cases and are infrequent PTEN loss and ERG protein expression (43). Patients with PDA presented with lower PSA, had more favorable pathological features, and similar overall survival compared to men with Gleason 8–10 acinar adenocarcinoma (44). It is reported that PDA respond to hormonal manipulation treatment.

PDA has morphological similarities to AC of other organs. It is important for therapeutic decisions to distinguish the prostatic origin with the metastases from other organs. Androgen receptor, prostatein, PSA, and PSAP were almost invariably expressed in PDA. Ki-67-labeling index was lower in PDA than in other AC (4,45,46). Positive rate of AMACR is in 77% of cases. Majority has

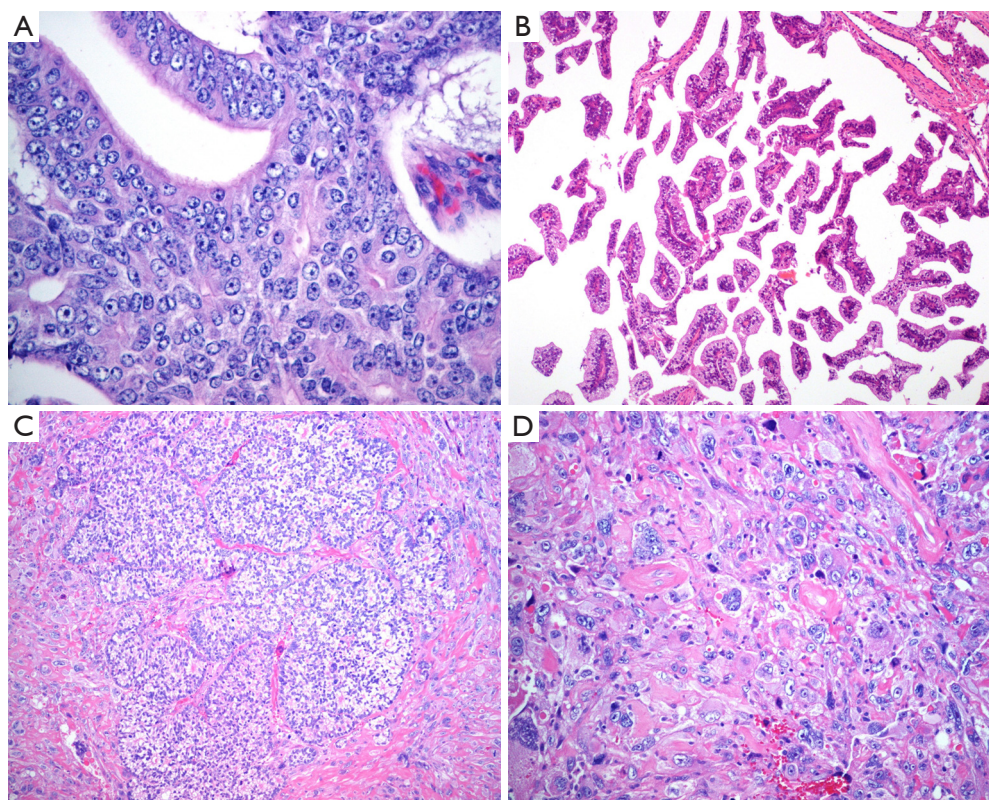


Figure 3 Ductal carcinoma and sarcomatoid carcinoma of prostate. A and B, ductal adenocarcinoma. (A) Large glandular and cribriform architecture lined by tall columnar cells, with pseudostratified growth; cytoplasm amphophilic and nucleus oblongated with variably prominent nucleolus (400 \times); (B) ductal adenocarcinoma with prominent papillary architecture (100 \times); (C) and (D) sarcomatoid carcinoma: carcinoma admixed with sarcomatoid spindle cell component (100 \times , 200 \times).

no detectable basal cells by p63 or HMCK (34 β E12). ISUP 2005 consensus recommends grading as Gleason pattern 4; if necrosis present, pattern 5.

Sarcomatoid carcinoma

Sarcomatoid carcinoma is a rare biphasic malignant or monophasic neoplasm of prostate demonstrating epithelial and mesenchymal differentiation by light microscopic or immunohistochemistry. Two elements of sarcomatoid carcinoma include a malignant epithelial component and a malignant mesenchymal or mesenchymal-like component. Overall, histologically, sarcomatoid carcinoma falls into three categories. The most common one is carcinoma admixed with sarcomatoid spindle cell component. The other is carcinoma admixed with sarcomatous component containing heterologous elements. The third one is the monophasic spindle cell tumor with immunohistochemical and/or electron microscopic evidence of epithelial

differentiation (*Figure 3C,D*). Sarcomatoid component frequently composed of undifferentiated spindle cell sarcoma. About 24% cases may contain heterologous elements that most frequently resemble osteosarcoma, or leiomyosarcoma, chondrosarcoma, rhabdomyosarcoma, and angiosarcoma. The combination of these sarcomatous elements is common. Heterologous elements typically merge with spindle cells. IHC findings in the 2 components are different, with adenocarcinoma showing diffuse CK and PSA/PAP positivity and the spindle cells exhibiting more focal CK positivity and rare PSA/PAP labeling (47-49). The prognosis of prostatic sarcomatoid carcinoma is poor with local recurrence not response to hormonal treatment (50).

Small cell carcinoma (SmCC)

Primary SmCC of prostate is very rare, the estimated incidence range from 0.3% to 1% of all prostatic carcinomas.

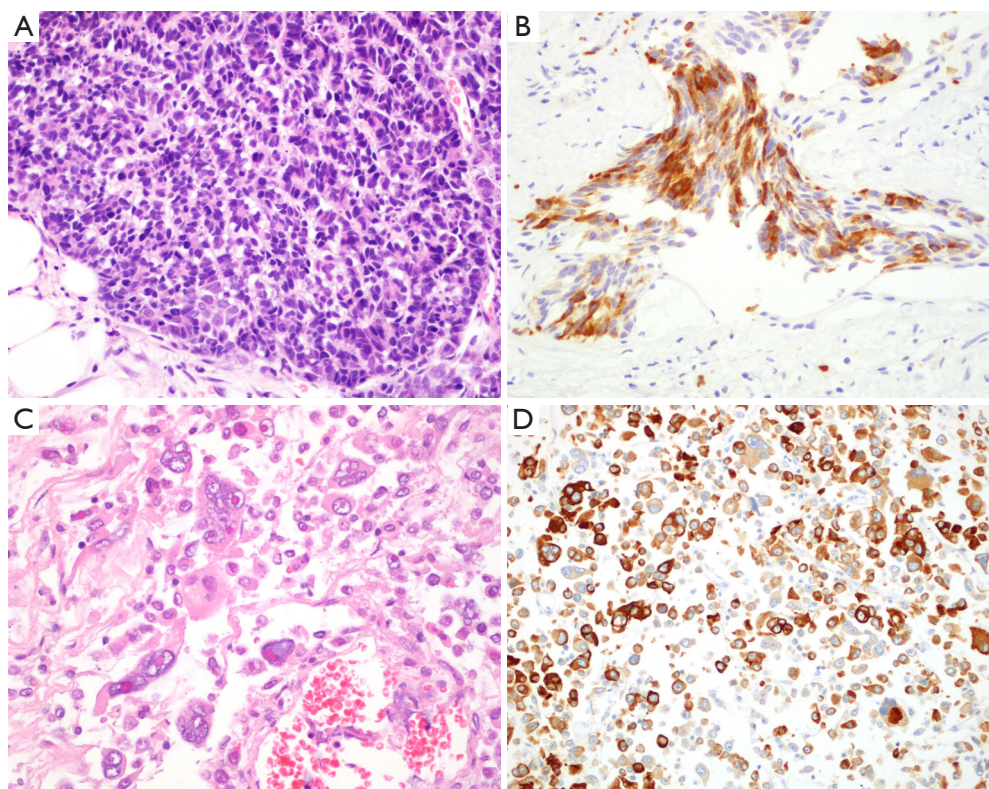


Figure 4 Small cell carcinoma and pleomorphic giant cell carcinoma of prostate. (A) Small cell carcinoma of prostate: small blue cell with scant cytoplasm, high nuclear to cytoplasmic ratio, “salt and pepper” chromatin, nuclear molding (200×); (B) synaptophysin is positive for the small cells (200×); (C) pleomorphic giant cell carcinoma: large bizarre tumor cells with prominent nucleoli (200×); immunohistochemistry staining of AE1/AE3; (D) (200×) and vimentin (not shown) are positive for the pleomorphic giant tumor cells.

In about one-half of cases, the carcinoma is pure SmCC, and in the other half it is admixed with prostatic acinar adenocarcinoma (33). SmCC is histologically similar to SmCC of lungs, including small blue cell tumor with scant cytoplasm, high nuclear to cytoplasmic ratio, “salt and pepper” chromatin, nuclear molding, single cell necrosis or geographic necrosis, and smearing artifacts (*Figure 4A,B*). Focal NE differentiation in acinar adenocarcinoma is characterized by scattered or focal cluster of NE cells mixing with adenocarcinoma cellular elements, highlighted by NE markers. Paneth cell-like change may occur (51).

Hormonal treatment or androgen deprivation therapy (ADT) for acinar adenocarcinoma may lead NE tumor cells to clonal propagation, for NE cells are devoid of androgen receptors; Possible clonal progression and evolution of subset of non-NE tumor cells that have been influenced by ADT (51).

It is reported that NE marker immunoreactivity in SmCC, that synaptophysin positive in 84–89% cases, chromogranin positive 61–75% cases, CD56 positive in

83–92% cases, NSE positive in 85% cases, and prostate specific markers (PSA, PAP, PSMA) positive in less than 20% cases. Approximately 50% of SmCCs are TTF-1 positive. So, it will be difficult to identify the derivation of the SmCC found in prostate. The test of *TMPRSS2-ERG* Gene Fusion in SmCC of Prostate will be helpful. *TMPRSS2* (transmembrane proteinase serine 2) is an androgen-regulated gene that is specifically expressed in the prostate. There is androgen responsive element in the 5' untranslated region of the *TMPRSS2* gene. Therefore, the fusion of 5' *TMPRSS2* to 3'*ERG* leads to the expression of *ERG* under the androgen control. Overall, in the prostate, the *TMPRSS2-ERG* gene fusion is seen in 50% (40–70%) of prostate adenocarcinoma, and is also reported in about 20% of high-grade PIN (52). But it is generally negative in the benign glands. On FISH analysis, the rearrangement of the *ERG* gene was found in 8 cases of prostatic SmCC (67%), and the rearrangement was associated with deletion of the 5' *ERG* gene in 7 cases, but rearrangement of the *ERG*

gene was not present in any SmCC of the urinary bladder (12 cases) or lung (11 cases) (52). So the FISH analysis of *TMPRSS2-ERG* gene rearrangement is helpful in identify the derivation of the SmCC in prostate.

Pleomorphic giant cell CA

This is a very rare variant of adenocarcinoma with large bizarre tumor cells with prominent nucleoli. In addition to the pleomorphic giant cell component, multiple coexistent histologic components may be seen including Gleason score 9 conventional PCa, SmCC, squamous carcinoma, and prominent ductal adenocarcinoma differentiation with intraductal spread (53). In immunohistochemical staining, PSA may be negative in the giant cells, or different degree positivity. The bizarre giant cells were strongly positive for cytokeratins AE1/AE3 and/or Cam 5.2 (*Figure 4C,D*). It is often more aggressive conventional PCa in clinical outcome (53).

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Footnote

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