

HISTOLOGIC VARIANTS OF BLADDER CANCER: DIAGNOSTIC, THERAPEUTIC AND PROGNOSTIC IMPLICATIONS

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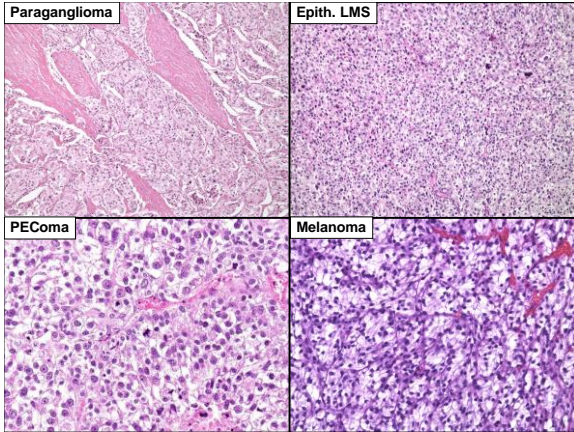
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UNUSUAL "EPITHELIAL" NEOPLASMS IN THE BLADDER

- **Primary:** Urothelial carcinoma & its variants, squamous cell carcinoma & adenocarcinoma
- **Metastatic**
- **Non-epithelial**
 - Paraganglioma*
 - PEComa*
 - Epith. LMS*
 - Prim. Melanoma*



UROTHELIAL CARCINOMA (Prim. or Metastatic site)

Challenges:

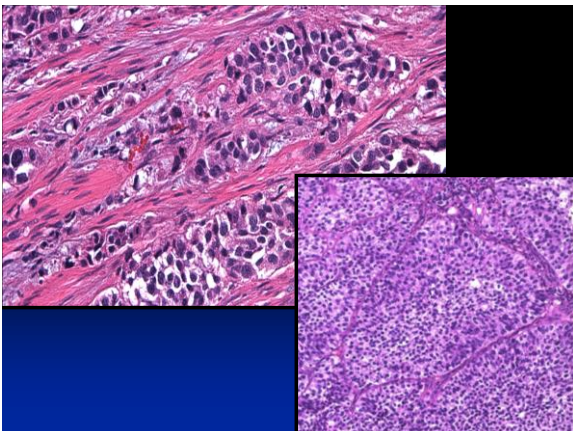
- Poorly differentiated carcinoma
- "Characterless": solid, nested & trabecular architecture

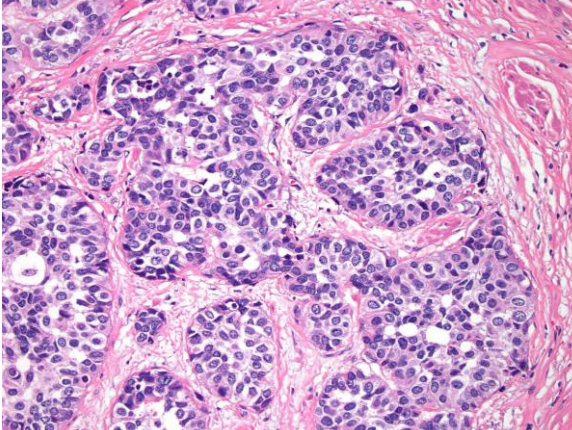
Hallmarks:

- Frequent squamous and / or glandular diff.
- Cells with nuclear grooves
- Nuclear atypia obvious +/- anaplasia

Approach

- Clinical history (invasive, usually high stage carcinoma)
- Compare with primary
- Judicious IHC: ? Best markers





CLASSIFICATION OF INVASIVE BLADDER CA

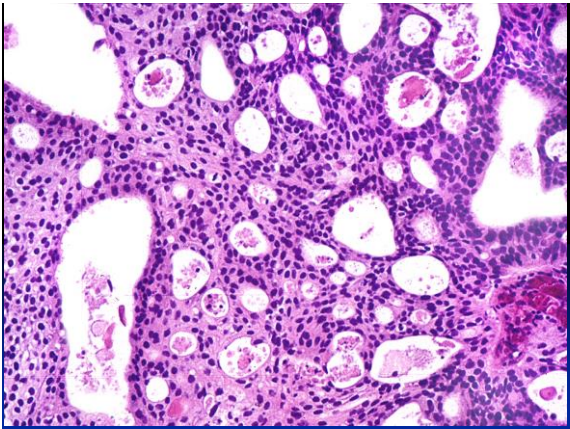
- **Urothelial carcinoma**
- **Squamous cell Ca**
 - conventional
 - verrucous
 - basaloid
- **Adenocarcinoma**
 - mucosal based
 - urachal
- **Neuroendocrine carcinoma**
 - Small cell
 - Large cell
 - Well differentiated tumor
 - Paraganglioma
- **Variants of urothelial Ca**
 - nested (incl. large nested)
 - microcystic
 - micropapillary
 - lymphoepithelioma-like
 - sarcomatoid
 - diffuse/plasmacytoid
 - signet ring cell
 - giant cell
 - lipid rich
 - clear cell
 - undifferentiated

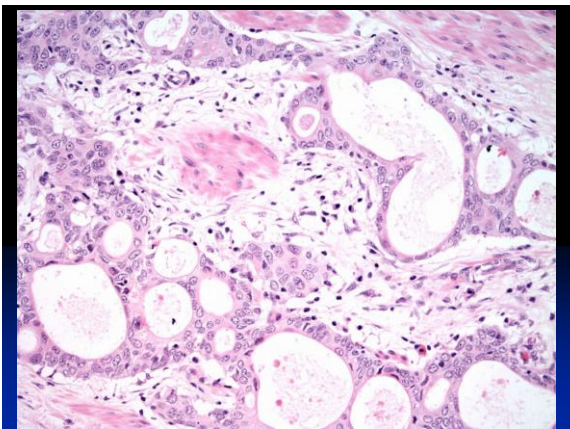
CARCINOMAS OF THE BLADDER WITH GLANDULAR HISTOLOGY

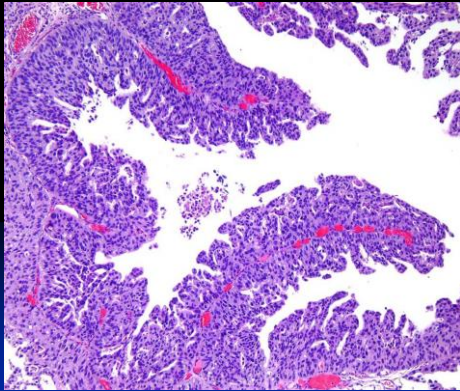
- **Histologic:**
 - Primary urothelial carcinoma with glandular differentiation – patterns
 - Primary adenocarcinoma of urinary bladder – subtypes
 - Metastatic adenocarcinoma

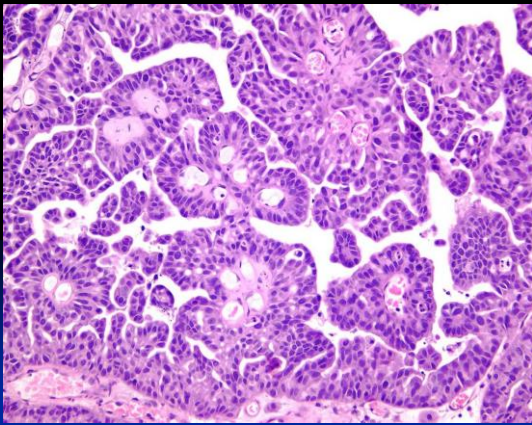
UROTHELIAL CARCINOMA WITH GLANDULAR FEATURES

- Gland-like lumina (NOS)
- Microcystic
- Small tubules
- With villoglandular features
- With specific adenocarcinoma pattern









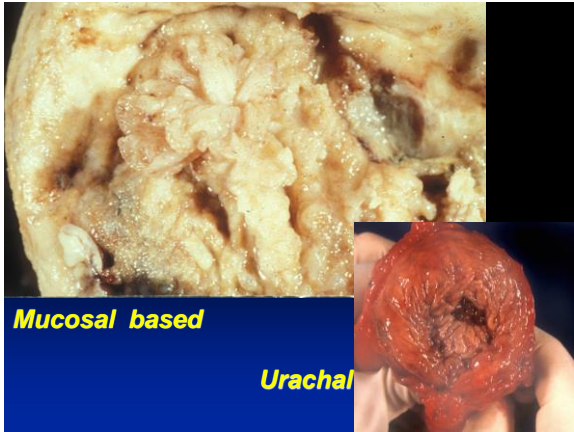
PRIMARY ADENOCARCINOMA OF THE BLADDER

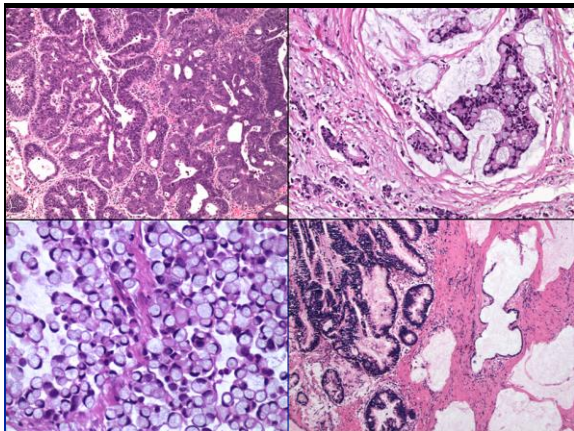
Anatomic:

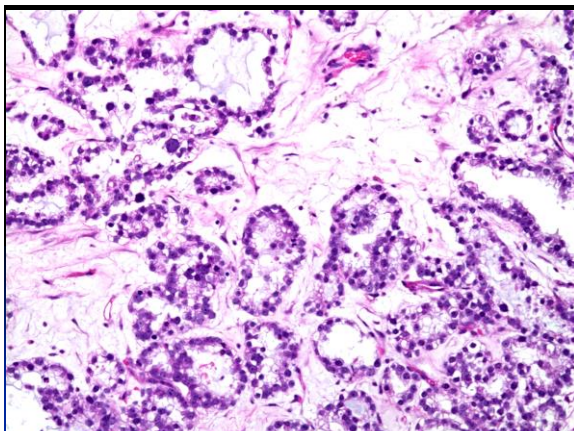
- Urachal
- Bladder mucosa

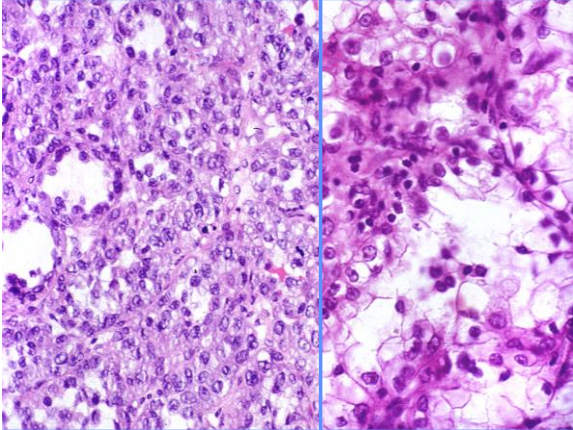
Histology:

- Adenocarcinoma NOS
- Enteric
- Mucinous
- Signet ring
- Clear cell
- Hepatoid
- Combined (from above)







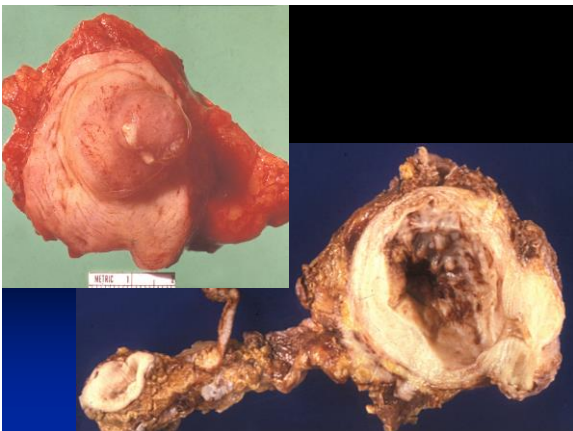


URACHAL CARCINOMA

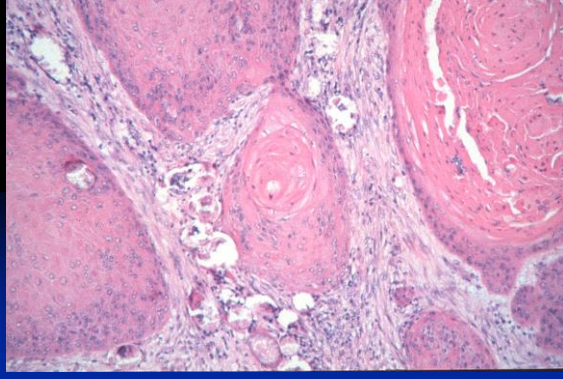
- **Clinicopathologic diagnosis**

- **Criteria:**

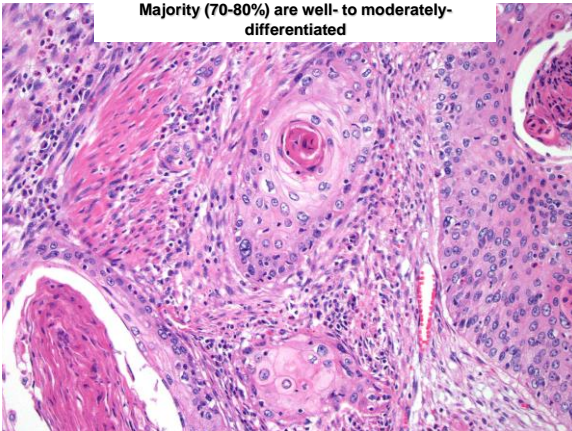
- *Dome or anterior location*
- *Absence of cystitis glandularis or intestinal metaplasia*
- *Absence of primary elsewhere*
- *Epicenter of mass in bladder wall*
- **> 90% are adenocarcinoma**



SQUAMOUS CELL CARCINOMA



Majority (70-80%) are well- to moderately-differentiated



HISTOLOGIC VARIANTS

Morphology not typical of usual or conventional type

Awareness: Diagnostic, prognostic or therapeutic importance

General rules:

- Document in report - facilitates association with histology of metastasis
- “Unusual” histology - rule out metastasis

Histologic Variants of Bladder Cancer

Prognosis:

- Aggressive
 - Micropapillary
 - Small cell
 - Sarcomatoid
 - With rhabdoid features
 - Signet ring adenocarcinoma
 - Giant cell carcinoma
- Favorable
 - Pure LELC
 - Verrucous Ca
 - Carcinoid tumor

Therapy:

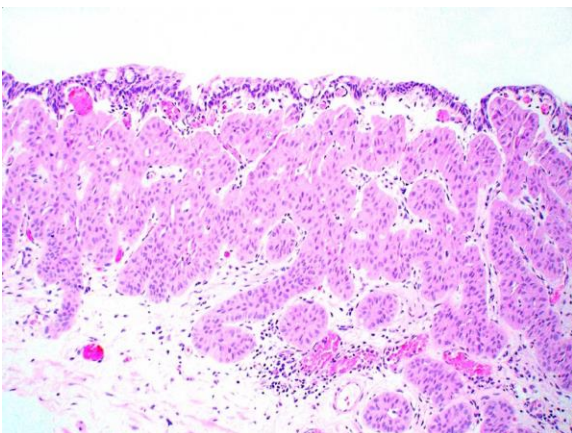
- Sarcomatoid Ca
- Small cell
- Large cell neuroendocrine
- Lymphoepithelioma-like
- Micropapillary

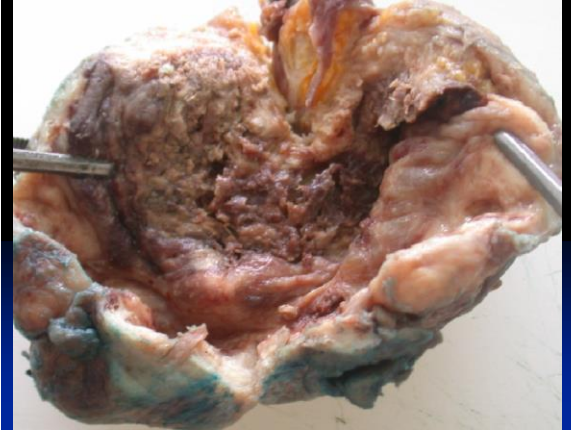
Diagnosis

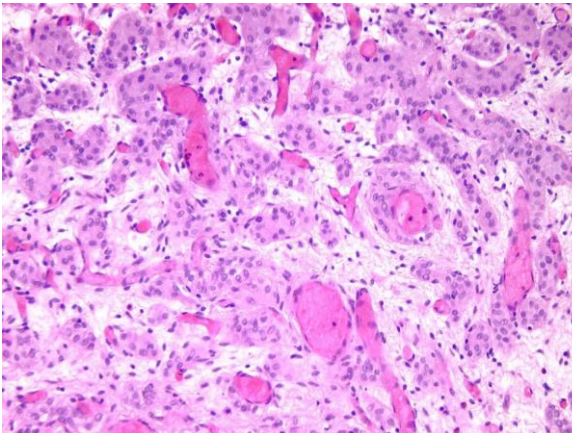
- Nested variant
- UCa with small tubules
- Plasmacytoid UCa
- UCa with clear cell features

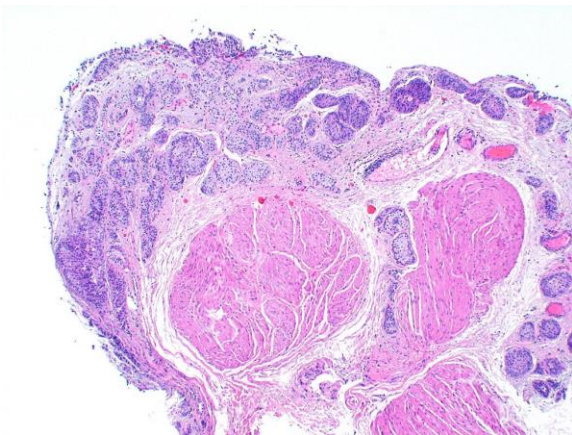
U Ca. WITH DECEPTIVELY BLAND FEATURES

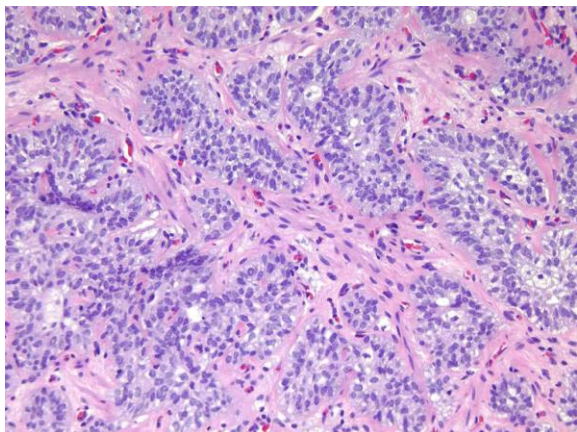
- Nested variant
- U Ca. with small tubules
- Microcystic variant

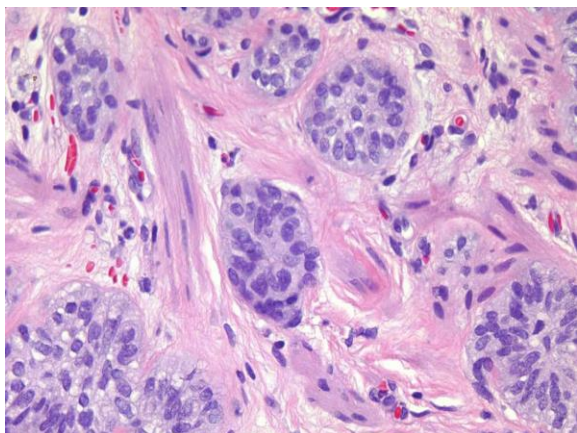


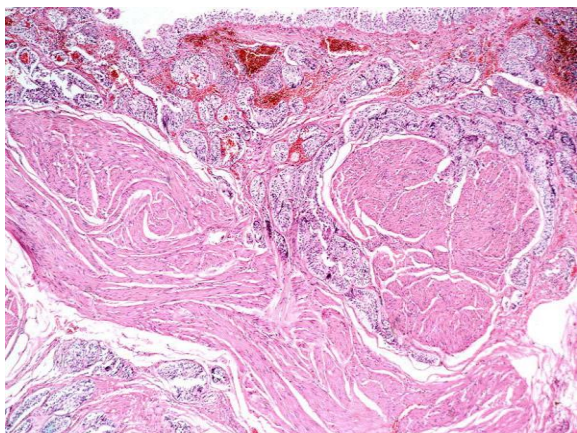


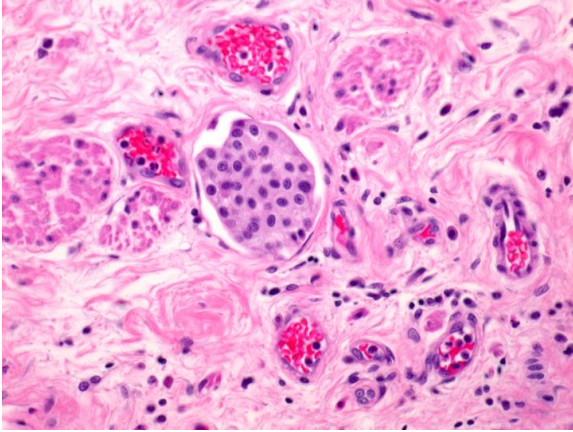


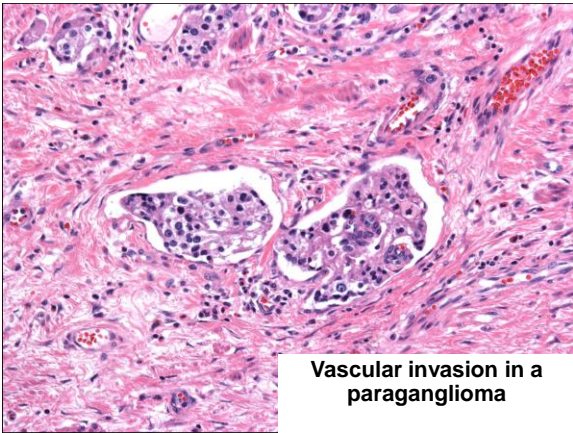




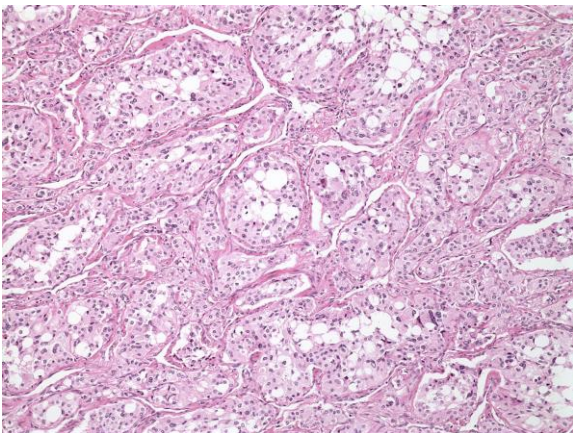


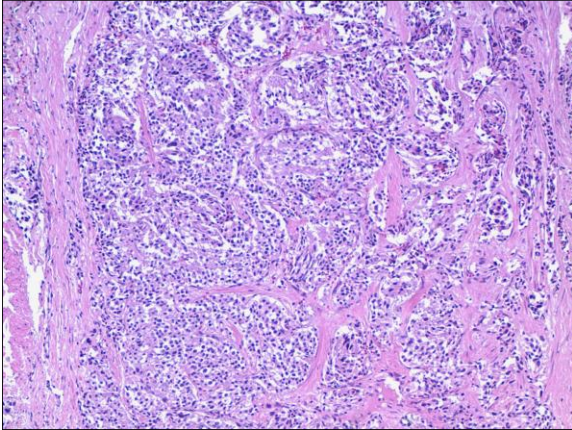


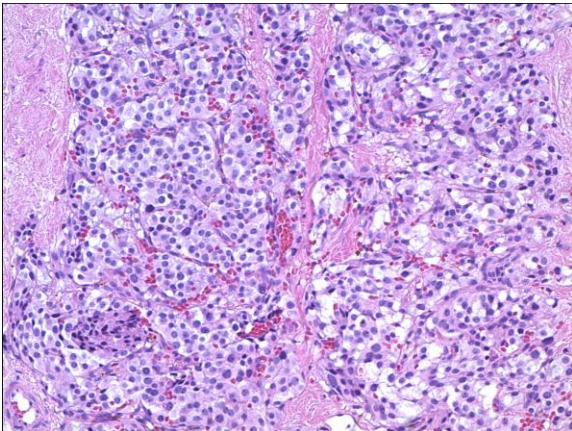




Vascular invasion in a paraganglioma

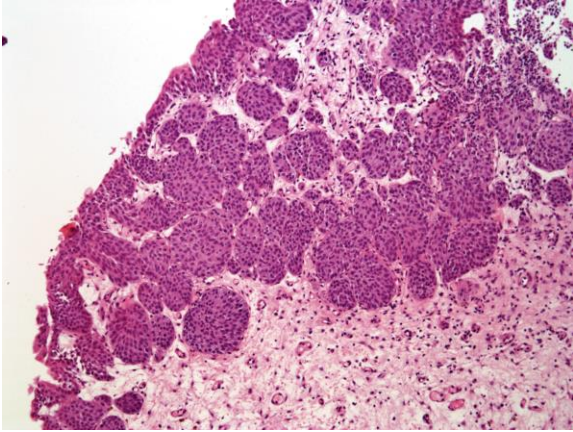


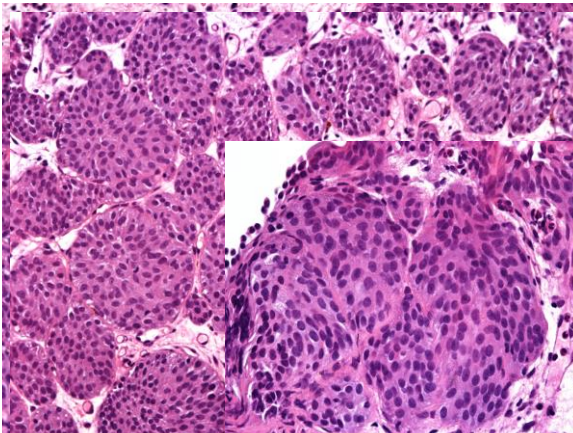




NESTED VARIANT OF U Ca.

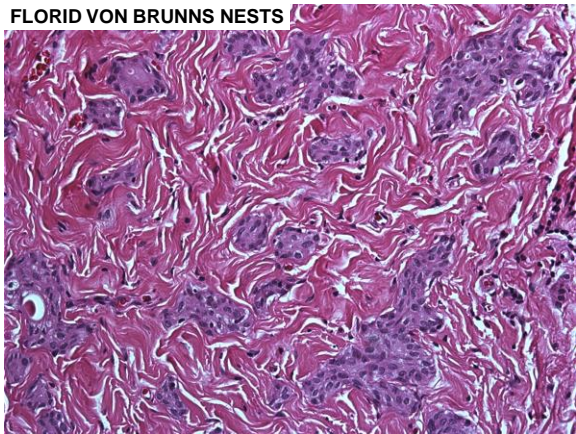
- **Diagnostic importance**
- Significant pitfall in limited biopsies
- **Differential diagnosis**
 - Von Brunn's nests
 - Post treatment pseudocarcinomatous hyperplasia
 - Paraganglioma
 - Nephrogenic adenoma
 - Metastatic prostate carcinoma
 - Carcinoid tumor





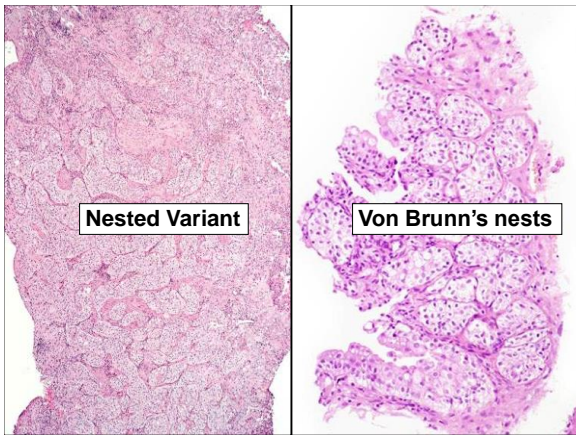


FLORID VON BRUNNS NESTS

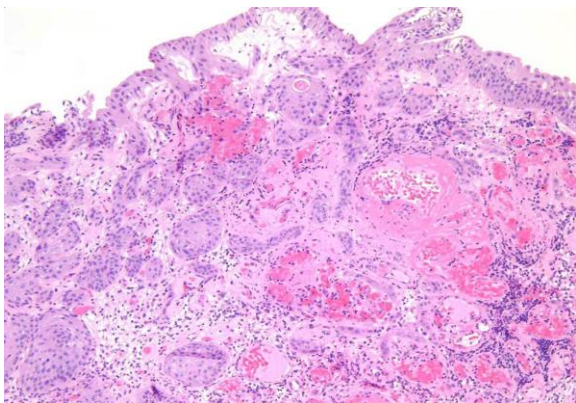


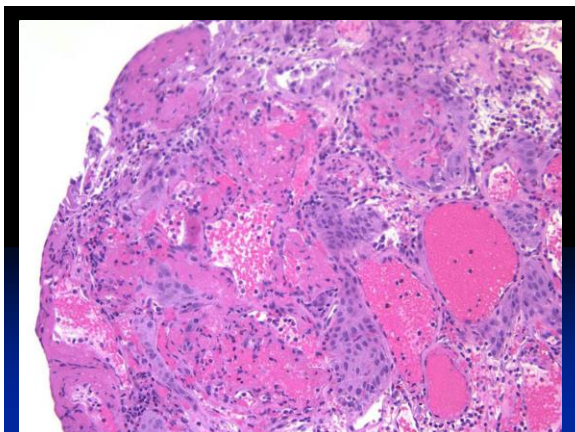
Nested Variant

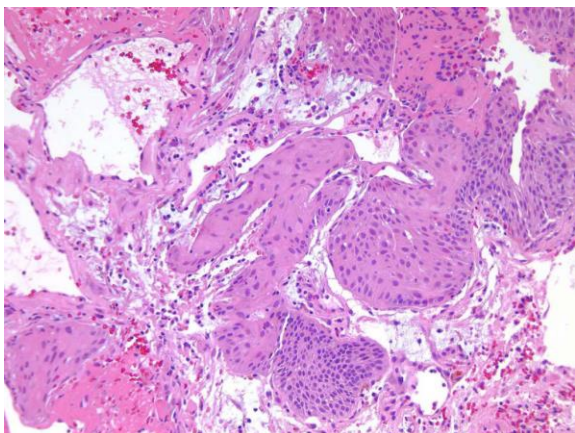
Von Brunn's nests

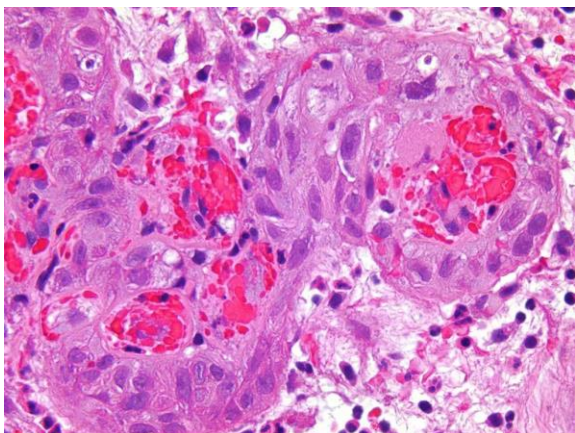


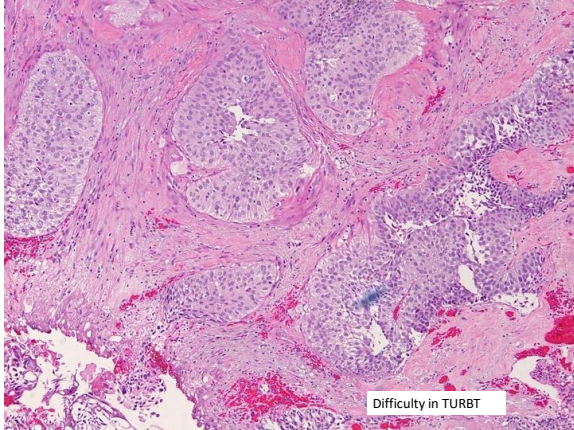
POST TREATMENT PSEUDOCARCINOMATOUS HYPERPLASIA

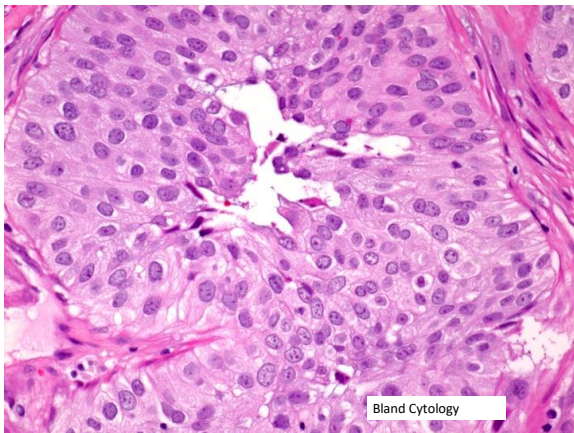


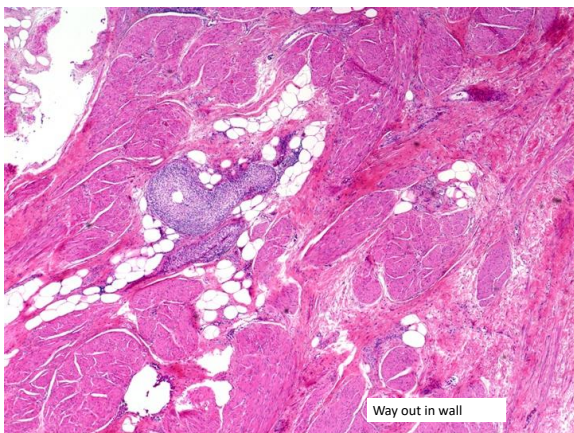


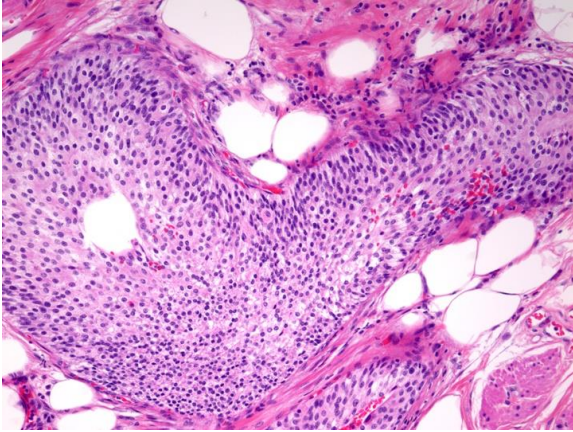


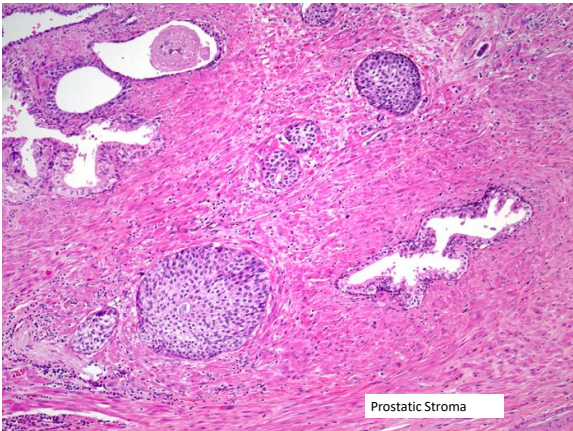










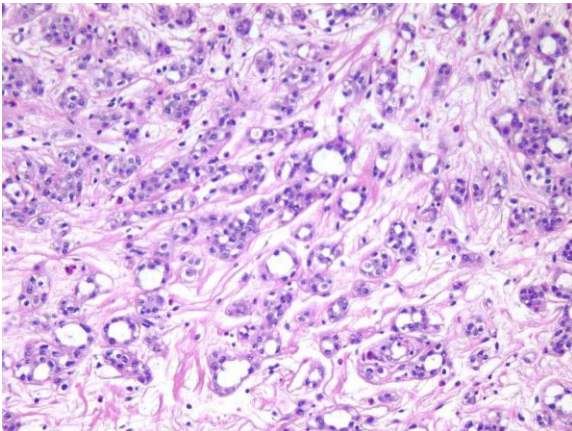


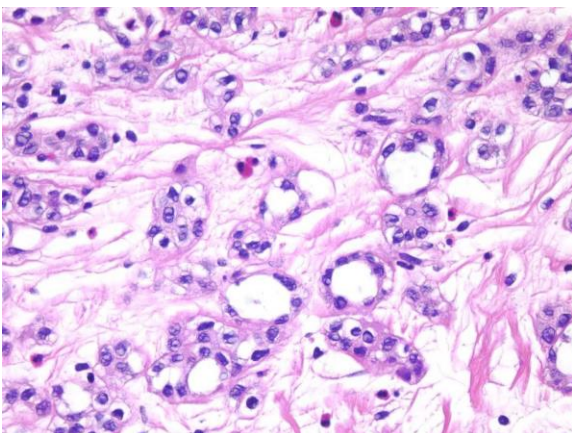
NESTED VARIANT OF U Ca.

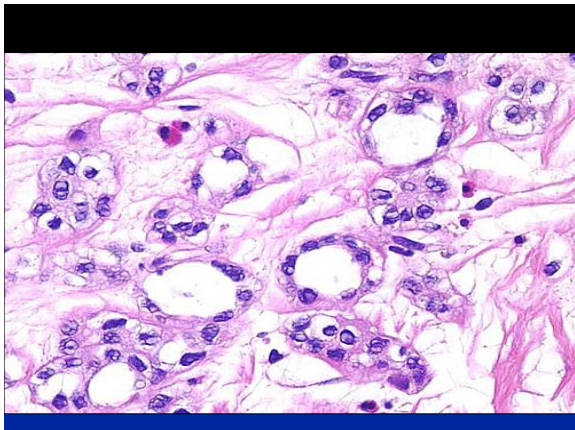
- **Prognostic significance**
 - Small number of cases, variable follow up
 - Aggressive clinical course in spite of low histologic grade
 - Distinct capability of progression with metastasis and death

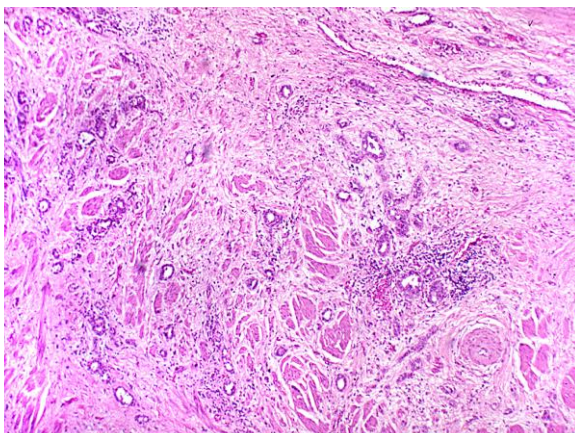
UROTHELIAL Ca. WITH SMALL TUBULES

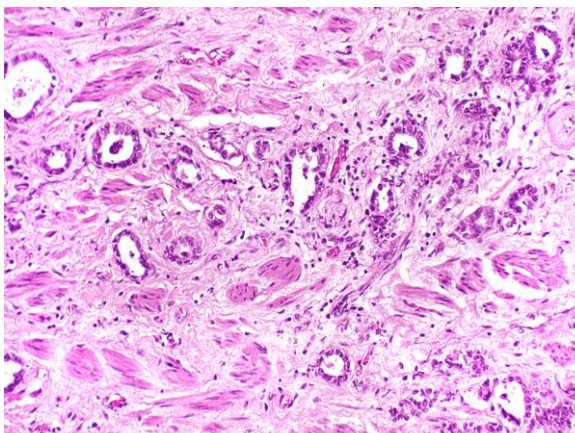
- Frequently admixed with nested variant
- **Differential diagnosis**
 - *nephrogenic adenoma*
 - *prostatic carcinoma*
- **Prognostic significance**
 - *unclear (stage of disease)*

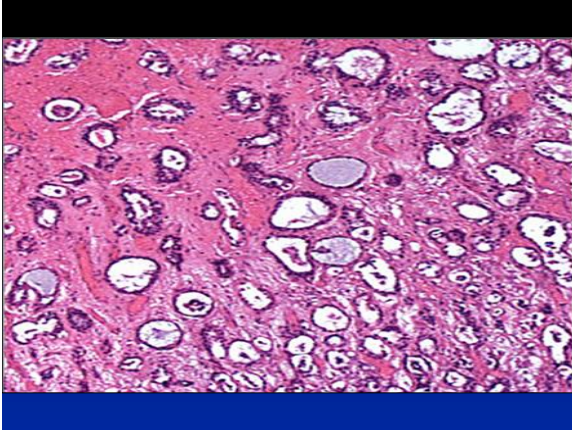


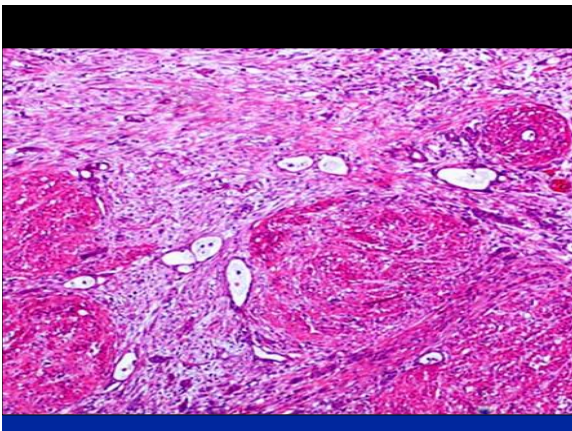


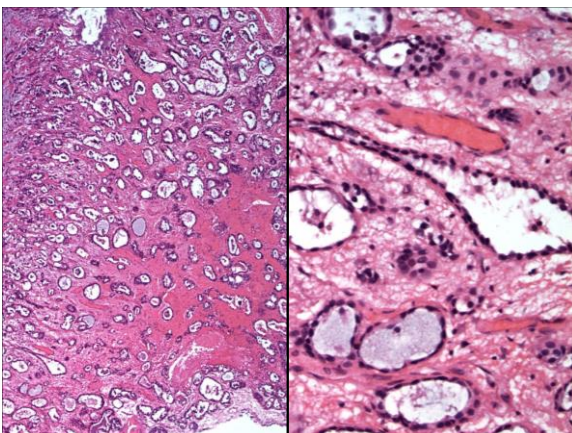


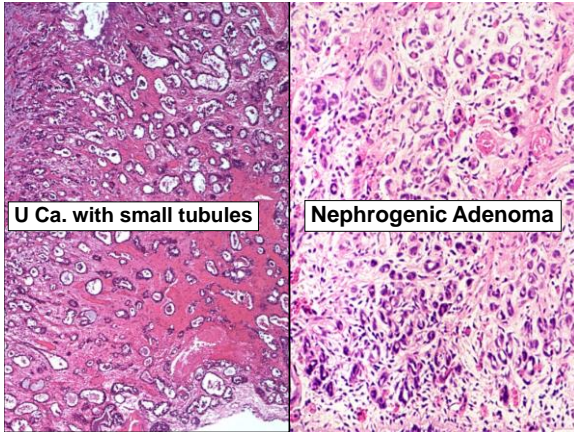


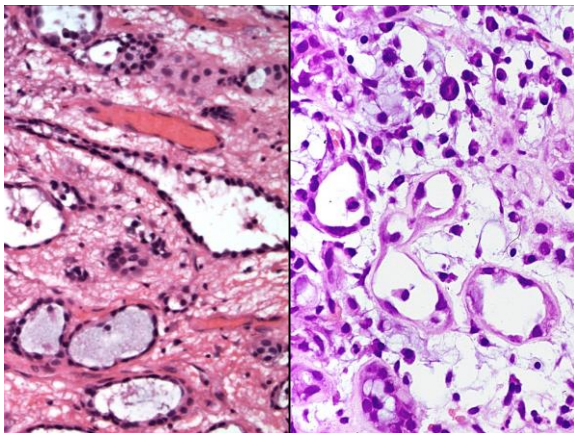










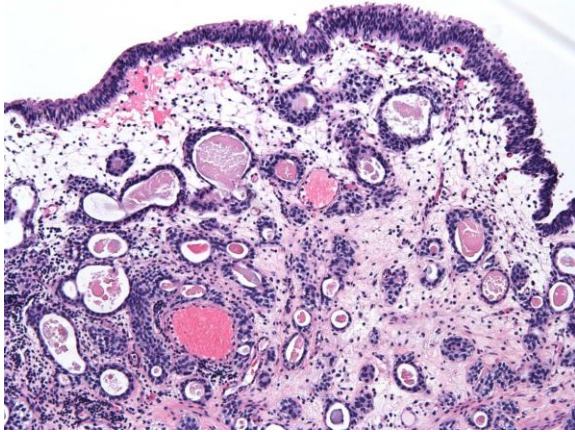


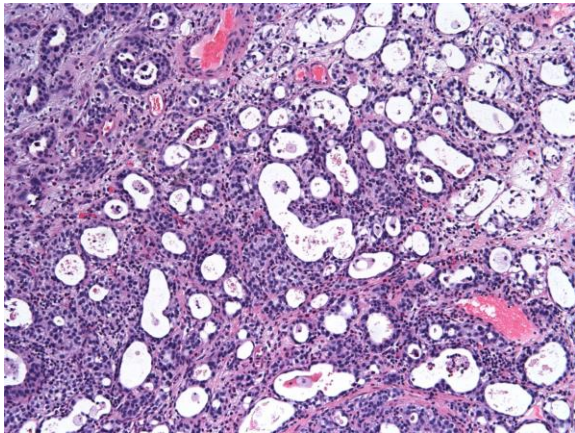
UROTHELIAL Ca. WITH MICROCYSTIC PATTERN

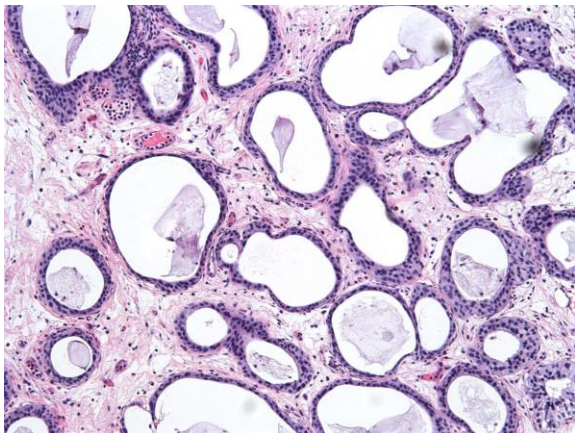
• Histologic features

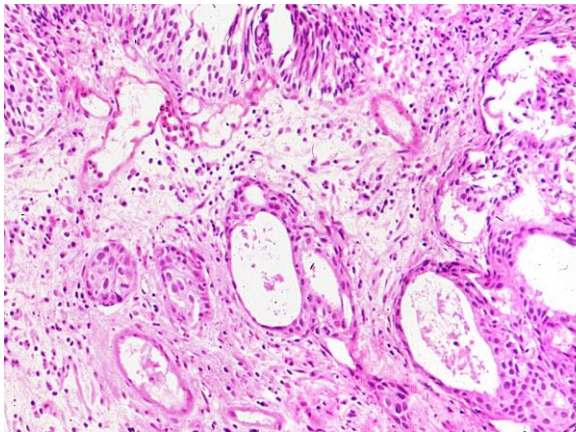
- Widespread cystic change within nests of U Ca. (urothelial lining) or U Ca. with glandular differentiation (columnar lining); or flattened lining
- Cysts oval to round, 1-2 mm, \pm secretions
- Cytologically bland by definition

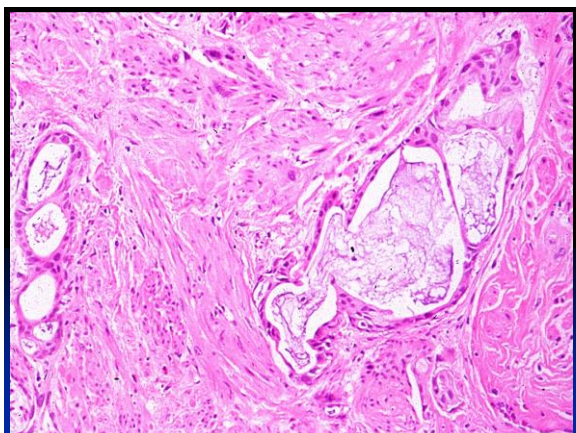
Cancer: marked variation in size
architectural complexity
haphazard growth
desmoplasia or myxoid reaction
muscularis propria invasion

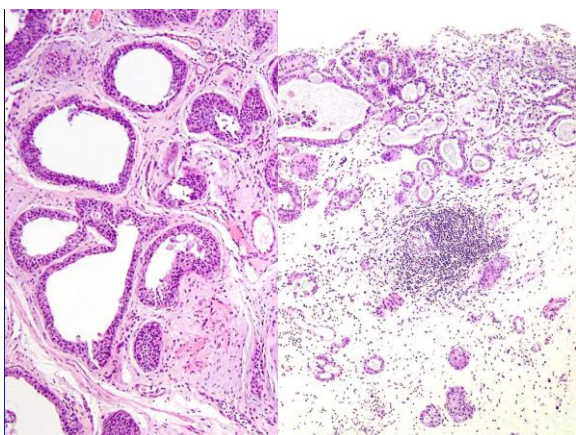


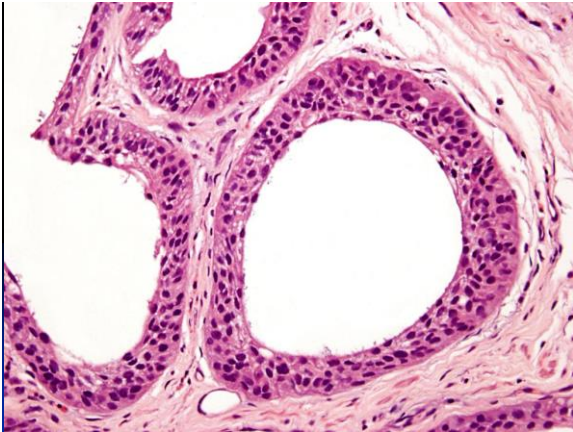






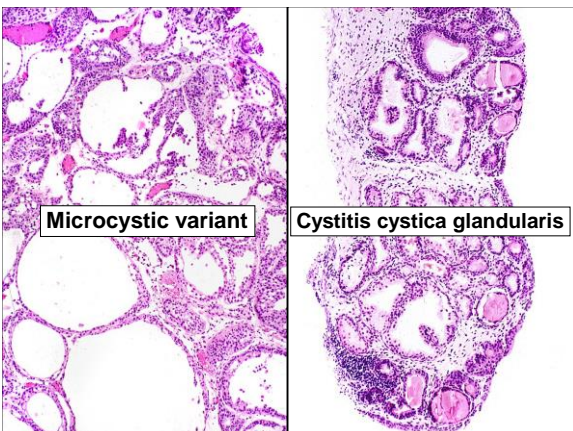




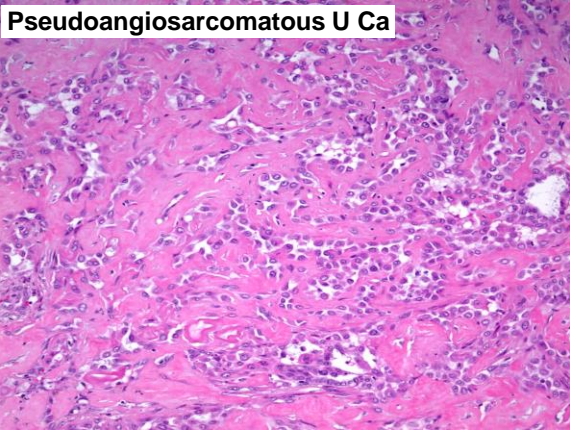


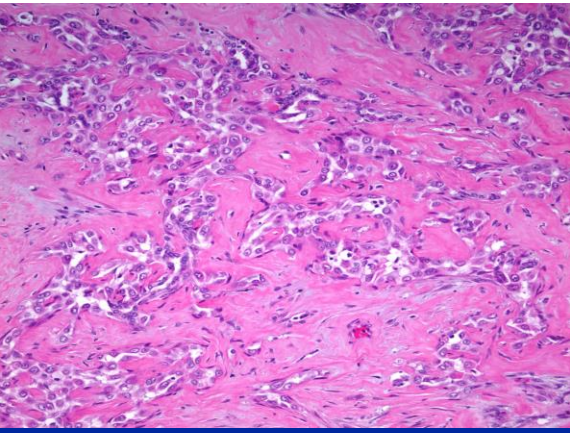
UROTHELIAL Ca. WITH MICROCYSTIC PATTERN

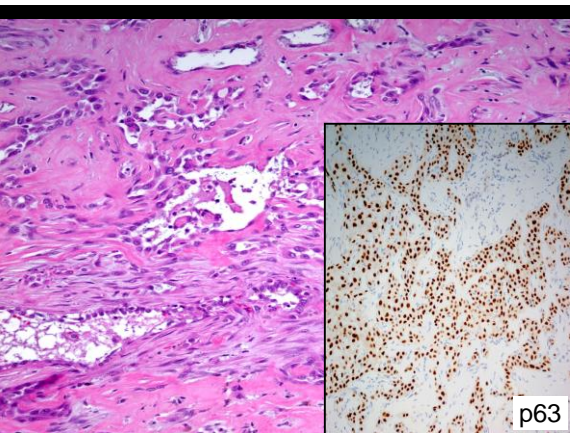
- Diagnostic Significance: Pitfall
- Differential diagnosis
 - *cystitis cystica / glandularis*
 - *adenocarcinoma*



Pseudoangiosarcomatous U Ca



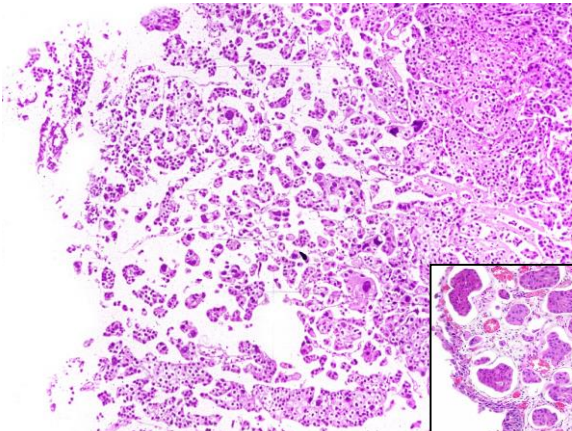


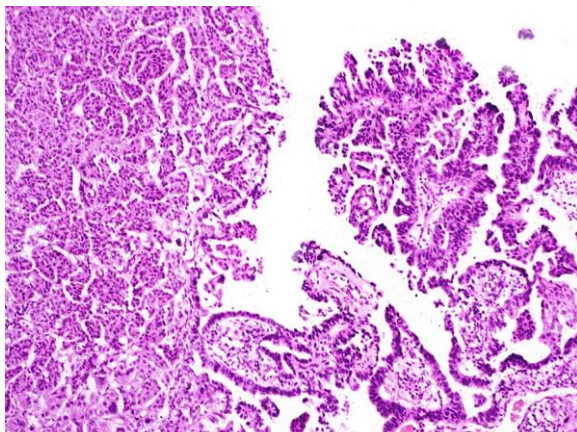


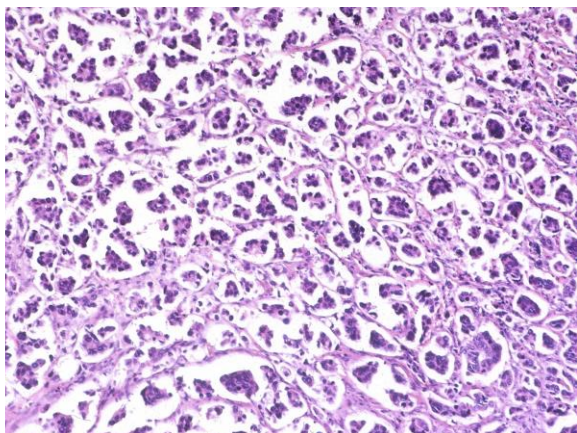


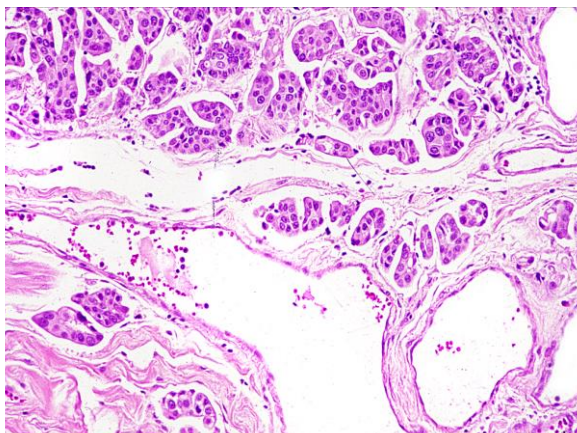
MICROPAPILLARY U Ca.

- **Histology:** Reminiscent of ovarian papillary serous tumors
- **Surface:** Slender, delicate, filiform processes, glomeruloid structures
- **Invasive:** Small tight nests/balls in lacunae mimic vascular invasion
- **Metastasis:** Micropapillary histology retained
- **Pattern may be focal, extensive or exclusive**









MICROPAPILLARY U Ca.

- **Prognostic significance**

- Most commonly high-stage with U Ca. frequent vascular invasion
- Metastasis frequently contain predominant micropapillary histology

- **Aggressive variant of U Ca.**

- **5- and 10- year survival: 51% and 24%** compared to 58% and 50% for invasive U Ca (> pT2,N0)

MICROPAPILLARY U Ca.

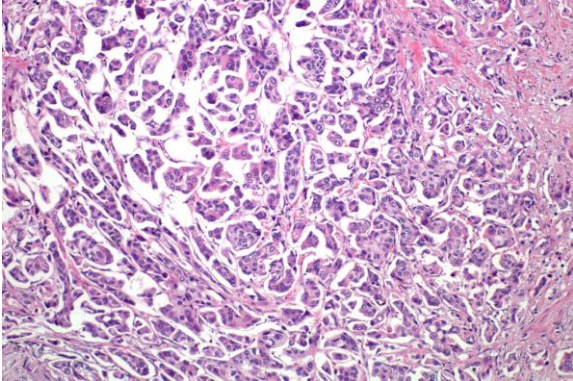
- **Dx & Prognostic significance**

- Patients with unknown primary - *consider MP U Ca. in males and in females with normal gyn. tract – along with lung, breast, pancreas & salivary gland Ca.*
- MP U Ca. in superficial biopsy without m. propria - *suggest rebiopsy*
- pTa/pT1- poor response to immunotherapy
- *? Early cystectomy for pTa/pT1 tumors*

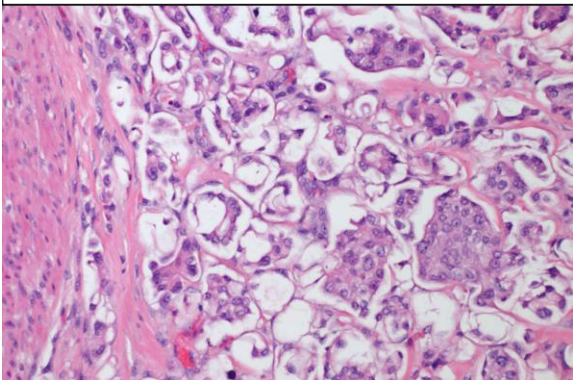
Whats new in Micropapillary UCa

- Distinctive molecular features: ERBB2 mutations and amplifications
- pT1 lesions: early surgery & poor response to intravesical therapy
- Refined criteria for increased diagnostic reproducibly

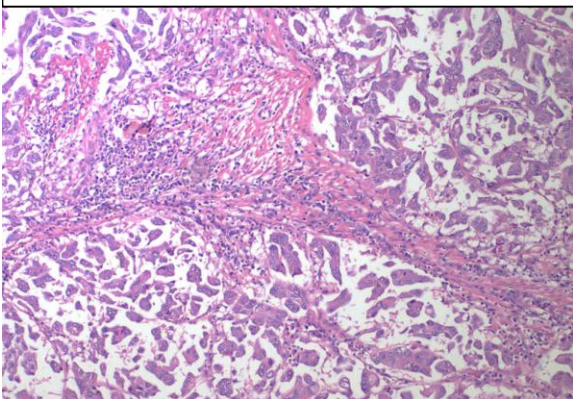
“Classic MP”: Multiple Nests in Same Lacunar Space



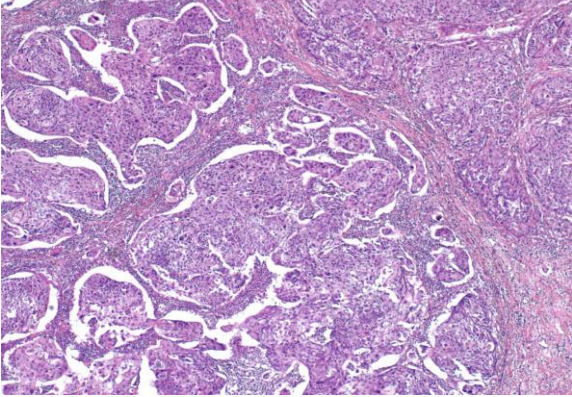
**“Classic MP”
Epithelial Ring Forms and Back-to-Back Lacunae**



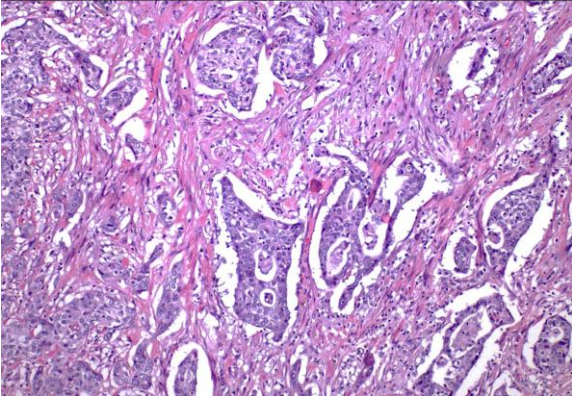
“Classic MP”



NOT Micropapillary



NOT Micropapillary

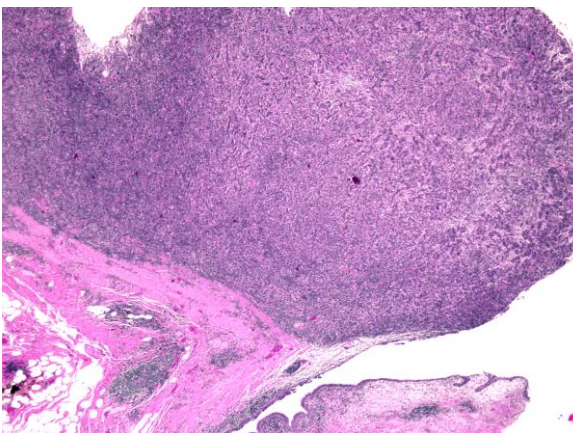
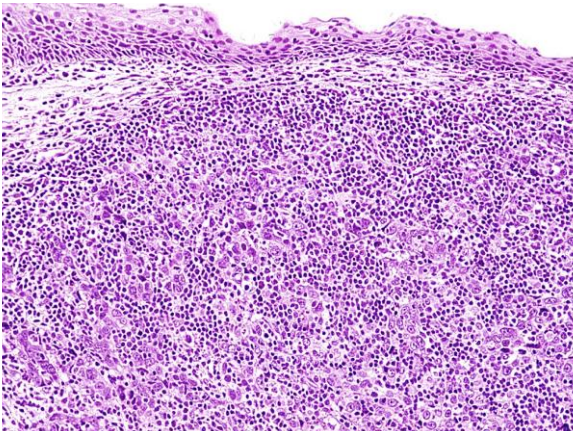


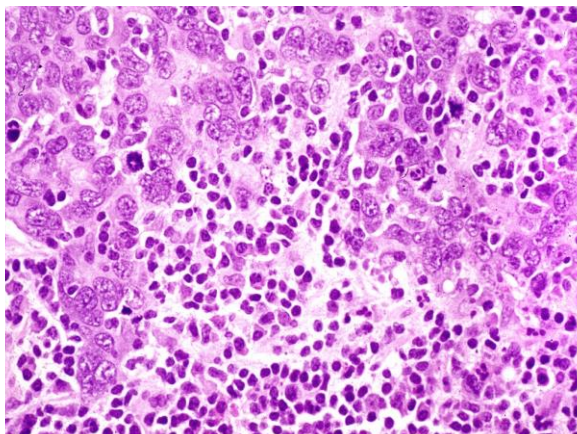
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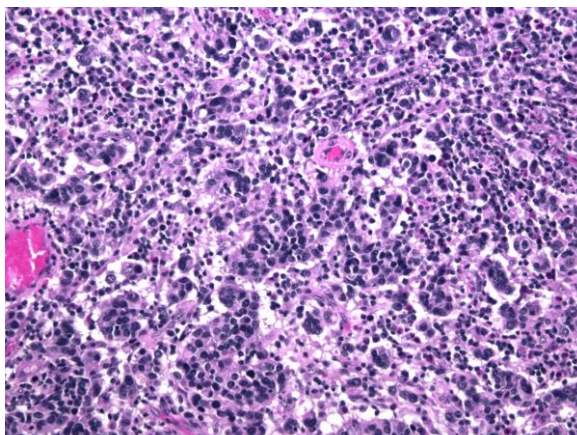
mamin5@uthsc.edu

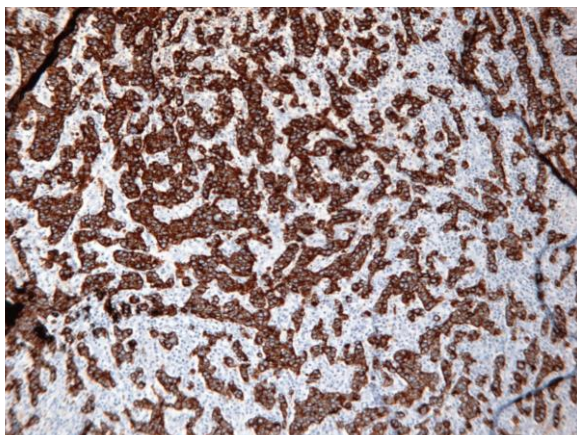
LYMPHOEPITHELIOMA-LIKE CARCINOMA OF THE BLADDER

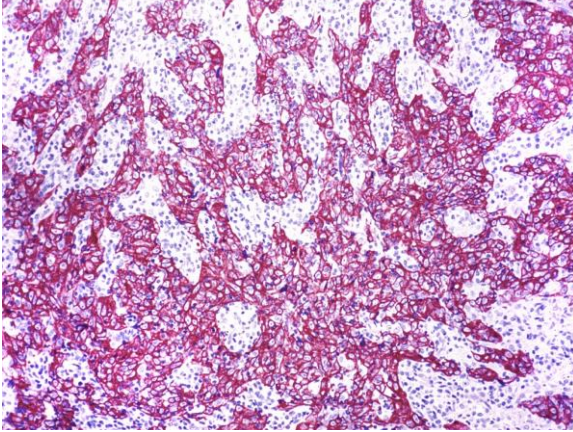
- Indistinguishable from nasopharyngeal counterpart
- Pure, predominant or focal
- Large cells arranged in syncytia, vesicular nuclei, prominent nucleoli
- Lymphoid infiltrate (predominantly T cell) - sine qua non
- Tendency for m. propria invasion (80% cases)
- No association with EBV





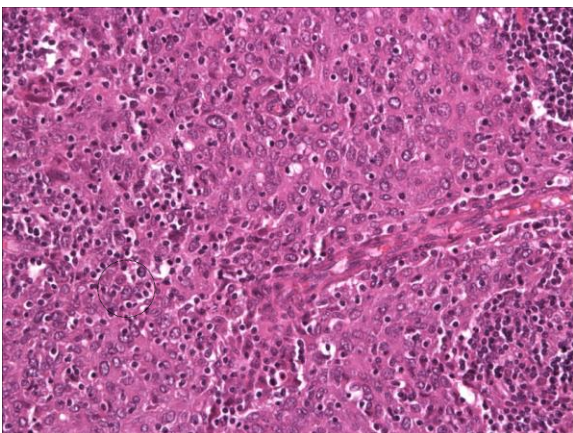


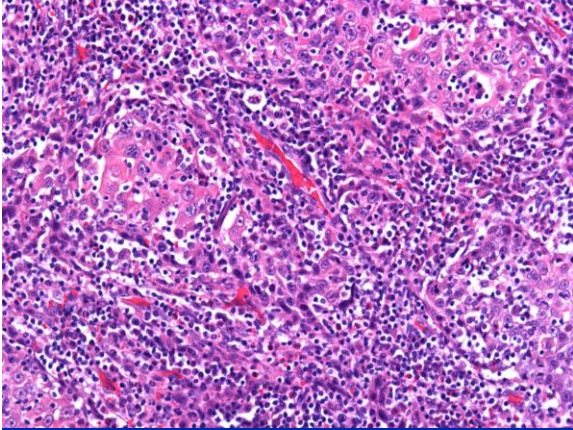




LYMPHOEPITHELIOMA-LIKE CARCINOMA OF THE BLADDER

- **Diagnostic significance**
 - Malignant lymphoma
 - U Ca. with prominent lymphoid infiltrate
 - Chronic cystitis (crushed/limited samples)





LYMPHOEPITHELIOMA-LIKE CARCINOMA OF THE BLADDER

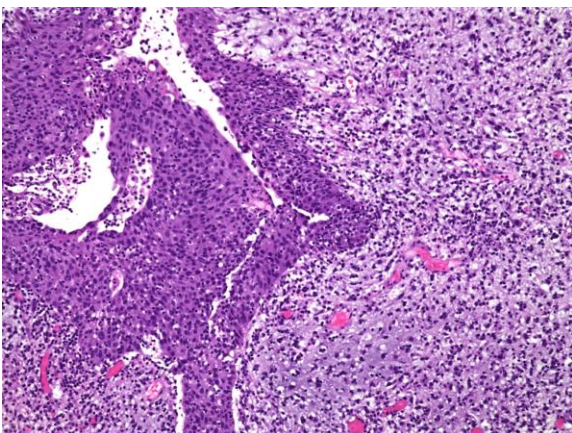
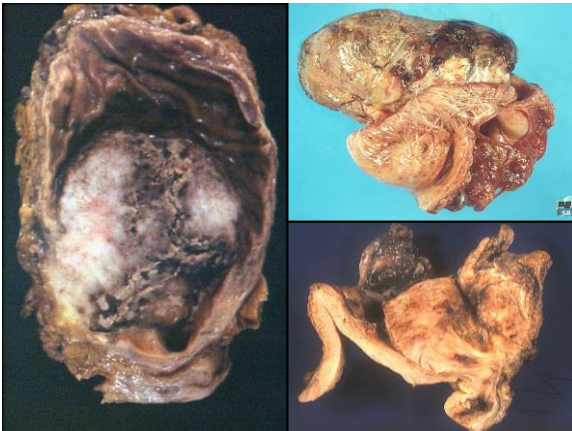
- **Prognostic significance**
 - Majority of tumors: high stage - pT2 or higher
 - Pure and predominant LELC: Better survival : ? host response - few studies
 - Focal LELC: like conventional U Ca. of similar stage

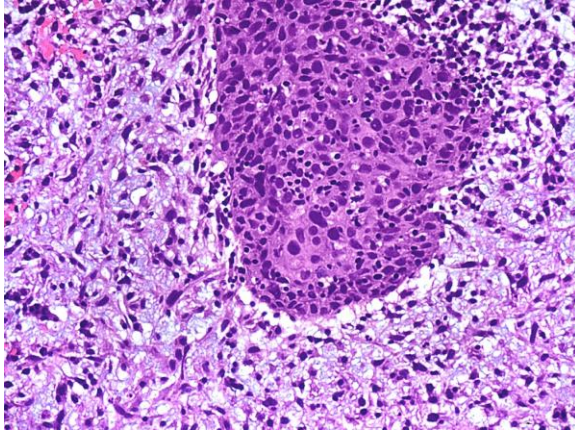
LYMPHOEPITHELIOMA-LIKE CARCINOMA OF THE BLADDER

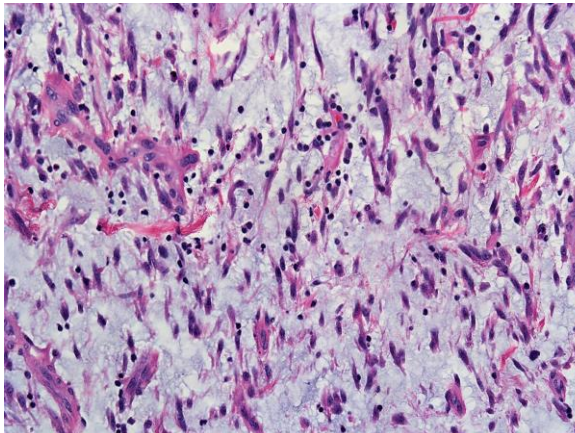
- **Therapeutic significance**
 - **Pure LELC:** Cisplatin-based chemotherapy : potential to salvage bladder function
 - *The diagnosis of pure LELC should be made after examination of entirely resected tumor in a TURBT*

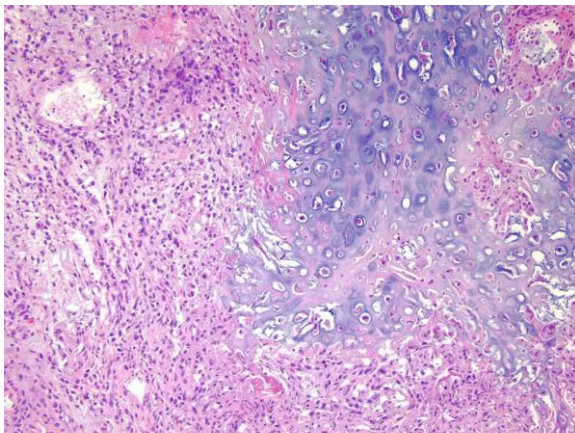
SARCOMATOID U Ca.

- **Biphasic histology**
 - Sarcomatoid component
 - High grade sarcoma, NOS
 - Heterologous differentiation: osteo, chondro, rhabdo, lipo & angiosarcoma
 - Poorly differentiated carcinoma
 - Urothelial carcinoma
 - Squamous, adeno- or small cell ca.
 - Mixed histology







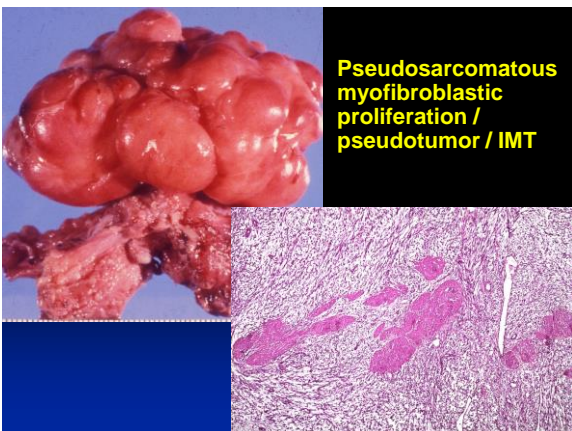


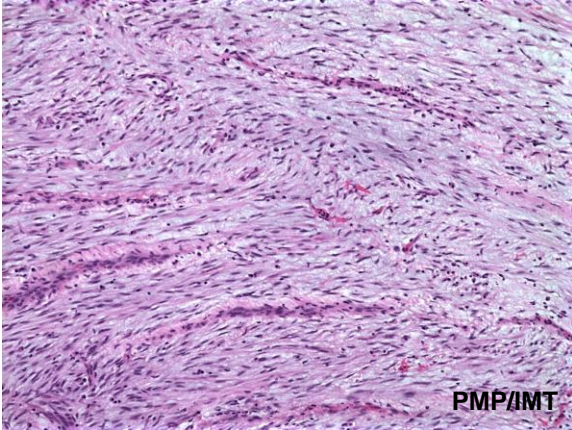
SARCOMATOID U Ca.

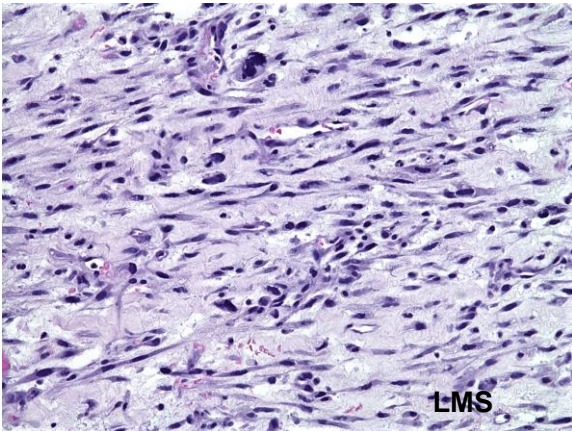
- **Prognostic significance**
 - Invariably presents at high stage
 - Crude 1- and 2-year survival 50% and 25%
 - No apparent difference in outcome if heterologous elements present
- **Therapeutic significance**
 - Different from carcinoma - many institutions

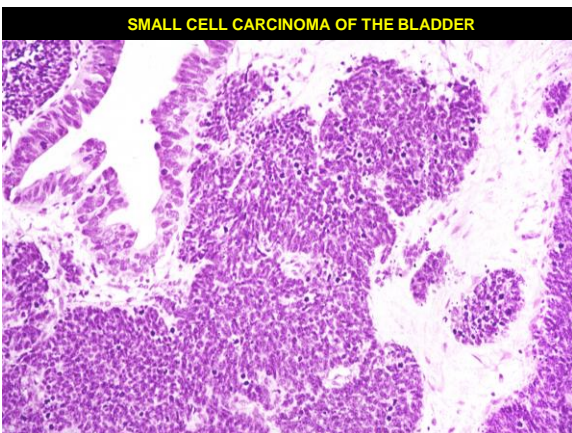
SARCOMATOID U Ca.

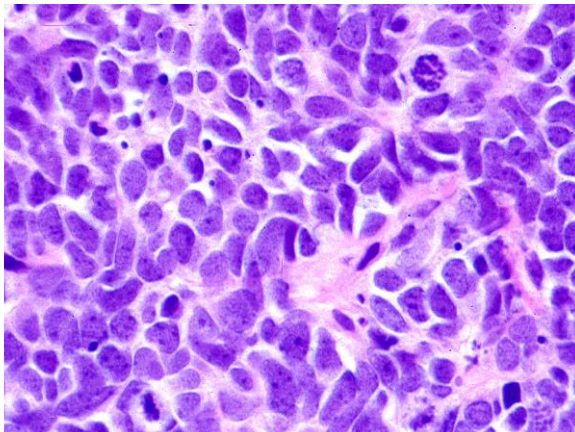
- **Differential diagnosis**
 - **Benign**
 - *Pseudosarcomatous myofibroblastic proliferation (post-operative spindle cell nodule & pseudotumor)*
 - **Carcinoma**
 - *UCa. with pseudosarcomatous stroma*
 - *UCa. with osseous/chondroid metaplasia*
 - **Sarcoma**
 - *Leiomyosarcoma and others*

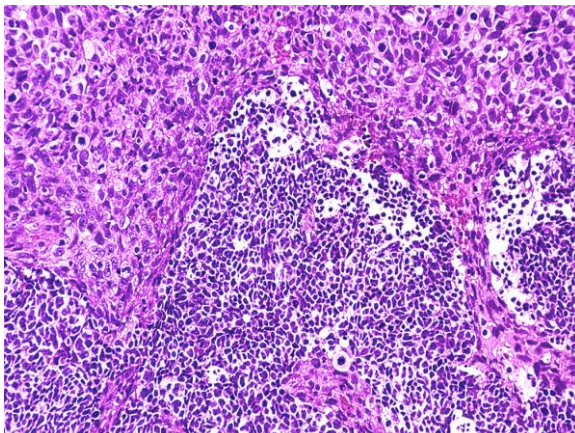












SMALL CELL CARCINOMA

• Differential diagnosis

- Inflammation (scant/crushed specimens)
- Malignant lymphoma
- High-grade (poorly differentiated) U Ca.
- Alveolar rhabdomyosarcoma (RMS)
- Metastasis
 - Lung
 - Prostate

SMALL CELL CARCINOMA

- **Prognostic significance**
 - Present as high-stage tumors (94%)
 - 25% present with metastasis, 67% develop them
 - Poor prognosis in pts without chemotherapy compared to U Ca. patients - mean survival 6-35 months
- **Therapeutic significance**
 - Pre-chemo era: 10% 2-year survival
 - Post-chemo era (cisplatin & etoposide): Longer survival, especially for low-stage tumors → 8-40% 5-year survival
 - Outcome depends on response to chemotherapy

SMALL CELL CARCINOMA


Therapeutic approach


- No formal studies

Chemotherapy



Surgery+/- radiation

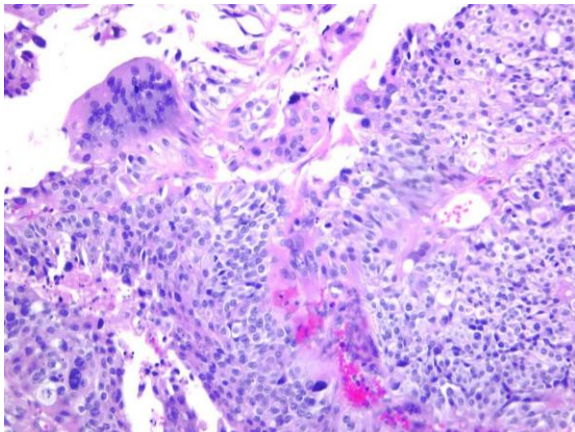
- 
- Small cell carcinoma component
 - Systemic control

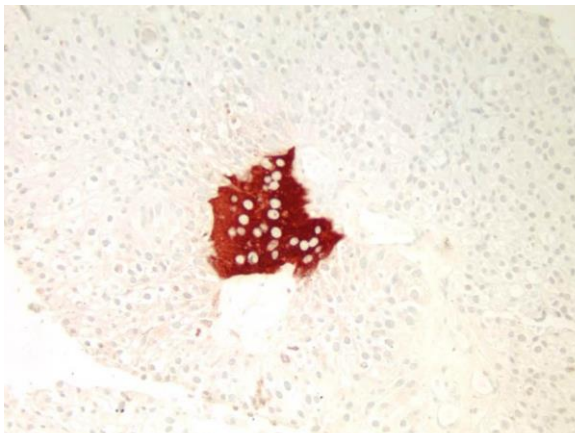
- 
- Sq/U Ca./glandular component
 - Aggressive local control

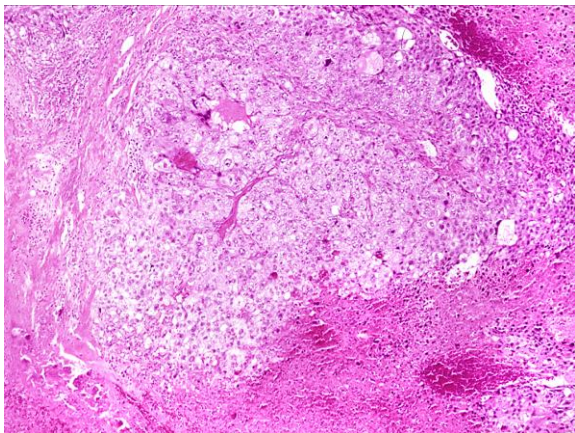
U Ca. WITH TROPHOBLASTIC DIFFERENTIATION

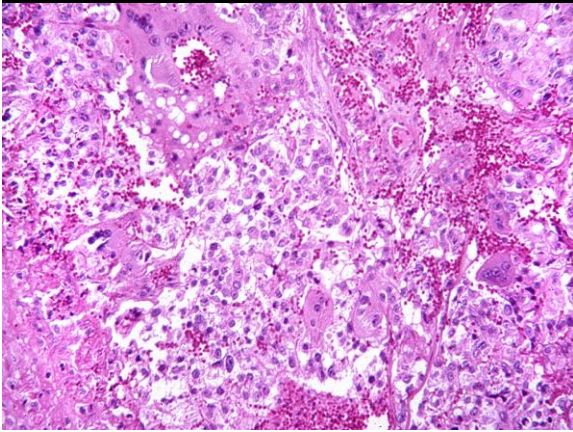
- High-grade U Ca. with HCG immunoreactivity
- High-grade U Ca. with syncytiotrophoblastic giant cells
- High-grade U Ca. with choriocarcinoma
- Pure choriocarcinoma

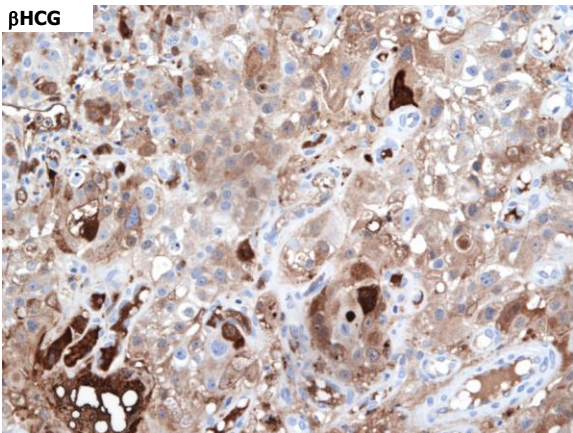
Metaplastic theory suggests a sequence











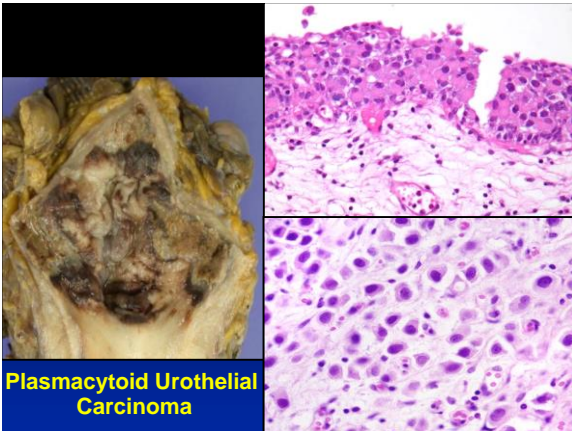
U Ca. WITH TROPHOBLASTIC DIFFERENTIATION

- **U Ca. with HCG positivity or syncytiotrophoblasts**
 - Poor prognosis (assoc. with high-grade U Ca.)
 - Resistance to radiotherapy
 - Serum levels correlate with response to chemotherapy
- **U Ca. with choriocarcinoma**
 - Rare, use strict criteria
 - Poor prognosis (all cases with 1 year follow-up - DOD)
 - Poor response to chemotherapy or radiotherapy

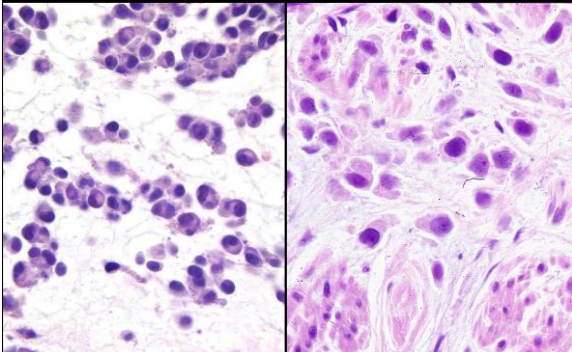
HISTOLOGIC VARIANTS OF U Ca.

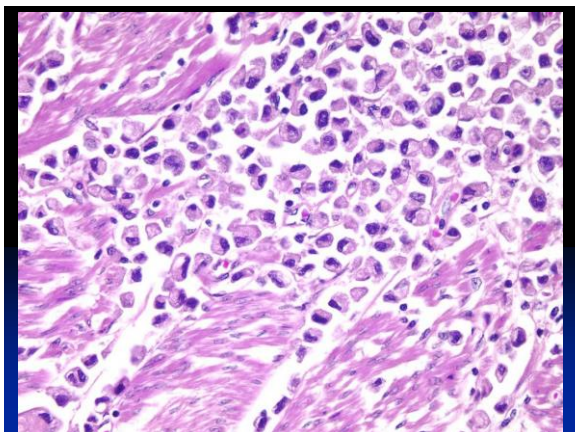
- Unusual cytoplasmic features

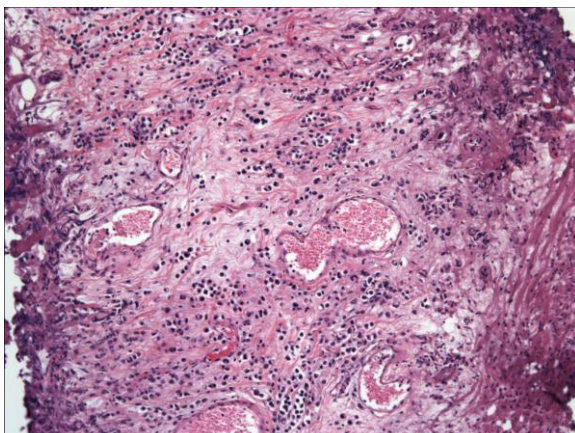
- Plasmacytoid
- Rhabdoid
- Clear cells
- Lipid-rich

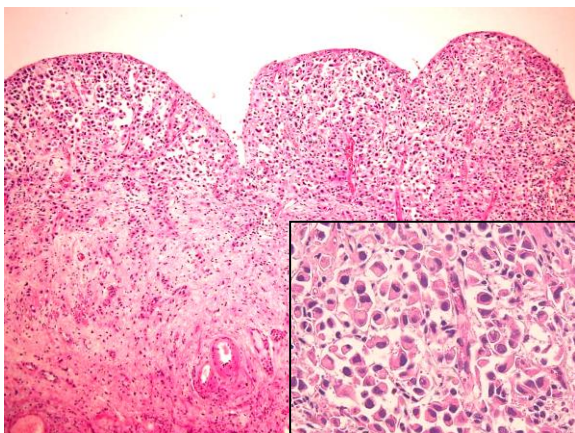


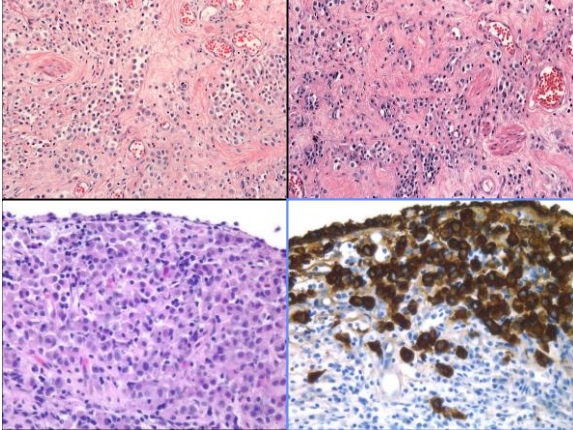
Plasmacytoid UCa now includes signet ring cell carcinoma without extracellular mucin





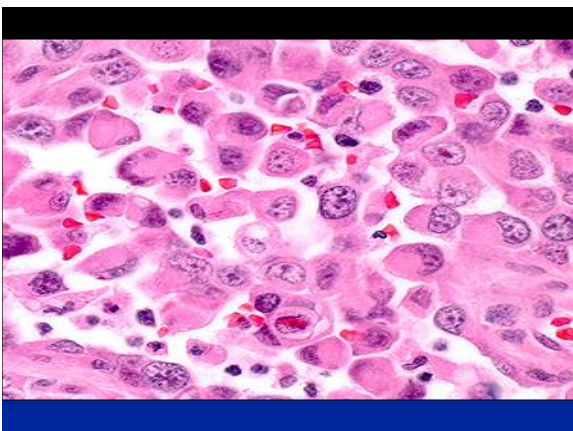


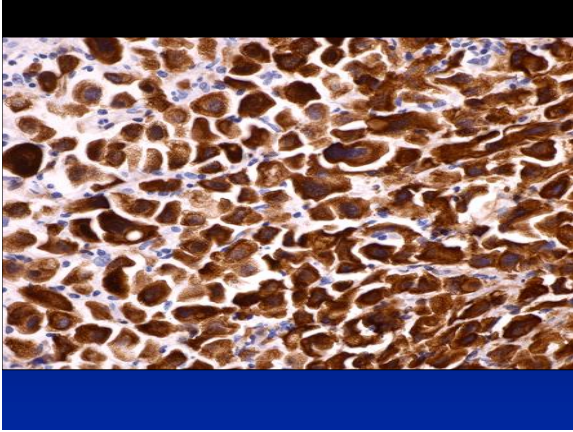


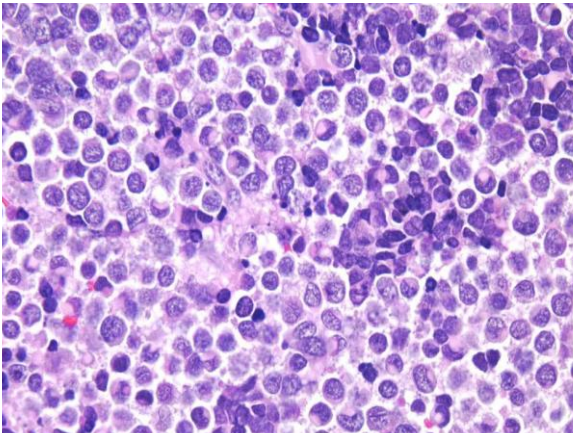


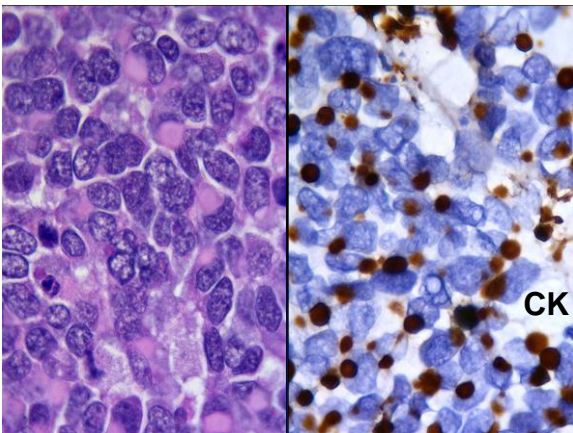
U Ca. WITH RHABDROID FEATURES

- Large discohesive cells with vesicular nuclei, +/- prominent nucleoli, +/- inclusions
- Poor prognosis
- **Differential diagnosis**
 - pure malignant rhabdoid tumor (INI 1+)
 - Other undifferentiated malignancies (e.g. melanoma)



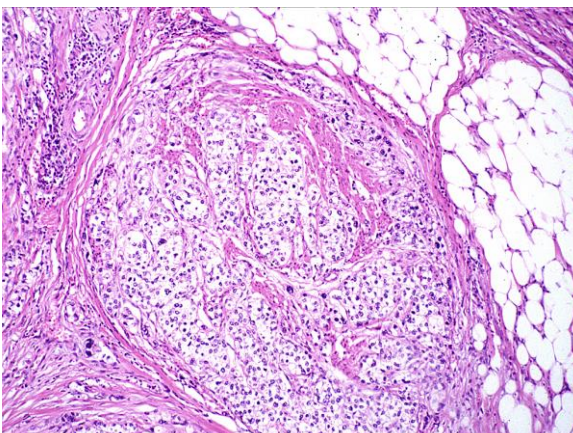
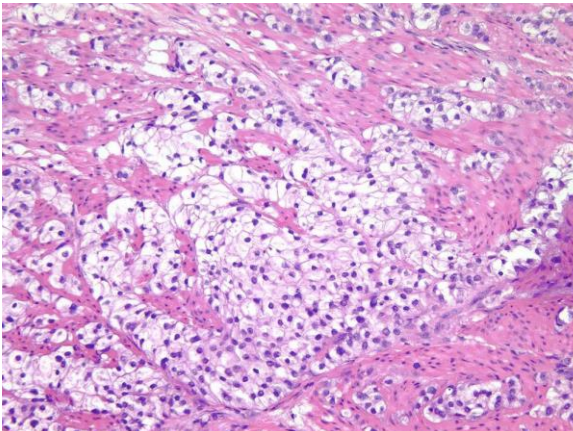


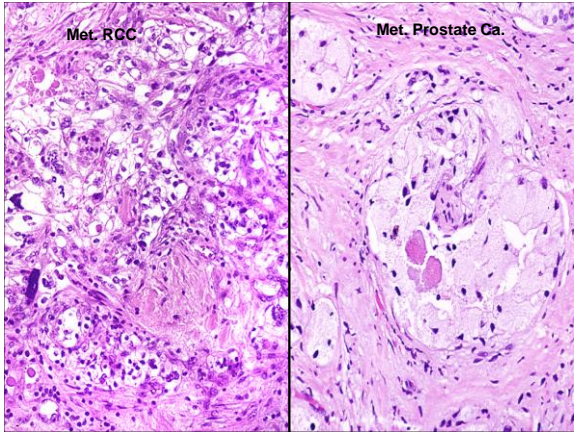


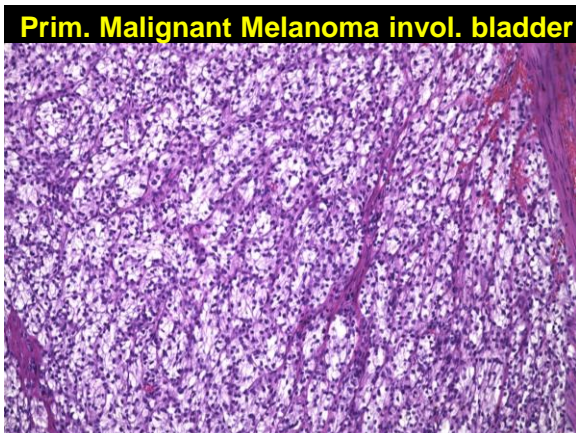


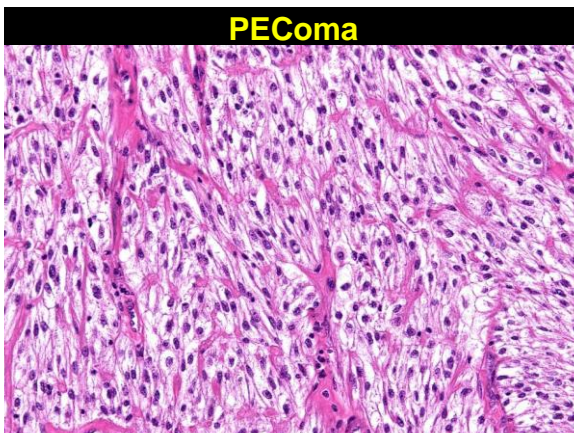
U Ca. WITH CLEAR CELLS

- U Ca. rich in glycogen
- **Differential diagnosis**
 - *Clear cell carcinoma of bladder/urethra*
 - *Metastatic renal cell carcinoma*
 - *Metastatic prostate cancer*
 - *Extension/metastasis from gynecologic primary*



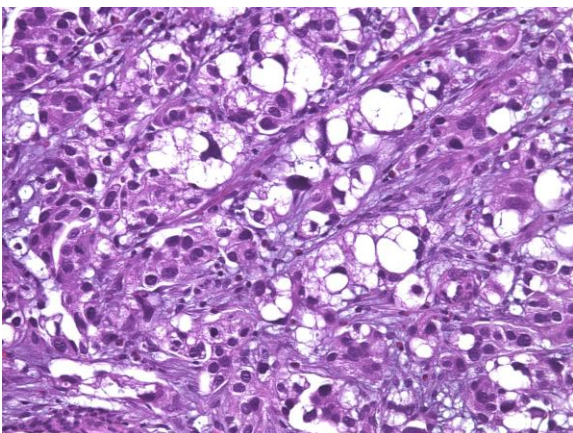
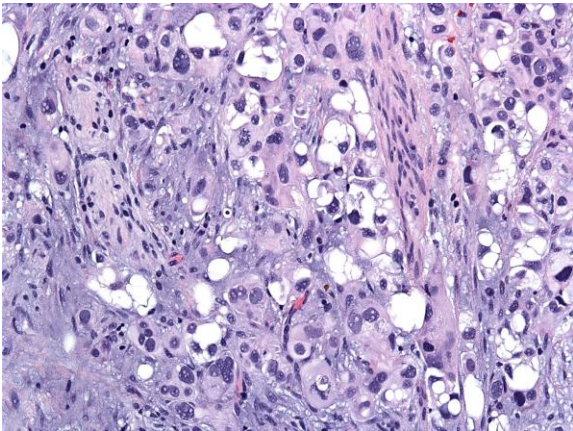


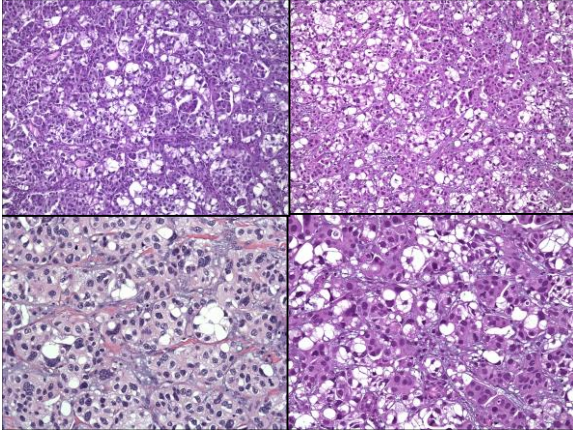




UROTHELIAL CARCINOMA WITH LIPID

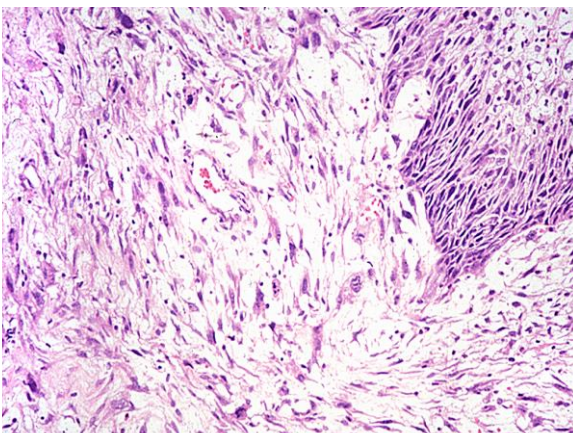
- Usually focal in invasive U Ca. : 10-50% of tumor
- **Differential Diagnosis**
 - *signet ring cell component*
 - *liposarcomatous heterologous component*
- No known clinical significance

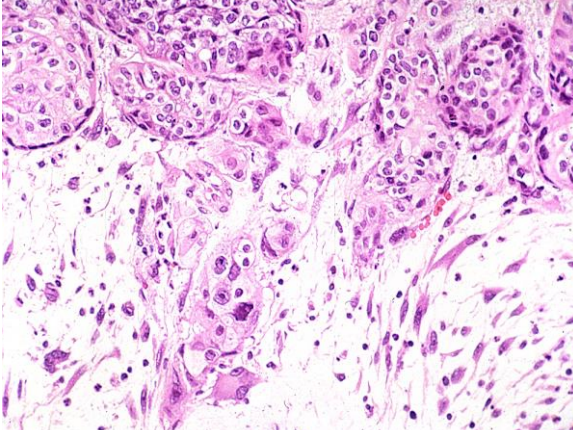


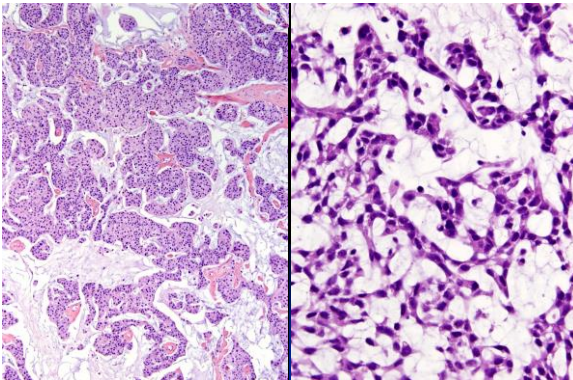


U Ca. WITH UNUSUAL STROMAL REACTIONS

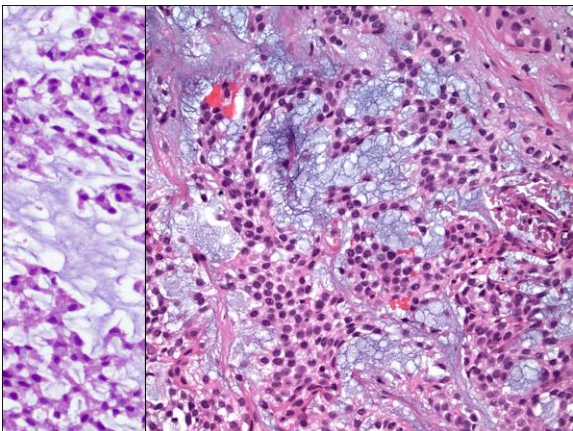
- Pseudosarcomatous stroma
- Myxoid stroma
- Chondroid/osseous metaplasia
- Osteoclast-like giant cells

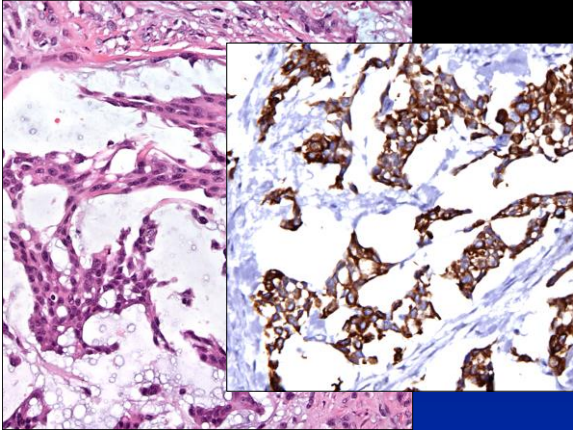






**UROTHELIAL CARCINOMA WITH MYXIOD STROMA :
"CHORDOID VARIANT"**



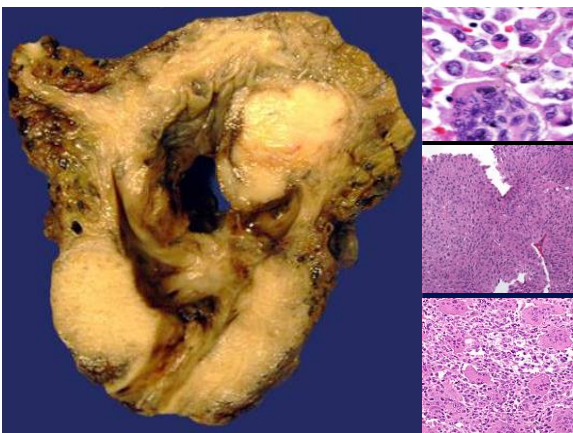


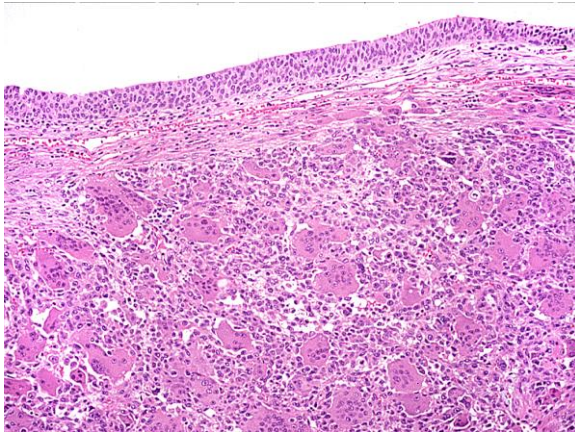
**OSTEOCLAST-RICH
UNDIFFERENTIATED CARCINOMA**

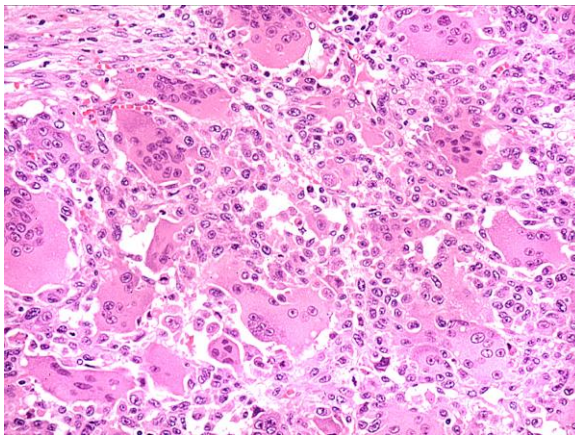
High stage tumors with variable admixtures of:

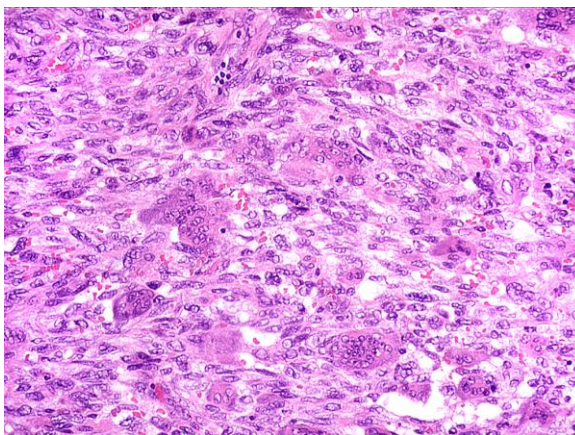
- Osteoclast - like giant cells (*often predominant*)
(CD68, CD51, CD54 +)
- Undifferentiated mononuclear cells
(frequently + for epithelial markers)
- Recognizable urothelial carcinoma
(CIS, papillary or invasive)
- May have blood filled spaces reminiscent of ABC

Most patients have metastasis or die of disease



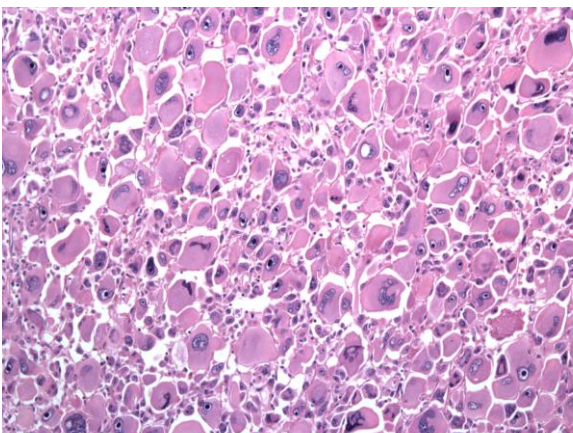
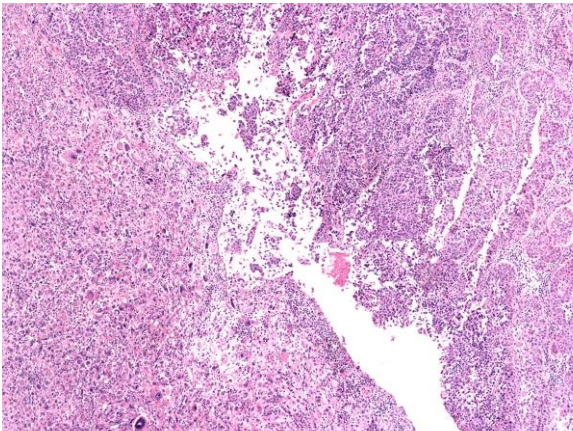


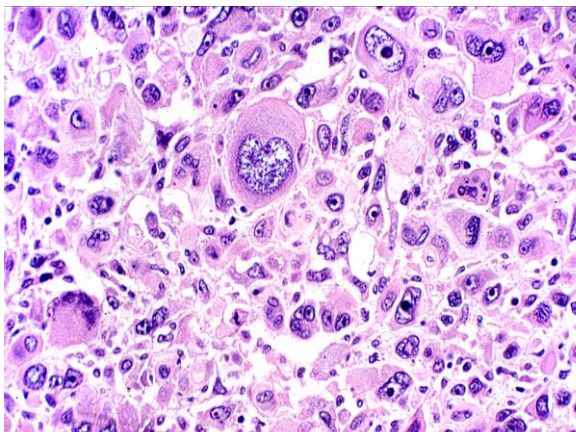




GIANT CELL CARCINOMA

- Large anaplastic, pleomorphic cells
 - Prognostic significance: poor outcome (few cases)





MORPHOLOGIC DIVERSITY OF U Ca

- U Ca. may show myriad patterns and divergent differentiation
- Wide range demonstrates the totipotentiality of the bladder mucosal lining
- Awareness of the histologic spectrum
 - Diagnostic
 - Prognostic
 - Therapeutic

RELEVANCE

Histologic Variants of Bladder Cancer

- It remains unclear what percentage of variant form impacts survival in most cases
- Hence the percentage of variant component required to make a diagnosis of a particular variant is not defined
- When mixed with conventional or other variants of U Ca, the relative percentages of the different histologies must be specified
 - e.g. "U Ca with micropapillary histology (40%), conventional U Ca histology (50%) and with squamous differentiation (10%)"

The treatment algorithm for based on variant histology

- Variant histology appears to inherently define “high risk” bladder cancer in both nonmuscle invasive & muscle invasive
- pT1 disease - consider early cystectomy for some
- pT2-4 - consider neo-adjuvant chemotherapy for some

Curr Opin Urol 2013;23:435-443



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