I. UROTHELIAL (TRANSITIONAL CELL) CARCINOMA

A. Usual or Conventional Type of Urothelial Carcinoma

Urothelial neoplasms of the urinary bladder may be subdivided into papillary (papillomas, low malignant potential and papillary carcinoma) and non-papillary (urothelial carcinoma in situ and invasive) categories. Papillary tumors are predominantly exophytic, with papillae containing well-defined fibrovascular cores. The lining urothelium may vary from one that is indistinguishable from normal (papilloma) to markedly anaplastic (high-grade urothelial carcinoma). The flat lesion of urothelial carcinoma in situ is characterized by extensive (often full thickness) replacement of the urothelium by cells demonstrating severe cytologic atypia. Invasive urothelial carcinoma may present as a polypoid, sessile, ulcerated or infiltrative lesion in which the neoplastic cells invade the bladder wall as nests, cords, trabeculae, small clusters or single cells that are usually separated by a desmoplastic stroma. The tumor sometimes grows in a more diffuse pattern, but even in these cases focal nests and clusters are generally present. Occasionally, carcinomas are associated with a pronounced chronic inflammatory cell infiltrate, which partially or substantially obscures the underlying tumor cells. The neoplastic cells in these typical or conventional patterns of invasive urothelial carcinoma are usually of moderate size and have modest amounts of pale to eosinophilic cytoplasm. In some tumors the cytoplasm is more abundant and may be clear or strikingly eosinophilic. The presence of clear cells should not lead to the diagnosis of the very rare clear cell adenocarcinoma, which has a very typical histology. Features indicative of the urothelial or transitional character of cells of urothelial carcinoma include the presence of longitudinal nuclear grooves that are often appreciable in low-grade tumors, but are more focally present in high-grade tumors. Lymphatic or vascular invasion is seen to varying degrees but is occasionally striking, as are bizarre hyperchromatic nuclei with marked anaplasia. Approximately 10% of urothelial carcinomas contain foci of glandular or squamous differentiation.
Glandular differentiation is usually in the form of small tubular or gland-like spaces in conventional urothelial carcinoma (urothelial carcinoma with gland-like lumina) or as a histology similar to enteric adenocarcinoma. Rarely, a coexistent signet ring cell or mucinous component may be present. In order to designate squamous differentiation, one must see clear-cut evidence of squamous production (intracellular keratin, intercellular bridges, or keratin pearls), and the degree of squamous differentiation, when present, parallels the grade of the urothelial carcinoma. In general, urothelial carcinomas have a relatively nondescript appearance, which when viewed in isolation cannot be differentiated from poorly differentiated carcinomas of other types. Therefore, the presence of squamous and/or glandular differentiation in a poorly differentiated neoplasm suggests the possibility of urothelial differentiation.

Listed below is a classification of carcinomas of the urinary bladder including urothelial carcinoma and its variants.

**Classification of Carcinomas of the Urinary Bladder Including Urothelial (Transitional Cell) Carcinoma and Its Variants**

I. **Urothelial (Transitional Cell) Neoplasia**
   A. Benign
      i. Transitional papilloma (WHO/ISUP, 1998; WHO, 1973, grade 0)
      ii. Inverted papilloma
   B. Papillary urothelial neoplasm of low malignant potential (WHO/ISUP, 1998; WHO, 1973, grade I)
   C. Malignant
      i. Papillary*  
         a. Typical (low grade or high grade, WHO/ISUP, 1998)
            1. Variant  
               (a) With squamous or glandular differentiation
            b. Micropapillary
      ii. Nonpapillary
         a. Carcinoma in situ
         b. Microinvasive carcinoma
         c. Frankly invasive carcinoma
            1. Variants containing or exhibiting
               (a) Deceptively benign features
                  • Nested pattern (resembling von Brunn’s nests)
                  • Small tubular pattern
                  • Microcystic pattern
                  • Inverted pattern
               (b) Squamous differentiation
               (c) Glandular differentiation
               (d) Micropapillary histology
(e) Sarcomatoid foci (“sarcomatoid carcinoma”)
(f) Urothelial carcinoma with unusual cytoplasmic features
   • Clear cell
   • Plasmacytoid
(g) Urothelial carcinoma with syncytiotrophoblasts
(h) Unusual stromal reactions
   • Pseudosarcomatous stroma
   • Stromal osseous or cartilaginous metaplasia
   • Osteoclast-type giant cells
   • With prominent lymphoid infiltrate

II. Squamous Cell Carcinoma
   A. Typical
   B. Variant
      i. Verrucous carcinoma
      ii. Basaloid squamous cell carcinoma
      iii. Sarcomatoid carcinoma

III. Adenocarcinoma
   A. Anatomic variants
      i. Bladder mucosa
      ii. Urachal
      iii. With exstrophy
      iv. From endometriosis
   B. Histologic variants
      i. Typical intestinal type
      ii. Mucinous (including colloid)
      iii. Signet ring cell
      iv. Clear cell
      v. Hepatoid
      vi. Mixture of above patterns – adenocarcinoma NOS

IV. Tumors of Mixed Cell Types

V. Undifferentiated Carcinoma
   i. Small cell carcinoma
   ii. Large cell neuroendocrine carcinoma
   iii. Lymphoepithelioma-like carcinoma
   iv. Giant cell carcinoma
   v. Not otherwise specified

VI. Metastatic Carcinoma

+ Modified from reference(5)
* Papillary tumors may be invasive or noninvasive, and when invasive may be microinvasive (invasive to a depth of 2 mm or less) or frankly invasive (like nonpapillary tumors)
↓ Refers to tumors that are undifferentiated by light microscopy
B. Variants of Urothelial Carcinoma

In recent years, with increasing experience with urothelial carcinomas, the spectrum of microscopic forms of urothelial carcinoma has been expanded to include several unusual histologic variants. The term “variant” is used to describe a distinctively different histomorphologic phenotype of a certain type of neoplasm. The recognition of histologic variants is important because: a) some types may be associated with a different clinical outcome, b) some may have a different therapeutic approach, or c) awareness of the unusual pattern may be critical in avoiding diagnostic misinterpretations. I recommend following two general rules when dealing with histologic variants: first, the “variant” histology should be documented in the pathology reports because metastatic tumors usually continue to exhibit the distinctive histologic pattern, and this knowledge of the variant histology facilitates association of the metastasis to the primary tumor; second, since the pattern of the neoplasm deviates from the conventional form, the possibility that this “unusual” morphology represents a metastasis should always be considered and ruled out.

1. Nested Variant of Urothelial Carcinoma

This variant has distinct patterns in the superficial and deep portions. In superficial biopsy samples and transurethral resectates, the superficial component appears as discrete nests, occasionally with tubules. The nests are tightly packed, often confluent and haphazardly arranged with little or no intervening stroma. Most nests have a relatively bland cytologic appearance, but at least some have more pleomorphic nuclei and large nucleoli. The architectural complexity, confluence and anastomosis between the nests are particularly helpful in distinguishing carcinoma from von Brunn’s nests or other benign conditions. In the deeper portion, the neoplasm usually shows greater cytologic atypia and an irregular infiltrative pattern. These tumors are frequently muscle-invasive and, in spite of their innocuous histology, are paradoxically associated with aggressive clinical outcome. Only 4 of 20 patients with follow-up have had no evidence of disease, and 7 patients died of disease. From a pathologist’s perspective, the nested variant should appropriately be recognized as a malignant process, particularly in superficial biopsies.

2. Urothelial Carcinoma with Small Tubules

Some urothelial carcinomas may have a prominent component of small- to medium-sized, round to elongated tubules that may be misdiagnosed as nephrogenic adenoma or cystitis glandularis. Furthermore, the tubules are lined by urothelial cells in contrast to the cuboidal, columnar or occasionally flattened cells that line the tubules of nephrogenic adenoma. The tumors may be widely invasive and usually have a deceptively bland histology. The biologic significance of this pattern is uncertain, but some of these cases occur in conjunction with the nested pattern and may result in an aggressive outcome.
3. **Microcystic Urothelial Carcinoma**

This is yet another deceptively benign form of urothelial carcinoma and is exemplified by the formation of numerous microcysts, which may lead to the misdiagnosis of cystitis cystica. The pattern is characterized by prominent widespread cystic change within nests of urothelial carcinoma or urothelial carcinoma with glandular differentiation. The cysts are round to oval, 1-2 mm, and contain secretions that may be targetoid. The cyst lining is urothelial; larger cysts may possess a flattened epithelium or a denuded lining. Cytologic blandness is present by definition, and the most critical feature in distinguishing this carcinoma type from benign conditions is the variation, often dramatic, in size and shape of the epithelial formations and the relatively haphazard infiltrative growth into the wall of the urinary bladder. There is no apparent or striking biologic significance associated with this pattern, except that it represents a potentially serious diagnostic pitfall, particularly in limited samples.

4. **Inverted Pattern of Urothelial Carcinoma**

This form of urothelial carcinoma is associated with two diagnostic concerns: 1) distinction from inverted papilloma and 2) difficulty in assessing invasion. Distinction from the inverted papilloma requires attention to architectural and cytologic features of the lesion. Urothelial carcinomas with inverted growth usually have thicker columns, with irregularity in width of the columns and/or transition of cords and columns into more solid areas. The characteristic orderly maturation, spindling, and peripheral palisading seen in inverted papilloma are generally absent or inconspicuous in urothelial carcinomas with inverted growth. Unequivocal stromal invasion into the lamina propria or muscularis propria rules out the diagnosis of inverted papilloma. Furthermore, cytologic atypia is an important feature for the diagnosis of carcinoma; and thus, carcinomas with inverted growth, like their exophytic counterparts, may be classified as low grade or high grade. Although the endophytic growth into the lamina propria caused by the inverted pattern may cause concern for the presence of invasion, similar to conventional urothelial carcinoma, unequivocal stromal invasion must be present for a neoplasm to be considered invasive. To diagnose stromal invasion, I recommend that unquestionable presence of irregularly shaped nests or single cells be required, along with a desmoplastic and/or inflammatory response. If a stromal response is absent, marked irregularity of the contours of the nests in question, architectural complexity, and presence of single cell invasion is helpful. Recognition of architectural abnormality, even subtle forms, is important, particularly in the deceptively bland patterns because they are most often cytologically banal. Another clue to recognize invasion is the presence of tumor cells within retraction spaces, which mimic vascular invasion. Early or limited invasion very frequently shows retraction artifact and, in this instance, this feature should not be overcalled as vascular invasion.
5. **Micropapillary Variant of Urothelial Carcinoma**

This histologic variant of urothelial carcinoma has a micropapillary architecture that is reminiscent of the papillary configuration seen in ovarian papillary serous tumors. This rare histologic variant comprises 0.6-1% of urothelial carcinomas and shows a definite male predominance (male to female ratio 5:1) which is higher than in conventional urothelial carcinoma (3:1). More than 95% of these tumors are muscle invasive at the time of presentation. Histologically, the micropapillary component (MPC) of these tumors may be encountered in the a) non-invasive component, b) invasive component, and c) in the metastasis. This pattern may be focal, extensive (>90%) or exclusive. Urothelial carcinoma in situ is demonstrable in greater than 50% of the cases and concurrent glandular differentiation is known to occur. Five histologic features of the micropapillary component are noteworthy: (i) The MPC has two distinct patterns; on the surface it forms slender, delicate filiform processes rarely with a fibrovascular core. When cut in cross-sections, these papillae appear as glomeruloid bodies. In the invasive component and in all metastatic sites, the tumor cells are arranged in small tight nests or balls. (ii) Psammoma bodies, a feature of ovarian papillary serous neoplasia, are exquisitely rare in the MPC. (iii) The tumor cells in the invasive and metastatic components are aggregated in lacunae which mimic vascular invasion. This feature is intriguing and extremely characteristic of the invasive MPC. The spaces may be lined focally by flattened spindled cells or may be devoid of any lining. In most instances, there is no host response to the tumor cells that merely seem to reside in hollow spaces at various random intervals within the tumor. This pattern of lacunae containing neoplastic cells is also seen in the metastatic sites. Awareness that lacunae of micropapillary urothelial carcinoma may mimic vascular invasion is important so as not to over-diagnose the presence of vascular invasion, which is considered to be an ominous sign in invasive urothelial carcinoma regardless of the stage of disease. (iv) The MPC always demonstrates a high nuclear grade (high grade by WHO/ISUP classification), although some areas within a neoplasm may parallel low-grade urothelial carcinoma. (v) Finally, most reported cases with MPC show at least focal unequivocal vascular invasion.

There are several important reasons for recognizing micropapillary variant of urothelial carcinoma: (i) these tumors are high grade and high stage and are always associated with vascular invasion; (ii) the MPC has a higher DNA index than conventional urothelial carcinoma (limited cases examined) and, because metastatic sites of tumors with MPC are predominantly composed of MPC, it is likely that this unique configuration of urothelial carcinoma connotes a more aggressive clone of neoplastic cells; (iii) the presence of micropapillary histology in metastatic sites forces us to consider the possibility of urothelial carcinoma, especially if the micropapillary configuration is encountered in the peritoneum, abdominal lymph nodes or mesentery of a male patient with an unknown primary, or in a female with normal appearing
ovaries; and (iv) the high association of MPC with muscle-invasive disease should alert the pathologists to its possibility. If the biopsy is superficial and lacks muscularis propria, there should be a suggestion for a rebiopsy.

6. **Lymphoepithelioma-Like Carcinoma**

Tumors with this histology are so termed because of their striking morphologic resemblance to the undifferentiated nasopharyngeal carcinoma or lymphoepithelioma. The neoplastic cells are large and arranged in syncytia, with vesicular nuclei, prominent nucleoli and numerous mitoses. The sine qua non for this histologic pattern of urothelial carcinoma is the presence of a prominent lymphoid infiltrate, although an admixture of other inflammatory cells including plasma cells and eosinophils is not uncommon. Relatively few series and cases of this subtype of urothelial carcinoma have been reported, but the aggregate data suggests that when these tumors occur in a pure form they respond to chemotherapy, providing the potential to salvage bladder function. When mixed with conventional urothelial carcinoma, their outcome is similar to that for conventional urothelial carcinoma and depends on the grade and stage of the associated conventional urothelial carcinoma. The differential diagnosis includes malignant lymphoma, and in limited and crushed biopsies with marked chronic cystitis. High-grade urothelial carcinoma of the usual type should not be termed lymphoepithelioma-like merely because of a brisk inflammatory infiltrate. The syncytial arrangement and typical cytology are essential for the diagnosis of lymphoepithelioma-like carcinoma, which as mentioned in its purest form may be treated differently than the usual or conventional invasive carcinoma.

7. **Sarcomatoid Carcinoma (Carcinosarcoma)**

Although rare, sarcomatoid carcinoma is more common than primary sarcoma of the urinary bladder. The sarcomatoid areas may merge with foci of urothelial carcinoma, squamous cell carcinoma, adenocarcinoma or small cell carcinoma. Heterologous differentiation may be present but has no prognostic significance. All sarcomatoid carcinomas present at a high stage and have a poor prognosis. These tumors do not demonstrate a difference in survival when compared stage-for-stage with urothelial carcinoma. In the absence of an obvious, invasive urothelial carcinoma or other epithelial differentiation, the history of prior urothelial carcinoma, the coexistence of urothelial carcinoma in situ, or strong cytokeratin immunoreactivity is helpful in making the diagnosis of sarcomatoid carcinoma over a primary sarcoma. The adjuvant therapy for sarcomatoid carcinoma tends to vary from institution to institution and may be different from therapy for a primary sarcoma. The differential diagnosis also includes benign or locally aggressive conditions, including post-operative spindle cell nodules and pseudotumors (inflammatory myofibroblastic tumors) of the bladder.
8. **Small Cell Carcinoma**
Morphologically, this tumor is identical to small cell carcinoma of the lung, but may be admixed with urothelial carcinoma, squamous cell carcinoma or adenocarcinoma. Both lymphoepithelioma-like carcinoma and small cell carcinoma may be mistaken for malignant lymphoma or with a poorly differentiated urothelial carcinoma with scant cytoplasm. Metastasis from lung or extension from adjacent viscera must be ruled out. Small cell carcinoma of the urinary bladder has been associated with paraneoplastic syndromes, high stage at presentation, and frequent disseminated metastases. An important reason for its recognition is the apparent response to newer chemotherapy protocols which, in combination with surgical resection, have shown encouraging results, and reports of long-term survivors are available. Chromogranin, synaptophysin and neuron-specific enolase immunohistochemistry may be helpful, but in most instances careful light microscopic evaluation and insistence on observing the typical and characteristic cytomorphology of small cell carcinoma is essential before this diagnosis is rendered.

9. **Urothelial Carcinoma with Trophoblastic Differentiation**
More than 20 cases of urothelial carcinoma with areas of trophoblastic differentiation have been reported. Although some of the early reports have described tumors that apparently were composed solely of tissue resembling choriocarcinoma, all tumors reported in the last 30 years have been composed of a mixture of urothelial carcinoma with trophoblastic elements. Thus, trophoblastic differentiation is today recognized as a variant of urothelial carcinoma rather than a neoplasm of germ cell origin. Immunohistochemistry often can detect human chorionic gonadotropin in typical urothelial carcinoma and some variants, including carcinoma in situ. This is more common in high-grade carcinoma, approaching 33% of cases. The presence of syncytiotrophoblasts has been associated with a poor prognosis; in most cases, less than 12 months have elapsed between the presentation and death. For this reason, the presence of elements with trophoblastic morphology and some estimate as to their quantity should be reported. In summary, trophoblastic differentiation in urothelial carcinoma spans a spectrum from immunohistochemical expression for human chorionic gonadotropin in an otherwise typical invasive urothelial carcinoma to the presence of syncytiotrophoblasts, to the presence of focal areas resembling choriocarcinoma, to the rare predominant or pure choriocarcinoma.

10. **Plasmacytoid Urothelial Carcinoma**
In the past few years, urothelial carcinomas with a striking resemblance to plasma cells have been described. Tumors are poorly differentiated, usually having a coexisting typical high-grade urothelial carcinoma or a sarcomatoid carcinoma histology. Immunohistochemical reactions for cytokeratin are confirmatory for epithelial differentiation versus that of a lymphoma.
11. Urothelial Carcinoma with Unusual Stromal Reactions

a. Pseudosarcomatous Stroma
Urothelial carcinomas may have a pseudosarcomatous stromal response in the primary or metastatic neoplasm. In these cases, the stroma contains atypical mesenchymal cells that are similar to those seen in giant cell cystitis. The chief reason for their awareness is that they should not be misinterpreted as the biphasic component of spindle cell or sarcomatoid carcinoma. The superficially very atypical appearing spindle cells often have abundant eosinophilic cytoplasm and pleomorphic hyperchromatic nuclei that have a degenerate appearance. The spindle cell component lacks mitotic activity, an expansile growth, and there is a lack of transition between the spindle cells and the carcinoma cells.

b. Osseous or Cartilaginous Metaplasia
The stroma of urothelial carcinomas or their metastases may rarely undergo osseous or cartilaginous metaplasia. This feature should not be mistaken for heterologous differentiation in a sarcomatoid carcinoma (carcinosarcoma).

c. Osteoclast-Type Giant Cells
Giant cells resembling osteoclasts occasionally are present in the stroma of bladder carcinoma. Rare cases of tumors with predominant osteoclast-type giant cell histology have been reported as osteoclastomas of the urinary bladder. Most experts believe that the giant cells are an unusual component of the stroma of the carcinoma rather than a separate neoplasm.

12. Giant Cell Carcinoma
Undifferentiated carcinoma of the bladder occasionally may be composed predominantly or purely of poorly differentiated large, cohesive pleomorphic and anaplastic cells with abundant eosinophilic or amphophilic cytoplasm. The tumor cells often contain multiple nucleoli and are similar to giant cell carcinomas seen in the lung and in other parts of the body. The high degree of nuclear anaplasia helps differentiate giant cell carcinoma from the osteoclast-type giant cells that may be seen in urothelial carcinoma.

II. SQUAMOUS CELL CARCINOMA
Typical squamous cell carcinoma accounts for less than 5% of bladder carcinoma, and such a designation requires that the bladder tumor be almost purely squamous in its histology. The gross appearance of squamous cell carcinoma varies from sessile and ulcerative to polypoid or polypoid to nodular. They are usually very large and deeply invasive. Invasion into the muscle or beyond is present in more than 90% of the patients. The microscopic appearance of these tumors is similar to that of squamous cell carcinomas seen elsewhere. The majority are moderate or well
differentiated and are often associated with abundant keratin production.

**Squamous Cell Carcinoma, Verrucous Type**

Only one series of verrucous carcinomas of the bladder has been reported. The 19 tumors in that report were encountered in Egypt, where squamous cell carcinoma of the bladder is common. The tumors were more common in males and cystoscopically and grossly were large, papillary or polypoid white tumors. Microscopic examination shows large, hyperkeratotic papillae that typically have bulbous, deep margins and a pushing border with the underlying tissue, where a variable amount of inflammatory infiltrate may be evident. The tumors typically show minimal cytologic atypia. The differential diagnosis is with condyloma acuminatum.

### III. ADENOCARCINOMA

The frequency of adenocarcinoma of the urinary bladder has varied from 0.5-2% of all primary carcinomas of the bladder. Urachal carcinoma is a distinct anatomic variant of adenocarcinoma of the bladder. Adenocarcinomas of the urinary bladder may have several histologic patterns including enteric, signet ring cell, mucinous, clear cell and hepatoid histology. Enteric carcinomas resemble colonic or prostatic duct adenocarcinomas with irregular interanastomosing or cribriform glands that have elongated to cigar-shaped nuclei with pseudostratification. The differential diagnosis of enteric-type adenocarcinoma includes metastatic colonic carcinoma, or direct extension from rectum, and extension from ductal carcinoma of the prostate. Clear cell adenocarcinomas of the urinary bladder are distinctly rare, more common in women, and a subset of these are associated with Müllерianosis (endometriosis, endosalpingiosis and/or endocervicosis). Microscopic examination shows an admixture of tubular glands, cysts, papillae and diffuse sheets of cells lined by or composed of cells that vary from those with abundant clear glycogen-rich cytoplasm to flattened and hobnail cells. Infrequently the tumor is composed predominantly of sheets of cells with more eosinophilic cytoplasm. A predilection for these tumors to be associated with urinary bladder diverticula is reported.

Adenocarcinoma of the urachus is more common in men than in women and typically occurs in the dome of the urinary bladder. Symptoms are often similar to those of urothelial carcinoma, but a suprapubic mass is palpable in a few patients. Mucous strands in urine, present in approximately 25% of cases, may suggest the diagnosis. Grossly and cystoscopically, the tumors are soft and gelatinous. Histologically, the tumors show extensive invasion of the muscularis propria and may have extension upward toward the umbilicus in the space of Retzius. High grade and high stage (invasion beyond the wall of the bladder or metastasis) are the principal determinants of poor prognosis. Enteric, mucinous or colloid histology, in variable combinations, is most commonly present. Although originally it was contended that urachal tumors had a better prognosis than non-urachal adenocarcinoma, the aggregate data suggests that the prognosis is not different stage for stage of cancer. The chief reason for suggesting urachal origin (criteria include tumor in dome of bladder, absence of metastasis, absence of cystitis
glandularis with intestinal metaplasia and adenocarcinoma histology) is that the therapy may consist of partial cystectomy with resection of urachal tract and the umbilicus.

IV. SECONDARY TUMORS OF THE BLADDER
The bladder may be involved by tumors from adjacent sites such as the prostate, seminal vesicles, lower intestinal tract and the female genital tract. Tumors may involve the bladder by direct extension or metastasis. The diagnostic problems posed for the pathologist in cases of secondary involvement vary according to the morphology of the primary neoplasm; e.g., female genital tract tumors or lower gastrointestinal tumors with squamous cell carcinoma histology may mimic or may be impossible to distinguish from a primary bladder tumor. Fortunately, in the vast majority of cases, clinical features aid in the diagnosis. Uncommon metastatic tumors to the bladder which enter the differential diagnosis of different types and variants of bladder carcinoma include malignant melanoma (with plasmacytoid variant), metastatic renal cell carcinoma (with urothelial carcinoma with clear cell change and clear cell adenocarcinoma) and metastatic small cell carcinoma. A not so uncommon differential diagnostic dilemma of a poorly differentiated carcinoma in transurethral resections of the bladder/prostate is between high-grade invasive urothelial carcinoma and a poorly differentiated prostatic adenocarcinoma. The presence of squamous and/or glandular differentiation, the presence of urothelial carcinoma in situ, and the high degree of nuclear anaplasia favor the diagnosis of urothelial carcinoma. Prostate carcinomas that are poorly differentiated may have a more diffuse growth, with only focal evidence of glandular differentiation. In these instances, the tumor cells are usually more homogeneous with very prominent nucleoli. A clinical history and assistance with immunohistochemical stains (PSA and PSAP) is important.

V. SUMMARY OF HISTOLOGIC VARIANTS OF UROTHELIAL CARCINOMA
Urothelial lesions have a pronounced ability for divergent differentiation. It is important that surgical pathologists be aware of this potential for multidirectional differentiation, as it may have diagnostic, therapeutic or prognostic implications. Outlined below are the histologic criteria and the clinical significance of these patterns.
<table>
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<tr>
<th>VARIANT</th>
<th>HISTOLOGIC CRITERIA</th>
<th>DIFFERENTIAL DIAGNOSIS</th>
<th>CLINICAL SIGNIFICANCE</th>
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</table>
| Small cell carcinoma          | • identical to small cell carcinoma of lung, including scant cytoplasm, nuclear molding, Azzopardi phenomenon and absence of prominent nucleoli  
• mixed pattern of urothelial carcinoma, squamous or adenocarcinoma (23-75%)  
• combination of cytokeratin, NSE, chromogranin, and synaptophysin immunostains may be helpful | • metastatic small cell carcinoma from lung, prostate, etc.  
• high-grade urothelial carcinoma with scant cytoplasm  
• lymphoma | • high stage at presentation  
• association with paraneoplastic syndromes  
• frequent disseminated metastasis  
• response to newer chemotherapy protocols |
| Lymphoepithelioma-like carcinoma | • undifferentiated malignant tumor indistinguishable from nasopharyngeal lymphoepithelioma  
• pattern may be pure, predominant or focal  
• large cells in syncytia, vesicular nuclei, prominent nucleoli, numerous mitoses  
• prominent lymphoid infiltrate (sine qua non) – lymphocytes, plasma cells, histiocytes, eosinophils  
• tendency to deep muscle invasion | • malignant lymphoma  
• chronic cystitis  
• urothelial cancer with prominent lymphoid stroma | • limited data  
• pure tumors may respond to chemotherapy alone – possible salvage of bladder function |
| Giant cell carcinoma          | • similar to giant cell carcinoma of the lung  
• pure or predominant component of giant cells with large pleomorphic, loosely cohesive cells | • urothelial carcinoma with syncytiotrophoblastic differentiation  
• urothelial carcinoma with osteoclast-like giant cells | • poor prognosis |
| Urothelial carcinoma with trophoblastic differentiation | a) Conventional urothelial carcinoma with positive immunostaining for β-HCG  
• morphologically garden variety urothelial carcinoma  
• no morphologic evidence of trophoblastic differentiation  
• positive immunostaining for β-HCG  
• urothelial carcinoma with syncytiotrophoblastic giant cells  
• typical pattern of invasive urothelial carcinoma, usually high grade, with associated syncytiotrophoblastic giant cells  
• urothelial carcinoma with coexistent choriocarcinoma  
• urothelial carcinoma with characteristic biphasic histology of choriocarcinoma | • pure choriocarcinoma of the urinary bladder  
• giant cell bladder carcinoma | a) significance unclear  
• resistance to radiation  
• some series indicate worse outcome  
• urine and serum HCG may be used to monitor patients for disease response and recurrence  
• poor prognosis, high morbidity |
| Micropapillary variant        | • pure, predominant or focal pattern  
• usually accompanied by conventional urothelial carcinoma  
• non-invasive: slender, delicate filiform processes often with fibrovascular core  
• invasive: nests and tight aggregates of cells residing within lacunae  
• high-grade nuclear features | • adenocarcinoma of the bladder | • high stage, high grade with frequent vascular invasion  
• metastasis frequently composed only of micropapillary histology |
<table>
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<tr>
<th>VARIANT</th>
<th>HISTOLOGIC CRITERIA</th>
<th>DIFFERENTIAL DIAGNOSIS</th>
<th>CLINICAL SIGNIFICANCE</th>
</tr>
</thead>
</table>
| Urothelial carcinoma with squamous differentiation | • presence of squamous differentiation, i.e., intercellular bridges, keratin pearls and intracytoplasmic keratin  
• conventional urothelial carcinoma or urothelial carcinoma in situ must be present (usually high grade)  
• no well-established cut-off value required for assigning this designation | pure squamous carcinoma                                    | unfavorable prognosis-?, because of association with high-grade urothelial carcinoma  
• limited series show poor response to chemotherapy and radiation |
| Urothelial carcinoma with glandular differentiation | • presence of unequivocal glandular spaces or  
• presence of multifocal mucin production  
• no well-established cut-off value required for assigning this designation | pure adenocarcinoma                                         | uncertain  
• ? poor response to chemotherapy (only one study)                                                   |
| Nested variant                  | • superficial portion – discrete nests, occasionally with tubules; nests may be closely packed with interanastomosis between nests by cords  
• deeper portion – greater cytologic atypia, irregular infiltrative pattern, muscle invasion | • von Brunn’s nests  
• paraganglioma                                                 | aggressive clinical course with frequent metastasis  
• potential diagnostic pitfall in limited samples                                                         |
| Tubular variant                 | • frequently coexists with nested variant, glandular differentiation may be present  
• tubules lined by transitional/urothelial cells  
• cytologic atypia or invasion is always present | • cystitis cystica  
• cystitis cystica glandularis  
• nephrogenic adenoma  
• adenocarcinoma                                               | unknown, similar to nested variant when concomitant nested component is present                           |
| Urothelial carcinoma with microcystic pattern | • prominent widespread cystic change within nests of urothelial carcinoma or urothelial carcinoma with glandular differentiation  
• cysts are oval to round, 1-2mm, and contain secretions that may be targetoid  
• cyst lining is transitional/urothelial, large cysts may possess a flattened epithelium or denuded lining  
• cytologic blandness is present by definition but marked variation in size is important to note | • cystitis cystica glandularis  
• nephrogenic adenoma  
• adenocarcinoma                                               | no biologic difference in outcome from usual urothelial carcinoma  
• potential diagnostic pitfall in limited sampling                                                        |
| Urothelial carcinoma with inverted pattern | • inverted pattern of growth  
• urothelial carcinoma in situ or exophytic (papillary) urothelial carcinoma may be present  
• nuclear pleomorphism, mitotic activity and architectural disorder  
• may or may not be associated with invasion | inverted papilloma                                           | depends on presence or absence of lamina propria or muscularis propria invasion  
• invasion may be overcalled                                                                                 |
| Sarcomatoid carcinoma (carcinosarcoma) | • high-grade urothelial carcinoma with undifferentiated spindle cell component with or without heterologous elements  
• in some cases epithelial component may be urothelial carcinoma in situ, squamous, adenocarcinoma or small cell carcinoma  
• heterologous differentiation most likely chondrosarcoma, osteosarcoma or rhabdomyosarcoma | • sarcoma  
• pseudosarcomatous fibromyxoid tumor (inflammatory pseudotumor)  
• urothelial carcinoma with pseudosarcomatous stroma | extremely aggressive  
• 2-year survival of 28%, median survival 1 year (one large study)                                         |
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