

**Variant morphology in upper urinary tract urothelial carcinoma: a fourteen-year case series of biopsy and resection specimens**

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**Abstract**

Upper urinary tract urothelial carcinoma exhibiting variant morphology, especially in higher-grade tumors, is a recognized phenomenon but has not been comparatively studied in biopsy versus resection material. We studied the morphologic patterns and clinicopathological features, and provide a comparison between biopsy and resection specimens. Consultation cases were evaluated separately to investigate for possible consultation bias. A total of 383 in-house cases from 352 patients including 314 resection specimens and 69 biopsies from 2001-2014 were reviewed from a single institution. Histologic type, tumor grade, invasion, pathologic stage, nodal status, metastasis, and the presence and type of variant morphology for each case were evaluated. Variant morphology was identified in 5 biopsy specimens (7.2%) and 42 resection specimens (13.4%). The most common variant morphologic pattern was squamous differentiation (16 cases, 4.5%) followed by an inverted growth pattern (8 cases, 2.2%). The presence of variant morphology in resection specimens had a significant association with higher tumor grade, higher pT stage, and non-papillary configuration. Out of 69 patients with biopsies, 31 had a subsequent resection. In comparison, 181 consultation cases from 168 patients showed variant morphology in six biopsies (7.1%) and twenty-seven resections (28.1%). In conclusion, the frequency of recognizing variant morphology in biopsies is about one-half of that in resections. The inclusion of consultation cases can inflate the incidence of variant morphology. As a result, the frequency of variant morphology in our in-house cases is lower than the percentage reported in the literature, most likely secondary to a consultation bias.

Keywords: Upper urinary tract, urothelial carcinoma; variant

## 1.1

### Introduction

Urothelial neoplasms of upper urinary tract are uncommon, accounting for approximately 5% of all epithelial tumors of the urinary tract [1]. Eighty percent of those are malignant, with urothelial carcinoma (UC) accounting for 90%. From 2004–2010, the percentage of in situ cases increased while stage IV cases have decreased [2]. Upper urinary tract urothelial carcinoma (UTUC) exhibiting variant morphology is a well-recognized phenomenon, and has been reported to be associated with a higher grade, higher stage, higher frequency of lymphovascular invasion, and increased recurrence [3-7].

Recognition of variant morphology is not only essential for management decisions but also necessary to rule out metastasis or secondary involvement from adjacent malignancies [8]. The reported frequency of UTUC variant morphology in surgical resections; i.e., nephroureterectomy or ureterectomy, has ranged from 12–40% in the larger published series [4-7]. However, the frequency of variant morphology in biopsies and their subsequent resection specimens has not been previously reported. We analyzed a large volume of cases from a single institution, comparing findings from both in-house and consultation cases, in order to investigate the true incidence of variant morphology in UTUC and determine the presence and significance of the consultation bias.

## 1.2

### Materials and Methods

An electronic data search was performed from our institutional files from January 2001 through December 2014 to include all biopsies and surgical resections with a final

diagnosis of UTUC. Included cases of UTUC were from nephrectomies, nephroureterectomies, and ureterectomies, as well as all biopsies from the portion of the urinary tract above the urinary bladder (renal pelvis and ureter). The cases were separated based on service type: in-house or consultation. In-house cases included all biopsy and resection procedures performed at the hospital sites within our institution and directly served by our department. Consultation cases were cases sent to our department from other institutions for expert interpretation.

All case documentation was analyzed and the diagnoses were confirmed by reviewing the corresponding hematoxylin and eosin–stained sections. The clinical information of each patient was reviewed from all available electronic medical records, and the following data points were recorded: (1) age at time of diagnosis, (2) gender, (3) stage, (4) development of recurrence and/or metastasis, and (5) status of disease at last follow-up.

These UTUC cases were reviewed for various histologic features, including configuration, grade of tumor, pathologic stage, vascular invasion, and the presence and type of variant morphology. The configuration was classified as papillary or non-papillary based on the architecture. Tumors were classified as low grade or high grade according to criteria set by the World Health Organization (WHO)/International Society of Urological Pathology (ISUP) grading system [9]. Tumor staging was performed according to the 2010 American Joint Committee on Cancer TNM staging system [10]. We defined low pT to be pTa, pTis, and pT1. Cases with a pT of pT2 or higher were designated as high pT for our analysis. Variant morphology was classified using the WHO 2016 classification and additional recently reported patterns in literature [8, 9, 11-13].

Statistical analysis between cases with and without variant morphology and for clinicopathologic factors was performed using the chi-square test or the Fisher exact test. For all data reported, results with a  $p$  value  $<0.05$  were considered statistically significant. All data was analyzed using EZR (Saitama Medical Center, Jichi Medical University), which is a graphical user interface for R (The R Foundation for Statistical Computing, version 3.1.2) [14].

In concordance with our institutional policy, all patients seen within our hospital system have given consent for materials to be used for research purposes in an anonymous fashion. Furthermore, this study is granted exemption status by our Institutional Review Board.

### 1.3

#### Results

Over the fourteen-year study period, a total of 383 in-house cases from 352 patients were identified. These included 69 biopsies and 314 resections (202 nephroureterectomies, 112 ureterectomies). The clinicopathological characteristics associated with variant morphology in biopsies and resections from in-house cases are provided in Table 1. The patients ranged in age from 37-95 years (mean 70.6 years); the male to female ratio was 1.6:1. The follow-up time ranged from 1–139 months (median, 8 months). The most common architecture was papillary, followed by infiltrative/nodular (Figure 1A, B). Overall, 46 cases (13%) showed the presence of variant morphology, of which 44 cases (95.6%) were high-grade, and 39 cases (84.7%) were invasive. The presence of variant morphology had a significant correlation with non-papillary configuration ( $P=0.013$ ), high grade ( $P=0.0127$ ),

and high pT stage ( $P=0.0002$ ) (Table 2).

During the same time period, a total of 181 consultation cases from 168 patients were identified. These included 85 biopsies and 96 resections (77 nephroureterectomies, 19 ureterectomies). Clinical information provided with consultation cases was often limited to age, sex, and operative procedure. The patients ranged in age from 14-87 years (mean 64.2 years); the male to female ratio was 1.1:1. The follow-up time was not available. The most common architecture was papillary. Overall, 33 cases (18%) showed the presence of variant morphology, of which 44 cases (87.9%) were of high-grade morphology.

### 1.3.1

#### **Biopsies:**

A total of 69 in-house biopsies from the upper urinary tract with a diagnosis of urothelial carcinoma were identified. Of these, 31 cases had subsequent resections. Patient age ranged from 52-80 years (mean 69.9 years), and the male to female ratio was 3:2. Five cases (7.3%) showed the presence of variant morphology and four of these cases (80.0%) were high-grade tumors. Three of these 5 cases (60.0%) showed invasion. Variant morphology in biopsy specimens showed no significant correlation with configuration ( $P=0.241$ ), grade ( $P=0.643$ ), or higher pT stage ( $P=0.211$ ) (Tables 2 and 3).

A total of 85 consultation biopsies diagnosed as UTUC were identified. Of these, 13 cases included subsequent resections. Patient age ranged from 14-87 years (mean 68.4 years), and the male to female ratio was 1.5:1. Six cases (7.1%) showed the presence of variant morphology and five of these cases (83.3%) were high-grade tumors.

### 1.3.2

**Resections:**

For the 314 in-house resection cases, the patient age ranged from 37-95 years (mean-70.6 years), and the male to female ratio was 2:1. Forty-two cases (13.4%) displayed variant morphology, 40 (95.2%) of which occurred in high-grade tumors, and 36 (85.7%) in invasive carcinomas. Unlike in the biopsy group, the presence of variant morphology had a significant correlation with non-papillary configuration ( $P=0.013$ ), high grade ( $P=0.0127$ ), and high pT stage ( $P=0.0002$ ) (Tables 2 and 4).

For the 96 consultation resection cases, the patient age ranged from 21-87 years (mean 66.0 years), and the male to female ratio was 0.96:1. Twenty-seven cases (28.1%) displayed variant morphology, 24 (88.9%) of which occurred in high-grade tumors.

**1.3.3****Variant morphologic patterns:**

Of 352 in-house patients, 306 were cases of usual urothelial carcinoma and the remaining 46 patients displayed variant morphology. Squamous differentiation (16 cases, 4.1%) was the most common, followed by inverted growth pattern (8 cases, 2.5%), sarcomatoid (7 cases, 1.8%), glandular differentiation (6 cases, 1.6%), and micropapillary (4 cases, 0.9%) (Table 5; Figure 1). Other less common patterns included plasmacytoid (2 cases, 0.6%), giant cell (1 case, 0.3%), and lymphoepithelioma-like (1 case, 0.3%) (Figure 2). Two cases with squamous differentiation also had sarcomatoid and glandular differentiation respectively. Only two of 31 cases that included both a biopsy and subsequent resection showed inverted growth pattern in both (Figure 1D). A summary of the types of divergent morphology over different grades and stages in biopsies and resections is provided in Table 6.

Among the 181 consultation UTUC cases reviewed, 33 cases displayed variant morphology. The most common variant types of these were squamous differentiation and sarcomatoid (9 cases, 4.8%, each), followed by inverted growth pattern (7 cases, 3.7%) and glandular differentiation (6 cases, 3.2%). Less common patterns were plasmacytoid (3 cases, 1.6%), small cell (2 cases, 1.1%), and trophoblastic (1 case, 0.5%). A mixture of variant patterns was seen in four cases. Each contained squamous differentiation and another component: sarcomatoid, glandular differentiation, or the combination of glandular differentiation and sarcomatoid (chondroid heterologous component). Of the sarcomatoid type cases, one contained osteoclast-like giant cells and another was composed of almost entirely rhabdoid cells. One case with squamous differentiation also contained abundant myxoid stroma. None of the consultation cases displaying variant morphology included both a biopsy and subsequent resection for comparison. A comparison of variant patterns from in-house and consultation cases is provided in Table 5.

#### 1.4

#### Discussion

The frequency of variant morphology in UTUC has previously been reported as being between 12.0% and 24.2% in a limited number of large resection series [6, 7, 15]. The incidence in the renal pelvis has been reported to be as high as 40% in the literature [4, 5]. However, our findings are that the frequency of variant morphology is nearer to the low end of the percentage range reported. It is possible that the reporting studies represent cohorts of patients not just from hospital and community practices, but also including unique consultations, thus leading to a higher percentage of variant morphology. It is also likely that

cases sent by general pathologists for expert consultation have a greater incidence of morphological variants because of their diagnostically challenging nature.

To investigate this source of bias we excluded all the consultation cases from statistical analyses and report consultation data separately from our in-house patients. To our knowledge, this study is one of the largest series examining variant UTUC patterns. In our opinion, the results of our in-house group provide an accurate incidence of this entity in general practice.

The spectrum of variant morphologies of UTUC is similar to that from the urinary bladder [1]. Previous reports from resection specimens have included examples of UC with squamous differentiation, UC with glandular differentiation, microcystic UC, micropapillary UC, UC with inverted growth pattern, UC with choriocarcinoma or syncytiotrophoblastic giant cells (now termed UC with trophoblastic differentiation [9]), sarcomatoid UC (including cases with heterologous components present such as rhabdoid cells or chondrosarcoma [9]), lymphoepithelioma-like UC, nested UC, plasmacytoid UC, signet ring cell (now included in plasmacytoid UC if no extracellular mucin component is present [9]), small cell carcinoma, clear cell UC, and lipid-rich UC, osteoclast-rich poorly undifferentiated carcinoma, and UC with pseudosarcomatous stromal changes [4-6, 16-35]. In our study, the most frequent type from in-house resections was squamous differentiation, as in a previously reported series [6]. The frequency of squamous differentiation has been reported to range from 9.9%–18%, but our study showed a lower frequency of squamous differentiation (4.5%), squamous differentiation combined with sarcomatoid (0.3%), and squamous differentiation combined with glandular differentiation (0.3%) patterns [3, 4, 6]. One possible explanation

for this variation in squamous differentiation recognition could be the use of varying criteria by different pathologists.

The presence of variant morphology in resection specimens (in-house cases) showed a significant correlation with high grade and high pT stage. In the urinary tract, variant differentiation frequently corresponds with higher grade and stage of urothelial cancer [9]. Sakano et al. reported that UTUC with variant histology was significantly associated with advanced pathological T stage ( $pT \geq 3$ ), higher tumor grade (G3), and more frequent lymphovascular invasion [7]. On univariable analysis, variant histology was associated with disease recurrence and cancer specific mortality; however, multivariate analysis did not show an association with cancer specific mortality [6, 7]. In our study, it is not possible to determine an association between prognosis and variant morphology because the follow-up time (mean 8 months) was too short for practical analysis. Variant morphology in resections also showed a significant correlation with the non-papillary configuration. Rink et al. also reported a similar correlation. Remzi et al. reported that pT2 and higher stage tumors tend to have the non-papillary pattern [30]. Tumor architecture has also been reported as an independent predictor of cancer recurrence and cancer-specific mortality [24, 30]. Therefore, it is important to pay attention to the configuration of UTUC cases to detect variant morphology and for accurate prognostication.

We assessed the frequency of variant morphologies of UTUC in biopsies and compared it to resections. The frequency in in-house biopsies was 7.2%, about a one-half of that found in in-house resections. Moreover, unlike in resections, variant morphology in a biopsy had no association with configuration, grade, or pT stage. The most likely explanation

is the smaller sample size and superficial nature of these specimens precluded thorough assessment. This is supported by our observations that grade and morphologic patterns are more accurately assessed in resection specimens as compared to biopsy material. In a larger study, it was documented that in the urinary bladder, out of 589 transurethral biopsies of UC, 115 cases (19.5%) demonstrated variant histologic differentiation [31]. Unlike these urinary bladder biopsies, upper urinary tract biopsies seem to have a lower detection rate of variant morphology and it is important to consider this when making management decisions. The fact that upper urinary tract biopsies are typically much smaller than bladder biopsies most likely contributes to this. Additionally, it might be difficult to distinguish cases of primary UC from metastasis, or direct invasion from another malignancy, on the basis of biopsy alone when findings demonstrate a variant morphology.

In this study, 31 patients had a biopsy followed by surgical resection (in-house). Two patients (6.5%) displayed variant morphology on the preoperative biopsy. One showed low-grade papillary UC with inverted growth pattern on biopsy. The final postoperative diagnosis was high-grade papillary UC with inverted growth pattern, and the stage was pT2pN2. The other showed high-grade papillary UC with inverted growth pattern both on biopsy and resection. This emphasizes that biopsy may provide limited information regarding grade and the extent of tumor.

In summary, our study shows that variant morphology is found in 12.6% of UTUC. This was more often recognized in the resections (13.2%) than in biopsies (7.2%). The presence of variant morphology in resections had a significant association with non-papillary configuration, higher grade, and high pT stage. We conclude that the incidence of variant

morphology is lower in the general population than previously reported, most likely due to a consultation bias. Lastly, biopsy specimens may provide low sensitivity information regarding the presence of variant morphology.

ACCEPTED MANUSCRIPT

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**Figure legends**

**Figure 1.** **A**, Papillary high grade urothelial carcinoma (right) adjacent to kidney parenchyma (left) (H&E 40X). **B**, High grade urothelial carcinoma with an infiltrative pattern (upper right) and nodular pattern (lower left) (H&E 100X). **C**, Urothelial carcinoma with keratinizing squamous differentiation (H&E 100X). **D**, Urothelial carcinoma showing predominant inverted growth pattern (H&E 200X). **E**, Urothelial carcinoma with a sarcomatoid component (H&E 40X). **F**, Urothelial carcinoma with glandular differentiation (H&E 200X).

**Figure 2.** Less commonly observed variant morphologies in upper urinary tract urothelial carcinoma. **A**, Plasmacytoid urothelial carcinoma, tumor cells with characteristic plasmacytoid morphology forming discohesive sheets infiltrating a fibrous stroma (H&E 200X). **B**, Lymphoepithelioma-like differentiation, an abundant lymphoid infiltrate surrounding and obscuring urothelial tumor cells (H&E 200X). **C**, Urothelial carcinoma with abundant myxoid stroma, single and groups of cells floating in mucin (H&E 100X). **D**, Giant cell urothelial carcinoma, large pleomorphic cells with prominent giant cell morphology (H&E 200X).

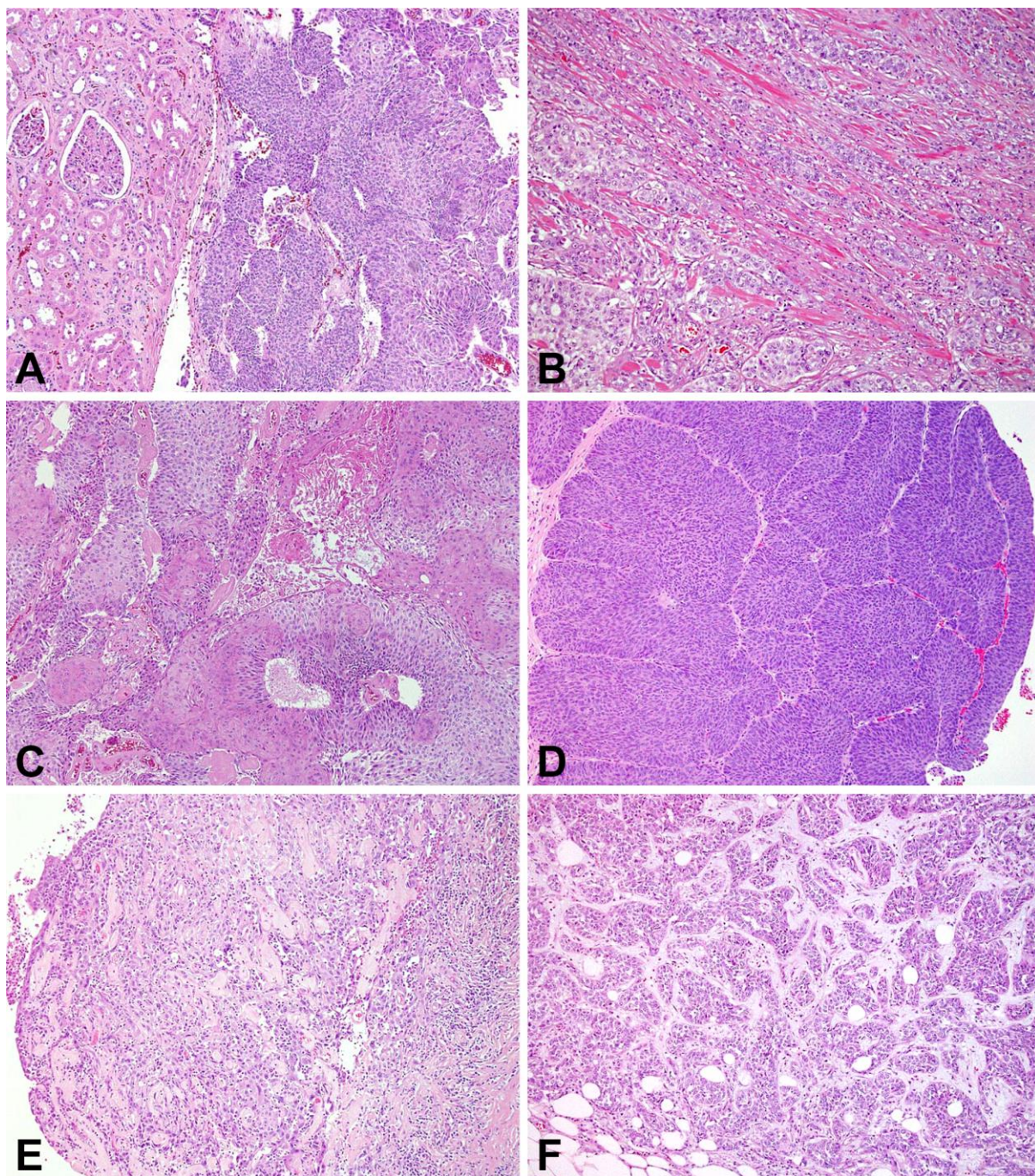


Figure 1

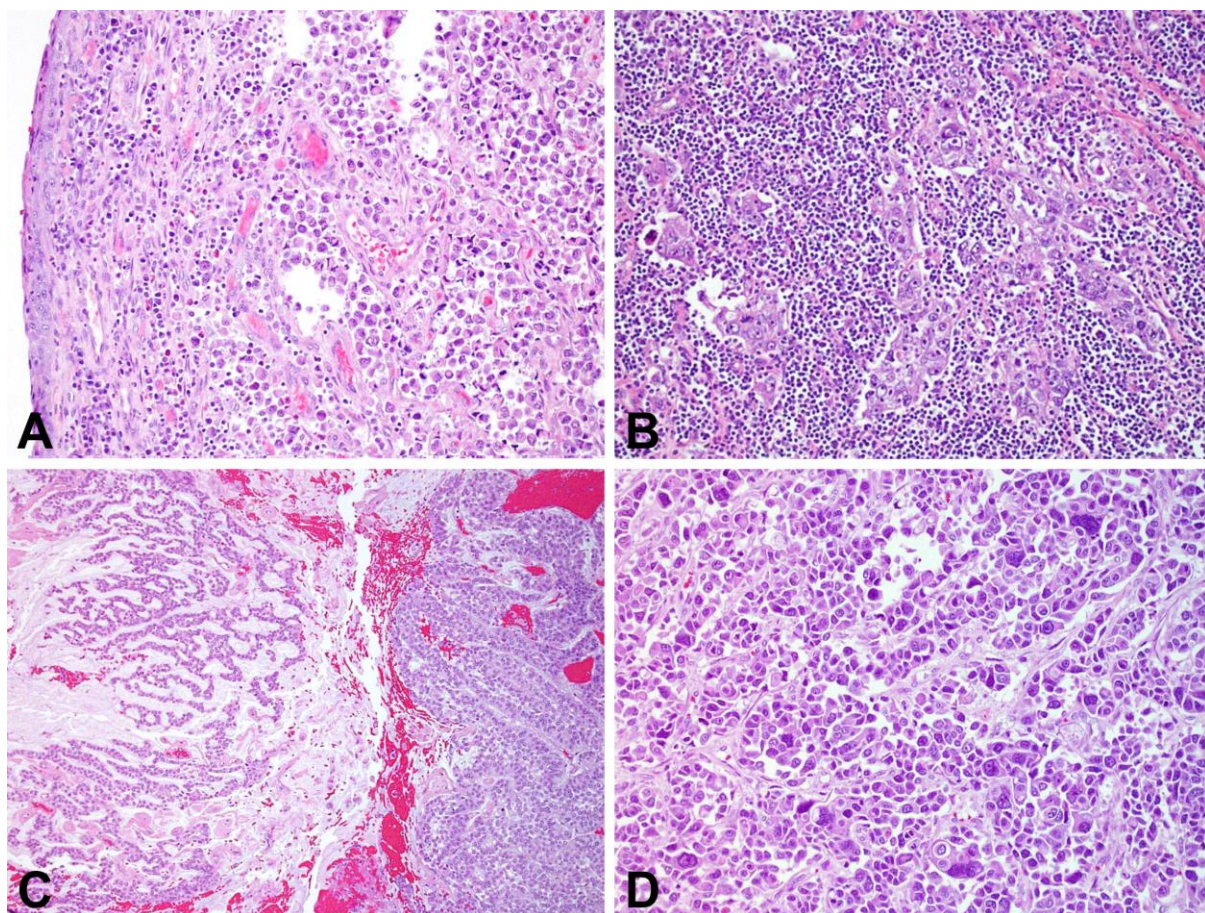


Figure 2

Table 1. Variant morphology and clinical characteristics of in-house cases of upper urinary tract urothelial carcinoma

	Variant morphology in biopsies n=69 (100%)		Variant morphology in resections n =314 (100%)	
	Present (%) 5* (7.3)	Absent (%) 64 (92.7)	Present (%) 42* (13.4)	Absent (%) 272 (86.6)
Age				
≤70	4 (80)	30 (46.9)	16 (38.1)	126 (46.2)
>70	1 (20)	34 (53.1)	26 (61.9)	146 (53.8)
Sex				
M	3 (60)	38 (59.4)	27 (64.3)	171 (62.9)
F	2 (40)	26 (40.6)	15 (35.7)	101 (37.1)
Surgery				
Nephroureterectomy			30 (71.4)	172 (63.3)
Ureterectomy			12 (28.6)	100 (36.7)
Chemotherapy				
None			30 (71.4)	221 (81.5)
Neoadjuvant			11 (26.2)	40 (14.5)
Unknown			1 (2.4)	11 (4.0)
Follow-up (month)			<1 - 139	<1 - 89
Died from UTUC			2 (4.8)	7 (2.5)

\*From 46 patients with variant tumors, 5 were identified on biopsy and 42 on resection. UTUC, upper urinary tract urothelial carcinoma.

Table 2. Statistical analysis of variant histology versus pathologic features for in-house cases of upper urinary tract urothelial carcinoma

<b>Variant vs Grade (n=352; P=0.00844)*</b>			<b>Grade vs Configuration (n=345; P&lt;0.001)</b>		
	<u>Grade low</u>	<u>Grade high</u>		<u>Papillary</u>	<u>Nonpapillary</u>
Variant absent	68/306	238/306	Low grade	69/70	1/70
Variant present	2/46	44/46	High grade	169/275	106/275
<b>Variant vs pT (n=352; P=0.0515)</b>			<b>Grade vs LVI (n=233; P&lt;0.001)</b>		
	<u>pT low</u>	<u>pT high</u>		<u>LVI not identified</u>	<u>LVI present</u>
Variant absent	164/306	142/306	Low grade	49/49	0/49
Variant present	17/46	29/46	High grade	120/184	64/184
<b>Variant vs Configuration (n=345; P=0.0315)</b>			<b>pT vs Configuration (n=345; P&lt;0.001)</b>		
	<u>Papillary</u>	<u>Nonpapillary</u>		<u>Papillary</u>	<u>Nonpapillary</u>
Variant absent	216/300	84/300	Low pT	155/175	20/175
Variant present	22/45	23/45	High pT	83/170	87/170
<b>Variant vs LVI (n=352; P=0.561)</b>			<b>pT stage vs LVI (n=233; P&lt;0.001)</b>		
	<u>LVI not identified</u>	<u>LVI present</u>		<u>LVI not identified</u>	<u>LVI present</u>
Variant absent	154/210	56/210	Low pT	117/117	0/117
Variant present	15/23	8/23	High pT	52/116	64/116
<b>Grade vs pT (n=352; P&lt;0.001)</b>			<b>Configuration vs LVI (n=233; P&lt;0.001)</b>		
	<u>Low pT</u>	<u>High pT</u>		<u>LVI not identified</u>	<u>LVI present</u>
Low grade	68/70	2/70	Papillary	143/169	26/169
High grade	113/282	169/282	Nonpapillary	26/64	38/64

LVI, lymphovascular invasion; Low pT, pTa/pTis/pT1; High pT: pT2/pT3/pT4

\* One variant case overlapping and 31 biopsies overlapping

Table 3. Variant morphology, grade, and stage correlation for in-house biopsy specimens

Grade (n)	High grade UC (42)						Low grade UC (27)		
Variant morphology (n)	Present (4)			Absent (38)			Present (1)	Absent (26)	
Configuration (n)	P (2)	NP (1)	NA (1)	P (7)	NP (22)	NA (9)	P (1)	NP (25)	NA (1)
Noninvasive	0	1	0	3	15	4	1	25	1
Invasive	2	0	1	4	7	5	0	0	0
Ta/Tis	0	1	0	3	15	4	1	25	1
T1	2	0	1	3	5	4	0	0	0
T2	0	0	0	1	2	1	0	0	0

NA = Not assessed due to the minute size and fragmentation of the specimen

NP = Non-papillary

P = Papillary

UC = Urothelial carcinoma

Table 4. Variant morphology, grade, and pathologic stage correlation for in-house resection specimens

Grade (n)	High grade UC (259)				Low grade UC (55)			
Variant morphology (n)	Present (40)		Absent (219)		Present (2)		Absent (53)	
Configuration (n)	P (20)	NP (20)	P (138)	NP (81)	P (1)	NP (1)	P (53)	NP (0)
Noninvasive	2	2	27	3	1	1	46	0
Invasive	18	18	111	78	0	0	7	0
pTa	2	0	27	0	1	1	46	0
pTis	0	2	0	3	0	0	0	0
pT1	5	2	44	7	0	0	5	0
pT2	5	1	30	20	0	0	2	0
pT3	5	7	33	36	0	0	0	0
pT4	3	8	4	15	0	0	0	0
pNx	11	11	84	37	1	1	32	0
pN0	4	4	45	23	0	0	21	0
pN1	1	1	7	9	0	0	0	0
pN2	4	3	2	12	0	0	0	0
pN3	0	1	0	0	0	0	0	0
Mx	20	20	138	80	1	1	53	0
M1	0	0	0	1	0	0	0	0

NP = Non-papillary

P = Papillary

UC = Urothelial carcinoma

Table 5. Summary of variant morphology in-house and consultation cases

	In-House	Consultation*
Total Cases	383	181
Conventional UC	337 (88%)	148 (82%)
Variant UC	46 (12%)	33 (18%)
Squamous differentiation	16 (4.1%)	9 (4.8%)
Inverted growth pattern	9 (2.5%)	7 (3.7%)
Sarcomatoid**	7 (1.8%)	9 (4.8%)
Glandular differentiation	6 (1.6%)	6 (3.2%)
Micropapillary	4 (0.9%)	0
Plasmacytoid	2 (0.6%)	3 (1.6%)
Giant cell	1 (0.3%)	0
Lymphoepithelioma-like	1 (0.3%)	0
Small cell	0	2 (1.1%)
Trophoblastic differentiation	0	1 (0.5%)
UTUC, upper urinary tract urothelial carcinoma; UC, urothelial carcinoma. *Several consultation cases exhibited more than one variant; therefore the variant types total is greater than the variant UC total. **Sarcomatoid variants identified included chondroid, rhabdoid, and spindled morphologies.		

Table 6. Overall in-house biopsy and resection correlation with variant morphology, grade, and stage

Grade (n)	High grade UC (282)						Low grade UC (70)		
Variant morphology (n)	Present (44)			Absent (238)			Present (2)		Absent (68)
Configuration (n)	P (21)	NP (22)	NA (1)	P (148)	NP (84)	NA (6)	P (1)	NP (1)	P (68)
Noninvasive	3	2	0	35	4	1	1	1	61
Invasive	18	20	1	113	80	5	0	0	7
Ta/Tis	3	2	0	35	4	1	1	1	61
T1	5	4	1	45	9	4	0	0	5
T2	5	1	0	31	20	1	0	0	2
T3	5	7	0	33	36	0	0	0	0
T4	3	8	0	4	15	0	0	0	0

NA = Not able to assess due to the minute size and fragmentation of the specimen

NP = Non-papillary

P = Papillary

UC = Urothelial carcinoma

**Variant morphology in upper urinary tract urothelial carcinoma: a fourteen-year case series of biopsy and resection specimens**

Highlights

- Upper urinary tract urothelial carcinoma exhibits a spectrum of variant morphology.
- Variant morphology frequency in biopsies and resections has not been reported.
- The frequency of variant morphology is around 12% in the general population.
- Previously reported incidences are most likely inflated due to a consultation bias.