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Outcomes of nonmetastatic micropapillary variant upper tract urothelial carcinoma

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Abstract

Purpose: Micropapillary variant upper tract urothelial cancer (MP-UTUC) is a rare malignancy with little known regarding its clinical course and/or optimal treatment. In this case series, we describe patient characteristics, surgical treatment, oncologic outcomes, and response to perioperative chemotherapy.

Materials and Methods: We conducted a review to identify patients with MP-UTUC treated at our center between January 1994 and October 2017. Clinicopathologic data was obtained. Descriptive statistics, Kaplan-Meier analysis, Cox proportional hazards, and nearest neighbor matching were used to examine the cohort.

Results: Eighteen, (4.3%) of 416 patients were found to have MP-UTUC at our institution over a 23-year period. The majority of patients had ≥pT3 disease at the time of extirpative surgery (13/18, 72%) and one was identified as MP-UTUC prior to surgery. Seven patients received neoadjuvant chemotherapy and six patients received adjuvant chemotherapy. Median overall, cancer specific, and recurrence free survival were 3.29, 3.29, and 1.69 years, respectively for MP-UTUC. There was no survival difference between conventional UTUC and MP-UTUC when matched for age, stage, grade, lymphovascular invasion, and margins (HR 1.18, $P = 0.567$). No MP-UTUC patients receiving neoadjuvant and adjuvant chemotherapy had apparent pathologic down staging, and of those receiving adjuvant chemotherapy two-thirds died of disease within 2 years.

Conclusions: MP-UTUC is a rare, and in most cases aggressive malignancy that commonly presents as locally advanced disease. In this case series, MP-UTUC does not appear to respond to perioperative chemotherapy as neoadjuvant and adjuvant chemotherapy did not result in apparent pathologic down staging and the majority of those receiving adjuvant chemotherapy died from MP-UTUC. © 2019 Elsevier Inc. All rights reserved.

Keywords: Upper tract urothelial cell carcinoma; Renal pelvis cancer; Ureter cancer; Micropapillary; Chemotherapy

1. Introduction

Historically, studies examining treatment and outcomes of upper tract urothelial carcinoma (UTUC) have viewed the disease as one histologic entity, not exploring the impact of histologic variants. To date, little is known regarding the clinical course of patients with variant upper tract histology.

Micropapillary urothelial cell variant was first reported by Amin et al. in 1994 [1]. In the subsequent three decades, studies have highlighted the aggressive behavior of this variant urothelial histology [2,3]. The incidence of MP-UTUC is very low resulting in a paucity of data addressing clinical behavior and/or the optimal treatment approach, in particular the use of perioperative chemotherapy.

Conflicts of interest: None

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Currently, the roles of neoadjuvant and adjuvant chemotherapy (NAC, AC) are rapidly evolving in UTUC, with level 1 evidence recently reported for both. A phase II NAC trial showed a pathologic complete response rate of 14% and 60% down staging to ≤ypT1 disease in those with high-grade (HG) disease. Another randomized AC trial demonstrated improved progression free survival in those at high risk of recurrence after nephroureterectomy receiving adjuvant chemotherapy (HR 0.49, P=0.003) [4,5]. Prior series have also reported pathologic down staging and improved survival in high-risk patients with NAC utilization [6,7]. Importantly, these studies do not specifically address the role of perioperative chemotherapy in patients with variant upper tract histology.

In this series, we describe the treatment, oncologic outcomes, and impact of perioperative chemotherapy in this rare group of patients. We also compare recurrence and/or survival outcomes to a matched cohort of conventional UTUC patients (C-UTUC).

2. Materials and methods

2.1. Population

After receiving institutional ethics approval, we retrospectively identified patients with MP-UTUC treated at MD Anderson Cancer Center by reviewing the records of patients diagnosed with MP variant histology between January 1994 and October 2017. The following clinical variables were recorded: age, gender, clinical T stage, and grade (based on ureteroscopic biopsy when available), clinical node status, hydronephrosis, NAC, surgical technique, AC, recurrence, date of last visit, or date, and cause of death when available. Patients with visceral metastasis at time of surgery were excluded.

2.2. Pathologic evaluation

All surgical specimens were evaluated by dedicated genitourinary pathologists. Pathologic re-review was performed for patients undergoing surgery at outside institutions (OSI). The following pathologic variables were assessed: TNM staging, histologic grade, disease location, lymphovascular invasion, carcinoma in situ, and surgical margin status.

2.3. Survival outcomes and comparison to conventional UTUC

Descriptive statistics were used to characterize the patient cohort. The methods of Kaplan and Meier were used to estimate survival outcomes. Cox proportional hazards models were conducted to estimate the Hazards ratio and corresponding 95% confidence intervals. Overall survival (OS) was measured from date of surgery to date of death or date of last follow-up. Recurrence-free survival was measured from date of surgery to date of first recurrence on imaging, date of death, or date of last follow-up. Cancer-specific survival (CSS) was measured from date of surgery to date of first death due to disease, date of other death (censored), or date of last follow-up. CSS was also estimated using competing risk regression (Fine and Gray) to model the cumulative incidence of recurrence. Death due to other causes was considered a competing event for death due to disease. To correct for biases in the data, nearest neighbor matched (conventional and micropapillary) pairs were first obtained. All models estimated standard errors using sandwich estimators. Variables used for matching were, age, pT grade, lymphovascular invasion, pN, and margins. With exception of matching, all statistical analyses were performed using Stata/MP v15.0 (College Station, TX). Nearest neighbor matching was carried out using the MatchIt package in R (MatchIt: Nonparametric Preprocessing for Parametric Causal Inference**,** R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Baseline demographics of MP-UTUC patients

Over a 23-year period (1994–2017), 19 cases of MP-UTUC were identified at our institution from a total of 416 UTUC patients, representing 4.6% of all cases. Eighteen cases were for definitive treatment and one case for palliation in a patient with metastatic disease and refractory hematuria. Of the 18 patients, 16 (88.9%) were treated with radical nephroureterectomy and two (11.1%) with ureterectomy. The majority of procedures (13/18, 72.2%) were performed using an open technique. One patient had a concurrent radical cystectomy as tumor invasion into the bladder was noted at the time of radical nephroureterectomy. Ten patients had their surgery performed at our center, while the remaining eight had surgery at an OSI and were referred to MD Anderson Cancer Center for further management. Demographics and clinical characteristics are detailed in Table 1. Median age was 69 years (IQR 59.5–73.3) and the median follow-up was 25.2 months (IQR 11–63).

3.2. Perioperative data

Nine patients (50%) had clinical tumor staging information available for review prior to extirpative surgery, of whom six underwent ureteroscopy with biopsy and three had upper tract cytology and/or brushings. All staging samples showed high-grade urothelial tumor and only one patient (0.5% of all clinical HG tumors) was found to have MP-UTUC histology on ureteroscopic biopsy.

Twelve (66.7%) patients had preoperative imaging available for re-review, of whom five (41.7%) were clinically node positive. Hydronephrosis was identified in six (50%) patients with imaging available.

Table 1
Baseline demographics and clinical staging

Case No.	Age at diagnosis	Year of treatment	Sex	Staging technique	Biopsy stage	Biopsy grade	Biopsy histology	Clinical node status	Hydro-nephrosis	Surgical technique	Surgery location
1	63	2008	M	*NA*	*NA*	*NA*	*NA*	N1	Yes	open	MDACC
2	51	2017	M	URS*	*NA*	*NA*	*NA*	N0	No	open	MDACC
3	53	2011	M	URS	Tx	HG	UCC	N1	No	lap	MDACC
4	72	1996	M	Brushing	*NA*	HG	*NA*	N0	Yes	open	MDACC
5	76	1997	M	*NA*	*NA*	*NA*	*NA*	Nx	*NA*	open	OSI
6	74	1999	M	*NA*	*NA*	*NA*	*NA*	Nx	*NA*	open	OSI
7	54	2001	M	*NA*	*NA*	*NA*	*NA*	Nx	*NA*	open	OSI
8	69	2005	M	*NA*	*NA*	*NA*	*NA*	N0	No	lap	OSI
9	58	2000	M	*NA*	*NA*	*NA*	*NA*	Nx	*NA*	open	OSI
10	73	1999	F	*NA*	*NA*	*NA*	*NA*	Nx	*NA*	open	OSI
11	70	2006	M	*NA*	*NA*	*NA*	*NA*	Nx	*NA*	open	OSI
12	69	2008	F	URS	Tx	HG	UCC	N1	No	open	MDACC
13	67	2013	F	URS	Tx	HG	UCC	N0	Yes	open	MDACC
14	72	2009	M	URS	Ta	HG	MPUC	N1	No	lap	MDACC
15	75	2010	M	URS	T1	HG	UCC	N0	No	lap	MDACC
16	60	2015	M	URS	Tis	HG	CIS	N0	Yes	lap	MDACC
17	76	1994	M	Upper tract cytology	*NA*	HG	*NA*	N1	Yes	open	MDACC
18	61	2005	M	Brushing	*NA*	HG	*NA*	N1	Yes	open	OSI

* URS without biopsy.Tx-depth of invasion not identified.HG = high grade; MDACC = MD Anderson Cancer Center; NA = not available; OSI = outside institution; URS = ureteroscopy.

Table 2
Pathologic information.

Case no.	pT-stage classification	Percent micropapillary	Histologic grade	LVI	CIS	Margin	pN
1	pT3	<25	HG	Yes	Yes	Negative	N3
2	pT2	<25	HG	No	Yes	Negative	N1
3	pT3	50	HG	No	Yes	Negative	N0
4	pT3	20	HG	No	No	Negative	N0
5	pT3	70	HG	Yes	Yes	Negative	Nx
6	pT4	50	HG	Yes	Yes	Positive	Nx
7	pT3	30	HG	Yes	No	Negative	Nx
8	pT3	30	HG	Yes	No	Positive	Nx
9	pT2	50	HG	No	No	Positive	N0
10	pT3	60	HG	Yes	No	Negative	N1
11	pT3	30	HG	Yes	No	Negative	N3
12	ypT2	<25	HG	No	No	Negative	N0
13	ypT2	25	HG	No	No	Negative	N0
14	ypT3	30	HG	No	No	Negative	N0
15	ypT2	50	HG	No	Yes	Negative	N0
16	ypT3	<25	HG	Yes	No	Negative	N2
17	ypT3	80	HG	Yes	Yes	Negative	N3
18	ypT3	<25	HG	Yes	No	Negative	N3

HG = high grade; ypT = postneoadjuvant chemotherapy.

Seven (38.9%) patients received NAC, including the one patient with clinically identified MP-UTUC. NAC regimens, number of cycles, and clinical responses are listed in Table 3. Six patients (33.3%) received AC (Table 3). An additional three (16.7%) patients received chemotherapy following the development of metastatic disease.

3.3. Pathologic findings

The majority of patients had ≥pT3 disease (13/18, 72.2%). Most tumors were located within the renal pelvis (10/18, 55.6%). Thirteen (72%) of patients had extensive MP-UTUC (defined as >25%). No patient had tumor down staging to ≤ypT1 following the use of NAC. Three positive margins (16.7%) were recorded, all ureteral. Retroperitoneal lymph node dissection (RPLND) was performed in fourteen patients (77.8%) with a median lymph node count of 10 (IQR 5–19). Six (42.9%) patients had lymph node positive disease. All pathological information is listed in Table 2.

3.4. Recurrence and outcomes

Seven (38.9%) patients recurred following surgery, the majority (71%) within 1 year. Four patients recurred distantly, two locoregionally, and one patient with both distant and locoregional recurrence (Table 4). Median survival for all patients was 3.29 years.

3.5. MP vs. conventional UTUC—survival outcomes of matched cohorts

A total of 18 MP-UTUC patients were matched 1:2 to C-UTUC patients. All matching variables and NAC utilization were well balanced across groups (Table 5). The median follow-up time for all subjects was 2.4 years. Of note, one patient in the C-UTUC group was lost to follow-up after surgery and therefore not included in survival analysis. The median OS for the conventional UTUC group was 3.08 years (95% CI: 1.41–6.08) vs. 3.29 (95% CI: 1.69–4.77) years for the micropapillary group (HR 1.18, $P = 0.567$ 95% CI 0.66–2.11). The 5-year OS probability was 0.36 (95% CI: 0.20–0.52) vs. 0.27 (95% CI: 0.09–0.49) for the conventional and micropapillary groups respectively (Supplemental Table 1a and b). Fig. 1 depicts the Kaplan Meier curves for all survival outcomes. There were no survival differences between matched C-UTUC and MP-UTUC patients.

4. Discussion

We identified 19 cases of MP-UTUC at our center over a 23-year period from 416 UTUC patients, directly speaking to the low incidence of this disease. Patients with MP-UTUC had HG disease identified on biopsy, but were rarely diagnosed as having MP-UTUC histology preoperatively. Most had advanced pathologic disease, high rates of positive margins, positive lymph nodes, and rapid recurrence when present. Patients did not appear to respond to NAC, with no patient undergoing down staging to ≤ypT1 at the time of surgery. Advanced disease was noted, with more than two-thirds harboring ≥pT3 disease and more than one-third having positive lymph nodes on final pathology. AC was administered to six patients, all of whom but one died of MP-UTUC. Indeed, our findings are consistent with prior series. Both Holmang and Sung found that ≥80% of patients had at least pT3 disease at the time of resection in $n = 26$ and $n = 7$ patients, respectively. Similar to our series

Table 3
Perioperative chemotherapy patients and regimens.

Case No.	Age	Tumor grade	TNM	NAC/AC	Chemotherapy regimen	Number of cycles	Cr (pre chemo)	Nodal status	Initial response
1	63	HG	pT3N3R0	AC	gemcitabine/cisplatin	4	1.3	pN3	Stable
2	51	HG	pT2N1R0	AC	ddMVAC	4	1.3	pN1	Stable
5	76	HG	pT3NxR0	AC	ddMVAC + gemcitabine/cisplatin	2+2+1	1.7	Nx	Progressed
6	74	HG	pT4NxR1	AC	taxol/carbo + taxol/adriamycin	3+3	2.1	Nx	Progressed
10	73	HG	pT3N1R0	AC	ddMVAC + gemcitabine/taxol	2+	1.5	pN1	Progressed
11	70	HG	pT3N3R0	AC	gemcitabine/taxol/ adriamycin + gemcitabine/cisplatin	1+3	2.0	pN3	Stable
12	69	HG	cTxN1	NAC	ddMVAC + gemcitabine/ifosfamide/ adriamycin	3+3	0.8	cN1	Complete nodal response
13	67	HG	cTxN0	NAC	cisplatin/gemcitabine/ ifosfamide	1	1.08	cN0	Discontinued secondary to nephrotoxicity
14	72	HG	cTaN1	NAC	ddMVAC	4	0.9	cN1	Partial nodal response
15	75	HG	cT1N0	NAC	ddMVAC	2	0.69	cN0	Stable disease
16	60	HG	cTisN0	NAC	ddMVAC	4	0.91	cN0	Stable disease
17	76	HG	NA	NAC	5-fluorouracil,adriamycin, cisplatin (FAP)	2	1.2	cN1	Partial nodal response
18	61	HG	NA	NAC	cisplatin/gemcitabine/ ifosfamide + taxol/ ifosfamide/cisplatin + ddMVAC	6+2+2	0.8	cN1	Complete nodal response

AC = adjuvant chemotherapy; Cr = creatinine; ddMVAC = dose-dense methotrexate, vinblastine, adriamycin, cisplatin; HG = high grade; NAC = neoadjuvant chemotherapy.

in which 61% of patients died of disease (DOD), 57% and 73% of patients in the Sung and Holmang series DOD, respectively [8,9].

Due to the rare nature of this variant histology in upper tract malignancy, the majority of series to date have pooled patients from multiple treatment centers [10,11]. The largest of these studies retrospectively identified 39 patients nationwide. In that series, they did not report on the use of NAC. Survival from that series showed no difference in 5-year-CSS between C-UTUC and MP-UTUC, with median follow-up of 19 months [11].

Not surprisingly, the majority of patients in our study were male (83%). Prior studies have also reported that the majority of their MP patients were male in both bladder and upper tract disease [9,12]. One potential, yet untested, hypothesis for the poor outcomes seen with this histology is that male patients harbor more aggressive biology that their female counterparts.

This report examines outcomes of patients who received NAC as part of their standard treatment for upper tract MP. NAC did not result in any pathologic down staging, however this finding could simply be due to small sample size as well as selection bias, whereby those with worse clinical findings, and doomed to respond poorly anyway, were recommended to undergo NAC. It is possible, though we think unlikely, that some MP-UTUC patients had a complete response with ypT0 disease and thus were not identified. The role of NAC is gaining traction in UTUC. Many clinicians view it as integral to the treatment of UTUC, while others remain skeptical due to the lack of level one evidence. Current knowledge is based on retrospective studies, small prospective studies, and a recent phase II study [5−7]. The latter demonstrated pathologic complete response (ypT0N0) of 14% in those receiving platinum-based NAC and a 60% rate of ≤ypT1N0 [5]. Intuitively, variant histology is considered as “high-risk”; however, data surrounding the effect of NAC in this group is lacking. In a recent study, Vetterlein et al. attempted to quantify the benefit of NAC in variant histology bladder cancer. Interestingly, they found no survival benefit with its use in MP histology despite increased pathologic downstaging [13]. In another study, Fernandez et al. found that NAC was not beneficial in all patients with MP bladder cancer, only in those with muscle-invasive disease and no evidence of hydronephrosis [12].

The role of AC in upper tract disease is shifting as well. Concerns exist regarding candidacy and tolerability following the loss of a renal unit. In our series, six patients received AC, all of whom did not receive NAC. Of these six patients, 4 DOD within 2 years, one died from disease 57 months following surgery, and the final patient finished chemotherapy recently with no evidence of disease 6 months later. A recent randomized study assessing the role of adjuvant chemotherapy in UTUC has reported preliminary results showing improved progression-free survival in those receiving AC (HR 0.49, $P = 0.003$) [4]. Although

Table 4
List of recurrences.

Case No.	pStage	Site of recurrence	Time to recurrence (months)
6	pT4NxR1	Pelvic lymph nodes + pulmonary	11.5
7	pT3NxR0	Retroperitoneal lymph nodes	1
8	pT3NxR1	Bladder + peritoneal	7.6
9	pT2N0R0	Retroperitoneal lymph nodes	1.3
10	pT3N1R0	Pulmonary	0.2
11	pT3N3R0	Pulmonary	39.4
12	ypT2N0R0	Pulmonary	14.7

very intriguing, and applicable to patients who have adequate renal function postoperatively, these results cannot be directly applied to those with variant histology as they were excluded from the trial.

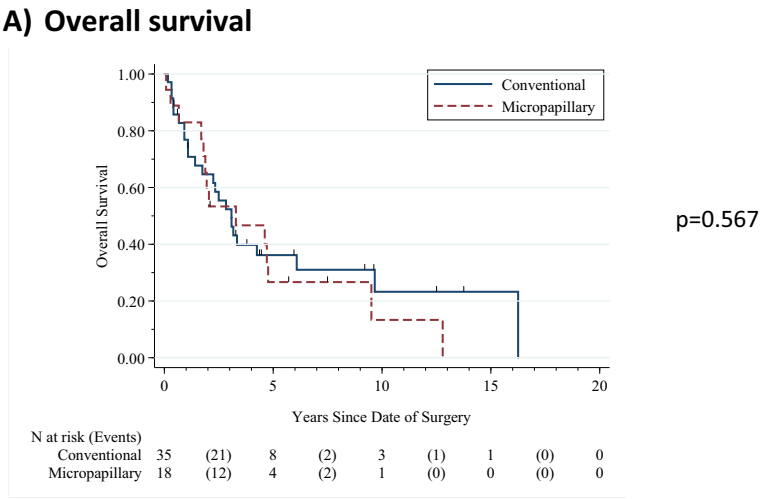
The utility of RPLND continues to be a topic of debate in the management of UTUC as well. Advocates cite resection of micrometastatic disease and enhanced prognostic information as reasons for performing RPLND [14]. In our series, almost half of those with preoperative staging available for review were clinically node positive (5/12). One of fourteen (7%) patients who received RPLND had a retroperitoneal recurrence. This patient had a positive ureteral margin at the time of surgery and the extent of lymph node dissection is unknown as their surgery was performed at an outside institution. All other recurrences following RPLND (3 patients) occurred outside the retroperitoneum. It is unclear what role RPLND has on survival in this setting, but it would be fair to assume that it may reduce local recurrences as has been shown for C-UTUC [15].

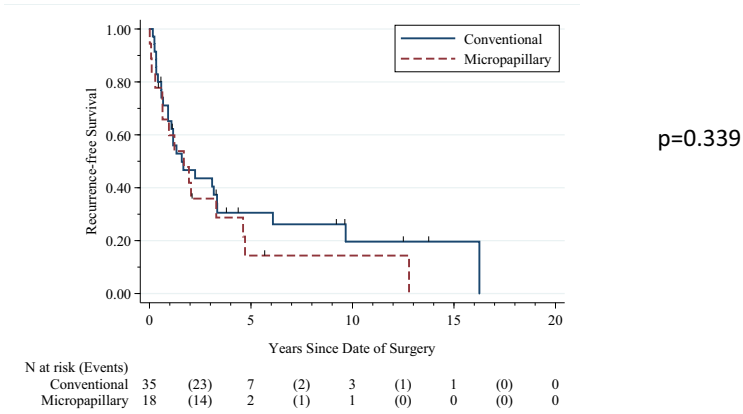
Unlike bladder cancer, upper tract tumors are notoriously difficult to stage preoperatively and identification of variant histology is challenging. The small biopsies obtained during ureteroscopy make it difficult for pathologists to accurately assess presence and/or depth of invasion or comment on the presence of histologic variants. This was the case in our series as well. Only one patient was diagnosed with MP variant based on biopsy alone. As a

Table 5
Clinical characteristics of matched cohorts.

Variable	Conventional (C-UTUC)	Micropapillary (MP-UTUC)	*P* value
Total no.	36	18	-
Mean age (SD)	68.39 (10.78)	66.28 (8.30)	0.470
Pathologic stage			0.395
pTis	1	0	
pT1	3	0	
pT2	7	5	
pT3	18	12	
pT4	7	1	
Grade			>0.999
Unknown	2	0	
High	34	18	
LVI			0.172
Unknown	4	0	
No	20	8	
Yes	12	10	
Nodal status			0.461
Nx	5	4	
N0	17	7	
N1	9	2	
N2	5	1	
N3	0	4	
Margins			0.319
Negative	34	15	
Positive	2	3	
NAC			0.845
No	21	11	
Yes	15	7	

LVI = lymphovascular invasion; NAC = neoadjuvant chemotherapy.





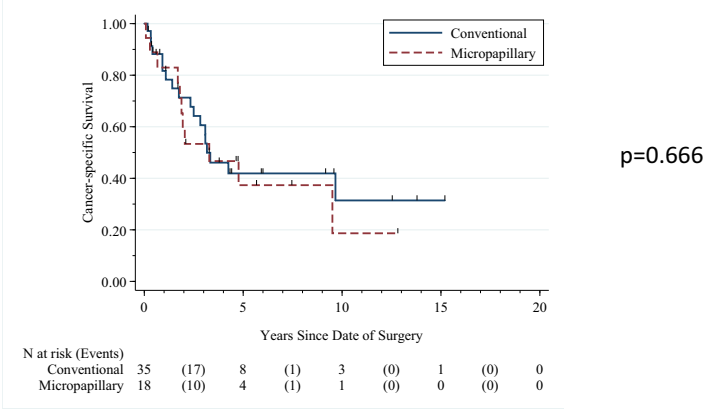


Fig. 1. Overall survival, recurrence free survival, cancer-specific survival of MP-UTUC and matched C-UTUC ($n = 18$ and 35 respectively).

result, treatment decisions regarding NAC are made using risk stratification based on clinical data [16].

Interestingly, when MP-UTUC patients were matched 1:2 to C-UTUC, no difference in survival was noted**.** A potential explanation for this is that by matching the C-UTUC to the advanced pathology observed in MP-UTUC, we selected for C-UTUC patients destined for poor prognosis, therefore making histology less of a prognostic factor. However, given the small numbers in the analysis the most likely explanation is that it is underpowered for the OS endpoint.

Limitations of our study include its retrospective design, which is subject to selection bias and lack of a control group. The small number of patients in this study limits the generalizability of its findings. Also, as a result of its retrospective design we were unable to gather all baseline data points on patients initially treated at outside institutions. We recognize that significant variability likely exists with regard to surgical technique as some patients received their extirpative surgery at outside institutions. Even within our own institution, surgical approaches vary between surgeons. Both of these factors add heterogeneity to the study; however reflect the real-world management of this disease. Pathologic re-review was a strength of this study however, our pathologists interpretations of OSI cases are limited by the sections they receive. Nonetheless, we believe this study serves as a depiction of upper tract MP-UTUC disease management and outcomes. With this pathologic variant being so rare, studies such as this provide some foundation for management decisions when confronted with this patient in the clinic.

5. Conclusions

MP-UTUC variant disease was aggressive, presented in advanced stages, recurred early, and with short survival. The benefit of perioperative chemotherapy in upper tract variant histology remains to be defined. In this small series, it did not appear to provide a benefit. The presence of MP-UTUC variant histology is often not recognized until final pathologic analysis, further evidence for the difficulty in identifying these tumors. Further studies are needed to confirm these findings, identify genomic signatures, druggable targets, and evaluate other existing therapeutic options such as checkpoint blockade in this rare variant histology.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2019.01.026.

References

[1] Amin MB, Ro JY, elSharkaway T, Lee KM, Troncoso P, Silva EG, et al. Micropapillary variant of transitional cell carcinoma of the urinary bladder. Histologic pattern resembling ovarian papillary serous carcinoma. Am J Surg Pathol 1994;18(12):1224–32.

[2] Kamat AM, Dinney CP, Gee JR, Grossman HB, Siefker-Radtke AO, Tamboli P, et al. Micropapillary bladder cancer: a review of the University of Texas M. D. Anderson Cancer Center experience with 100 consecutive patients. Cancer 2007;110(1):62–7.

[3] Guo CC, Tamboli P, Czerniak B. Micropapillary variant of urothelial carcinoma in the upper urinary tract: a clinicopathologic study of 11 cases. Arch Pathol Lab Med 2009;133(1):62–6.

[4] Birtle AJ, Chester JD, Jones RJ, Johnson M, Hill M, Bryan RT, et al. Results of POUT: a phase III randomised trial of perioperative chemotherapy versus surveillance in upper tract urothelial cancer (UTUC). J Clin Oncol 2018;36.

[5] Hoffman-Censits J, Puligandla M, Trabulsi E, Plimack E, Kessler E, Matin SF, et al. LBA26 Phase II trial of neoadjuvant chemotherapy followed by extirpative surgery for patients with high grade upper tract urothelial carcinoma (HG UTUC): results from ECOG-ACRIN 8141. J. Urol. 2018;199(4, Supplement):e1166–7.

[6] Porten S, Siefker-Radtke AO, Xiao L, Margulis V, Kamat AM, Wood CG, et al. Neoadjuvant chemotherapy improves survival of patients with upper tract urothelial carcinoma. Cancer 2014;120(12):1794–9.

[7] Siefker-Radtke AO, Dinney CP, Shen Y, Williams DL, Kamat AM, Grossman HB, et al. A phase 2 clinical trial of sequential neoadjuvant chemotherapy with ifosfamide, doxorubicin, and gemcitabine followed by cisplatin, gemcitabine, and ifosfamide in locally advanced urothelial cancer: final results. Cancer 2013;119(3):540–7.

[8] Holmang S, Thomsen J, Johansson SL. Micropapillary carcinoma of the renal pelvis and ureter. J Urol 2006;175(2):463–6:discussion 466-7.

[9] Sung HH, Cho J, Kwon GY, Jeon HG, Jeong BC, Seo SI, et al. Clinical significance of micropapillary urothelial carcinoma of the upper urinary tract. J Clin Pathol 2014;67(1):49–54.

[10] Perez-Montiel D, Hes O, Michal M, Suster S, et al. Micropapillary urothelial carcinoma of the upper urinary tract: clinicopathologic study of five cases. Am J Clin Pathol 2006;126(1):86–92.

[11] Masson-Lecomte A, et al. Impact of micropapillary histological variant on survival after radical nephroureterectomy for upper tract urothelial carcinoma. World J Urol 2014;32(2):531–7.

[12] Fernandez MI, Williams SB, Willis DL, Slack RS, Dickstein RJ, Parikh S, et al. Clinical risk stratification in patients with surgically resectable micropapillary bladder cancer. BJU Int 2017;119(5):684–91.

[13] Vetterlein MW, Wankowicz SAM, Seisen T, Lander R, Loppenberg B, Chun FK, et al. Neoadjuvant chemotherapy prior to radical cystectomy for muscle-invasive bladder cancer with variant histology. Cancer 2017;123(22):4346–55.

[14] Roscigno M, Shariat SF, Margulis V, Karakiewicz P, Remzi M, Kikuchi E, et al. Impact of lymph node dissection on cancer specific survival in patients with upper tract urothelial carcinoma treated with radical nephroureterectomy. J Urol 2009;181(6):2482–9.

[15] Kondo T, Takagi T, Tanabe K. Therapeutic role of template-based lymphadenectomy in urothelial carcinoma of the upper urinary tract. World J Clin Oncol 2015;6(6):237–51.

[16] Margulis V, Youssef RF, Bagrodia A, Kapur P, Darwish OM, Krabbe LM, et al. Preoperative multivariable prognostic model for prediction of nonorgan confined urothelial carcinoma of the upper urinary tract. J Urol 2010;184(2):453–8.