






Upper tract urothelial cancer (UTUC) genomic profiling and correlation regarding benefit of platinum-based chemotherapy

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Academic Editor: Nicola Normanno, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Italy

Received: July 10, 2024 **Accepted:** September 16, 2024 **Published:** October 17, 2024

Cite this article: Hwang MW, Kauffeld J, Belay S, de Jong JJ, Davicioni E, Li W, et al. Upper tract urothelial cancer (UTUC) genomic profiling and correlation regarding benefit of platinum-based chemotherapy. *Explor Target Antitumor Ther.* 2024;5:1261–70. <https://doi.org/10.37349/etat.2024.00274>

Abstract

Upper tract urothelial cancer (UTUC) are rare subsets of urothelial cancer, which typically present with more aggressive course. Molecular markers stratifying urothelial tumors as luminal subtype and non-luminal subtype tumors have been proposed to select patients who may have greater or lesser benefit from neoadjuvant systemic therapy in bladder cancer, though not yet evaluated in UTUC. Here, a single-institution study retrospectively obtained clinical and genomic information in patients with UTUC and evaluated four patient tumors using the Decipher Bladder[®] assay and Foundation Medicine[®] test. All four patients had non-luminal molecular subtype including basal ($N = 4$) and mixed basal/claudin-low ($N = 2$) subtypes. The best clinical response achieved was stable disease in a patient who had basal/claudin-low subtype with residual ypT3 after neoadjuvant chemotherapy. For the remaining three patients, all were treated with platinum-based chemotherapy for eventual metastatic disease but all three showed progressive disease with limited overall survival, highlighting their aggressive course. The non-luminal subtype and lack of *FGFR* alteration may partly explain the poor overall outcomes while the real-world benefit of next generation sequencing for clinical use in UTUC patients require further clarification in a larger cohort study.

Keywords

Upper tract urothelial cancers, neoadjuvant chemotherapy, molecular subtypes, Decipher Bladder[®]

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Introduction

Upper tract urothelial cancer (UTUC) is a relatively rare manifestation of urothelial cancer (UC) that tends to be more aggressive [1]. The standard treatment for high-grade disease involves surgery in the form of radical nephroureterectomy (NU). There is also level 1 evidence on the use of adjuvant chemotherapy based on the POUT trial, which has showed improvement in disease-free survival (DFS) [2]. Additionally, a meta-analysis revealed better evidence for adjuvant chemotherapy than there is for neoadjuvant chemotherapy (NAC) at this time [3]. Although the use of cisplatin-based NAC is considered nephrotoxic and there is currently no published level 1 evidence supporting the use of NAC in the management of high-grade UTUC (HG UTUC), a neoadjuvant approach may still be beneficial prior to definitive surgery [4]. Therefore, NAC followed by surgery is often used in clinical practice [5]. Nevertheless, much of our understanding of NAC benefit in UTUC is extrapolated from bladder-UC data and from retrospective or small prospective UTUC cohort studies.

Of interest, several molecular biomarkers, such as transcriptome-based molecular subtypes, have been evaluated for use in urothelial bladder cancer. At the highest level, bladder tumors can be classified among luminal and non-luminal subtypes and non-luminal tumors have been suggested to benefit most from NAC [6]. In the present study, we assessed molecular subtyping classifications of UTUC patients who underwent NU with or without NAC, by using Decipher Bladder[®], a clinical-grade, transcriptome-wide assay that has been validated in the peri-operative setting for bladder cancer [7]. The validated signatures include classes of Luminal, Infiltrated, Basal, Claudin-Low [8, 9] and Neuroendocrine-like (NE-like) [10, 11].

We conducted a small, single institutional, retrospective pilot study to obtain information regarding genomic profiling and molecular subtypes of four consecutive patients with a final diagnosis of UTUC who underwent NU and platinum-based chemotherapy [12]. A supplement to an existing IRB retrospective protocol was submitted to evaluate molecular subtypes in these patients. Four FFPE archival tissue samples were assayed through the commercially available Decipher Bladder[®] test (Veracyte Inc, San Diego, CA). The tissue block with the highest grade and volume of disease was selected, and a region of interest for the assay was selected after pathological review of the hematoxylin & eosin tissue slide. The Foundation One[®] next generation sequencing test was available for two of the four patients (Foundation Medicine, Cambridge MA). Further evaluation included clinical phenotypes of response, demographics, clinical staging, imaging results, final pathologic grade, and tumor stage. Overall survival and progression-free survival were evaluated though no formal statistical analyses were conducted given the small sample size of the study.

Case report

Four patient samples that were sent for transcriptome-wide analysis are reported herein. [Table 1](#) summarizes clinical characteristics, and [Figure 1](#) depicts selected marker expression from the Bladder Decipher[®] Grid from these four cases.

Clinical case 1

Case 1 was a 74-year-old male with coronary artery disease presented with a left upper tract mass with positive urine cytology showing high-grade UC (HGUC). He underwent four cycles of gemcitabine and cisplatin, with imaging findings showing stable left renal pelvis mass. A radical NU was performed, and the final pathology showed ypT3pNxMx HG UTUC with glandular and focal squamous differentiation ([Figure 2](#)). While stable findings were seen without evidence of distant disease, eventual death ensued from cardiovascular disease.

Clinical case 2

Case 2 was a 58-year-old male who underwent biopsy of a left kidney tumor, which revealed HG UTUC. He then underwent left NU, which showed pT3NxMx UC with squamous differentiation of 40%. A re-staging computed tomography (CT) scan showed multiple lung nodules, a liver mass, and retroperitoneal (RP)

Table 1. Clinical, genomic characteristics, and Decipher® results

Case characteristics	Case 1	Case 2	Case 3	Case 4
Age/Sex	72/Male	57/Male	80/Female	64/Male
Upper tract location	Renal pelvis and ureter	Renal pelvis and ureter	Renal pelvis	Renal pelvis
Initial stage	III	IV	III	IV
Metastatic (Y/N); N; N/A sites		Y; lung, bronchus	Y; RP nodes, liver	Y; spine osseous
Neoadjuvant chemo (Y/N); cycles	Y; 3	N; N/A	N; N/A	N; N/A
Treatment response	Residual ypT3 after NAC but without metastatic disease	Progressive disease	Progressive disease	Initial stable disease then progressive disease
Final clinical stage	Stage III	Stage IV	Stage IV	Stage IV
Final pT stage	ypT3	pT3cN1cM1	pT3cN2Mx	pT3aNxM1
Variant histology	HG UTUC with glandular and focal squamous differentiation	HG UTUC with squamous differentiation of 40%	Pure HG UTUC	HG UTUC with 30% sarcomatoid features and 20% necrosis
Decipher® subtype probability	Basal probability 53.4%/Basal Claudin-low 43%	Basal probability 80.4%	Basal probability 82.4%	Basal probability 39.4%/Basal Claudin-low probability 43.5%
Decipher subtype	Basal/Basal Claudin-low	Basal	Basal	Basal/Basal Claudin-low
Consensus subtype	Stroma-rich	Basal/Squamous	Basal/Squamous	Stroma-rich
UNC subtype	Basal	Basal	Basal	Basal
FGFR3 activity class	inactive	inactive	inactive	inactive
Immune190 score	0.70	0.27	0.68	0.48
ESTIMATE stromal score	3,675	-875	1,889	2,245
Foundation medicine (NGS results)	N/A	PD-L1 TPS 1%; MS-Stable; TMB—6 Muts/Mb; CASP8 loss exons 3-7; CDKN2A loss; CDKN2B loss; HRAS G12S; MTAP loss; TERT promoter -124C>T; VUS: BTK Y418H; CDH1 V794I; CSF1R V48M; HRAS L163fs*52; MITF E207G; NOTCH3 S872F; RBM10 G280V; RPTOR D821N; SNCAIP R269Q; TSC2 R1268H	MS-Stable; TMB—11 Muts/Mb; AKT2 amplification; CDKN2A loss; CDKN2B loss; ERBB3 E332K; KDM6A Q670*; MTAP loss; RAF1 amplification; TERT promoter -124C>T; TP53 loss	N/A
Overall survival	36.6 mos	8.7 mos	10.8 mos	14.2 mos
Progression free survival	N/A	6 mos	0.7 mos	2.5 mos
Decipher gene outlier category	Immune activation/angiogenesis	FGF/ADC	Immune activation/angiogenesis	Immune activation

HG UTUC: high-grade upper tract urothelial carcinoma; mos: months; N/A: not applicable; NAC: neoadjuvant chemotherapy; RP: retroperitoneal; TPS: tumor proportion score; VUS: variants of unknown significance; UNC: University of North Carolina; NGS: next generation sequencing; PD-L1: programmed death ligand 1; TMB: tumor mutational burden; FGFR: fibroblast growth factor receptor

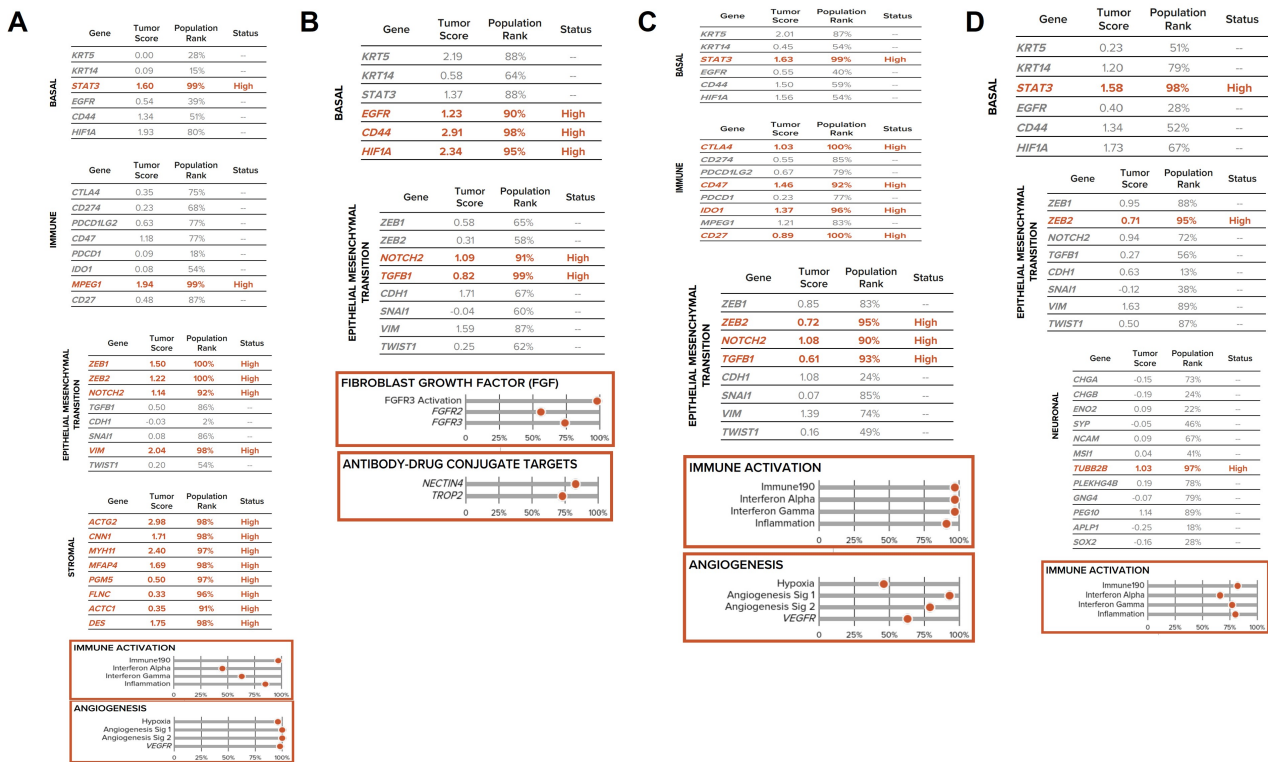


Figure 1. Bladder Decipher® GRID. A. Pertains to clinical case 1; B. pertains to clinical case 2; C. pertains to clinical case 3; D. pertains to clinical case 4. Selected marker expression from the Bladder Decipher® Grid which contains RNA expression values with the list of 48 genes grouped according to biological modules of luminal, basal, immune, epithelial-mesenchymal transition, stromal, and neuronal. The population rank refers to the percentage of tumor RNA profiles in the GRID Reference population. The bottom panel shows the genomic atlas or gene expression signatures that defines tumor biology

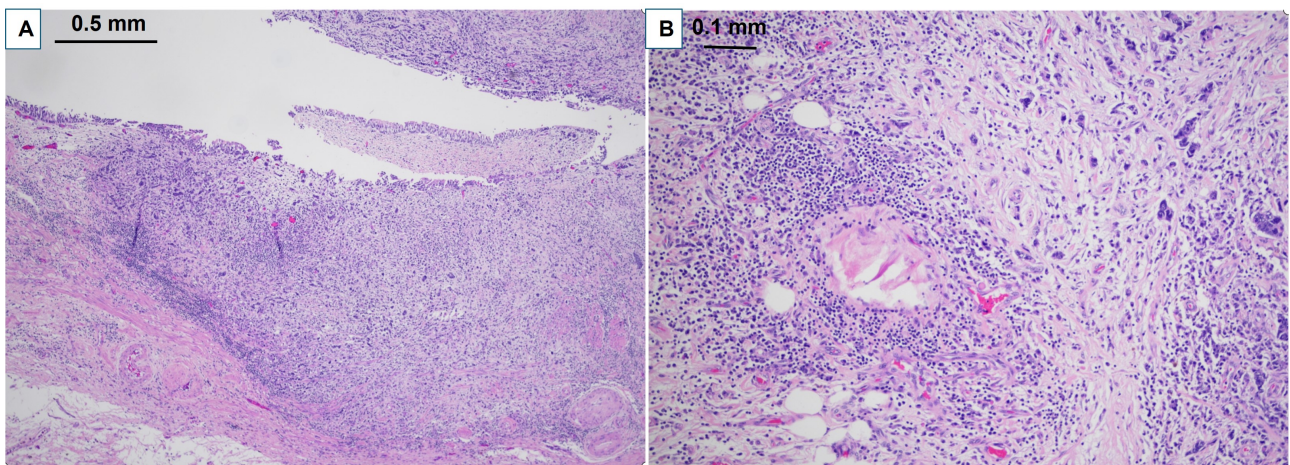


Figure 2. Pathological findings on H&E for clinical case 1. A. Clinical case 1 pathological staging ypT3 high grade urothelial carcinoma with glandular and focal squamous differentiation involving the renal pelvis (40× H&E); B. high grade urothelial carcinoma extending into peri pelvic adipose tissue (100× H&E)

adenopathy. A subsequent CT-guided liver biopsy showed benign liver tissue, but a follow-up re-staging scan identified a new left hilar mass (Figure 3) and enlarging lung nodules. An endobronchial ultrasound-guided fine-needle aspiration biopsy of the hilar mass confirmed metastatic HGUC. He was started on four cycles of gemcitabine and carboplatin, with a bronchial stent placement required due to worsening lung lesions. The patient transitioned to comfort care given lack of response to treatment.

Clinical case 3

Case 3 involved an 80-year-old female who presented with a left renal pelvis mass and underwent left renal pelvis washing and biopsy, which showed HGUC. Further staging CT scan showed a small, non-specific 3 mm lung nodule. She then proceeded with left NU, which showed pT3pNxMx UC (Figure 4) with

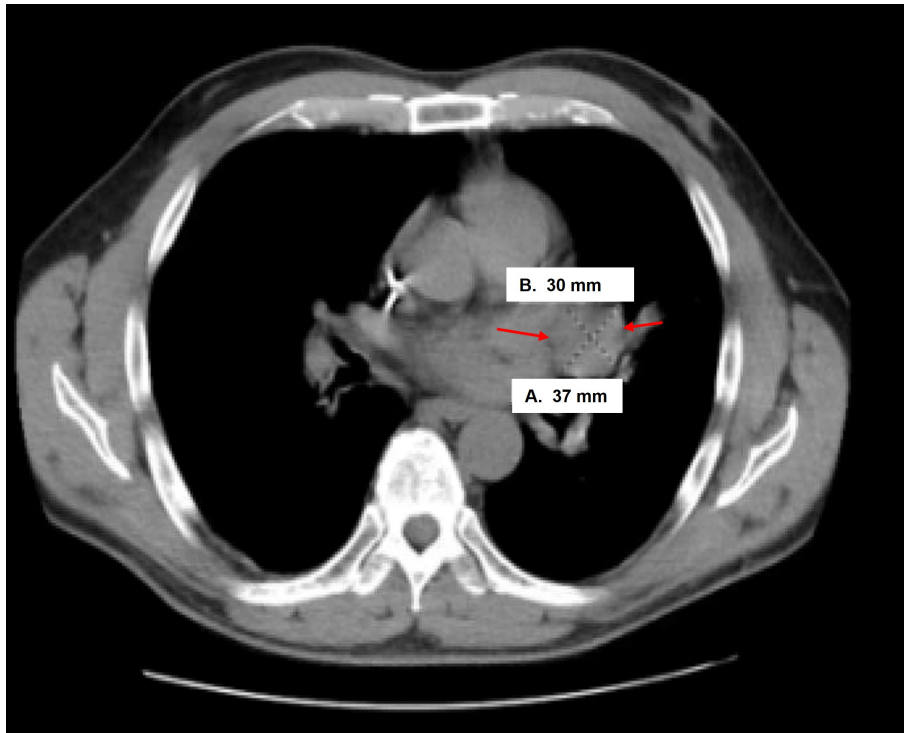


Figure 3. Computed tomography (CT) scan findings of clinical case 2 with enlarging hilar mass at 30 mm × 37 mm size (arrows)

carcinoma in situ. She opted not to undergo adjuvant chemotherapy, but then subsequent re-staging CT showed prominent RP adenopathy, prompting the initiation of chemotherapy with gemcitabine and carboplatin for three cycles. However, due to worsening pain, another scan was performed which revealed an interval increase in RP and left periaortic adenopathy. Given these results, she was switched to pembrolizumab but only received two cycles before developing new liver metastases (Figure 5). This new development led to the patient’s eventual transition to hospice care.

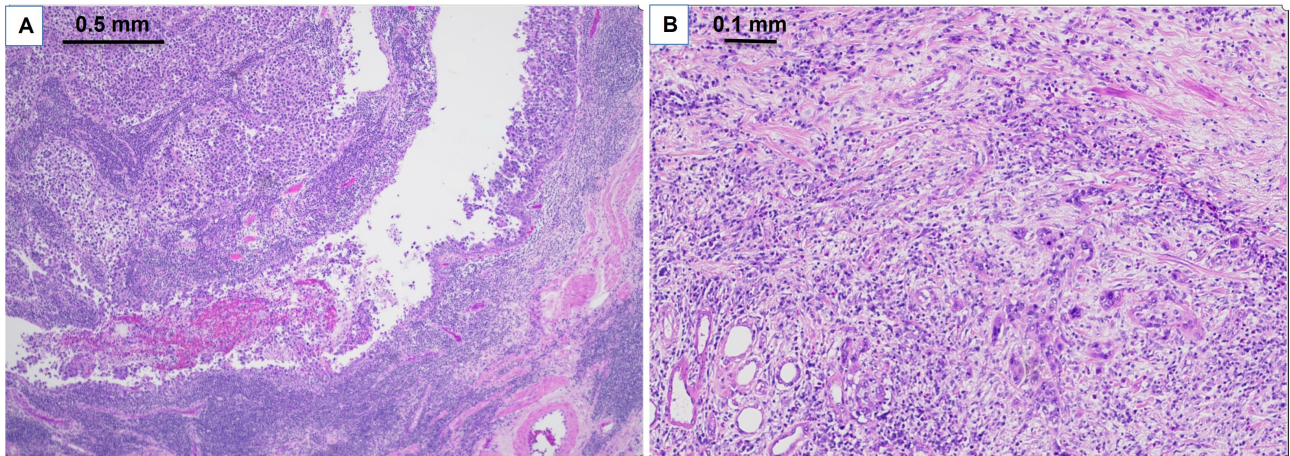


Figure 4. Pathologic findings on H&E for clinical case 3. A. Clinical case 3 pathological staging pT3 high grade papillary urothelial carcinoma of renal pelvis (40× H&E); B. high grade papillary urothelial carcinoma invades renal parenchyma (100× H&E)

Clinical case 4

Case 4 is a 66-year-old male without significant prior history presented with a heterogeneously enhancing mass in the left renal pelvis with a biopsy showing papillary UC. He underwent a left radical NU, which showed pT3pN0Mx UC with 30% sarcomatoid features and 20% necrosis. Following surgery, he presented with back pain, and a subsequent scan demonstrated L3 lesion consistent with metastatic UC. He underwent an L3 partial vertebrectomy and laminectomy and received palliative radiation. He was then

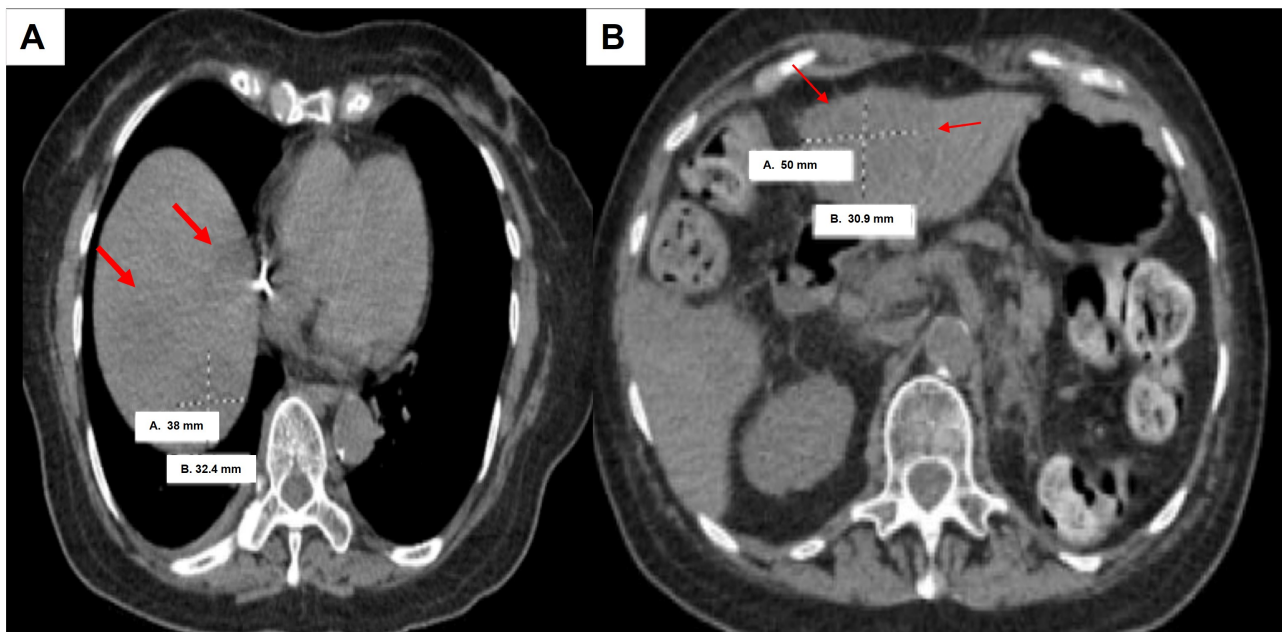


Figure 5. Computed tomography (CT) scan of clinical case 3 showing liver metastases (red arrows) and largest size measuring 38 mm × 32.4 mm

treated with six cycles of gemcitabine and carboplatin, but experienced worsening weakness and an enlargement of a soft tissue mass at T12, requiring additional palliative radiation. Despite these efforts, further progression of the disease led to his eventual transition to hospice care.

Discussion

UTUC makes up only a fraction of cases of UC but tends to be more aggressive in its course [13]. Systemic therapy follows closely the treatment used in bladder cancers [1]. Decipher Bladder[®] assay is a genomic subtyping tool that has been shown to predict response to NAC in muscle-invasive bladder cancers (MIBC) [6]. In addition, the standard treatment for UTUC involves surgery with NU in early stages for high-grade disease though NAC followed by surgery is frequently used in clinical practice [1]. Patients in this series all received chemotherapy, but only case 1 underwent NAC followed by NU. While all three other cases underwent NU upfront, all eventually got diagnosed with metastatic disease and received further platinum-based chemotherapy for metastatic disease but all cases quickly progressed thereafter.

The four cases presented in our series (Table 1) had mixed stages and clinical course. Only case 1 remained locally advanced stage (stage III) and underwent NAC with residual ypT3 disease after NU. Unfortunately, this patient succumbed to cardiovascular morbidity, resulting in a non-cancer-related death. The remaining three cases, none of whom have prior NAC exposure, quickly progressed to metastatic disease, and showed poor overall response to systemic therapy.

All four cases had basal molecular markers, although two patients had additional mixed claudin-low molecular subtype with increased stromal markers on the Decipher Bladder[®] GRID (Figure 1). This led to their classification among the stroma-rich subtype by the consensus subtyping model [14]. Of interest, both case 1 and 4 had basal and basal/claudin-low molecular subtype but their clinical course and phenotype differed. Case 1 manifested residual ypT3 HGUC after NAC but remained non-metastatic, whereas case 4 showed a sarcomatoid component on immunohistochemistry. These factors likely portended poor outcomes regardless of chemotherapy treatment.

The co-occurrence of non-luminal subtype and sarcomatoid variant histology has been reported in other series where basal MIBC have been enriched with both squamous and sarcomatoid features, which can be associated with metastatic disease or advanced stage at presentation [15, 16]. Furthermore, low expression of keratin 5/6 (KRT 5/6) and KRT14 is also consistent with sarcomatoid transition with loss of

epithelial markers [17]. While several mutations were notable in case 2, the rapid progression of the disease did not allow for any further switch in treatment.

The genomic characteristics of patients who undergo NU and their association with response to systemic chemotherapy in UTUC have not been studied extensively. In contrast, molecular markers in bladder cancer have been evaluated and suggested to predict both pathological upstaging at radical cystectomy and response to NAC. Non-luminal tumors have shown higher rates of pathological upstaging in the cystectomy-only setting without NAC [9] and were suggested to benefit most from NAC in a separate multi-institutional MIBC study [18]. Notably, all four cases within the present UTUC profiling study had a non-luminal subtype, with only one out of four cases being treated with NAC. Although none of these cases showed a convincing response, the aggressive behavior of non-luminal tumors was validated in the present study as reflected by high pathologic tumor stage. Moreover, whereas previous efforts on transcriptomic subtyping revealed many luminal-type tumors among UTUC [19], the present study solely included non-luminal tumors.

In addition to observing a luminal subtype in UTUC, Robinson et al. [19] described UTUC having a T-cell depleted contexture. In our study, two out of four non-luminal cases harbored substantial signal for the claudin-low subtype, a subtype previously described to have increased levels of immune signatures and suggested to benefit from systemic neoadjuvant pembrolizumab [20]. Lastly, although activated *FGFR3* signaling has been observed in UTUC [19], it was not evident in the present study when evaluating an *FGFR3* activity signature (Table 1) [21]. Furthermore, Foundation DNA analysis results did not show any *FGFR*-related DNA alterations. As such, both the non-luminal transcriptomic subtypes and lack of *FGFR*-related DNA alterations in the present case-series may represent UTUC cases with more aggressive biology, reflected by their clinical course associated with poor outcomes.

The initial goal of this small pilot project was to determine feasibility and pave the way for a future prospective trial to predict the response to NAC in UTUC. However, since the initiation of this project, additional studies, including the POUT trial, have demonstrated the benefits of adjuvant chemotherapy, revealing an improvement in three-year DFS in favor of adjuvant chemotherapy [2]. In addition, the CheckMate 274 trial showed that adjuvant nivolumab improved DFS, although the subgroup of UTUC patients who were capped at 20% enrollment had seemingly suboptimal responses with subgroup analyses hazard ratios for disease recurrence or death of 1.23 and 1.56 for renal pelvis and ureter, respectively [22].

Understanding the biologic aspects may help prioritize UTUC patients to certain types of systemic therapy in a prospective manner. It is important to note that this case series has several limitations, including the small retrospective nature, the wide heterogeneity of the population with mixed stages, and inconsistent availability of genomic sequencing platform other than the molecular subtyping.

In summary, our study evaluated the feasibility of obtaining molecular subtyping information from UTUC specimens and provided potential feasibility and increased understanding of genomics in UTUC. While a prospective trial may assess whether molecular biomarkers could predict response to NAC, it is yet unclear whether these studies could facilitate future sparing of completion NU in those who achieve complete or partial response. In addition, the real-world application of next generation sequencing as a tool to be used for clinical judgement in UTUC patients requires further clarification in a larger cohort study. Furthermore, the future role of biomarkers including ctDNA, may help further refine the molecular landscape of the UTUC patient population.

Abbreviations

CT: computed tomography

DFS: disease-free survival

HG UTUC: high-grade upper tract urothelial carcinoma

HGUC: high-grade urothelial cancer

MIBC: muscle-invasive bladder cancers

NAC: neoadjuvant chemotherapy

NU: nephroureterectomy

RP: retroperitoneal

UC: urothelial cancer

UTUC: upper tract urothelial cancer

Declarations

Acknowledgments

Special thanks to Inova Schar Cancer Institute Clinical trials research office under Stephanie Van Bebbler. Acknowledgement to Ewan Gibb, PhD, former Vericyte Scientist for the conduct of this study. This study was in part included as presented Belay et al., *Journal of Clinical Oncology*; 41 (16) suppl e16578 at the American Society Clinical Oncology (ASCO) Annual Meeting 2023 (cited Reference # 12).

Author contributions

JBAC: Conceptualization, Investigation, Writing—original draft, Writing—review & editing, Validation, Supervision. JJdJ and ED: Conceptualization, Investigation, Writing—original draft, Writing—review & editing, Validation. WL: Writing—original draft, Writing—review & editing, Visualization, Investigation. MWH, SB, and JK: Writing—original draft, Writing—review & editing, Investigation. All authors read and approved the submitted version.

Conflicts of interest

JBAC received Speakers' Bureau and Advisory board fees from BMS, Astellas/Seagen Pfizer, EMD Serono, Merck KGaA; and also received advisory board fees from Pfizer, EMD Serono, Merck, AVEO, Immunomedics, Astellas/Seagen, Janssen, Bayer, Novartis. JJdJ reports being a consultant for Veracyte. ED reports employee of Veracyte. All other authors declare that they have no conflicts of interest.

Ethical approval

This study was approved by the Inova IRB (Inova IRB # 16-2259).

Consent to participate

Consent to participate was waived and exempt according to the section 46.116 (d) conditions of the IRB approval and review expedited.

Consent to publication

Consent to publication was waived and exempt according to the section 46.116 (d) conditions of the IRB approval and review expedited.

Availability of data and materials

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

Funding

This project was funded by the Inova Institutional Research Seed Grant. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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References

1. Campbell MT, Shah AY, Matin SF, Siefker-Radtke AO. Optimizing management of upper tract urothelial carcinoma. *Urol Oncol*. 2017;35:492–8. [DOI] [PubMed]
2. Birtle A, Johnson M, Chester J, Jones R, Dolling D, Bryan RT, et al. Adjuvant chemotherapy in upper tract urothelial carcinoma (the POUT trial): a phase 3, open-label, randomised controlled trial. *Lancet*. 2020;395:1268–77. [DOI] [PubMed] [PMC]
3. Leow JJ, Chong YL, Chang SL, Valderrama BP, Powles T, Bellmunt J. Neoadjuvant and Adjuvant Chemotherapy for Upper Tract Urothelial Carcinoma: A 2020 Systematic Review and Meta-analysis, and Future Perspectives on Systemic Therapy. *Eur Urol*. 2021;79:635–54. [DOI] [PubMed]
4. Coleman JA, Yip W, Wong NC, Sjoberg DD, Bochner BH, Dalbagni G, et al. Multicenter Phase II Clinical Trial of Gemcitabine and Cisplatin as Neoadjuvant Chemotherapy for Patients With High-Grade Upper Tract Urothelial Carcinoma. *J Clin Oncol*. 2023;41:1618–25. [DOI] [PubMed] [PMC]
5. NCCN Guidelines: Bladder Cancer [Internet]. National Comprehensive Cancer Network; 2024 [cited 2024 Jul 1]. Available from: <https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1417>
6. Lotan Y, de Jong JJ, Liu VYT, Bismar TA, Boorjian SA, Huang HC, et al. Patients with Muscle-Invasive Bladder Cancer with Nonluminal Subtype Derive Greatest Benefit from Platinum Based Neoadjuvant Chemotherapy. *J Urol*. 2022;207:541–50. [DOI] [PubMed]
7. Decipher Bladder[®] Test [Internet]. Veracyte, Inc; 2024 [cited 2024 Jul 1]. Available from: <https://decipherbio.com/bladder/>
8. Seiler R, Ashab HAD, Erho N, van Rhijn BWG, Winters B, Douglas J, et al. Impact of Molecular Subtypes in Muscle-invasive Bladder Cancer on Predicting Response and Survival after Neoadjuvant Chemotherapy. *Eur Urol*. 2017;72:544–54. [DOI] [PubMed]
9. Lotan Y, Boorjian SA, Zhang J, Bivalacqua TJ, Porten SP, Wheeler T, et al. Molecular Subtyping of Clinically Localized Urothelial Carcinoma Reveals Lower Rates of Pathological Upstaging at Radical Cystectomy Among Luminal Tumors. *Eur Urol*. 2019;76:200–6. [DOI] [PubMed]
10. Batista da Costa J, Gibb EA, Bivalacqua TJ, Liu Y, Oo HZ, Miyamoto DT, et al. Molecular Characterization of Neuroendocrine-like Bladder Cancer. *Clin Cancer Res*. 2019;25:3908–20. [DOI] [PubMed]
11. Grivas P, Bismar TA, Alva AS, Huang HC, Liu Y, Seiler R, et al. Validation of a neuroendocrine-like classifier confirms poor outcomes in patients with bladder cancer treated with cisplatin-based neoadjuvant chemotherapy. *Urol Oncol*. 2020;38:262–8. [DOI] [PubMed]
12. Belay S, Li W, Aragon-Ching JB. Upper tract urothelial cancer (UTUC): Role of sequencing, molecular subtyping and treatment outcomes. *J Clin Oncol*. 2023;41:e16578. [DOI]
13. Aragon-Ching JB, Wang H. Contemporary treatment and survival differences in patients with urothelial versus nonurothelial bladder and upper tract carcinomas: Analyses from the National Cancer Database (NCDB). *J Clin Oncol*. 2022;40:463. [DOI]
14. Kamoun A, de Reyniès A, Allory Y, Sjödaahl G, Robertson AG, Seiler R, et al.; Bladder Cancer Molecular Taxonomy Group. A Consensus Molecular Classification of Muscle-invasive Bladder Cancer. *Eur Urol*. 2020;77:420–33. [DOI] [PubMed] [PMC]
15. Choi W, Czerniak B, Ochoa A, Su X, Siefker-Radtke A, Dinney C, et al. Intrinsic basal and luminal subtypes of muscle-invasive bladder cancer. *Nat Rev Urol*. 2014;11:400–10. [DOI] [PubMed]
16. Narayan VM, Gupta S, Davicioni E, Murugan P, Gibb EA, Konety B. Genomic Analysis and Treatment Response of a Bladder Urothelial Carcinoma With Sarcomatoid Variant Histology. *Clin Genitourin Cancer*. 2019;17:e888–92. [DOI] [PubMed]
17. Genitsch V, Kollár A, Vandekerckhove G, Blarer J, Furrer M, Annala M, et al. Morphologic and genomic characterization of urothelial to sarcomatoid transition in muscle-invasive bladder cancer. *Urol Oncol*. 2019;37:573.e19–29. [DOI] [PubMed]

18. McConkey DJ, Choi W, Shen Y, Lee IL, Porten S, Matin SF, et al. A Prognostic Gene Expression Signature in the Molecular Classification of Chemotherapy-naïve Urothelial Cancer is Predictive of Clinical Outcomes from Neoadjuvant Chemotherapy: A Phase 2 Trial of Dose-dense Methotrexate, Vinblastine, Doxorubicin, and Cisplatin with Bevacizumab in Urothelial Cancer. *Eur Urol.* 2016;69:855–62. [DOI] [PubMed] [PMC]
19. Robinson BD, Vlachostergios PJ, Bhinder B, Liu W, Li K, Moss TJ, et al. Upper tract urothelial carcinoma has a luminal-papillary T-cell depleted contexture and activated FGFR3 signaling. *Nat Commun.* 2019; 10:2977. [DOI] [PubMed] [PMC]
20. Necchi A, Raggi D, Gallina A, Ross JS, Farè E, Giannatempo P, et al. Impact of Molecular Subtyping and Immune Infiltration on Pathological Response and Outcome Following Neoadjuvant Pembrolizumab in Muscle-invasive Bladder Cancer. *Eur Urol.* 2020;77:701–10. [DOI] [PubMed]
21. de Jong JJ, Liu Y, Robertson AG, Seiler R, Groeneveld CS, van der Heijden MS, et al. Long non-coding RNAs identify a subset of luminal muscle-invasive bladder cancer patients with favorable prognosis. *Genome Med.* 2019;11:60. [DOI] [PubMed] [PMC]
22. Bajorin DF, Witjes JA, Gschwend JE, Schenker M, Valderrama BP, Tomita Y, et al. Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma. *N Engl J Med.* 2021;384:2102–14. [DOI] [PubMed] [PMC]