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Validation of Keratin 17 as a tissue biomarker in the diagnosis of upper tract urothelial carcinoma

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ABSTRACT

Upper tract urothelial carcinoma (UTUC) has a relatively low incidence but presents significant surveillance and treatment challenges. Therefore, novel biomarkers for the accurate detection of upper tract urothelial tumors are urgently needed. We evaluated the expression of Keratin 17 (KRT17), an oncoprotein implicated in the cell cycle progression of multiple human cancers and previously studied in bladder urothelial carcinoma, by immunohistochemistry in 139 UTUC cases, including noninvasive, invasive papillary urothelial carcinoma and urothelial carcinoma in situ. KRT17 expression pattern (basal/negative vs. nonbasal) and H-score were evaluated. The expression pattern was significantly different in normal (NL) compared to malignant urothelium. Nonbasal KRT17 expression was significantly higher in pTa ($p < 0.001$) and invasive (pTinv) ($p = 0.0023$) urothelial carcinoma compared to NL, and in pTinv compared to pTa ($p = 0.0391$). Sensitivity and specificity for distinguishing benign from malignant tumors were 85% and 82, respectively, with an area under the curve of 0.83 ($p < 0.001$). The KRT17 H-score was significantly higher in pTa and pTinv compared to NL ($p < 0.001$ and $p = 0.0035$, respectively). Sensitivity and specificity for distinguishing benign from malignant carcinoma were 91% and 69%, respectively, with an AUC of 0.81 ($p = 0.0010$). KRT17 was not associated with tumor site, grade, or stage.

In summary, K17 is a sensitive and specific marker of neoplastic upper tract urothelium, and its potential use in routine diagnostics should be explored in larger studies.

1. Introduction

Upper tract urothelial carcinoma (UTUC) is an uncommon, but burdensome and potentially lethal cancer. Though overall population incidence is low at approximately 2 cases per 100,000, among patients with urothelial tumors, upper tract tumors make up about 5–10% of diagnoses [1]. Up to 30% of upper tract tumors are multifocal (involving multiple areas in the ureter or renal pelvis) [2]. Furthermore, about 1.6% of patients with UTUC develop bilateral disease affecting both kidneys/ureters [3], presenting significant surveillance and treatment challenges, as does metachronous development of UTUC in the contralateral kidney or ureter after surgical treatment due to the presence of a solitary renal unit.

Initial diagnosis and post-treatment monitoring of UTUC frequently requires a combination of imaging studies (computed tomography urography, magnetic resonance urography), endoscopic evaluation using diagnostic ureteroscopy, and monitoring of urine cytology [4]. The burden of surveillance and associated costs for patients with this disease are high, with many patients requiring endoscopic surveillance in the operating room as frequently as every 3 months [4]. Furthermore, diagnostic evaluation of the upper tract presents difficulties on both cytology and biopsies. Challenges in accessing the upper tract with complicated retrograde access secondary to ureter anatomy render sampling technically difficult [5] and have been shown to affect reliability, especially as it pertains to concordance between endoscopic biopsy and final surgical specimen for low-grade disease [6].

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Table 1
Clinico-pathologic characteristics of the patients' cohort.

Variable	N (%)	N (%)	Total N
Site			139
Pelvis	73 (52)		
Pelvis-ureter	20 (15)		
Ureter	46 (33)		
Grade			139
High grade papillary	96 (69)		
Low grade papillary	38 (27)		
CIS (pure)	5 (4)		
pT Stage (HG)			101
pTa	23 (23)		
pTis (pure)	5 (5)		
pT1	26 (26)		
pT2	16 (16)		
pT3	27 (27)		
pT4	4 (4)		

Furthermore, differing morphologic features may limit urine cytology interpretation from this region [7]. Thus, there is currently a significant need to utilize novel biomarkers for both initial diagnosis as well as surveillance after treatment due to the burden of endoscopic or imaging-based surveillance.

Keratin 17 (KRT17) is an oncoprotein that has been implicated in the cell cycle progression of multiple human cancers [8–13]. Keratins are members of the intermediate filament protein family, which, along with microfilaments (composed by actin), and microtubules (composed by tubulin), compose the cytoskeleton. Intermediate filaments are coded by 70 genes with tissue- and differentiation-dependent expression patterns [14], of which 54 code for keratins expressed in epithelia. These epithelial-specific keratin genes are classified into 28 type I and 26 type II genes. Type I keratin genes, except K18 gene, are clustered on the long arm of human chromosome 17, whereas type II keratin genes and type I K18 gene are clustered on the long arm of human chromosome 12 [14]. KRT17 belongs to the type I intermediate family and is mainly localized in the epithelial appendages, such as hair follicles and sebaceous glands [15]. KRT17 is not expressed in normal skin, but its expression can be induced under stress [16]. In recent years, KRT17 expression has been found to be increased or decreased in several tumor types, including breast, oropharyngeal, esophageal, gastric, pancreatic, thyroid, lung, colorectal, endometrial, cervical, and ovarian carcinoma, Ewing's sarcoma and osteosarcoma [17–20]. KRT17 has also been associated with tumor growth, invasiveness, pathologic predictors of poor prognosis [21], decreased survival and relapse-free survival [8,17–19,22]. In prior work reported by Babu et al. in bladder specimens, tissue and urine evaluation was performed using immunohistochemistry on formalin-fixed, paraffin-embedded tissue and in urine samples from patients with both normal tissue and biopsy-proven urothelial carcinoma of the bladder (both low and high-grade). This analysis demonstrated that KRT17 detection was both sensitive and specific for detecting low or high-grade urothelial carcinoma compared to normal cells [9].

The previous validation of KRT17 in urothelial carcinoma of the bladder provides the closest insights into the potential diagnostic validity of the oncoprotein in UTUC, although genomic differences driving oncogenesis between urothelial carcinoma and UTUC warrant further independent investigation of KRT17 in upper tract specimens Therefore, we sought to determine the diagnostic performance of KRT17 in UTUC tissue specimens obtained for diagnosis (endoscopic biopsy) and/or at the time of treatment (radical nephroureterectomy).

2. Methods

The study was approved by the Vanderbilt Institutional Review Board (IRB #212141). A retrospective search of the pathology files at Vanderbilt University Medical Center from 2005 to 2021 for consecutive nephroureterectomy specimens was conducted to identify histologically confirmed cases of low and high-grade UTUC. Variant urothelial histology, malignancy of non-upper tract urothelial origin, and cases with inadequate tissue for immunohistochemical analysis were excluded. All cases were re-reviewed by a urologic pathologist (GAG), and re-evaluation was performed based on contemporary criteria. One representative tumor block per case containing the best representation of the tumor was selected for immunohistochemistry (IHC).

KRT17 IHC was performed on Autostainer Link 48 (Agilent, Santa Clara, CA, USA) based on method previously described [9]. Briefly, formalin-fixed, paraffin-embedded tissue blocks were sectioned, mounted on charged glass slides, and deparaffinized. Antigen retrieval was performed on Autostainer Link 48 at 97 °C for 20 min using the manufacturer's standard protocol (Agilent, Santa Clara, CA, USA). Sections were incubated for 60 min with mouse monoclonal anti-human KRT17 antibody (KDX1 URO17 antibody, KDx Diagnostics, San Jose, CA USA). Following incubation with the primary antibody, slides were processed by Autostainer Link 48 using EnVision FLEX + reagent system including FLEX + Mouse LINKER (Agilent, Santa Clara, CA, USA), developed in 3,3 diaminobenzidine (DAB), and counterstained with hematoxylin. Scoring of KRT17 expression was carried out by analysis of two variables, namely H-score and expression pattern. H-score was determined as follows: $H = 3 \times$ [% strong stain] $+ 2 \times$ [% moderate stain] + [% weak stain] [23]. Cytoplasmic stain in >10% of cells was considered positive. The expression pattern was dichotomized into basal/negative and nonbasal, the latter including basal/parabasal, full-thickness, full--thickness with basal accentuation, full-thickness/patchy, and patchy focal. Basal distribution in invasive tumors was evaluated as KRT17 expression in the basal layer of the invasive nests, where applicable. As for noninvasive tumors, invasive tumors with KRT17 expression above the basal layer within the invasive nests were classified as having nonbasal distribution. KRT17 expression was independently evaluated on

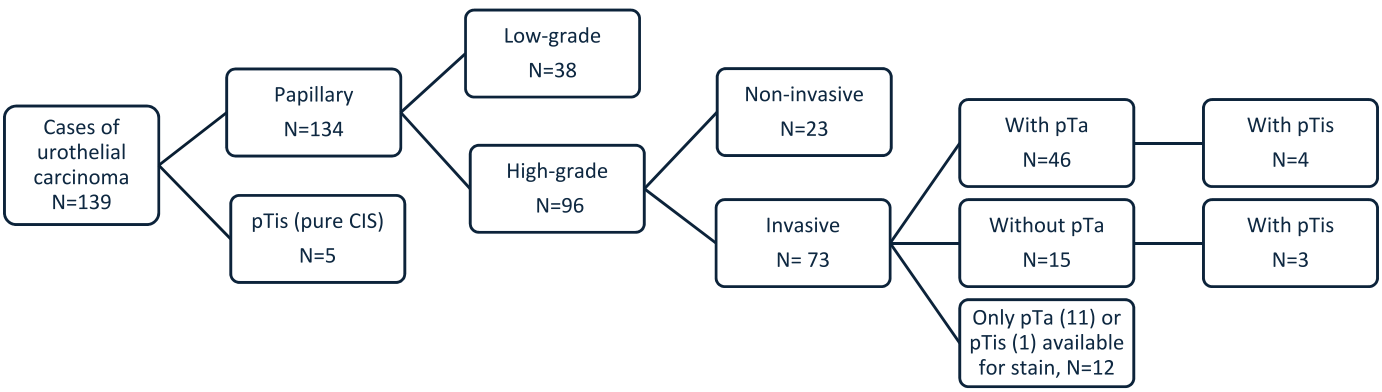

Fig. 1. Flow chart illustrating the distribution of cases included in the study.

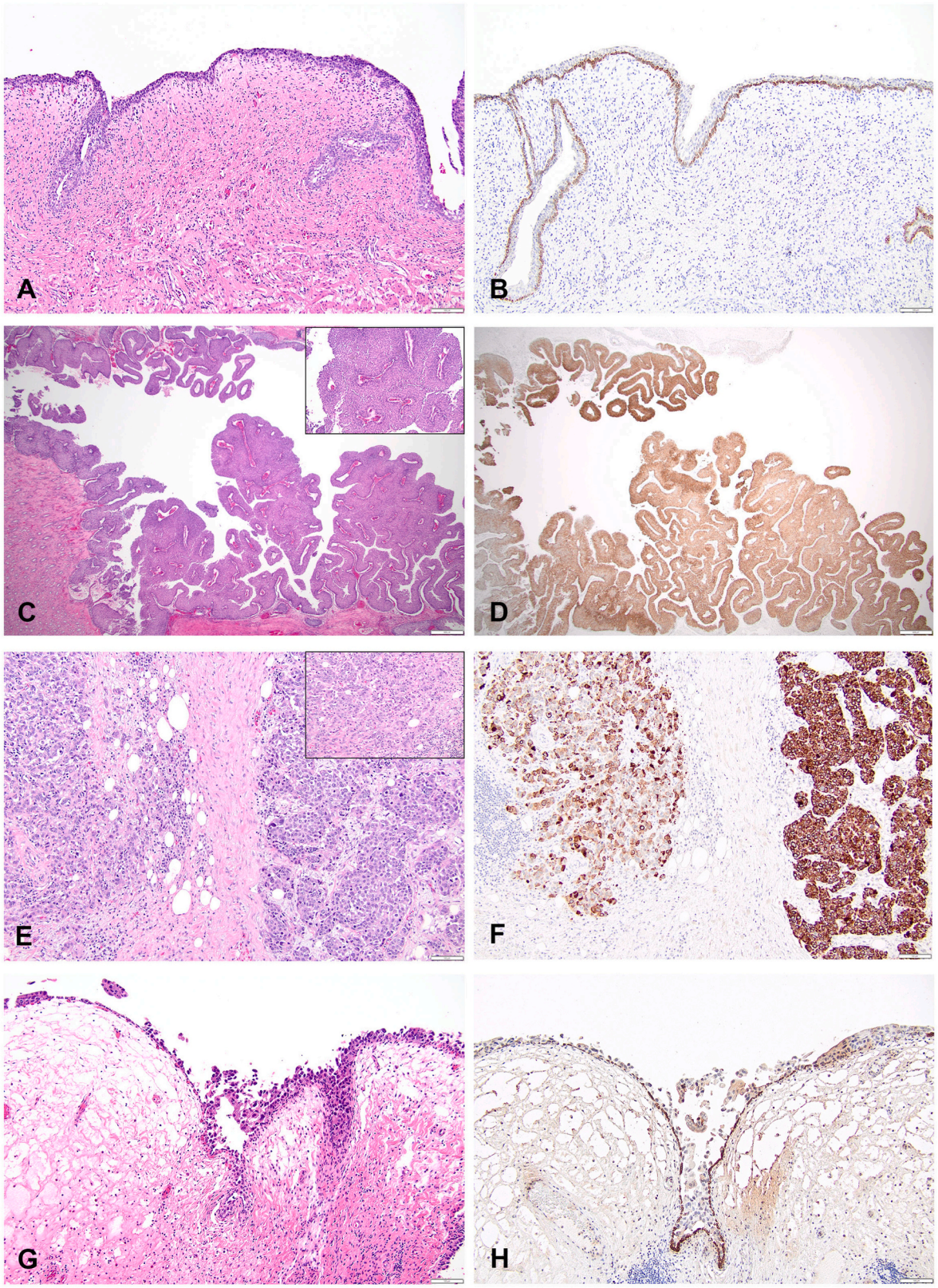

Fig. 2. A) Normal urothelium. B) KRT17 expression with basal distribution. (Magnification, ×100). C) Non-invasive low-grade papillary urothelial carcinoma of the renal pelvis. The inset shows a high-power view of the tumor's cytologic features. D) KRT17 full-thickness expression (Magnification, ×20). E) Invasive component into the peri-pelvic fat of a high-grade papillary urothelial carcinoma of the renal pelvis. Inset shows a high-power view of the tumor cytologic features. F) KRT17 full-thickness expression in the lower half of the picture, and patchy full-thickness expression in the upper half (Magnification, ×100). G) Urothelial carcinoma in situ. H) This case showed KRT17 basal expression with tumor sparing (Magnification, ×100).

Table 2
Keratin 17 expression patterns in normal urothelium and urothelial carcinoma.

	Normal urothelium N (%)	pTa	pTis	pTinv
Basal	45 (82)	18 (15)	5 (38)	3 (5)
Nonbasal	8 (14)	89 (76)	6 (46)	51 (84)
Negative	2 (4)	11 (9)	2 (15)	7 (11)
Total	55 (100)	118 (100)	13 (100)	61 (100)

Abbreviations: pTa = noninvasive papillary urothelial carcinoma or noninvasive component of an otherwise invasive papillary urothelial carcinoma; pTinv = invasive papillary urothelial carcinoma; pTis = urothelial carcinoma in situ or flat in situ component of an otherwise invasive urothelial carcinoma.

Table 3
Comparisons of KRT17 expression pattern in different stages of urothelial carcinoma.

Comparison	Proportion of cases with nonbasal KRT17 expression N (%)				
	pTa	pTinv	pT1is	NL	p[a]
pTa vs NL	89 (75)			8 (15)	< **0.001**
pTinv vs NL		51 (84)		8 (15)	**0.0023**
pTis vs NL			6 (46)	8 (15)	1.0000
pTa vs pTinv	89 (75)	51 (84)			**0.0391**
pTa vs pTis	89 (75)		6 (46)		1.0000
pTinv vs pTis		51 (84)	6 (46)		0.5637

Abbreviations: NL, benign urothelium; pTinv, invasive urothelial carcinoma of various stages.
[a] Wilcoxon matched-pairs signed-rank test.

the in situ and invasive components of the same tumor in cases where these components co-existed.

For H-score assignment, cases with only basal distribution were assigned a score based on the percent of basal cells having strong, moderate, and weak stains. Given that the basal layer represents a small percent of the full-thickness urothelium, these cases tended to have low total H-scores. In addition to assigning an H-score based on the percentage of positive cells, the pattern was also further qualified as "basal". Cases with complete lack of KRT17 expression were assigned an H-score of 0, and the case was further qualified as "negative." Statistical analysis was carried out using STATA version 18 (StataCorp LLC, College Station, TX), NCSS version 2020 (NCSS Inc., Kaysville UT), JMP version 5.0.1 (SAS Institute, Cary NC). Continuous variables were reported as mean, SD, median, min-max for continuous expressions, and N (%) by category for categorical expression. Continuous variables were analyzed using Aspin-Welch and non-parametric Wilcoxon rank-sum test for differences between groups. Categorical expressions were analyzed using Pearson chi-square for differences between groups. Matched pairs analyses were analyzed using *t*-test and Wilcoxon signed-rank test. KRT17 expression levels and their discriminatory power between benign and malignant urothelium were compared by calculating sensitivity and specificity in a receiver operating characteristic (ROC) curve analysis at different intensity cutoffs over the range of observed values for separation (DeLong method). A p value less than 0.05 was regarded as statistically significant.

3. Results

KRT17 was evaluated in 139 UTUC cases, including 38 low-grade noninvasive papillary urothelial carcinomas (LG-pTa), 96 high-grade papillary urothelial carcinomas, including 23 non-invasive (HG-pTa) and 73 invasive (HG-pTinv), and 5 pure carcinomas in situ (pTis). The 73 HG-pTinv included foci of pTa and pTis, which were also used to independently evaluate KRT17 expression. pTis in total were 13. Benign urothelium was present in 55 cases and served as internal control (NL). Tumor site was pelvis (73, 52%), pelvis-ureter (20, 15%), and ureter (46, 33%). Grade was high (101, 73%), including papillary (96, 69%) and flat (5, 4%), and low (38, 28%). Stage was pTa (61, 44%, including the above-mentioned 38 LG and 23 HG-pTa), pTis (5, 5%), pT1 (26, 26%), pT2 (16, 16%), pT3 (27, 27%) and pT4 (4, 4%). Table 1 and Fig. 1 describe the details of the cases included in the study.

Analysis of KRT17 expression pattern showed a basal distribution in most NL cases (Fig. 2A–B), whereas pTa (Fig. 2C–D) and pTinv (Fig. 2E–F) showed nonbasal distribution in most cases. In pTis (Fig. 2G–H), a similar number of cases had basal and nonbasal KRT17 expression (Table 2). In matched pair analysis, the staining pattern (basal/negative vs. nonbasal) was significantly different between NL and malignant urothelium, with nonbasal KRT17 expression being significantly more likely in pTa and pTinv compared to NL (pTa vs. NL, $p < 0.001$; pTinv vs. NL, $p = 0.0023$), but with similar expression in pTis and NL (pTis vs. NL, $p = 1.00$). Amongst malignant histologies, pTinv was significantly more likely to have nonbasal stain ($p = 0.039$) compared to pTa (Table 3). Based on expression pattern, sensitivity, specificity, positive and negative predictive value for distinguishing benign from malignant histology for pTa were 85%, 82%, 91%, and 71%, respectively, with an area under the curve of 0.83 ($p < 0.001$) (Fig. 3A). KRT17 expression pattern was similar in low- and high-grade tumors ($p = 0.74$) as well as in different tumor sites ($p = 0.36$), and stages ($p = 0.31$).

When analyzing the expression intensity in matched pair analysis, the H-score was significantly higher in pTa and pTinv compared to NL ($p < 0.001$ and $p < 0.0035$, respectively). However, there was no significant H-score difference between pTis and NL, pTa vs. pTinv and pTis, and pTinv vs. pTis (Table 4). Sensitivity and specificity for distinguishing benign from malignant (pTa) were 91% and 69%, respectively, with an AUC of 0.81 ($p=<0.0010$) (Fig. 3B). H-score was similar in low- and high-grade tumors ($p = 0.23$), as well as in different tumor sites ($p = 0.42$), and stages ($p = 0.68$).

The H-score distribution by pattern is shown in Fig. 4A. A higher H-score was present in cases with full-thickness distribution. The density plot indicates lower H-score values in pT4, whereas the other stages display values spread through the distribution, suggesting dimming in higher-stage tumors (Fig. 4B). Mosaic plots showed changes from basal or basal/parabasal to full thickness from pTa to pTinv ($p < 0.0001$) (Fig. 4C).

4. Discussion

In prior studies analyzing bladder urothelium, KRT17 expression by immunohistochemistry was found to have a sensitivity of 89% and a specificity of 88% for distinguishing malignant from normal urothelium. Normal urothelium expressed KRT17 in 12% of cases in a basal distribution, while PUNLMP expressed KRT17 in all sampled cases (100%). Furthermore, KRT17 expression was significantly higher in non-papillary compared to papillary and in muscle-invasive compared to non-muscle invasive urothelial carcinoma with a sensitivity of 89% and a specificity of 88% for distinguishing malignant from benign urothelium. KRT17 expression was not associated with patient age or gender. In the same study, KRT17 demonstrated a sensitivity of 100% and a specificity of 96% for urothelial carcinoma in urine specimens [9].

In this study, we show that, similarly to bladder urothelium, KRT17 is expressed in UTUC in a nonbasal distribution in 76% of cases, as opposed to normal urothelium, which demonstrated basal or negative KRT17 expression in 85% of cases. The latter finding supports and validates prior literature [9,24]. KRT17 expression pattern had a sensitivity and specificity of 85% and 82% for distinguishing benign from malignant urothelium, respectively (AUC = 0.83). Furthermore, the expression pattern differed in noninvasive compared to invasive urothelial carcinoma, with invasive carcinoma showing significantly more frequent full-thickness expression than noninvasive carcinoma. Although our pTis cohort was small, and results would require larger scale validation, it is of note that the KRT17 pattern of expression in this

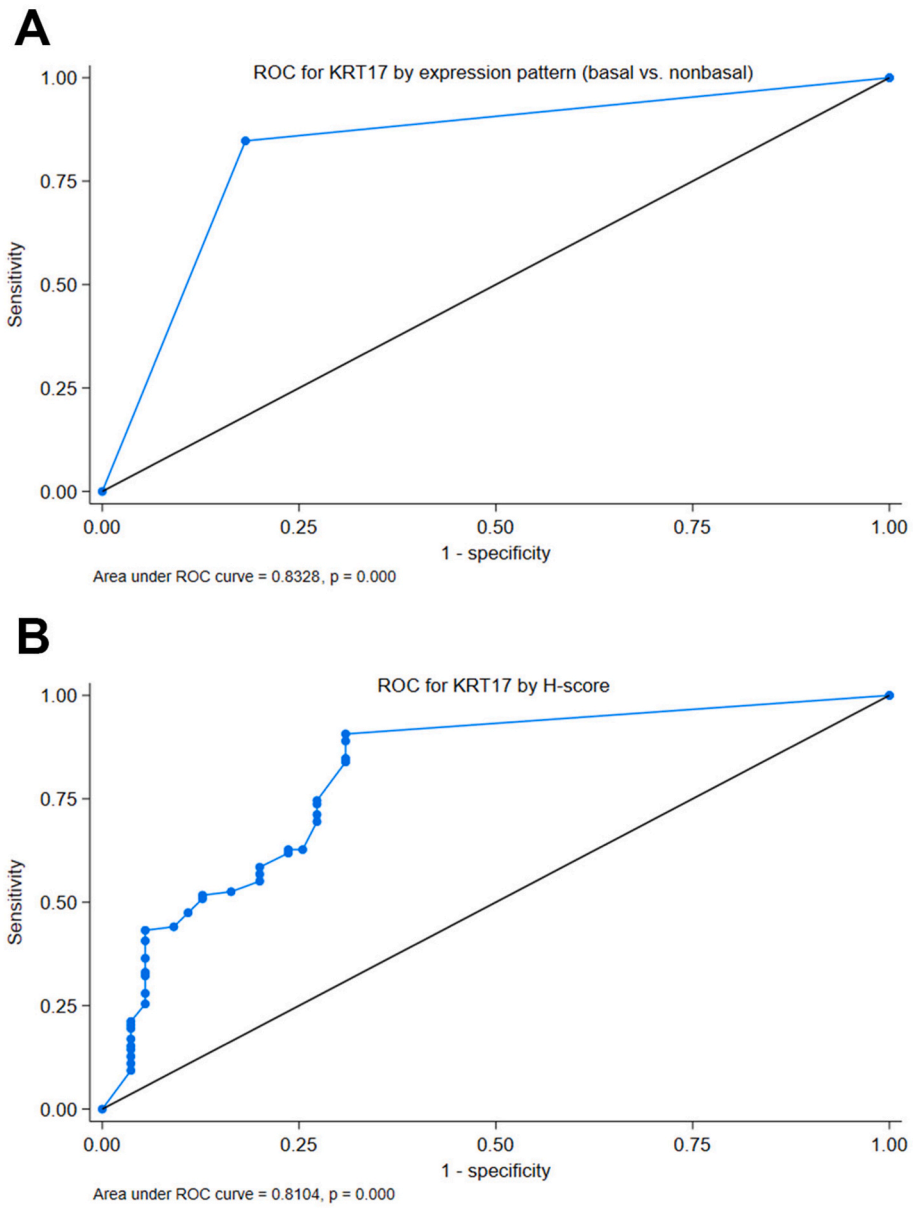

Fig. 3. A) Receiver operating characteristic analysis for Keratin-17 by expression pattern (basal vs. nonbasal) in malignant and normal urothelium. B) Receiver operating characteristic analysis for Keratin-17 by H-score in malignant and normal urothelium. C) Mosaic plots showed changes from basal or basal/parabasal to full-thickness from pTa to pTinv.

Table 4
Comparisons of KRT17 H-scores in different stages of urothelial carcinoma.

Comparison	Mean KRT17 H-Score				
	pTa	pTinv	pT1is	NL	p[a]
pTa vs NL	119			34	< **0.001**
pTinv vs NL		127		34	**0.0035**
pTis vs NL			132	34	0.3961
pTa vs pTinv	119	127			0.2316
pTa vs pTis	119		132		0.1615
pTinv vs pTis		127	132		0.3109

Abbreviations: NL, benign urothelium; pTinv, invasive urothelial carcinoma of various stages.
[a] Wilcoxon matched-pairs signed-rank test.

group was significantly more frequently basal/negative than in pTa and pTinv. These preliminary findings should be further explored. These findings suggest that pattern rather than intensity characterized invasive vs. noninvasive urothelial carcinoma, and that KRT17 could be a useful diagnostic biomarker in routine assessment of urothelial malignancy.

Genomic profiling data have identified differential expression signatures in non-muscle invasive and muscle-invasive bladder cancer. In the latter group, there are two broad molecular subtypes with distinct biological behavior, namely luminal and basal. Over the years, this classification has progressed from an initial mRNA-based to a protein expression-based classification with different class reiteration evolving into the five Lund bladder cancer taxonomy subtypes [25]. These five subtypes have been integrated into six biologically relevant molecular classes in a recent international consensus scheme, namely luminal papillary, luminal nonspecified, luminal unstable, stroma-rich, basal/squamous, and neuroendocrine-like [26]. Tumors from the three luminal classes overexpress urothelial differentiation signatures, including PPARG/GATA3/FOXA1. Basal/squamous and neuroendocrine-like tumors, overexpress gene signatures associated with basal (KRT14, KRT5/6, and a lack of GATA3 and FOXA1) and neuroendocrine differentiation, both with strong enrichment of genomic

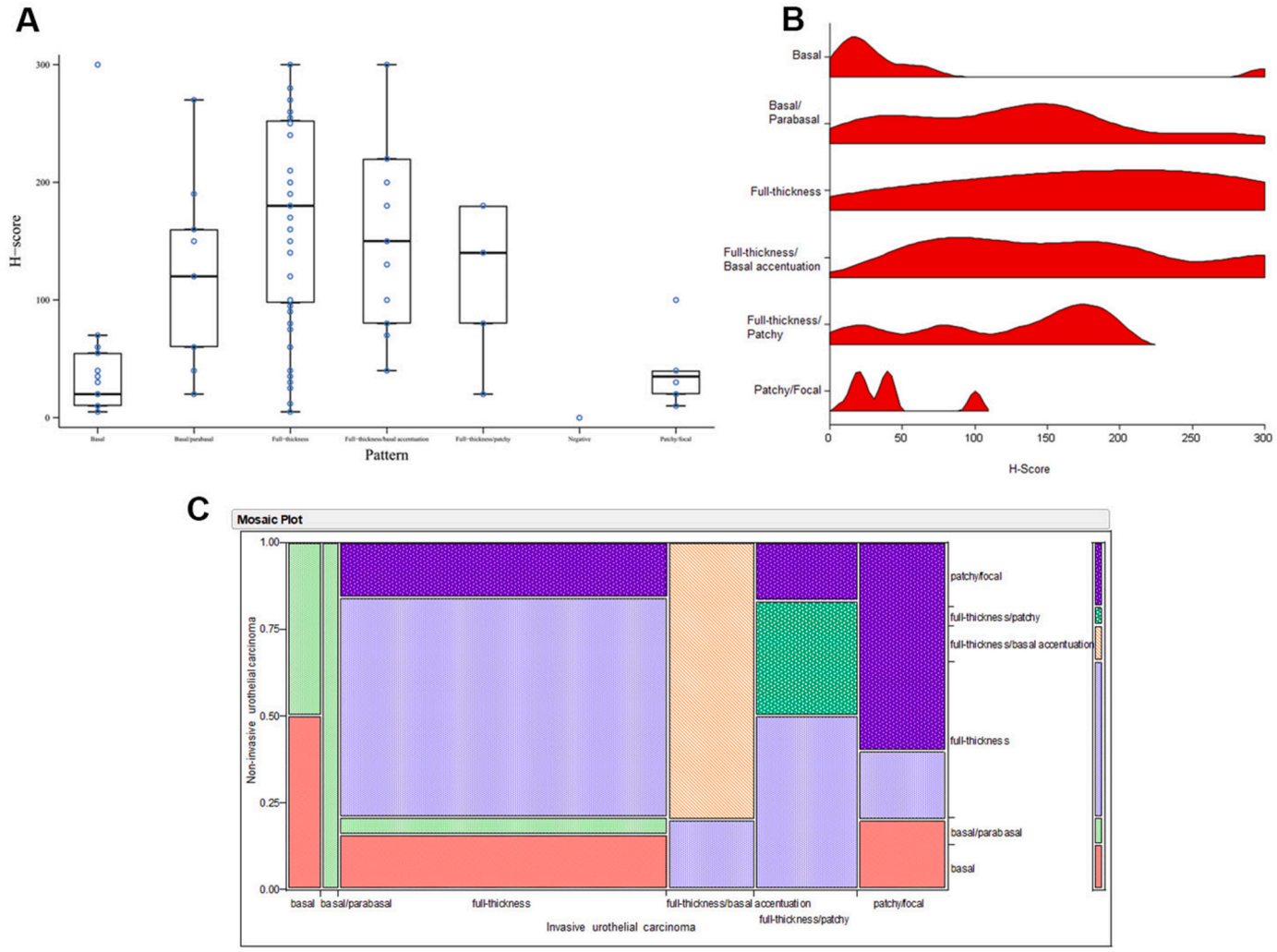

Fig. 4. A) H-score distribution by pattern in non-invasive papillary urothelial carcinoma (pTis). B) Density plot showing higher H-scores in cases with full thickness distribution and lower H-score in pT4. Other stages display values spread through the distribution, suggesting dimming in higher stage tumors. C) Mosaic plots showing changes from basal or basal/parabasal to full-thickness from pTa to pTinv.

alterations of TP53 and RB1. In contrast to these studies, as well as those highlighting the prognostic significance in other non-urothelial tumors [8,17–19,21,22], KRT17 did not have prognostic significance in our study, in that it was not associated with either stage or grade, similar to previous reports in bladder [9]. However, although correlation with molecular classes was outside of the scope of this study, additional studies exploring the role of KRT17 in this setting would be of particular interest.

Several immunohistochemical biomarkers are available in routine diagnostic evaluation of urothelial cancer. These markers have been employed in the differential diagnosis of benign versus malignant urothelial lesions and in the metastatic setting to identify urothelial differentiation. At this regard, CK7, CK20, CD44, HMWCK clone 34BE12, P63, p53, thrombomodulin, uroplakin II and III, and GATA3 are some of the markers utilized. CK20, CD44, and p53 have been suggested as useful markers in the differential diagnosis between reactive urothelium and urothelial carcinoma in situ with loss of CD44, full-thickness CK20, and p53 overexpression favoring the latter over benign/reactive processes [27]. However, a recent meta-analysis of 15 eligible studies with 35 datasets and 661 patients showed that the overall rate of CK20, CD44, Ki67 and p53 expression in CIS was 43%, 31%, 44%, 38%, respectively [28]. Therefore, although this panel has potential utility, it is variably used and has limitations [29]. Similarly, p53 abnormal overexpression or loss has been evaluated as a marker for urothelial carcinoma in situ in a few studies with conflicting results [27,30–33]. In the metastatic setting, discrimination of urothelial differentiation is carried out using cytokeratin 7, CK20, HMWCK clone 34BE12, p63, thrombomodulin, uroplakin II and III, and GATA3. However, except for uroplakin II and III, which are highly specific for urothelial differentiation (95–100%) but scarcely sensitive (63–68% and 19–23%, respectively) [34,35], all other markers lack specificity, as their expression may be identified in multiple organs as well as in benign urothelium [36]. As an example, GATA3, a commonly used urothelial biomarker has a reported sensitivity of 80% but low specificity in the metastatic setting due to its expression mammary carcinoma (96%), cutaneous basal cell carcinoma (98%) squamous cell carcinoma (75%), skin adnexal tumors, malignant mesothelioma (58%), chromophobe renal cell carcinoma (51%), and ductal carcinomas of salivary gland (43%) and pancreas (37%) [37]. Although in our study the specificity of KRT17 for distinguishing between benign from malignant urothelium was 82%, additional studies are needed to define the specificity of this marker in the metastatic setting.

Limitations of this study include the small sample size of some of the study groups, e.g. foremost pTis and invasive carcinoma. Therefore, these findings will require large scale validation. Furthermore, the study represents a single institution analysis. Multi-institutional validation to account for variable tissue processing protocols will be required.

In conclusion, KRT17 is a sensitive and specific marker of urothelial

neoplasia, as it is preferentially expressed in carcinoma but not in benign urothelium. Pattern of expression rather than positive/negative expression has the most discriminatory pattern. As opposed to other organ systems, KRT17 does not appear to have prognostic value. These findings anticipate the potential use of this marker in routine diagnosis of urothelial carcinoma.

CRediT authorship contribution statement

Woodson Smelser: Writing – review & editing, Writing – original draft, Project administration, Investigation, Data curation. **Nam Kim:** Writing – review & editing. **Sholeh Jahanfard:** Writing – review & editing. **Mark Sarno:** Writing – review & editing, Validation, Formal analysis, Conceptualization. **Sam S. Chang:** Writing – review & editing, Conceptualization. **Giovanna A. Giannico:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Ethics approval/consent to participate

This study did not require ethical approval.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Declaration of competing interest

N.K. and S.J. are employees of KDx Diagnostics Inc. M.S. is Chief Executive Officer at Vision Clinical Research, LLC. The remaining authors declare that they have no conflict of interest.

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