Primary Female Urethral Carcinoma

Proposed Staging Modifications Based on Assessment of Female Urethral Histology and Analysis of a Large Series of Female Urethral Carcinomas

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Abstract: Primary female urethral carcinoma is rare. Limited clinicopathologic information has hindered development of staging criteria in this disease. We analyzed 29 primary female urethral carcinoma resections from 3 academic medical centers to characterize histopathologic features, clinical outcomes, and applicability of current and a novel modified staging criteria. We complemented this analysis with review of fully embedded female autopsy urethras to detail anterior and posterior urethral wall histology. Primary female urethral carcinoma subtypes included urothelial carcinoma in situ (3/29, 10%), adenocarcinoma in situ (1/29; 3%), invasive urothelial carcinoma (13/29, 45%), clear cell carcinoma (5/29, 17%), adenocarcinoma not otherwise specified (4/29, 14%) and squamous cell carcinoma (3/29, 10%). Only 6/29 cases (21%) were originally assigned a stage at diagnosis. Using histologic landmarks specific to the female urethra, we modified existing eighth edition American Joint Committee on Cancer urethral staging to a histology-based female urethral carcinoma staging (UCS) system. UCS stages were defined as pTa/pTis$_{UCS}$ (noninvasive carcinoma), pT1$_{UCS}$ (subepithelial tissue invasion), pT2$_{UCS}$ (periurethral muscle invasion), pT3$_{UCS}$ (vaginal adventitia or surrounding fibrovascular tissue), and pT4$_{UCS}$ (anterior wall fibroadipose tissue or posterior vaginal wall). UCS staging was applicable to all cases and showed stepwise changes in disease recurrence with increasing stage and was statistically significant for disease-specific and overall survival in contrast to the American Joint Committee on Cancer staging system. This study of one of the largest cohort of primary female urethral carcinomas provides a modified histology-based staging system specific to female urethral anatomy that provides outcomes-related information, which may be further validated by larger multi-institutional studies.

Key Words: urethra, urethral carcinoma, urinary tract, staging, urothelial carcinoma

Primary female urethral carcinoma represents <1% of female malignancies, but encompasses a diagnostically challenging set of lesions with a poor prognosis.[1] Currently, as per the eighth edition of the American Joint Committee on Cancer (AJCC) manual the staging of female urethral carcinoma is grouped with the staging of nonprostatic male urethra into a single staging category.[2] However, given the distinct anatomic and histologic differences between the male and female urethra, use of the current AJCC system is not optimally and uniformly applicable to the female urethra.

There is a paucity of published literature regarding primary female urethral carcinomas, especially with respect to the relevance of the existing pathologic staging criteria for this organ. The reasons for this are manifold and include the uncommon nature of these carcinomas and the relative underrepresentation of the descriptions of the histology of the normal female urethra in medical literature.[3,4] Consequently, the unique anatomic/histologic differences between the anterior and posterior female urethra has also not been addressed and analyzed in the context of the pathologic staging of these cancers.

Since prognosis and treatment of urethral carcinomas vary by pathologic stage, a relevant staging system specific for female urethral carcinoma is needed. To address this need, we first evaluated a series of fully embedded female urethras obtained at autopsy to define anterior and posterior urethral histology landmarks. We next evaluated 29 cases of female urethral carcinomas to determine extent of invasion into surrounding histologic layers of the anterior and posterior urethral wall using our proposed female urethral carcinoma staging (UCS) system and tested how this staging system predicted outcomes. Our results indicate that the UCS modified staging criteria

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for female urethral carcinomas can be uniformly applied to all urethral carcinoma specimens, by using histologic features that reflect the anatomy of the female urethral wall, and can be used to predict outcomes that differ between low-stage and high-stage disease.

MATERIALS AND METHODS

Analysis of Female Autopsy Urethra Specimens

Urethras were dissected from 4 female cadavers that lacked precedent or concurrent carcinoma of the genitourinary and rectal organs. Urethras were fully dissected in continuity with the bladder, using a dissection field that extended anteriorly to the pubic bone and posteriorly into the vaginal wall. Urethras were sectioned at 4 mm intervals and fully embedded from distal to proximal up to the bladder neck to generate sequential hematoxylin and eosin (H&E) sections of formalin-fixed paraffin-embedded material. H&E slides were reviewed to document histologic landmarks of the anterior, lateral and posterior urethral walls from distal to proximal. Ten to 18 sequential sections were obtained from each urethra.

Urethral Carcinoma Patient Cohort

This study was approved by the Institutional Review Boards at each of the 3 institutions involved in the study. Twenty-nine female patients with a diagnosis of urethral carcinoma were identified, including those with non-invasive carcinoma, who underwent resection. Patients with secondary involvement of the urethra from a carcinoma arising in another location either by contiguous spread or by metastasis were excluded. H&E slides were re-reviewed by 5 urologic pathologists to confirm the diagnosis, and stage the tumors according to the current AJCC and the UCS modified staging parameters.[2] Histopathologic subtyping was performed according to the World Health Organization (WHO) classification.[5] Retrospective data collection on patient demographics, type of surgery, tumor location, pathology diagnosis, clinical history, and follow-up were obtained from the electronic medical records. Only patients who underwent surgery with curative intent were included.

Twenty-eight patients had follow-up data available, including clinical notes and laboratory or tissue analysis. Recurrence was determined by evidence of new disease confirmed on imaging and/or tissue sampling following evidence of response to primary treatment. Survival was measured from the date of diagnosis to the date of death. Data for surviving patients were recorded at the time of their last visit.

The disease-specific and overall survival of the patients, using the 2 staging systems were compared using Kaplan-Meier curves, log-rank tests, and multivariate analyses based on the Cox proportional-hazards method. Kaplan-Meier analysis was performed using lifelines python package version 0.14.6. The results were independently validated with R statistical software (R version 3.6.1; 2019-07-05). Statistical significance of the differences between the groups was computed using log-

rank test. Univariate and multivariate survival analysis was performed using R survival package.

RESULTS

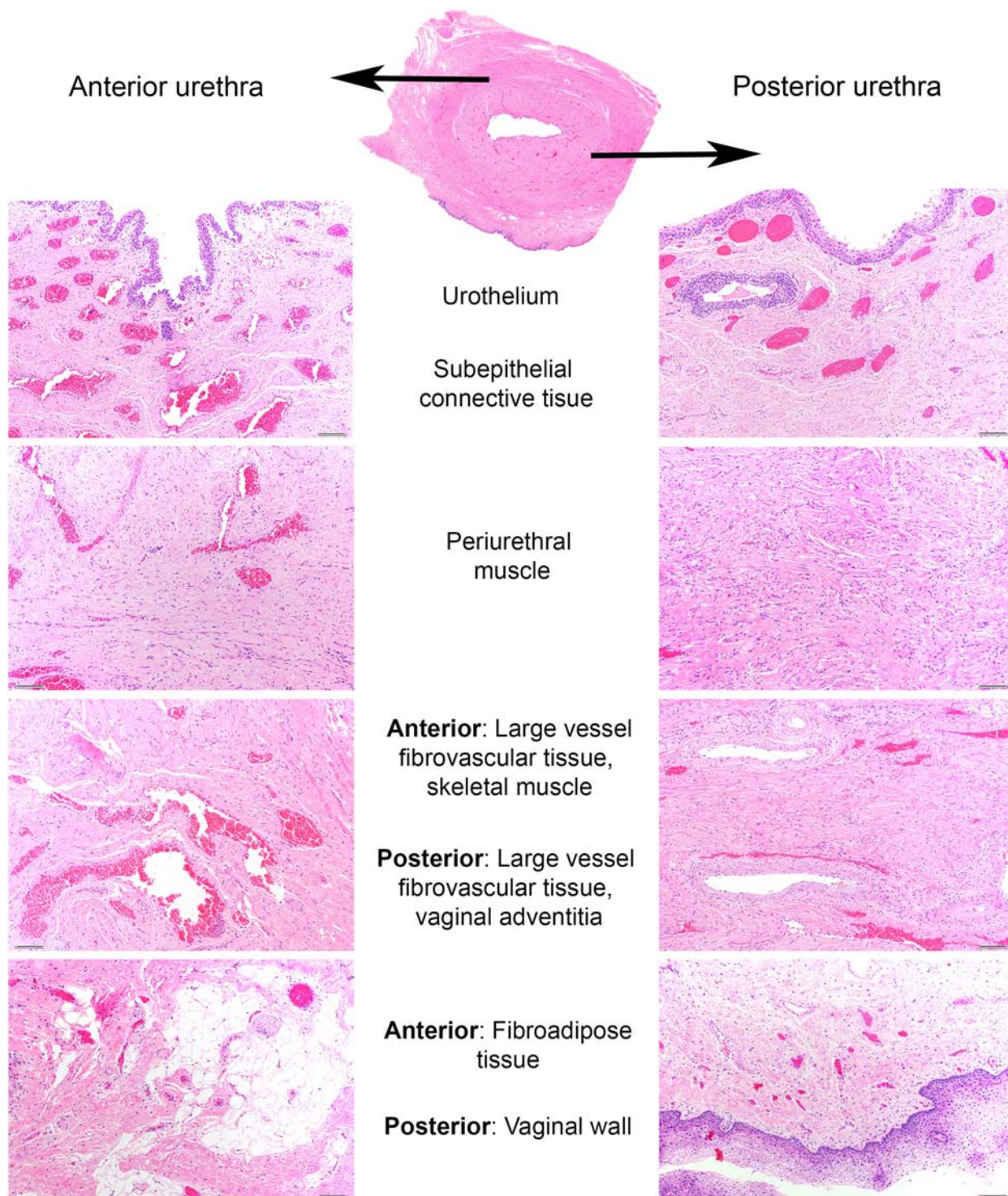### Histology of the Female Urethra

We analyzed the histology of 4 female urethras that were entirely dissected and fully embedded at the time of autopsy. The relevant demographic and clinical details of the cadavers dissected are listed in Table 1. We evaluated the histology from distal to proximal urethra and evaluated differences between anterior and posterior urethra with an effort to identify histologic landmarks that could be applied for staging purposes (Fig. 1). When comparing anterior and posterior urethral histology, the innermost layers were similar, consisting of the urothelium and its invaginations, subepithelial connective tissue, and multi-layered periurethral muscle. However, beyond the periurethral muscle, there was significant difference in the layers constituting and surrounding the anterior and posterior urethra. The anterior urethra is connected to the pubic periosteum by thick ligaments, associated striated urogenital sphincter muscle, and fibroadipose tissue. The posterior urethra transitions from the periurethral muscle to the submucosal vaginal muscle of the anterior vaginal wall with an intervening layer of fibroconnective and fibrovascular tissue containing large vessels. No fibroadipose tissue is seen along the posterior urethra. Differences unique to the distal urethra include a less distinct appearance of the periurethral muscle, enhanced visibility of the bulbocavernosus muscle that partially encircles the urethra at this location, presence of thin strands of striated muscle, and an increased presence of periurethral glands (Skene glands).[6]

Definition of Modified Female UCS Criteria

A major change in the most recent AJCC staging system of urethral carcinomas is the separation of the staging of prostatic urethral carcinomas from staging of carcinomas involving other portions of the urethra.[7] However, staging of carcinomas involving the penile urethra and the female urethra remain combined, given lack of evidentiary data supporting the need of distinct staging systems for these 2 distinct entities. We propose using histologic landmarks unique to the female urethra to test the application of a modified staging system (UCS) (Fig. 1). The modifications included in the UCS system are presented and compared with the current eighth edition AJCC staging system in Table 2.

TABLE 1. Summary of Relevant Cadaver Information

Cadaver	Race	Age	Cause of Death	Prior Pregnancy
1	White	60	Lung cancer	No
2	White	78	Myocardial infarction	Yes, terminated
3	Asian	70	Lung cancer	Unknown
4	White	75	Pulmonary infarction	Yes, vaginal delivery

FIGURE 1. Histologic layers of the anterior and posterior urethral wall. These layers were used to derive the female UCS system and correlate to pTa/pTis$_{UCS}$ (noninvasive carcinoma involving the urothelium), pT1$_{UCS}$ (subepithelial tissue invasion), pT2$_{UCS}$ (periurethral muscle invasion), pT3$_{UCS}$ (vaginal adventitia, surrounding fibrovascular tissue, striated muscle), and pT4$_{UCS}$ (anterior wall fibroadipose tissue or posterior wall vaginal wall).

The criteria for staging pTa/pTis, pT1, and pT2 tumors in both the systems remain the same. However, several major modifications are proposed to the pT3 and pT4 staging based on the histologic landmarks of the anterior and posterior urethra. Given that the anterior urethra underlies the pubic bone and the posterior urethra overlies the

TABLE 2. Comparison of the Eighth Edition AJCC Urethral Staging and Female UCS Systems

T Stage	AJCC Eighth edition	Female UCS
pTa/Tis	Intraepithelial carcinoma	Same
pT1	Subepithelial tissue invasion	Same
pT2	Periurethral muscle	Same
pT3	Anterior vagina	Anterior urethra: Fibrovascular tissue with large vessels, skeletal muscle Posterior urethra: Vaginal adventitia, fibrovascular tissue with large vessels
pT4	Other adjacent organ invasion (eg, bladder wall)	Anterior urethra: Fibroadipose tissue; anterior pelvic muscle; bladder wall Posterior urethra: Vaginal muscle, lamina propria or epithelium (mucosa); bladder wall

TABLE 3. Clinicopathologic Features of 29 Female Urethral Carcinoma Cases

Age, median (range) (y)	73 (41-96)
Type of resection, n (%)	
Wide local excision	4 (14)
Urethrectomy (± cystectomy)	13 (45)
Anterior pelvic exenteration	12 (41)
Tumor location, n (%)	
Proximal	14 (48)
Distal	6 (20)
Both	4 (14)
Unknown	5 (17)
Invasive tumor size, mean (range) (cm)	2.9 (0.1-5.5)
No. cases assigned stage at diagnosis	6 (21)
Histology, n (%)	
Urothelial carcinoma in situ	3 (10)
Adenocarcinoma in situ	1 (3)
Invasive urothelial carcinoma	13 (45)
Clear cell carcinoma	5 (17)
Adenocarcinoma NOS	4 (14)
Squamous cell carcinoma	3 (10)
Arising in diverticulum, n (%)	3 (10)
Angiolymphatic invasion, n/N (%)	11/29 (38)
Margin status, n (%)	
Negative	9 (31)
Positive	2 (7)
Not applicable	18 (62)
Concurrent bladder involvement	3 (10)
Lymph node status, n (%)	
Negative	6 (38)
Positive	10 (62)
Dissection not performed	13 (45)

vagina, it is obvious that using involvement of the anterior vagina as a prerequisite for staging a tumor as pT3 would lead to under staging tumors involving the anterior urethra. In the UCS system, the fibrovascular tissue with large vessels surrounding the periurethral muscle is an important landmark used to identify tumors that have spread beyond the urethra. In the posterior urethra this relates to the vaginal adventitia and in the anterior urethra this relates to an admixture of skeletal muscle and large vessels. Another major difference between the UCS system and the AJCC system is that in the former system the vagina is considered a separate organ, which is a concept commonly applied in the setting of pT4 cancer staging in other organs. Bladder wall involvement remains unchanged as pT4.

We have used this new female UCS to test its application to one of the largest series of female urethral carcinomas evaluated to date and determine its association with outcomes.

Summary of Female Urethra Carcinoma Cases Included in Staging Analysis

The clinicopathologic features of cases that were used to test the UCS criteria are presented in Table 3. All patients were over the age of 40 years, with a median age of 73 years. Surgeries were curative in intent and included wide local excision, urethrectomy with or without cystectomy, and anterior pelvic exenteration. The majority of cases were located in the proximal urethra.

Twenty-five resections showed invasive carcinoma, whereas 4 cases showed noninvasive disease that included carcinoma in situ (CIS) and/or high-grade papillary urothelial carcinoma in 3 cases and adenocarcinoma in situ in 1 case (Figs. 2A, B). Inverted growth and colonization of von Brunn nests was also staged as noninvasive disease (Fig. 2C). The most frequent form of invasive carcinoma was urothelial carcinoma (13/29, 45%), which included 4 cases with squamous and/or glandular differentiation (Fig. 3A). Clear cell carcinoma was identified in 5 cases (17%; Fig. 3B). Four cases

were classified as adenocarcinoma not otherwise specified (14%), including 1 case with extensive mucinous features (Figs. 3C, D). Invasive squamous cell carcinoma was identified in 3 cases (10%) and consisted of well-differentiated to moderately differentiated carcinoma (Fig. 3E). Urothelial carcinoma was more frequent in the 14 proximal-only urethral carcinomas (11/14; 79%) as compared with the 6 distal-only carcinomas (3/6 cases; 50%). The other subtypes of carcinomas did not appear to cluster by location; however, the small number of cases in this study may limit this distinction.

Angiolymphatic invasion was identified in 11 patients (38%; Fig. 3F). Three carcinomas arose in a clinical diverticulum (10%). Resection margin status was evaluated in 11 patients and 2 of these patients showed a positive margin. Concurrent mucosal involvement of the bladder by urothelial CIS was seen in 2 cases (one of urothelial carcinoma of the urethra and one of squamous cell carcinoma of the urethra), while in a third case, there was contiguous involvement of the bladder neck mucosa by clear cell adenocarcinoma arising from the proximal urethra. Lymph node dissection was performed in 16 patients and metastatic carcinoma was identified in 6 patients.

Applicability of AJCC and UCS Staging Systems to Female Urethral Carcinomas

Re-review of reports issued on the evaluated cases showed that only 6 of 29 patients (21%) were assigned an AJCC stage at the time of diagnosis. We subsequently re-evaluated all of the specimens that were included for study
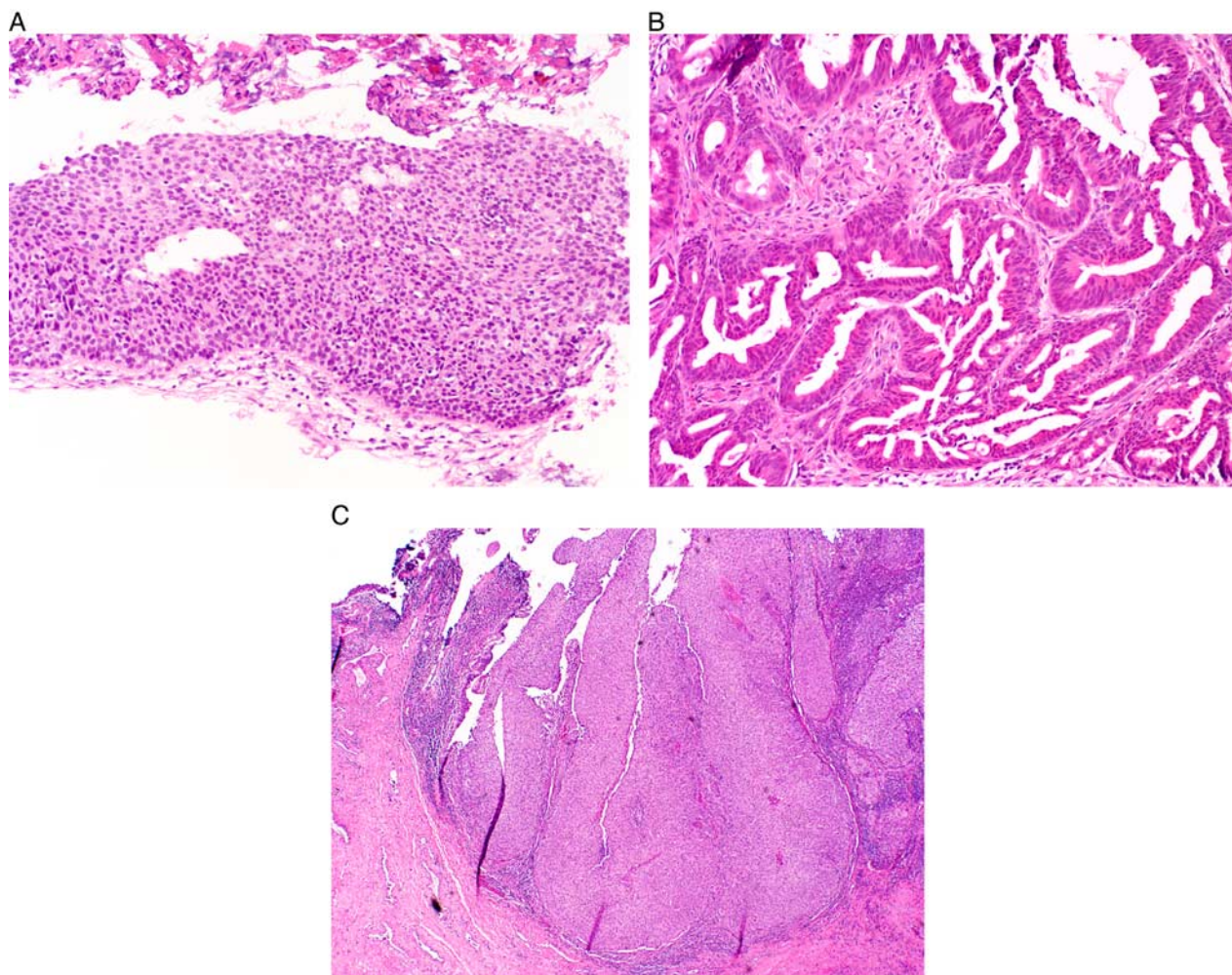
FIGURE 2. Noninvasive lesions of the female urethral included urothelial carcinoma in situ (A), adenocarcinoma in situ (B), and high-grade papillary urothelial carcinoma with an inverted growth pattern (C).

and assigned an AJCC and a UCS stage to each case irrespective of histologic subtype. This data is presented in Table 4. Several challenges existed, including the fragmented nature of many resected specimens, lack of annotation of tumor location in a subset of pathology reports, and the possibility of an incomplete resection in the subset of cases with excisional resections. However, use of histologic landmarks could assign a UCS stage and, in advanced cases, distinguish anterior fibroadipose tissue from posterior vaginal wall involvement.

Using the UCS system, we classified 4 cases as $pTa/pTis_{UCS}$ (noninvasive carcinoma), 3 cases as $pT1_{UCS}$ (subepithelial tissue invasion), 9 cases as $pT2_{UCS}$ (periurethral muscle invasion), 5 cases as $pT3_{UCS}$ (vaginal adventitia, surrounding fibrovascular tissue, skeletal muscle), and 8 cases as $pT4_{UCS}$ (anterior wall fibroadipose tissue or posterior vaginal wall). A summary of AJCC and UCS stage for the cases is presented in Table 4. pTa/pTis and pT1 stage classification remained the same between the 2 systems. In anterior urethral carcinoma cases, AJCC grouped all anterior cancers beyond the periurethral muscle as pT2, whereas the UCS system further separated these into pT2, pT3, and pT4 categories. In posterior urethral carcinoma cases, the AJCC staging system classified all vaginal involvement as pT3 disease, whereas the UCS system expanded categorization to pT3 and pT4 disease by taking into account the fibrovascular and adventitial layer of the vaginal wall and classifying vaginal wall involvement as pT4 disease. Examples of application of the UCS system are provided in Figure 4. The net result of this comparison shows that use of the AJCC staging system as currently described compresses the staging categories to lower stage disease, whereas use of all histologic layers in the UCS staging system stratifies cancer stage to a greater degree.

Association of AJCC and UCS Staging Systems to Urethral Carcinoma Outcomes

Although the UCS staging system provides a more detailed and accurate histologic application of female urethral anatomy, its relevance to outcomes was unclear. To address
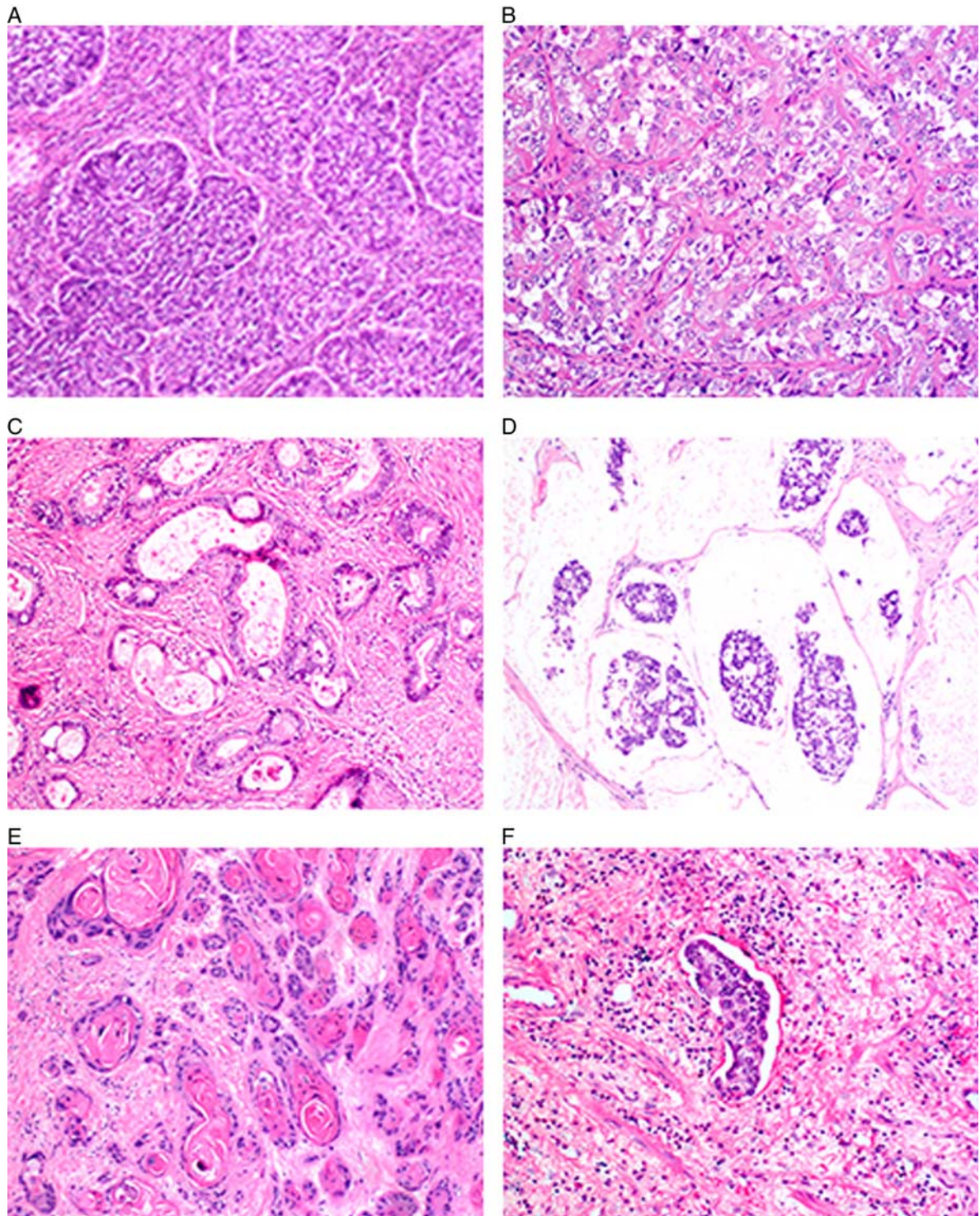
FIGURE 3. Histologic subtypes of female urethral carcinoma included in staging analysis included urothelial carcinoma (A), clear cell carcinoma (B), adenocarcinoma NOS (C), adenocarcinoma with mucinous features (D), and squamous cell carcinoma (E). F, Angiolymphatic invasion was identified in 38% of cases. All images.

this, we next examined the frequency of negative histologic indicators and clinical outcomes in relation to AJCC and UCS staging.

Clinical follow-up was available for 28 patients and ranged from 3 to 559 months (mean, 109 mo; median, 65 mo). Local recurrence was documented in 5/28 patients

TABLE 4. Stage Assignment of Cases Using AJCC Staging and UCS Staging Systems

	Eighth Edition AJCC Staging	UCS Staging
pTa/pTis	4	4
pT1	3	3
pT2	13	9
pT3	8	5
pT4	1	8

(18%) and subsequent metastasis was documented in 9/28 patients (32%). At the time of last follow-up, 7/28 patients were alive without disease (24%), 8/28 patients died of disease (28%), and 6 patients died of other causes in the absence of disease (20%). One patient was lost to follow-up.

Angiolymphatic invasion which is considered a negative prognostic indicator in bladder cancer[8] was identified in 11/29 patients (38%). Five of these patients did not have subsequent disease recurrence, whereas 5 patients had either local recurrence or metastasis. The remaining patient was lost to follow-up. Distribution of cases with angiolymphatic invasion using the AJCC system included 5 cases in pT2, 5 cases in pT3 and 1 case in pT4. Distribution of these cases using the UCS system included 3 cases in pT2, 2 cases in pT3 and 6 cases in pT4 disease.

We next examined recurrence rates, disease-specific survival, and overall survival in cases of invasive urethral carcinomas using both the AJCC and UCS staging systems. The AJCC system plateaued at pT2 for recurrence rates and did not provide additional information for the pT3 stage. There was only 1 case that was staged as pT4 using the AJCC staging system, which was lost to follow-up and therefore could not be further analyzed in this setting. By contrast, using the UCS system, stratification of patients with and without recurrences was more robust (Table 5). Figure 5 shows the Kaplan-Meier curves and Cox proportional hazard analysis for disease-specific and overall survival using the UCS and AJCC staging system. Multiple groups based on the different stages (pTa to pT4) were compared with each other in the Kaplan-Meier analysis using log-rank test in disease-specific survival (Figs. 5A, B) and overall survival (Figs. 5C, D). UCS system of staging revealed significant differences between outcome of the different staging groups (pTa to pT4) in both disease-specific survival (Fig. 5A, $P = 0.017$) and overall survival (Fig. 5C, $P = 0.031$). However, AJCC system did not show any significant differences between outcome of the different staging groups (pTa to pT4) in both disease-specific survival (Fig. 5B, $P = 0.39$) and overall survival (Fig. 5D, $P = 0.96$). Cox proportional hazard analysis revealed significant association to outcome only in the context of UCS univariate (Fig. 5E, $P = 0.00939$) and multivariate (Fig. 5E, $P = 0.00929$) disease-specific survival. AJCC system of staging was not significantly associated with outcome in both disease-specific survival and overall survival. Using the UCS system, the disease-specific survival rates approximate those described for bladder carcinoma staging.[9]

DISCUSSION

In this study, we examined fully embedded female urethras from autopsy cases and used one of the largest series of female urethral carcinoma cases reported to date to test a modification of the AJCC staging system. This modified UCS staging system incorporates more detail of the female urethral histology and anatomy into staging landmarks, including distinction between the anterior and posterior urethra. The results from this study show that this system based on histologic features is applicable to fragmented specimens, is reproducible among a set of urologic pathologists, and can better stratify disease-specific survival by stage.

Documentation of the anatomy and histology of the urethral wall is essential for staging of female urethral carcinomas. However, there are limited resources that have analyzed this in detail. Within the published literature, the urethra has been described to contain an inner longitudinal and outer circular smooth muscle layer, with an outermost striated urogenital sphincter layer.[6,10,11] This outermost circular striated muscle layer, the so-called striated urogenital sphincter complex, consists of the urethrovaginal sphincter, compressor urethrae, and sphincter urethrae that range in prominence from proximal to distal and within the anterior and posterior regions.[6] The urethrovaginal sphincter and compressor urethrae partially surround the urethra anteriorly and laterally, while the sphincter urethrae completely encircles the urethra.[6,12,13] These muscle layers show no direct continuation to the bladder detrusor muscle, the periurethral muscle, or the pelvic muscles in humans and are separated from the periurethral muscle by connective tissue and adventitia that contain large vessels.[14–17] Age-related changes have been described, including a reduction in the dorsal muscle fibers of the striated urogenital sphincter and a reduction in the density of circular smooth muscle.[18,19] Our study cohort showed a reduced volume of dorsal striated muscle tissue, but we could not confirm a decrease in periurethral smooth and striated muscle.

In addition to the lack of published data regarding the female urethra, there is also some lack of clarity about the histologic layers of the vagina.[20–23] Although some authors suggest that the vaginal wall consists of 3 layers (epithelium, mucosa, and muscle layer),[20,22] others suggest a fourth layer of adventitia.[21,23] This adventitial layer contains connective tissue and blood vessels and lies between the vaginal muscle and surrounding tissue,[20] and corresponds to the UCS pT3 designation described in the posterior urethra in our study.

The eighth edition AJCC staging system for female urethral carcinomas has several limitations. The first limitation is that the histologic landmarks unique to the female urethra are not applied, beyond the pT2 stage, which limits its application to fragmented specimens and in the evaluation of anterior urethral disease. In our study, an initial AJCC pT stage was not assigned in a majority of the resection cases, which may reflect this challenge. The second limitation is that vaginal wall involvement has been categorized as pT3 disease, which
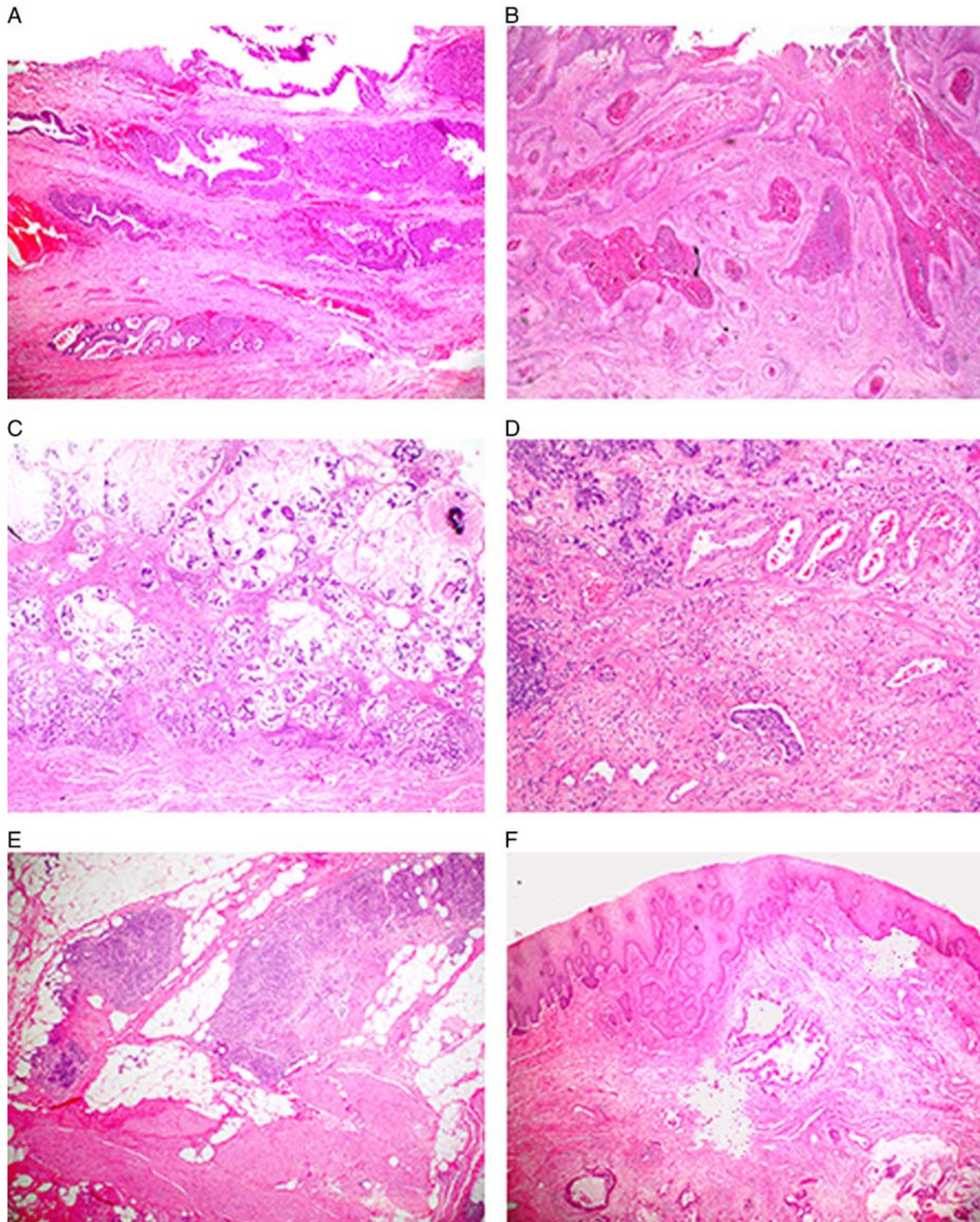
FIGURE 4. Examples of pT_{UCS} staging. A, $pTis_{UCS}$ stage consists of urothelial carcinoma with colonization of underlying von Brunn nests and periurethral glands in some instances. This is identical to $pTis_{AJCC}$. B, $pT1_{UCS}$ is identical to $pT1_{AJCC}$ and involves invasion of the subepithelial tissue. C, $pT2_{UCS}$ is identical to $pT2_{AJCC}$ and involves invasion of the periurethral muscle layers. D, $pT3_{UCS}$ includes invasion into the adjacent fibrovascular and striated muscle layers that surround the periurethral muscle in the anterior and posterior urethra. By contrast, $pT3_{AJCC}$ includes only invasion of the vaginal wall. E, $pT4_{UCS}$ of the anterior female urethra includes invasion of the anterior fat and/or bladder wall, while $pT4_{UCS}$ of the posterior female urethra includes invasion of the vaginal wall or bladder wall (F). By contrast, $pT4_{AJCC}$ includes only invasion of the bladder wall.

TABLE 5. Disease Recurrence and Disease-specific Survival of Invasive Urethral Carcinoma by AJCC Staging and UCS Systems

	Recurrence Rates, n/N (%)	
	Eighth Edition AJCC	**UCS**
pT1	0/3 (0)	0/3 (0)
pT2	8/13 (62)	5/9 (56)
pT3	5/8 (62)	4/5 (80)
pT4	— (LTF)	4/7 (57)

LTF indicates 1 case lost to follow-up.

compresses the stage categories and classifies the vaginal wall as a local extension of the urethral wall rather than a separate organ. The third limitation is that the fibrovascular, striated muscle, and connective tissue that exists between the periurethral muscle and the anterior fat and posterior vaginal wall has been ignored in stage assignment. These layers have been taken into account in our proposed UCS staging system and assigned a pT3 stage. Finally, the unique landmarks of the anterior urethral wall, including the fibroadipose tissue that is present underlying the pubic ramus, has not been included in the current AJCC staging system. Thus, the highest stage for carcinomas involving the anterior urethra, but not involving the bladder wall by default will be pT2, irrespective of their size. In our study, fibroadipose tissue appeared specific to the anterior and lateral urethral walls. However, one prior study, has described a distinct layer of fibroadipose tissue separating the anterior vagina and posterior urethra, although no figures documenting this finding was provided in this publication.[22]

One important feature of a staging system is that it provides information related to clinical outcomes. In this setting, we examined recurrence rates, disease-specific, and overall survival. Application of the AJCC staging criteria to these specimens showed that clinical outcomes plateaued at pT2. This is most likely caused by a clustering of cases at the pT2 stage given the condensed staging criteria and absence of detail surrounding staging criteria for the anterior urethra. By contrast, the UCS staging system could provide stepwise changes in disease-specific survival and overall survival with stage, which was similar to outcomes reported for stage with bladder carcinoma. These findings suggest that incorporation of the UCS staging system for female urethral carcinomas, which uses expanded histologic information of the urethral wall, may be more useful and relevant to all morphologic subtypes of female urethral carcinoma.

In our study, we could apply staging criteria for all specimens using the AJCC and the UCS systems. In fragmented specimens, the presence of large vessels was occasionally used as a surrogate for pT3 staging. The urethral lumen, periurethral muscle, striated muscle, fibroadipose tissue, and vaginal wall were readily identified in fragmented specimens.

Finally, we would like to comment on carcinomas arising in urethral diverticula. These are extremely rare and constitute ~5% of urethral carcinomas in women, with the majority presenting as pT2 or above using the AJCC staging system.[24] In our study there were 3 cases with cancer arising in urethral diverticula, and included 1 case each of urothelial carcinoma, mucinous adenocarcinoma and clear cell carcinoma. Only one of these cases was assigned a stage at initial assessment. This was a 5 cm tumor, which was grossly identified, filling a large diverticulum and involving the anterior vagina that was staged as a pT3 tumor using the AJCC staging system. On reassessing the case, the tumor was seen to involve only the vaginal adventitia, without involvement of the vaginal muscle and therefore was not upgraded using the UCS system to pT4 (pT3$_{UCS}$). In the remaining 2 cases the tumors were small (0.5 and 1 cm in greatest dimension) and were not assigned a stage at initial assessment. Both these tumors showed invasion of the lamina propria with focal extension into the attenuated periurethral muscle without involvement of the fibrovascular soft tissue. These were staged as pT2$_{UCS}$. Although the number of cases in our series is small, it is our opinion that the UCS system is also applicable to tumors arising in urethral diverticula and just like in urethral carcinomas may provide more meaningful information with regards to prognosis compared with the AJCC system.

Given the findings of this study, use of the UCS system for female urethral carcinoma may be of value. However, the current study also has several limitations. This study was performed retrospectively and future validation using prospective clinical outcomes may be valuable. The confounding effect of the presence of a concurrent or previous history of urothelial carcinoma of the bladder on the clinical outcome could not be completely evaluated because of the absence of this information in 5/16 cases of urothelial carcinoma in this study. However, of the 7 cases with adverse outcomes in this cohort (3 with recurrences or metastasis and 4 who died of their disease), 3 cases had no evidence of bladder involvement, 1 had a history of cystectomy 10 years prior for bladder CIS, 1 had concurrent CIS of the bladder (with UCS stage 2 urethral cancer) while in 2 cases this information was not available. In addition, differences in treatment between proximal and distal urethral carcinomas may also influence outcomes, although this degree of detail was not always available for our analysis. Finally, despite this study representing one of the largest series of female urethral carcinomas, the sample size is relatively small given the rarity of this tumor. However, the stratification of outcomes between UCS and AJCC staging is encouraging.

In conclusion, our findings indicate that our new proposed UCS staging system is a useful approach for staging female urethral carcinomas. Further multi-institutional studies using large cohorts should be undertaken to validate clinical outcomes. Regardless, the use of correct histologic parameters in female UCS should be seriously considered in evaluation of future staging guidelines in the female genitourinary system.
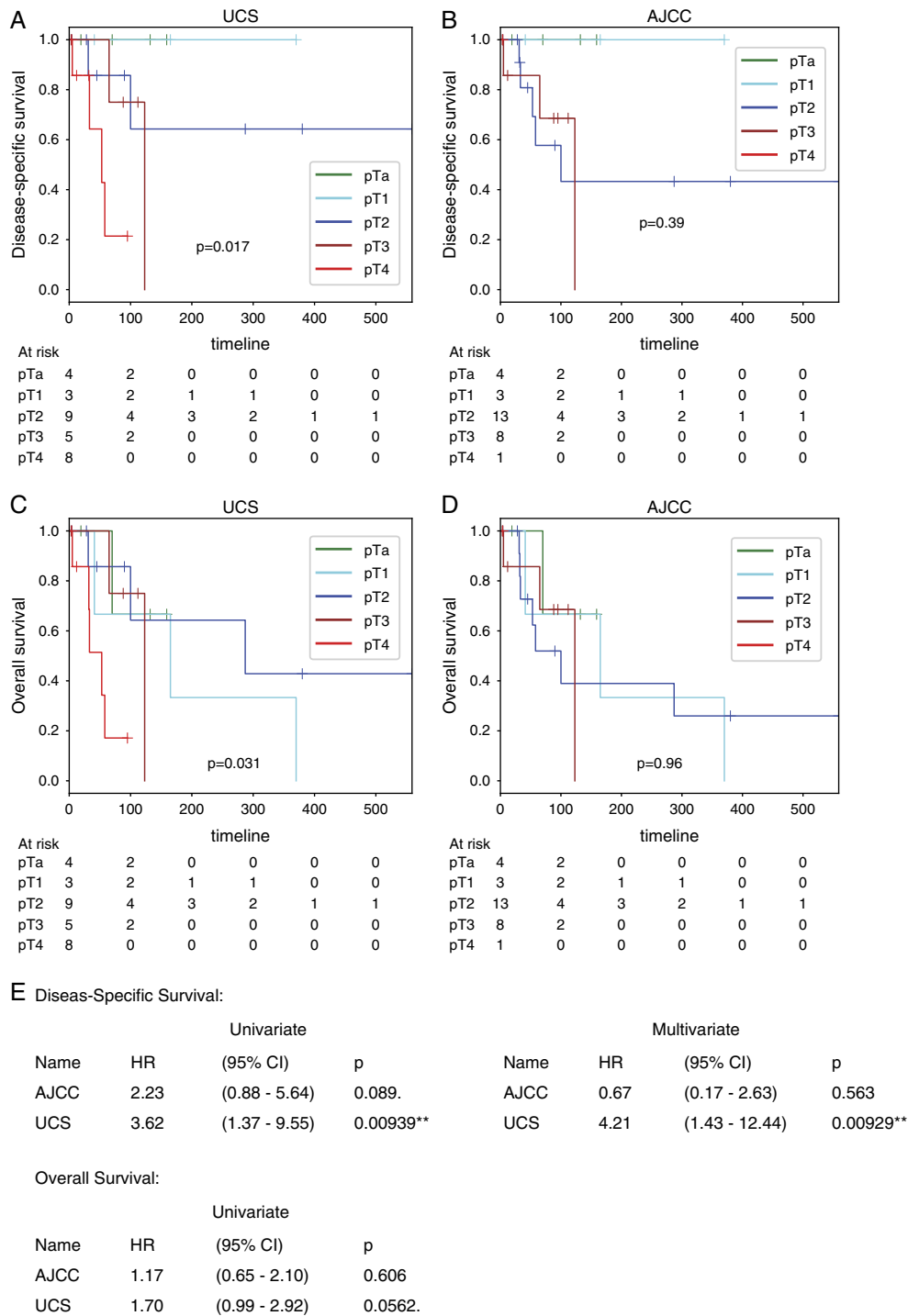
FIGURE 5. Kaplan-Meier curves for disease-specific survival and overall survival using UCS and AJCC staging systems. CI indicates confidence interval; HR, hazard ratio.

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