Review Article

Urethral diverticulum carcinoma in females—a case series and review of the English and Japanese literature

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Abstract: The aims of our study were to describe our case series of three urethral diverticulum carcinomas (UDC) in women and to review the literature on UDC in females to determine patient characteristics, presenting symptoms and outcomes along with optimal investigations and treatment modalities. A literature search was performed utilizing Medline, EMBASE and the Cochrane library for all papers including case reports on UDC in women published to date. The results along with those of our three cases are detailed. A total of 126 cases of UDC in women have been reported; 75% adenocarcinoma (Adenoca), 15% transitional cell carcinoma (TCC) and 10% squamous cell carcinoma (SCC). Median age at presentation was 53 years (range, 14–81 years). The commonest presenting symptoms were bleeding and retention. Cystoscopy, MRI and trans-urethral biopsy were the commonest methods of diagnosis. Treatment was radiotherapy +/– chemotherapy alone in 21%, local excision +/– radiotherapy in 44%, urethrectomy in 3% and anterior exenteration +/– radiotherapy in 32%. At last follow-up 63% were alive and well, 10% were alive with recurrent cancer and 25% had died from their disease. UDC is rare in women. It is predominantly adenocarcinoma. There is no established treatment and survival is at best moderate. An international registry and consensus on management is needed if this is to be improved.

Keywords: Urethral diverticulum carcinoma (UDC); urethral diverticulum (UD); carcinoma

Submitted Jun 05, 2018. Accepted for publication Jul 08, 2018.
doi: 10.21037/tau.2018.07.08
View this article at: http://dx.doi.org/10.21037/tau.2018.07.08

Introduction

Urethral diverticulum carcinoma (UDC) in women is extremely rare with only 123 cases previously reported (*Table 1*). Relatively little is known about UDC in women. We detail three additional cases of UDC in women and review the literature on the subject to more clearly define patient characteristics, presenting symptoms, diagnostics, treatments and outcomes to determine optimal management strategies.

Methods

We performed a literature search using the keywords; urethral diverticulum, cancer, carcinoma, tumour and malignancy. Databases searched were Medline, EMBASE and the Cochrane library. The data collected included patient demographics, presenting symptoms, diagnostic investigations, treatment modality and outcome at last follow-up in terms of disease free survival, recurrence and mortality. Ethnicity was determined according to the Office

Table 1 Signs and symptoms of female urethral diverticulum cancer

Author	Age (years)	Race	Symptom 1	Symptom 2	Duration (months)	Histology
Allen and Nelson, 1978 (1)	68	–	Bleeding	–	–	Adenoca
	69	–	Bleeding	–	–	Adenoca
Awakura *et al.*, 2003 (2)	75	A	Bleeding	Retention	7	Adenoca
Bracken *et al.*, 1976 (3)	–	–	–	–	–	TCC
Brown *et al.*, 1956 (4)	40	C	Bleeding	–	–	Adenoca
Carneiro Neto *et al.*, 1973 (5)	–	H	–	–	–	Not known
Catalano *et al.*, 1992 (6)	–	–	–	–	–	TCC
Cea *et al.*, 1977 (7)	48	C	Bleeding	–	2	Adenoca
	53	C	Bleeding	–	–	Adenoca
Christofferson, 1974 (8)	–	–	–	–	–	Adenoca
Clayton *et al.*, 1992 (9)	63	B	Urgency	Mass	–	SCC
	44	B	Bleeding	–	18	SCC
	35	B	Bleeding	UTIs	–	SCC
	44	B	Pain	–	–	Adenoca
	47	B	Bleeding	–	–	SCC
	67	B	Bleeding	–	–	Adenoca
Collado *et al.*, 2000 (10)	65	–	Bleeding	–	–	Adenoca
Cruz-Ruiz *et al.*, 2010 (11)	–	H	–	–	–	Adenoca
Davis *et al.*, 2003 (12)	58	–	UTIs	–	–	Adenoca
Davis *et al.*, 1999 (13)	48	–	UTIs	–	–	Adenoca
	48	–	Bleeding	–	–	Adenoca
Prudente de Toledo *et al.*, 1978 (14)	65	C	Urgency	–	–	TCC
Dodson *et al.*, 1995 (15)	–	–	–	–	–	Adenoca
Evans *et al.*, 1981 (16)	47	B	Bleeding	–	–	Adenoca
Faulkner *et al.*, 1959 (17)	57	–	Bleeding	–	–	TCC
Geisler *et al.*, 1998 (18)	70	–	–	–	–	Adenoca
Ghoniem *et al.*, 2004 (19)	71	–	Retention	Mass	–	Adenoca
Godec *et al.*, 1984 (20)	52	C	Dysuria	–	2	Adenoca
Gonzalez *et al.*, 1985 (21)	70	C	Bleeding	–	–	Adenoca
	14	C	Urgency	–	–	Adenoca
	27	C	Mass	–	–	Adenoca
	37	C	Bleeding	–	–	TCC
	40	H	Bleeding	Dyspareunia	5	TCC
	48	C	Retention	–	–	SCC
	36	C	Mass	–	–	SCC

Table 1 *(continued)*

Table 1 *(continued)*

Author	Age (years)	Race	Symptom 1	Symptom 2	Duration (months)	Histology
Graf *et al.*, 1962 (22)	65	C	Frequency	–	–	TCC
Ha *et al.*, 2010 (23)	60	A	UTIs	Bleeding	36	Adenoca
Hamilton *et al.*, 1951 (24)	53	–	Bleeding	–	–	Adenoca
Hickey *et al.*, 2000 (25)	50	–	UTI	Bleeding	–	Adenoca
Hinman *et al.*, 1960 (26)	40	–	Bleeding	–	–	Adenoca
	44	–	Bleeding	–	–	TCC
Hruby *et al.*, 2000 (27)	–	–	–	–	–	Adenoca
						Adenoca
Huvos *et al.*, 1969 (28)	58	B	Mass	–	–	SCC
Jensen *et al.*, 1981 (29)	–	–	–	–	–	Adenoca
						Adenoca
Jimenzez de Leon *et al.*, 1989 (30)	–	H	Bleeding	–	–	Adenoca
Kanno *et al.*, 2002 (31)	81	A	Bleeding	–	–	Adenoca
Kasahara *et al.*, 2017 (32)	48	A	Voiding dysfunction	–	5	Adenoca
Kato *et al.*, 1998 (33)	71	A	Frequency	Dysuria	1	Adenoca
Klotz *et al.*, 1974 (34)	67	C	Bleeding	–	–	Adenoca
Lang *et al.*, 2008 (35)	54	C	Dysuria	Frequency	72	Adenoca
Manning *et al.*, 2012 (36)	56	–	UI	Dysuria	60	TCC
Murayama *et al.*, 1978 (37)	42	A	Pain	–	–	Adenoca
Marshall *et al.*, 1977 (38)	64	–	Ulcer	–	12	Adenoca
	72	–	Bleeding	–	12	TCC
McLoughlin, 1975 (39)	51	B	UTI	–	–	TCC
Melnick and Birdsall, 1960 (40)	50	–	Bleeding	–	–	TCC
Nakamura *et al.*, 1995 (41)	50	A	–	–	–	Adenoca
Nakatsuka *et al.*, 2012 (42)	42	A	Bleeding	Pain	3	Adenoca
Ney *et al.*, 1971 (43)	59	–	Retention	–	–	Adenoca
Noguchi and Ida, 1983 (44)	58	A	Dysuria	–	–	Adenoca
Okubo *et al.*, 1996 (45)	44	A	Bleeding	Retention	3	Adenoca
Oliva and Young, 1996 (46)	–	–	–	–	–	Adenoca
						Adenoca
						Adenoca
						Adenoca
						Adenoca
						Adenoca
						Adenoca
						Adenoca
						Adenoca
						Adenoca
						Adenoca
						Adenoca

Table 1 *(continued)*

Table 1 *(continued)*

Author	Age (years)	Race	Symptom 1	Symptom 2	Duration (months)	Histology
Patanephan *et al.*, 1983 (47)	74	C	Retention	UTIs	–	Adenoca
	58	B	Mass	–	18	Adenoca
Rajan *et al.*, 1993 (48)	31	B	Dyspaerunia	–	–	Adenoca
	47	B	Bleeding	–	–	Adenoca
	65	H	Bleeding	–	–	Adenoca
	52	B	Mass	–	–	Adenoca
Reheis *et al.*, 1981 (49)	61	C	Bleeding	–	–	Adenoca
Rhamy *et al.*, 1973 (50)	61	C	–	–	–	TCC
	72	B	Bleeding	–	–	Adenoca
Rosenfeld and Frachtman, 1964 (51)	52	B	Mass	Dyspareunia	10	TCC
Roth, 1955 (52)	40	B	Bleeding	–	–	TCC
Salvador Alvarez *et al.*, 2011 (53)	57	H	Retention	Pyrexia	–	Adenoca
Scantling *et al.*, 2013 (54)	47	B	UTI	Bleeding	–	Adenoca
Schileru *et al.*, 1984 (55)	–	–	–	–	–	Adenoca
Schnoy and Leistenschneider, 1982 (56)	39	C	–	–	–	Adenoca
Seballos and Rich, 1995 (57)	58	–	Bleeding	–	3	Adenoca
Sekowska and Golajewski, 1961 (58)	–	–	–	–	–	Adenoca
Shalev *et al.*, 2002 (59)	38	–	UTIs	Urgency	–	SCC
Sheahan and Vega Vega, 2013 (60)	54	–	Bleeding	Voiding dysfunction	12	Adenoca
Srinivas and Dow, 1983 (61)	52	–	Dysuria	–	–	TCC
Tanabe *et al.*, 1982 (62)	50	C	Mass	Bleeding	2	Adenoca
Tesluk, 1981 (63)	46	–	Frequency	Urgency	–	Adenoca
	46		Frequency	Bleeding	2	Adenoca
	62		Retention	–	–	Adenoca
Thomas and McGuire, 1991 (64)	–	–	–	–	–	Adenoca
Thomas *et al.*, 2008 (65)	Average 45	–	UI	UTIs	–	Adenoca
			UI	UTIs	–	Adenoca
			UTIs	UTIs	–	Adenoca
			Pain	UTIs	–	Adenoca
			–	UTIs	–	Adenoca
Thompson and Bivings, 1962 (66)	65	C	Mass	–	–	TCC
	46	C	Mass	–	–	SCC
Tines *et al.*, 1982 (67)	56	B	Bleeding	–	–	Adenoca
	71	B	Bleeding	–	–	Adenoca

Table 1 *(continued)*

Table 1 *(continued)*

Author	Age (years)	Race	Symptom 1	Symptom 2	Duration (months)	Histology
Torres and Quattlebaum, 1972 (68)	53	C	Pain	Dysuria	3	Adenoca
Uesaka *et al.*, 2011 (69)	49	A	Asymptomatic—detected on smear	–	–	Adenoca
von Pechmann *et al.*, 2003 (70)	69	–	UI	Voiding dysfunction	–	Adenoca
Washino *et al.*, 2007 (71)	49	A	Dysuria	Bleeding	–	Adenoca
Weng *et al.*, 2013 (72)	65	A	Bleeding	Frequency	6	Adenoca
Wheeler *et al.*, 1992 (73)	56	C	Bleeding	Dyspareunia	5	Adenoca
	75	C	Bleeding	Urgency	5	Adenoca
Wishard and Nourse, 1952 (74)	39	C	Retention	–	–	TCC
Wishard *et al.*, 1960 (75)	54	C	Bleeding	–	–	Adenoca
Wishard *et al.*, 1963 (76)	43	–	Bleeding	–	–	SCC
Yamigawa *et al.*, 1988 (77)	54	A	Dysuria	–	3	Adenoca
Young *et al.*, 2007 (78)	41	–	Dysuria	UTI	24	SCC
UCLH, 2018	52	B	UTIs	Dysuria	18	Adenoca
	55	B	UTIs	Dysuria	20	Adenoca
	38	Ar	Pain	Dysuria	24	Adenoca

A, Asian; Ar, Arabic; B, Black; C, Caucasian; H, Hispanic; Adenoca, adenocarcinoma.

of National Statistics recommendations (79). For our own case series, we retrospectively reviewed patient records to glean symptoms at presentation, diagnostic modalities utilised, pathological stage and grade and management. Written informed consents were obtained from the patients for publication of their cases and any accompanying images.

Case presentations

Case 1

A 38-year-old Arabic female presented with an 18-month history of a palpable vaginal lump, dysuria, dyspareunia, urinary dribble, mixed urinary incontinence (UI), urinary tract infections (UTIs) and pain during urination. Per vaginal examination revealed a palpable hard and indurated mass.

Trans urethral (TUR) biopsy performed prior to referral revealed inflammation only. Pre-operative pelvic magnetic resonance imaging (MRI) showed a circumferential complex urethral diverticulum (UD) and videourodynamics (VUDS) indicated the presence of both idiopathic detrusor overactivity (IDO) and bladder outflow obstruction (BOO).

Initial management was excision of the UD with a modified Martius labial fat pad flap (MFP). Histological examination demonstrated a G3 adenocarcinoma of the UD with positive vaginal and proximal margins. She was counseled regarding all treatment and reconstructive options and went on to have a radical cystourethrectomy, pelvic lymph node dissection and ileal conduit formation 4 weeks after preliminary diverticulum excision. Formal histological analysis revealed a pT3N0M0 G3 adenocarcinoma. She remains under surveillance and is alive with a solitary lung recurrence at 72 months post diverticulectomy.

Case 2

A 55-year-old black female presented with a 9-month history of dysuria, urethral pain and poor flow. Clinical examination revealed a palpable non-tender vaginal mass. MRI pelvis showed a circumferential loculated complex UD and VUDS indicated the presence of BOO. Transvaginal biopsy indicated inflammation only.

She proceeded to excision of the UD with MFP interposition. Histological examination revealed pT2 G3 adenocarcinoma of the UD with negative margins. Formal staging with CT chest, abdomen and pelvis and bone scan indicated her to be N0M0. She was counseled regarding

all treatment options and declined any further therapy. She died from metastatic adenocarcinoma 22 months following her diverticulectomy.

Case 3

A 52-year-old black female presented with an 8-month history of dysuria, dyspareunia, UTIs and urethral pain. On clinical examination she had a palpable vaginal mass.

She underwent simple excision of her UD at her local hospital and was referred when histological review revealed a pT3 G2 adenocarcinoma with positive urethral margins. Post excision MRI performed at our centre indicated partial excision of a circumferential complex UD. Additional staging with CT chest, abdomen and pelvis and bone scan indicated that she was N0M0. After full counseling regarding treatment options she elected to undergo radical urethrectomy, bladder neck closure with MFP interposition, pelvic lymph node dissection and formation of Mitrofanoff channel. Histological examination of the excised specimen confirmed pT3N0 G2 adenocarcinoma. She remains alive and disease free at 21 months post diverticulectomy.

Epidemiology

Primary urethral carcinoma in females is extremely rare, accounting for only 0.02% of genitourinary tract malignancies (2-6). Squamous cell carcinoma (SCC) predominates, accounting for 70% of urethral carcinoma, followed by urothelial (20%) and then clear cell adenocarcinoma (CCA) (10%) (1,3,78,80,81).

UDC represents just 5% of all female urethral carcinoma or 0.001% of female genitourinary tract malignancies (81,82). Unlike in primary urethral carcinoma, adenocarcinoma is the commonest type of UDC, accounting for 75% of UDC (*Tables 1-4*). Transitional cell carcinoma (TCC) (15%) is the next most common and SCC the least common (10%) (9,16,42,59). The first patient with UDC was reported by Hamilton in 1951 (24), and since then only 124 cases (including the 3 in this current series) have been reported in the world literature.

Female urethral diverticula are in themselves rare entities—affecting between 0.02–6% of the female population (83,84). First described in 1805, they are benign, localized, epithelium-lined urethral outpouchings (85,86). Histologically, they are difficult to distinguish from paraurethral cysts. Their lining is composed of squamous epithelial cells in 42%, columnar epithelial cells in 32%, a combination of both squamous and columnar cells in 18% and cuboidal cells alone in 14% (87). The majority of diverticula (77%) show signs of inflammation, and ulceration is often present (87).

Rarely, diverticula are congenital, arising from embryonic Gartner duct remnants, persistence of Müllerian rest cells or the faulty union of primordial folds (88). The majority of diverticula are acquired; arising from rupture of chronically obstructed and infected periurethral glands into the lumen of the urethra (89,90). Risk factors for the development of urethral diverticula are: recurrent infection of the periurethral glands, vaginal birth trauma and previous vaginal or urethral surgery (91-95).

Pathogenesis

There are 3 theories regarding the origin of UDC (15,81,94). The first is that they arise from periurethral gland changes occurring due to persistent/continued infection and obstruction to drainage (20,21,61). The second theory suggests a metaplastic origin with neoplastic squamous, glandular or TCC development resulting from chronic inflammation and urethritis glandularis (65). The final theory is that the malignant change originates in retained Gartner or mesonephric duct remnants (78,96).

Many UDC are considered to originate from the paraurethral duct, which may be homologous to the prostate gland because it is prostate-specific antigen (PSA) positive in some cases (33,42,97). Ogihara and Kato suggested that the adenocarcinomas that arise from urethral diverticula are either CEA-positive columnar and/or mucin-producing and originate from the proximal portion of the paraurethral duct, or are PSA positive clear cell-type arising from the distal part of the paraurethral duct (96).

Occasionally premalignant lesions such as villous adenomas, intestinal metaplasia and high-grade dysplasia may arise (9,65). There are very occasional instances of benign tumour, such as leiomyoma and nephrogenic adenoma (9,65).

Age and race

The median age at presentation of UDC is 53 years (range, 14–81 years). There may be a higher incidence in the black population, possibly related to the higher incidence of UD amongst black women (9,21) although this is disputed (25).

Table 2 Diverticulum location and diagnostic modalities

Author	Location	Diagnostics	Findings	Histology
Allen and Nelson, 1978 (1)	Proximal; UK	–	–	–
Awakura *et al.*, 2003 (2)	Proximal	Cytology	Malignant cells	Adenoca
		Cystoscopy	Mass in diverticulum	
		Urethrogram	Filling defect	
		MRI	Urethral mass	
		TUR biopsy	Adenoca	
		OE	Anterior vaginal wall mass	
Bracken *et al.*, 1976 (3)	Proximal	–	–	TCC
Brown *et al.*, 1956 (4)	Distal	–	–	Adenoca
Carneiro Neto *et al.*, 1973 (5)	UK	–	–	UK
Catalano *et al.*, 1992 (6)	UK	–	–	TCC
Cea *et al.*, 1977 (7)	Middle	–	–	Adenoca
	Proximal	–	–	Adenoca
Christofferson, 1974 (8)	UK	–	–	Adenoca
Clayton *et al.*, 1992 (9)	Middle	OE	Anterior vaginal wall mass	SCC
	Middle	Cystoscopy	Tumour in diverticulum	SCC
		OE	Anterior vaginal wall mass	
		TUR Biopsy	SCC	
	Proximal	OE	Anterior vaginal wall mass	SCC
	Middle	OE	Anterior vaginal wall mass	Adenoca
	Middle	OE	Anterior vaginal wall mass	SCC
	Proximal	OE	Anterior vaginal wall mass	Adenoca
Collado *et al.*, 2000 (10)	UK	USS	Mass in urethra	Adenoca
		Urethrogram	Intravesical cavity	
		Cystoscopy	Diverticulum in urethra	
		CT	Mass in anterior vaginal wall	
		TV Biopsy	Adenoca	
		OE	Anterior vaginal wall mass	
Cruz-Ruiz *et al.*, 2010 (11)	UK	–	–	Adenoca
Davis *et al.*, 2003 (12)	UK	CT	Mass in urethra	Adenoca
		TV biopsy	SCC	
		OE	Anterior vaginal wall mass	
Davis *et al.*, 1999 (13)	Distal	–	–	Adenoca
	UK	–	–	Adenoca

Table 2 *(continued)*

Table 2 *(continued)*

Author	Location	Diagnostics	Findings	Histology
Prudente de Toledo *et al.*, 1978 (14)	Proximal	VCUG	Diverticulum	TCC
		IVU	NAD	
		OE	Anterior vaginal wall mass	
		TUR biopsy	TCC	
Dodson *et al.*, 1995 (15)	UK	–	–	Adenoca
Evans *et al.*, 1981 (16)	Middle	–	–	Adenoca
Faulkner *et al.*, 1959 (17)	Distal	–	–	TCC
Geisler *et al.*, 1998 (18)	Posterior	–	–	Adenoca
Ghoniem *et al.*, 2004 (19)	UK	MRI	Mass in urethra	Adenoca
		OE	Anterior vaginal wall mass	
		TV Biopsy	Adenoca	
Godec *et al.*, 1984 (20)	Middle	–	–	Adenoca
Gonzalez *et al.*, 1985 (21)	Anterior	–	–	Adenoca
	Middle	–	–	Adenoca
	Distal	–	–	Adenoca
	Distal	–	–	TCC
	Distal	Cystoscopy	Mass in diverticulum	TCC
		TUR biopsy	TCC	
	Distal	–	–	SCC
	Middle	–	–	SCC
Graf *et al.*, 1962 (22)	Middle	–	–	TCC
Ha *et al.*, 2010 (23)	UK	Cystoscopy	Mass in diverticulum	Adenoca
		Urethrogram	Urethral stricture	
		MRI	Urethral mass	
		OE	Anterior vaginal wall mass	
Hamilton *et al.*, 1951 (24)	Posterior	–	–	Adenoca
Hickey *et al.*, 2000 (25)	Posterolateral	Cytology	Malignant cells	Adenoca
		Cystoscopy	Mass in diverticulum	
		USS	Mass in diverticulum	
		OE	Anterior vaginal wall mass	
		TV biopsy	Adenoca	
Hinman *et al.*, 1960 (26)	Middle	–	–	Adenoca
	Middle	–	–	TCC
Hruby *et al.*, 2000 (27)	UK	–	–	Adenoca
	UK	–	–	Adenoca

Table 2 *(continued)*

Table 2 *(continued)*

Author	Location	Diagnostics	Findings	Histology
Huvos *et al.*, 1969 (28)	Proximal	OE	Anterior vaginal wall mass	SCC
Jensen *et al.*, 1981 (29)	UK	–	–	Adenoca
	UK	–	–	Adenoca
Jimenez de León *et al.*, 1989 (30)	UK	OE	Anterior vaginal wall mass	Adenoca
		TUR biopsy	Adenoca	
Kanno *et al.*, 2002 (31)	UK	MRI	Urethral mass	Adenoca
		CT	Urethral mass	
		OE	Anterior vaginal wall mass	
		TV biopsy	Adenoca	
Kasahara *et al.*, 2017 (32)	Proximal	MRI	Urethral mass	Adenoca
		OE	Anterior vaginal wall mass	
		TV biopsy	Adenoca	
Kato *et al.*, 1998 (33)	UK	Cytology	Malignant cells	Adenoca
		Cystoscopy	Mass in diverticulum	
		MRI	Mass in diverticulum	
		OE	Anterior vaginal wall mass	
		TUR biopsy	Adnoca	
Klotz *et al.*, 1974 (34)	Middle	–	–	Adenoca
Lang *et al.*, 2008 (35)	UK	MRI	Mass in diverticulum	Adenoca
		OE	Anterior vaginal wall mass	
Manning *et al.*, 2012 (36)	UK	Cytology	NAD	TCC
		MRI	Diverticulum	
		OE	Anterior vaginal wall mass	
Murayama *et al.*, 1978 (37)	Posterior	–	–	Adenoca
Marshall *et al.*, 1977 (38)	Middle	–	–	Adenoca
	Middle	–	–	TCC
McLoughlin, 1975 (39)	Middle	–	–	TCC
Melnick and Birdsall, 1960 (40)	Proximal	–	–	TCC
Nakamura *et al.*, 1995 (41)	UK	–	–	Adenoca
Nakatsuka *et al.*, 2012 (42)	UK	Cytology	Adenoca	Adenoca
		MRI	Mass entire urethra	
		Cystoscopy	Mass in diverticulum	
		CT	Mass entire urethra	
		TUR biopsy	Adenoca	
Ney *et al.*, 1971 (43)	Proximal	–	–	Adenoca

Table 2 *(continued)*

Table 2 *(continued)*

Author	Location	Diagnostics	Findings	Histology
Noguchi and Ida, 1983 (44)	UK	OE	Anterior vaginal wall mass	Adenoca
Okubo *et al.*, 1996 (45)	Proximal	Cytology	Malignant cells	Adenoca
		Cystoscopy	Mass in diverticulum	
		OE	Anterior vaginal wall mass	
		TUR biopsy	Adenoca	
Oliva and Young, 1996 (46)	UK	–	–	Adenoca
	UK	–	–	Adenoca
	UK	–	–	Adenoca
	UK	–	–	Adenoca
	UK	–	–	Adenoca
	UK	–	–	Adenoca
	UK	–	–	Adenoca
	UK	–	–	Adenoca
	UK	–	–	Adenoca
	UK	–	–	Adenoca
	UK	–	–	Adenoca
	UK	–	–	Adenoca
Patanephan *et al.*, 1983 (47)	UK	–	–	Adenoca
	UK	–	–	Adenoca
Rajan *et al.*, 1993 (48)	Proximal	OE	Anterior vaginal wall mass	Adenoca
	Proximal	OE	Anterior vaginal wall mass	Adenoca
	Proximal	OE	Anterior vaginal wall mass	Adenoca
	UK	OE	Anterior vaginal wall mass	Adenoca
Reheis *et al.*, 1981 (49)	Proximal	–	–	Adenoca
Rhamy *et al.*, 1973 (50)	UK	–	–	TCC
	Proximal	–	–	Adenoca
Rosenfeld and Frachtman, 1964 (51)	Proximal	Urethrogram	Diverticulum	TCC
		OE	Anterior vaginal wall mass	
Roth, 1955 (52)	Proximal	–	–	TCC
Salvador Álvarez *et al.*, 2011 (53)	UK	MRI	Cystic mass between vagina and urethra	Adenoca
		PET-CT	High metabolic rate	
		Cystoscopy	Mass in urethra	
		OE	Anterior vaginal wall mass	
		TUR biopsy	Adenoca	

Table 2 *(continued)*

Table 2 *(continued)*

Author	Location	Diagnostics	Findings	Histology
Scantling *et al.*, 2013 (54)	UK	Cystoscopy	Mass in diverticulum	Adenoca
		MRI	Mass in diverticulum with enlarged LN	
		CT	As per MRI	
		Bone scan	NAD	
		OE	Anterior vaginal wall mass	
Schileru *et al.*, 1984 (55)	UK	–	–	Adenoca
Schnoy and Leistenschneider, 1982 (56)	Proximal	–	–	Adenoca
Seballos and Rich, 1995 (57)	UK	Cystoscopy	Diverticulum	Adenoca
		Urethrogram	Diverticulum	
		OE	Anterior vaginal wall mass	
Sekowska and Golajewski, 1961 (58)	UK	–	–	Adenoca
Shalev *et al.*, 2002 (59)	UK	Urinalysis	Microhaematuria	SCC
		IVU	Diverticulum	
		OE	Anterior vaginal wall mass	
Sheahan and Vega Vega, 2013 (60)	UK	USS	Mass in urethra	Adenoca
		MRI	Mass in urethral diverticulum	
		Cytology	Malignant cells	
		Cystoscopy	Mass in diverticulum	
		OE	Anterior vaginal wall mass	
		TUR biopsy	Adenoca	
		TV biopsy	Adenoca	
Srinivas and Dow, 1983 (61)	Middle	–	–	TCC
Tanabe *et al.*, 1982 (62)	Proximal	–	–	Adenoca
Tesluk, 1981 (63)	Proximal	–	–	Adenoca
	Proximal	–	–	Adenoca
	Proximal	–	–	Adenoca
Thomas and McGuire, 1991 (64)	UK	–	–	Adenoca
Thomas *et al.*, 2008 (65)	UK	–	–	Adenoca
	UK	–	–	Adenoca
	UK	–	–	Adenoca
	UK	–	–	Adenoca
	UK	–	–	Adenoca
Thompson and Bivings, 1962 (66)	UK	–	–	TCC
	UK	–	–	SCC

Table 2 *(continued)*

Table 2 *(continued)*

Author	Location	Diagnostics	Findings	Histology
Tines *et al.*, 1982 (67)	Middle	–	–	Adenoca
	Middle	–	–	Adenoca
Torres and Quattlebaum, 1972 (68)	Middle	Cystoscopy; urethrogram	Diverticulum	Adenoca
Uesaka *et al.*, 2011 (69)	Proximal	PET-CT	Proximal urethral uptake	Adenoca
		Cystoscopy	Mass in diverticulum	
		MRI	Mass in diverticulum	
		OE	Anterior vaginal wall mass	
		TUR Biopsy	Adenoca	
von Pechmann *et al.*, 2003 (70)	Middle	Urinalysis	Microscopic haematuria	Adenoca
		Cystoscopy	Diverticulum	
		Urethrogram	Urethral stricture	
		OE	Anterior vaginal wall mass	
		TUR biopsy	Adenoca	
Washino *et al.*, 2007 (71)	UK	Cytology	Malignant cells	Adenoca
		MRI	Mass in diverticulum	
		Cystoscopy	Mass in diverticulum	
		CT	Mass in diverticulum	
		OE	Anterior vaginal wall mass	
		TUR biopsy	Adenoca	
Weng *et al.*, 2013 (72)	UK	Cystoscopy	Mass in diverticulum	Adenoca
		IVU	NAD	
		MRI	Mass anterior to vagina	
		TUR biopsy	Adenoca	
Wheeler *et al.*, 1992 (73)	Proximal	Urinalysis	Microscopic haematuria	Adenoca
		IVU	Filling defect bladder base	
		Urethrogram	Mass in diverticulum	
		Cystoscopy	NAD	
		OE	Anterior vaginal wall mass	
		TV biopsy	No malignancy	
	Posterior	Urinalysis	Microscopic haematuria	Adenoca
		IVU	Elevated bladder base	
		Cystoscopy	Diverticulum	
		TUR biopsy	Mass in urethra	
			Adenoca	

Table 2 *(continued)*

Table 2 *(continued)*

Author	Location	Diagnostics	Findings	Histology
Wishard and Nourse, 1952 (74)	Proximal	–	–	TCC
Wishard *et al.*, 1960 (75)	Distal	–	–	Adenoca
Wishard *et al.*, 1963 (76)	Proximal	–	–	SCC
Yamigawa *et al.*, 1988 (77)	Proximal	IVU	Elevated bladder	Adenoca
		Cystoscopy	Mass in diverticulum	
		OE	Anterior vaginal wall mass	
		TUR biopsy	Adenoca	
Young *et al.*, 2007 (78)	Anterior	VCUG	Diverticulum	SCC
		Cystoscopy	Mass in diverticulum	
		OE	Anterior vaginal wall mass	
UCLH, 2018	Proximal	Urinalysis	Microhaematuria	Adenoca
		OE	Anterior vaginal wall mass	
	Proximal	MRI	Suspicious diverticulum	Adenoca
		Cystoscopy	Diverticulum	
		OE	Anterior vaginal wall mass	
		TV biopsy	Negative	
	Proximal	MRI	Suspicious diverticulum	Adenoca
		Cystoscopy	Diverticulum	
		OE	Anterior vaginal wall mass	
		TUR biopsy	Negative	

UK, unknown; TUR, transurethral resection; OE, on examination; TV, transvaginal; VCUG, voiding cystourethrogram; IVU, intravenous urogram; NAD, no abnormality detected.

Our latest review of the literature indicates that 38% of cases are in white women, 32% in black women, 22% in Asian women and 8% in Hispanic women (N=65). In our series of 100 women having UD excision 82% with benign UD were white whilst UDC was found in 2 black and 1 Asian female suggesting a preponderance of UDC in black and Asian women. The median age of presentation of women with benign diverticulum also tended to be younger than those with UDC at 44 years (N=97). This contrasts with a median age at diagnosis of 53 in those with UDC (N=3) (98).

Presentation

There are no pathognomonic signs and symptoms of UDC. As can be seen in *Table 1* UDC may present with signs and symptoms of UD—classically dysuria (13%), dyspareunia (7%) and/or post micturition dribble/UI (3%). UDC more commonly presents with urethral bleeding or hematuria in 55%, urethral obstruction/voiding dysfunction in 16%, urethral/introital mass in 13%, UTIs in 13% and localized pain in 6% (N=89). A painless mass of the anterior vaginal wall can be found on examination in the majority of patients (1,9,16,80,81,90,96). This mass may feel much like a benign diverticulum but is noted to be firm or hard in some cases.

Preoperative diagnosis of UDC remains difficult because of its nonspecific presentation. The differential diagnosis of a peri-urethral mass in women includes; UD, urethrocele and/or cystocele, vaginal inclusion cyst, Müllerian cyst, endometriosis, and urethral or vaginal carcinoma. (33,61,81,88,97).

Table 3 Stage and grade of female urethral diverticulum carcinoma

Author	Histology	Stage	Grade
Allen and Nelson, 1978 (1)	Adenoca	T1	–
	Adenoca	T1	–
Awakura *et al.*, 2003 (2)	Adenoca	T3N0M0	–
Bracken *et al.*, 1976 (3)	TCC	T1	–
Brown *et al.*, 1956 (4)	Adenoca	T2	–
Carneiro Neto *et al.*, 1973 (5)	UK	–	–
Catalano *et al.*, 1992 (6)	TCC	–	–
Cea *et al.*, 1977 (7)	Adenoca	T3N0MO	–
	Adenoca	T2N0MO	–
Christofferson, 1974 (8)	Adenoca	–	–
Clayton *et al.*, 1992 (9)	SCC	T2	–
	SCC	T3	–
	SCC	T4N+M0	G3
	Adenoca	T3	–
	SCC	T3	–
	Adenoca	T3	–
Collado *et al.*, 2000 (10)	Adenoca	T2N0MO	–
Cruz-Ruiz *et al.*, 2010 (11)	Adenoca	–	–
Davis *et al.*, 2003 (12)	Adenoca	T2N1M0	–
Davis *et al.*, 1999 (13)	Adenoca; Adenoca	–	–
Prudente de Toledo *et al.*, 1978 (14)	TCC	T4	–
Dodson *et al.*, 1995 (15)	Adenoca	–	–
Evans *et al.*, 1981 (16)	Adenoca	T2	–
Faulkner *et al.*, 1959 (17)	TCC	T2	G1
Geisler *et al.*, 1998 (18)	Adenoca	–	–
Ghoniem *et al.*, 2004 (19)	Adenoca	–	–
Godec *et al.*, 1984 (20)	Adenoca	T3N0M0	G2
Gonzalez *et al.*, 1985 (21)	Adenoca	–	G1
	Adenoca	–	G1
	Adenoca	–	G3
	TCC	–	G3
	TCC	–	G3
	SCC	–	G1
	SCC	–	G3
Graf *et al.*, 1962 (22)	TCC	T1	G2
Ha *et al.*, 2010 (23)	Adenoca	T3N0M0	–
Hamilton *et al.*, 1951 (24)	Adenoca	–	–
Hickey *et al.*, 2000 (25)	Adenoca	–	–

Table 3 *(continued)*

Table 3 *(continued)*

Author	Histology	Stage	Grade
Hinman *et al.*, 1960 (26)	Adenoca	–	–
	TCC	–	G3
Hruby *et al.*, 2000 (27)	Adenoca	–	–
	Adenoca	–	–
Huvos *et al.*, 1969 (28)	SCC	T3N+	G1
Jensen *et al.*, 1981 (29)	Adenoca	–	–
	Adenoca	–	–
Jimenez de León *et al.*, 1989 (30)	Adenoca	–	–
Kanno *et al.*, 2002 (31)	Adenoca	–	–
Kasahara *et al.*, 2017 (32)	Adenoca	T4N2	–
Kato *et al.*, 1998 (33)	Adenoca	–	–
Klotz *et al.*, 1974 (34)	Adenoca	T3	G3
Lang *et al.*, 2008 (35)	Adenoca	T3	–
Manning *et al.*, 2012 (36)	TCC	Tis	G3
Murayama *et al.*, 1978 (37)	Adenoca	T3N0M0	–
Marshall *et al.*, 1977 (38)	Adenoca	T2	G1
	TCC	T1	–
McLoughlin, 1975 (39)	TCC	–	–
Melnick and Birdsall, 1960 (40)	TCC	–	–
Nakamura *et al.*, 1995 (41)	Adenoca	–	–
Nakatsuka *et al.*, 2012 (42)	Adenoca	–	–
Ney *et al.*, 1971 (43)	Adenoca	–	–
Noguchi and Ida, 1983 (44)	Adenoca	–	–
Okubo *et al.*, 1996 (45)	Adenoca	–	–
Oliva and Young, 1996 (46)	Adenoca	–	–
	Adenoca	–	–
	Adenoca	–	–
	Adenoca	–	–
	Adenoca	–	–
	Adenoca	–	–
	Adenoca	–	–
	Adenoca	–	–
	Adenoca	–	–
	Adenoca	–	–
	Adenoca	–	–
	Adenoca	–	–

Table 3 *(continued)*

Table 3 *(continued)*

Author	Histology	Stage	Grade
Patanephan *et al.*, 1983 (47)	Adenoca	–	–
	Adenoca	–	–
Rajan *et al.*, 1993 (48)	Adenoca	–	–
	Adenoca	–	–
	Adenoca	–	–
	Adenoca	–	–
Reheis *et al.*, 1981 (49)	Adenoca	T3	G1
Rhamy *et al.*, 1973 (50)	TCC	–	–
	Adenoca	–	–
Rosenfeld and Frachtman, 1964 (51)	TCC	T2	–
Roth, 1955 (52)	TCC	–	–
Salvador Álvarez *et al.*, 2011 (53)	Adenoca	–	–
Scantling *et al.*, 2013 (54)	Adenoca	T3N0M0	G2
Schileru *et al.*, 1984 (55)	Adenoca	–	–
Schnoy and Leistenschneider, 1982 (56)	Adenoca	T2	–
Seballos and Rich, 1995 (57)	Adenoca	–	–
Sekowska and Golajewski, 1961 (58)	Adenoca	–	–
Shalev *et al.*, 2002 (59)	SCC	–	–
Sheahan and Vega Vega, 2013 (60)	Adenoca	T2N1M0	G2
Srinivas and Dow, 1983 (61)	TCC	T3	G3
Tanabe *et al.*, 1982 (62)	Adenoca	T3N0M0	G3
Tesluk, 1981 (63)	Adenoca	T3	G3
	Adenoca	T3	G3
	Adenoca	T3	G3
Thomas and McGuire, 1991 (64)	Adenoca	–	–
Thomas *et al.*, 2008 (65)	Adenoca	–	–
	Adenoca	–	–
	Adenoca	–	–
	Adenoca	–	–
	Adenoca	–	–
Thompson and Bivings, 1962 (66)	TCC	T2	–
	SCC	T3N0M+	–
Tines *et al.*,1982 (67)	Adenoca	–	–
	Adenoca	–	–
Torres and Quattlebaum, 1972 (68)	Adenoca	T3N0M0	–

Table 3 *(continued)*

Table 3 *(continued)*

Author	Histology	Stage	Grade
Uesaka *et al.*, 2011 (69)	Adenoca	T2	–
von Pechmann *et al.*, 2003 (70)	Adenoca	T3N2M0	–
Washino *et al.*, 2007 (71)	Adenoca	T3	–
Weng *et al.*, 2013 (72)	Adenoca	T4N0M0	G3
Wheeler *et al.*, 1992 (73)	Adenoca	–	–
	Adenoca	–	–
Wishard and Nourse, 1952 (74)	TCC	T2	G1
Wishard *et al.*, 1960 (75)	Adenoca	T2	G1
Wishard *et al.*, 1963 (76)	SCC	T3	G3
Yamigawa *et al.*, 1988 (77)	Adenoca	–	–
Young *et al.*, 2007 (78)	SCC	CIS	–
UCLH, 2018	Adenoca	T3N0M0	G2
	Adenoca	T3N0M0	G3
	Adenoca	T3NOM0	G3

TCC, transitional cell carcinoma; SCC, squamous cell carcinoma; Adenoca, adenocarcinoma; UK, unknown; CIS, carcinoma in situ.

Diagnosis

Diagnostic modalities used in the diagnosis and pre-operative planning of UDC are outlined in *Table 2*. Urine cytology may be a useful initial screening test and has been reported to be positive in 10/11 (91%) cases in which it was utilised (2,25,31,36,41,42,45,60,69,71,77,96,98). Imaging modalities that have been used to aid the diagnosis of UDC include ultrasound, intravenous urography, voiding cystourethrography, computed tomography (CT), MRI, and cystourethroscopy (2,9,25,31,36,41,45,60,69,71,77,80, 96,98,99). The gold standard investigations to date appear to be a combination of gadolinium-enhanced MRI which can be used for diagnosis, staging and surveillance followed by transvaginal trucut or transurethral biopsies of the UD mass for definitive diagnosis. Case 2 above describes a 55-year-old lady with UD diagnosed on an initial MRI (*Figure 1*) with a follow up contrast enhanced study 2 months later (*Figure 2*). The differential diagnosis of increasing debris or thickening within the diverticulum includes infection and inflammatory change within the UD and biopsies may yield no evidence of malignancy as in 2/3 of our UDC cases. Cystoscopy was unhelpful in our cases but may play an important role in the pathological diagnosis and in localization of the tumor origin (1) with neoplasm in the diverticulum or urethra noted on cystoscopy in 23/29 (79%) cases in those series reporting its use (7,9,10,12,21,23,31,42,53,54,57,72,73,77, 96,98,100).

A CT or an isotope bone scan may be used to assess for lymph node enlargement, distant tissue and bone metastasis (80). In our experience a T2 weighted thin slice post void pelvic MRI should be performed to diagnose the presence of a UD and if history, examination or MRI are suspicious for cancer an urgent urethral diverticulectomy should be performed as a definitive "excision biopsy".

Pathology

Macroscopically

There is usually a mass within the diverticulum, which may be encroaching into the true urethral lumen or invading past the diverticulum walls into the surrounding paraurethral or paravaginal tissues (80).

Microscopically

Whilst only 10% of urethral cancers are adenocarcinoma, 30% of these originate from UD (1,3,78,80,81). Adenocarcinoma has two subtypes; clear cell and mucin

producing (33). The microscopic features of the CCA are similar to those of other CCA of the female genital tract and include; cells with abundant clear cytoplasm, some forms of pleomorphism, mitotic activity and a mostly flat shape. Focally, a hobnail appearance may be present. CCA of a UD may present patterns that are either tubule-cystic, papillary or diffuse (78). In a urine sample, the presence of malignant clear cells with the appearance of mirror balls is

Table 4 Treatment modalities and survival patterns iTn urethral diverticulum carcinoma

Author	Primary treatment	Survival in months	Outcome at last review	Histology
Allen and Nelson, 1978 (1)	Radiotherapy	48	Alive and well	Adenoca
	Radiotherapy	24	Alive and well	Adenoca
Awakura *et al.*, 2003 (2)	Chemotherapy + radiotherapy	24	Alive and well	Adenoca
Bracken *et al.*, 1976 (3)	Radiotherapy	30	Died	TCC
Brown *et al.*, 1956 (4)	Excision	30	Alive and well	Adenoca
Carneiro Neto *et al.*, 1973 (5)	UK	–	–	UK
Catalano *et al.*, 1992 (6)	UK	–	–	TCC
Cea et al., 1977 (7)	Excision + cystourethrectomy 12 m	24	Alive with recurrence	Adenoca
	Cystectomy	12	Alive and well	Adenoca
Christofferson, 1974 (8)	UK	–	–	Adenoca
Clayton *et al.*, 1992 (9)	Excision	36	Died	SCC
	Radiotherapy	30	Died	SCC
	Excision	24	Died	SCC
	Excision + radiotherapy	12	Alive and well	Adenoca
	Excision + radiotherapy	12	Died	SCC
	Excision	18	Died	Adenoca
Collado *et al.*, 2000 (10)	Cysto-urethrectomy + ileal conduit	16	Alive and well	Adenoca
Cruz-Ruiz *et al.*, 2010 (11)	UK	–	–	Adenoca
Davis *et al.*, 2003 (12)	Chemotherapy + radiotherapy + anterior exenteration + gracilis flap	10	Alive and well	Adenoca
Davis *et al.*, 1999 (13)	Excision	–	–	Adenoca
	Excision + vaginal wall reconstruction	39	Alive and well	Adenoca
Prudente de Toledo *et al.*, 1978 (14)	Chemotherapy + radiotherapy + cysto-urethrectomy + ureterosigmoidostomy	30	Alive and well	TCC
Dodson *et al.*, 1995 (15)	UK	–	–	Adenoca
Evans *et al.*, 1981 (16)	Excision	–	–	Adenoca
Faulkner *et al.*, 1959 (17)	Radiotherapy	12	Alive and well	TCC
Geisler *et al.*, 1998 (18)	Cystourethrectomy	3	Died	Adenoca
Ghoniem *et al.*, 2004 (19)	Anterior exenteration + Florida pouch	12	Alive and well	Adenoca
Godec *et al.*, 1984 (20)	Cystourethrectomy	12	Alive and well	Adenoca

Table 4 *(continued)*

Table 4 *(continued)*

Author	Primary treatment	Survival in months	Outcome at last review	Histology
Gonzalez *et al.*, 1985 (21)	Radiotherapy	60	Alive and well	Adenoca
	Radiotherapy	120	Alive and well	Adenoca
	Excision	12	Died	Adenoca
	Radiotherapy	30	Died	TCC
	Radiotherapy	12	Alive and well	TCC
	Radiotherapy	120	Alive and well	SCC
	Radiotherapy	12	Died	SCC
Graf *et al.*, 1962 (22)	Excision	12	Alive and well	TCC
Ha *et al.*, 2010 (23)	Laparoscopic anterior exenteration	6	Alive and well	Adenoca
Hamilton *et al.*, 1951 (24)	Excision	18	Alive with recurrence	Adenoca
Hickey *et al.*, 2000 (25)	Excision and radiotherapy	18	Alive and well	Adenoca
Hinman *et al.*, 1960 (26)	Excision	48	Alive and well	Adenoca
	Excision	72	Alive and well	TCC
Hruby *et al.*, 2000 (27)	Excision + radiotherapy	–	–	Adenoca
				Adenoca
Huvos *et al.*, 1969 (28)	Radiotherapy	12	Died	SCC
Jensen *et al.*, 1981 (29)	–	–	–	Adenoca
				Adenoca
Jimenez de León *et al.*, 1989 (30)	Radical urethrectomy + pelvic and inguinal LN dissection + urethral reconstruction	–	–	Adenoca
Kanno *et al.*, 2002 (31)	Urethrectomy + TAH + BSO + anterior vaginal wall excision	8	Alive and well	Adenoca
Kasahara *et al.*, 2017 (32)	Anterior exenteration + pelvic LN dissection + chemotherapy	5	Alive and well	Adenoca
Kato *et al.*, 1998 (33)	Anterior exenteration+ continent diversion	12	Alive and well	Adenoca
Klotz *et al.*, 1974 (34)	Cystourethrectomy	–	–	Adenoca
Lang *et al.*, 2008 (35)	Excision + radiotherapy	18	Alive and well	Adenoca
Manning *et al.*, 2012 (36)	Excision	–	–	TCC
Murayama *et al.*, 1978 (37)	Cystectomy	–	–	Adenoca
Marshall *et al.*, 1977 (38)	Excision	60	Alive and well	Adenoca
	Excision	12	Alive and well	TCC
McLoughlin, 1975 (39)	Excision	12	Alive and well	TCC
Melnick, Birdsall, 1960 (40)	Radiotherapy	–	–	TCC
Nakamura *et al.*, 1995 (41)	Excision	–	–	Adenoca
Nakatsuka *et al.*, 2012 (42)	Cystourethrectomy + partial resection of vaginal wall	–	–	Adenoca

Table 4 *(continued)*

Table 4 *(continued)*

Author	Primary treatment	Survival in months	Outcome at last review	Histology
Ney *et al.*, 1971 (43)	Radiotherapy	24	Alive and well	Adenoca
Noguchi and Ida, 1983 (44)	Excision	9	Alive and well	Adenoca
Okubo *et al.*, 1996 (45)	Anterior exenteration + pelvic LN dissection + Indiana pouch + radiotherapy	16	Alive and well	Adenoca
Oliva and Young, 1996 (46)	–	–	–	Adenoca
				Adenoca
				Adenoca
				Adenoca
				Adenoca
				Adenoca
				Adenoca
				Adenoca
				Adenoca
				Adenoca
				Adenoca
				Adenoca
				Adenoca
Patanephan *et al.*, 1983 (47)	–	–	–	Adenoca
				Adenoca
Rajan *et al.*, 1993 (48)	Radiotherapy + chemotherapy	12	Died	Adenoca
	Cystourethrectomy	29	Alive and well	Adenoca
	Cystourethrectomy	44	Alive and well	Adenoca
	–	–	–	Adenoca
Reheis *et al.*, 1981 (49)	Cystourethrectomy	12	Alive and well	Adenoca
Rhamy *et al.*, 1973 (50)	Radiotherapy	72	Alive and well	TCC
	Radiotherapy	12	Alive and well	Adenoca
Rosenfeld and Frachtman, 1964 (51)	Excision	12	Died	TCC
Roth, 1955 (52)	Excision	24	Alive and well	TCC
Salvador Álvarez *et al.*, 2011 (53)	Anterior exenteration	–	–	Adenoca
Scantling *et al.*, 2013 (54)	Robotic anterior exenteration + Indiana pouch	12	Alive and well	Adenoca
Schileru *et al.*, 1984 (55)	–	–	–	Adenoca
Schnoy and Leistenschneider 1982 (56)	Cystourethrectomy	24	Alive and well	Adenoca
Seballos and Rich, 1995 (57)	Excision	–	–	Adenoca
Sekowska and Golajewski, 1961 (58)	–	–	–	Adenoca

Table 4 *(continued)*

Table 4 *(continued)*

Author	Primary treatment	Survival in months	Outcome at last review	Histology
Shalev *et al.*, 2002 (59)	Excision	6	Alive with recurrence	SCC
Sheahan and Vega Vega, 2013 (60)	Anterior exenteration + pelvic LN dissection + ileal conduit	12	Alive with recurrence	Adenoca
Srinivas and Dow, 1983 (61)	Radiotherapy + cystourethrectomy	4	Alive and well	TCC
Tanabe *et al.*, 1982 (62)	Radiotherapy	30	Alive and well	Adenoca
Tesluk, 1981 (63)	Cystourethrectomy	36	Died	Adenoca
	Cystourethrectomy	–	–	Adenoca
	Cystourethrectomy	12	Alive and well	Adenoca
Thomas and McGuire, 1991 (64)	–	–	–	Adenoca
Thomas *et al.*, 2008 (65)	Anterior exenteration + ileal conduit	36	Died	Adenoca
	Anterior exenteration + ileal conduit	11	Died	Adenoca
	Anterior exenteration + ileal conduit	–	–	Adenoca
	Anterior exenteration + ileal conduit	–	–	Adenoca
	Anterior exenteration + ileal conduit	–	–	Adenoca
Thompson and Bivings, 1962 (66)	Excision	12	Died	TCC
	Radiotherapy	12	Died	SCC
Tines *et al.*, 1982 (67)	Cystourethrectomy	–	–	Adenoca
	Radiotherapy	–	–	Adenoca
Torres and Quattlebaum, 1972 (68)	Anterior pelvic exenteration with ureterosigmoidostomy and adjuvant radiotherapy	–	Alive and well	Adenoca
Uesaka *et al.*, 2011 (69)	Urethrectomy + cutaneous vesicostomy	5	Alive and well	Adenoca
von Pechmann *et al.*, 2003 (70)	Cystourethrectomy + vaginectomy + partial vulvectomy + TAH + pelvic LN dissection +ileal conduit	3	Alive with recurrence	Adenoca
Washino *et al.*, 2007 (71)	Excision	6	Alive with recurrence	Adenoca
Weng *et al.*, 2013 (72)	Urethrectomy + anterior exenteration + ileal conduit	24	Alive and well	Adenoca
Wheeler *et al.*, 1992 (73)	Excision + radical cystourethrectomy	30	Alive and well	Adenoca
	Anterior exenteration + pelvic LN dissection	24	Alive and well	Adenoca
Wishard and Noursem 1952 (74)	Excision	96	Alive and well	TCC
Wishard *et al.*, 1960 (75)	Excision	12	Alive and well	Adenoca
Wishard *et al.*, 1963 (76)	Excision	24	Died	SCC
Yamigawa *et al.*, 1988 (77)	Cystourethrectomy + pelvic LN dissection + ileal conduit	17	Alive and well	Adenoca
Young *et al.*, 2007 (78)	Excision	24	Alive and well	SCC

Table 4 *(continued)*

Table 4 *(continued)*

Author	Primary treatment	Survival in months	Outcome at last review	Histology
UCLH, 2018	Excision + urethrectomy + bladder neck closure + Mitrofanoff	21	Alive and well	Adenoca
	Excision	22	Died	Adenoca
	Excision + anterior exenteration + ileal conduit	72	Alive with recurrence	Adenoca

TCC, transitional cell carcinoma; SCC, squamous cell carcinoma; Adenoca, adenocarcinoma; UK, unknown; LN, lymph node; TAH, total abdominal hysterectomy.

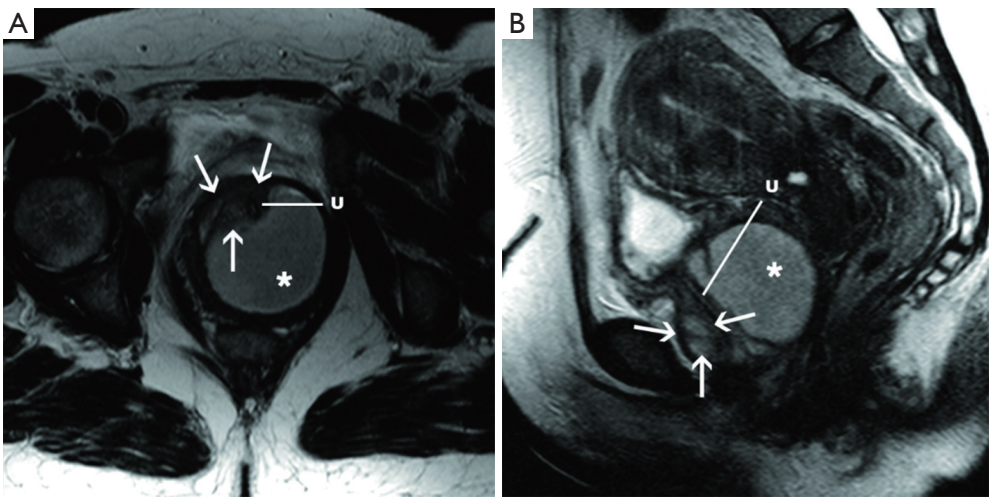


Figure 1 MRI at presentation. Axial (A) and sagittal (B) fast spin-echo T2-weighted sequence show a large fluid filled urethral diverticulum (*) displacing the urethra (U) anteriorly. Heterogeneous low T2 signal in the anterior portion (arrows).

highly suggestive for CCA arising from UD (9,16,42).

TCC accounts for around 15% of UDC and is histologically the same as that originating in the bladder although with a tendency to be of a higher stage at diagnosis due to the absence of a muscle layer within a UD. SCC is the least common form of UDC. SCC may be associated with the presence of calculus in a UD; Clayton found this to be the case in 56% (9).

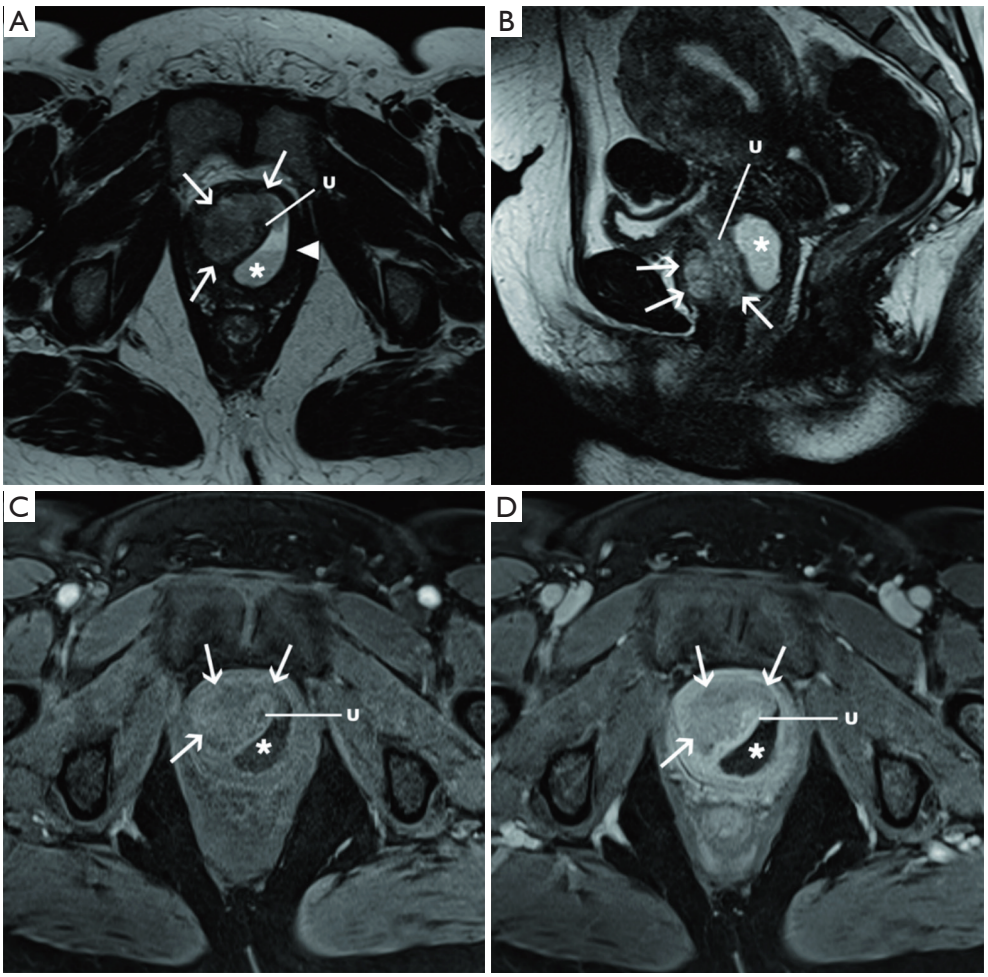
Staging

Staging of UDC is very difficult because of the location of the periurethral glands inside the periurethral space abutting the paravaginal fascia. The TNM staging system has been used in some cases (83). Most cancers are at an advanced stage at diagnosis because there is little muscle underlying them; 83% of UDC were T2 and above at time of presentation in the 54 patients in whom the stage was known at diagnosis (*Table 3*) (9,16,99). They also tend to be high grade with 73% grade 2 or 3 at presentation (N=40) (9,16,99).

Treatment

The mainstay of treatment is surgical with the options including:

(I) Urethral diverticulectomy alone or with adjuvant radiotherapy or chemotherapy (9,36,100);
(II) Urethrectomy +/– pelvic or inguinal lymph node dissection +/– adjuvant therapy (31,81);
(III) Anterior exenteration (excision of the urethra, bladder, anterior vaginal wall, uterus and pelvic lymph nodes) +/– inguinal lymph node dissection +/– adjuvant therapy (12,13,31,45,68);



Figures 2 MRI study performed 2 months later. Axial (A) and sagittal (B) fast spin-echo T2-weighted sequences show the posterior fluid component (*) has reduced in size and now contains a fluid level (arrowhead) due to debris. The anterior intermediate signal (arrows) has significantly increased in size and displaces the urethra (U) posteriorly; (C,D) axial T1 spin-echo fast suppressed pre- (C) and post- (D) contrast sequences. The solid anterior component (arrows) is isointense on the pre-contrast sequence and shows heterogeneous enhancement on the post-contrast studies, confirming this is a solid tumour rather than simple debris.

(IV) Radiotherapy +/– adjuvant chemotherapy alone (1,3,9).

The results from the various treatment options are summarized in *Table 4*. Accepting the limited (generally < 2 years) length of follow-up in most series, simple urethral diverticulectomy appears to be curative in 55% of the 22 patients who underwent same in which follow up was specified with a further 14% alive with recurrence at a mean of 26 months follow-up (4,9,16,21,22,24,26,36,38,39,41,44, 51,52,57,59,66,71,74-76,78). Urethrectomy appears to be curative in 100% at a mean of 13 months follow up (N=3) (30,31,69).

Occasionally cisplatinum-based chemotherapy alone and chemoradiotherapy has been used, without formal documentation of its effectiveness (3,80). Other chemotherapeutic agents utilized include 5-fluorouracil and leucovorin.

Prognosis

Patients with adenocarcinoma and TCC of a UD fare better than those with SCC. The % of patients alive with no evidence of disease (NED) at last follow-up is:

(I) 72% for those with adenocarcinoma (median

48 months) (N=54);
(II) 78% for those with TCC (median 18 months) (N=18);
(III) 25% for those with SCC (median 48 months) (N=12).

Conclusions

UDC is an extremely rare condition and presents a serious situation due to non-specific presentation and delayed diagnosis. UDC needs aggressive treatment as survival is at best moderate and is particularly poor for those with SCC. Optimal treatment remains to be determined but appears to be radical surgery. Consideration should be given to adjuvant radiotherapy +/– chemotherapy in patients with SCC or high-grade adenocarcinoma or TCC. An international registry and consensus on treatment would greatly aid the management of this problematic condition.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: O'Connor E, Iatropoulou D, Hashimoto S, Takahashi S, Ho DH, Greenwell T. Urethral diverticulum carcinoma in females—a case series and review of the English and Japanese literature. Transl Androl Urol 2018;7(4):703-729. doi: 10.21037/tau.2018.07.08

