Urethral Neoplasms

Editors:

Janet Baack Kukreja, MD, MPH

Authors:

Mary E. Westerman, MD; Andrea Kokorovic, MD, FRCSC, MSc

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male urethral cancer, female urethral cancer, urethrectomy

1. Introduction and Epidemiology

This core curriculum section addresses malignant tumors of the urethra. Urethral carcinomas account for less than 1% of all genitourinary malignancies.[1] Urothelial urethral carcinoma is more common in men with two-thirds of the cases being male.[2] A recent study based on SEER data suggested that men have a 3-fold increased incidence of all types of urethral cancer[3] and that women of African American descent have an increased age-adjusted incidence when compared to White women (4.3 vs 1.3 per million).

2. Anatomy

2.1 Epithelium

Both the male and female urethra are composed of an epithelial layer that changes throughout its length. Although the male and female urethras are anatomically divided by the urogenital diaphragm into anterior and posterior segments (discussed below), histologic differences do not conform to these divisions. **In the male, the prostatic urethra is lined by urothelium (transitional epithelium), the membranous urethra to the fossa navicularis is lined by stratified and pseudostratified columnar epithelium, and the fossa navicularis is lined by stratified squamous epithelium. In the female, the proximal third is lined by transitional epithelium and the distal two thirds is lined by squamous epithelium** .[4]

2.2 Lymphatic Drainage

The anterior and posterior divisions of the male and female urethra are demarcated by the **urogenital diaphragm**. In females, the posterior urethra comprises the majority of the urethral length (proximal two-thirds). Conversely, in men the inverse is true (proximal one-third). Although there is lymphatic drainage overlap, generally, anterior tumors are drained first by the superficial inguinal lymph nodes followed by the deep inguinal and pelvic nodes (analogous drainage to penile

carcinoma in men and vulvar carcinoma in females). The posterior urethral drainage is first to the external iliac lymph nodes followed by the obturator and internal iliac nodes. The bulbar urethra is an area of variable drainage and studies have demonstrated drainage to the retrofemoral nodes and those overlying the dorsum of the prostate. [4,5]

Table 1. Summary of Anatomy of the Male Urethra

	Anterior Urethra (Distal)	Posterior Urethra (Proximal)
Anatomic Delineation	Caudal to Verumontanum	Cranial to Verumontanum
Cellular Lining	SSE-->SCU-->PSCU	urothelial cells
Blood Supply	internal iliac--> internal pudendal--> common penile artery--> 3 branches: (1) bulbuourethral artery, (2) Cavernosal Artery, (3) dorsal artery	inferior vesical and middle rectal
Lymphatic Drainage	superficial and deep inguinal lymph nodes	pelvic lymph nodes

SSE-Stratified Squamous Epithelium, SCU-Stratified Columnar Epithelium, PSCU-Pseudostratified Columnar Urothelium

Table 2. Summary of anatomy of female urethra

	Distal Urethra	Proximal Urethra
Anatomical delineation	Approximate anatomical distal-third	Approximate anatomical proximal two-thirds
Cellular Lining	Non-keratinized stratified squamous cells	Urothelial cells
Blood Supply	Vaginal artery	Internal pudendal artery
Lymphatic Drainage	Superficial and deep inguinal nodes	External iliac, internal iliac and obturator nodes

From Appendix 1 of AUA Update 2019-Lesson 23[5]

SSE: stratified squamous epithelium; SCU: stratified columnar epithelium; PSCE: pseudostratified columnar epithelium

3. Sites of Disease and Histologies

The most common histology of primary male urethral carcinoma is *urothelial carcinoma* with the most common location in males being the proximal urethra (posterior). For distal tumors, the most common histology is squamous cell carcinoma. In females, urethral carcinoma is most likely to occur along the entire length of the urethra.[6]

Histologic and location distributions are listed in **Table 3**.[7,8,9] A recent SEER (2004 to 2016) analysis demonstrated that 52.9% of primary urethral carcinomas are of urothelial origin. The second most common histology overall was SCC (23.9% of cases),[10] followed by adenocarcinoma (14.6%) and other histologies (8.7%).[10] Urothelial carcinoma was the most common histology in both males (64.1%) and females (28.8%).[10] Adenocarcinoma occurred more commonly in women than in men, representing 27.4% and 8.6% of cases, respectively.[10] These findings are in contrast to historical data, which suggested that adenocarcinoma predominated in females.[10] Although rare, the **most common histology in urethral diverticulum is adenocarcinoma**. These tumors can be further divided histologically into clear cell variant adenocarcinoma (thought to be derived from Mullerian ducts) or mucin-producing adenocarcinomas (thought to be derived from the Skene's gland) which may stain for PSA or PSAP.[11]

Table 3. Urethral Cancer Histology and Location		
	Male	**Female**
Location		
Proximal	55%	30%
Distal	35%	70%
Both	10%	1%
Histology		
Urothelial	50%	25%
Squamous	30%	25%
Adenocarcinoma	10%	45%
Other	10%	<5%

4. Risk Factors and Pathophysiology

Given the rarity of urethral cancer, risk factors are not well described. Studies have demonstrated an association with **chronic inflammation, sexually transmitted disease, urethritis, urethral stricture disease and human papilloma virus (particularly subtypes 16 & 18)**.[6] Recent data found that 31% of urethral tumors were positive for high-risk HPV. In men, external beam radiotherapy (EBRT) and brachytherapy have also been associated with urethral cancer. In women, urethral diverticulum, recurrent urinary tract infections, and chronic irritation have all been associated with increased with of urethral cancer.

Additionally,[12,13] **smoking** has been implicated as it is a known causative agent for urothelial and squamous cell carcinomas in other locations. A prior history of urothelial carcinoma represents a risk factor for development of urethral carcinoma, with a recurrence rate in the urethra of 4.9%.[14]

5. Clinical Presentation

Urethral cancer is frequently symptomatic at presentation in both men and women (~95%). Common symptoms include **irritative or obstructive voiding, hematuria, and primary urethral bleeding**. Additionally, especially in women, masses may be palpable and cause pain. The rare presentations of urethral carcinoma within **urethral diverticula** typically present with **dyspareunia, dysuria, dribbling** (the 3 D's of urethral diverticulum). Solid components within a diverticulum can raise suspicion of concomitant malignancy and prompt biopsy (**Urethral Diverticulum** in the AUA Core Curriculum).

6. Evaluation and Staging

Table 4. 2016 TNM/AJCC (8th Ed.) Staging System For Urethral Cancer		
T stage		
Tis	Female urethra or male anterior urethra *male posterior urethra*	-Carcinoma in situ -Prostatic urethra or periurethral or prostatic ducts without stromal invasion
Ta	-	Non-invasive papillary or verrucous carcinoma
T1	-	Invades lamina propria (subepithelial connective tissue)
T2	Female urethra or male anterior urethra *male posterior urethra*	-invades corpus spongiosum, or periurethral muscle -invades prostatic stroma (either by ducts or direct extension)
T3	Female urethra or male anterior urethra *male posterior urethra*	-invades corpus cavernosum or anterior vagina -invades periprostatic fat
T4	-	Invades adjacent organs (bladder, rectum, uterus)
N stage		
N0	-	Negative nodes
N1	-	Single Node
N2	-	Multiple Nodes
M stage		

M0	-	No metastases
M1	-	Distant metastases

The TNM/AJCC 2016 (8th Ed.) staging system is the current consensus system for staging urethral cancer. **Regional nodes for N staging include the inguinal, external iliac, obturator, internal iliac, common iliac, and presacral nodes** (**Table 4**).[15]

6.1 Physical Exam

On physical examination of the male, the penis and perineum should be carefully palpated. The **presence of a palpable mass usually indicates an invasive tumor (≥T2)** and occasionally clear invasion of the corpora cavernosa is palpable (T3). **DRE** should be performed to evaluate for palpable prostatic invasion.

In women, a bimanual examination and careful speculum examination are required. A urethral diverticulum may be palpable and vaginal invasion is usually easily detectable (T3).

In both men and women, **palpation of the inguinal nodes** should be performed to rule out nodal involvement. **Lymphedema** of the lower extremities may suggest inguinal or pelvic nodal involvement.

6.2 Endoscopy

Endoscopic evaluation of the urethra (cystourethroscopy) is critical to making the correct diagnosis. **Urethral cancer can have the appearance of an idiopathic stricture and biopsies of such areas should be performed**. In women, care should be taken to look for a urethral diverticulum ostium, which are generally located posteriorly (vaginal side) and can be very subtle. A guidewire or ureteral catheter can be used to probe a urethral diverticulum, which may also be palpated with a careful bimanual exam. Men can occasionally have papillary tumor emanating from the verumontanum, indicating a tumor of the prostatic ducts. **All patients should have a complete endoscopic evaluation of the bladder in addition to the urethra to rule out multifocality.** In addition to endoscopic biopsy, **transvaginal needle core biopsy can be useful for female urethral carcinomas (solid mass) within a diverticulum.**

6.3 Retrograde Urethrography (RUG)

RUG can be a very useful tool in men with tumors of the bulbar and pendulous urethra. First, it establishes the length of urethral involvement, which is important if primary excision with urethral re-anastomosis is being considered. Second, approximately 50% of men with urethral cancer have associated strictures and RUG can locate and characterize these. Third, RUG will show the distance from the urogenital diaphragm to the tumor, which can occasionally be too short to allow perineal urethrostomy.

6.4 Ultrasonography

Penile ultrasonography can be used to establish the local T stage of distal urethral tumors but is seldom done as MRIs are preferred. Rarely, transrectal ultrasound is used to evaluate the prostate for invasion in cases where there appears to be prostatic ductal or urethral cancer. Prostate biopsies

are usually performed at the same time.

6.5 Abdominal-pelvic-inguinal imaging (CT, MRI, PET)

Patients with tumors that are pathologically non-invasive and low-grade often do not require axial imaging since their probability of being locally advanced or metastatic is low. In contrast, **any patient with a palpable tumor or pathologic presence of invasion should undergo axial imaging for local and systemic staging. Contrast-enhanced MRI provides the best resolution images of the urethra** and is favored over CT in most circumstances. **Pelvic MRI** (including the inguinal region/mid-upper thigh) **is the preferred imaging modality to assess the local extent of the urethral tumor and regional lymph node involvement**. PET/CT is an attractive modality for identifying systemic and nodal metastases in urothelial tumors, although data for urethral primaries is lacking.

In patients with ***urothelial carcinoma*** **of the urethra**, **upper tract imaging (CT urogram, retrograde pyelogram, or MR-urogram) is recommended to evaluate the remainder of the urothelium for potential disease.**

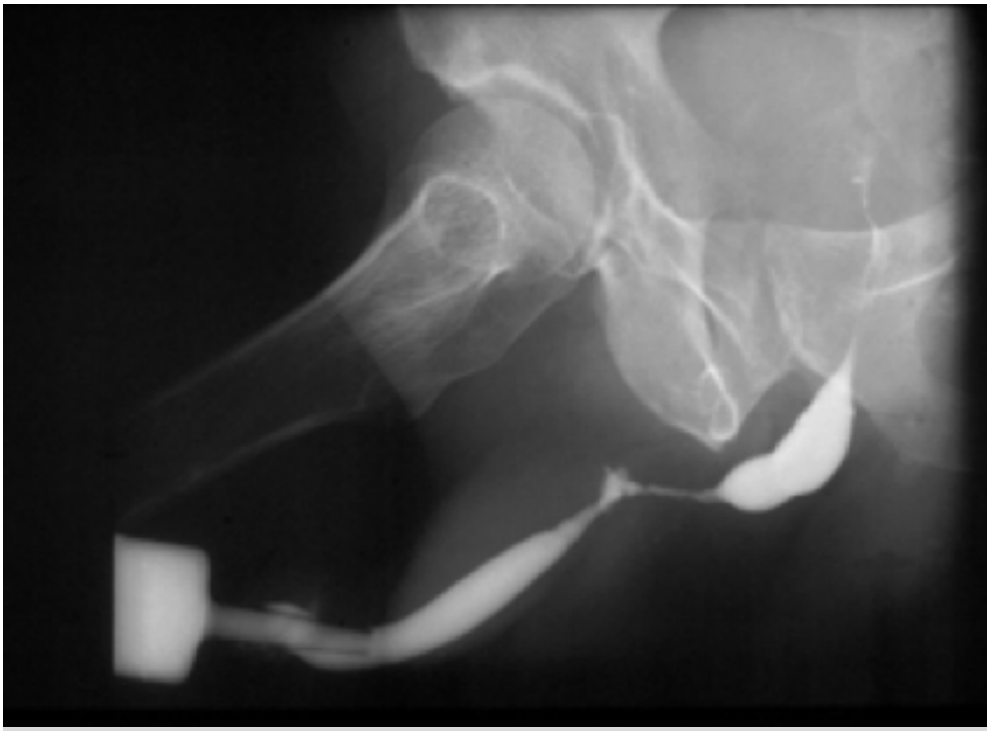

Figure 1: RUG of a bulbar urethral carcinoma (from Uzzo Penile Carcinoma 2019 AUA Board Review Course)

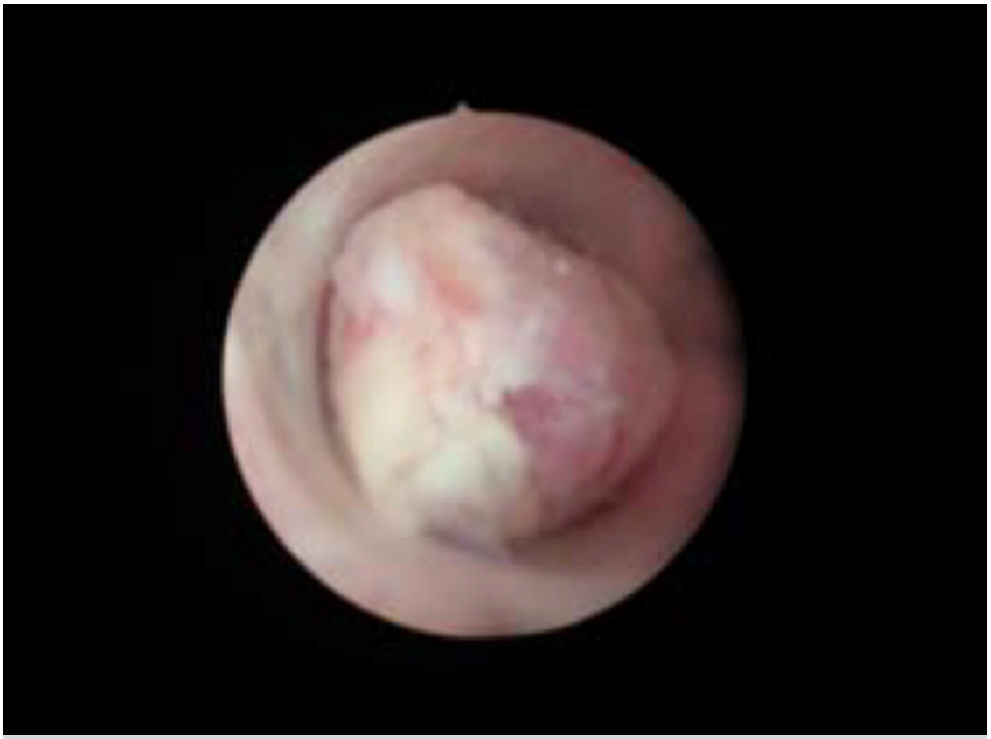

Figure 2: Cystoscopic view of bulbar urethral carcinoma (from Uzzo Penile Carcinoma 2019 AUA Board Review Course)

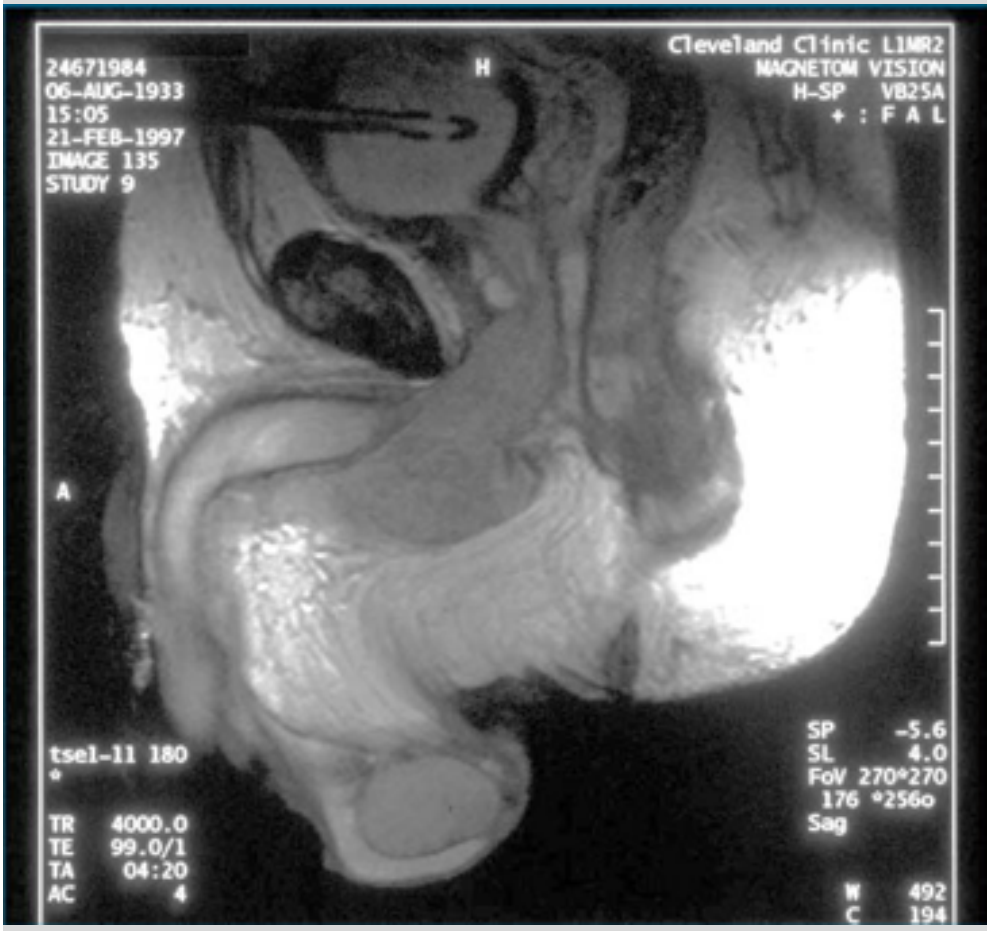

Figure 3: Sagittal MRI of a urethral mass extending from the bulbar urethra through the GU diaphram to the prostatic urethra. (from Uzzo Penile Carcinoma 2019 AUA Board Review Course)

6.6 Urinary Cytology

Urinary cytology has a limited role in the detection of urethral cancer. Cytology is 55-59% sensitive and this is dependent on histology. In women, sensitivity for squamous cell carcinoma is the highest (77%), while in men, sensitivity has been highest for urothelial carcinoma (80%). [16]

7. Treatment of Male Urethral Cancer

The treatment of urethral cancer in men depends on tumor histology, stage, grade, and location (anterior versus posterior urethra). For patients with **locally advanced tumors, multimodal therapy is preferred** based on small retrospective series.[17,18] Although there are no randomized trials to guide treatment, **patients with locally advanced nonmetastatic urothelial carcinoma of the urethra are most often treated with Cisplatin-based neoadjuvant chemotherapy followed by surgery with curative intent**.

Patients with squamous cell carcinoma can be treated with either chemo-radiation or neoadjuvant chemotherapy followed by surgical consolidation. Triple therapy (chemoradiation therapy followed by surgery) is sometimes used for bulky yet localized urethral cancer with direct extension into the pubis or genitourinary diaphragm. [19,20,21,22] Recent cohort studies demonstrated a survival benefit with triple therapy[23] compared to monotherapy or dual therapy.

7.1 Transurethral resection (TUR)

TUR is the treatment of choice for all small non-invasive tumors of the distal urethra. Additionally, TUR is the primary method used to stage and treat prostatic urethral and ductal cancer, obtain tissue for histology, and relieve urethral obstruction. **According to the 2016 AUA/SUO guideline for the diagnosis and treatment of non-muscle invasive bladder cancer, in patients with a history of NMIBC with normal cystoscopy and positive cytology, a clinician should consider prostatic urethral biopsies since tumor recurrences can involve the prostatic urethra in 24-39% of cases.**[24] Such biopsies are normally done at the 5 and 7 o'clock positions to ensure sampling of the prostatic ducts.

For cases of non-invasive[25] prostatic urethral carcinoma or carcinoma in situ, mucosal tumors, located in the prostatic urethra, a TUR of the prostate (including the bladder neck to allow contact of intravesical agents to the posterior urethra/prostatic urethra) is followed by adjuvant intravesical BCG with maintenance therapy. Prostatic duct involvement is often seen with carcinoma in situ of the prostatic urethra (confined to the urothelium of the prostatic duct shown below). Based on small retrospective series CIS of the prostatic ducts may be treated with TUR followed by intravesical BCG with caution as there is high risk of progression, and patients may benefit from radical therapy.

In patients with **urothelial carcinoma of the prostatic urethra with prostate stromal invasion, neoadjuvant cisplatin-based chemotherapy followed by radical cystoprostatectomy is the**

treatment of choice.

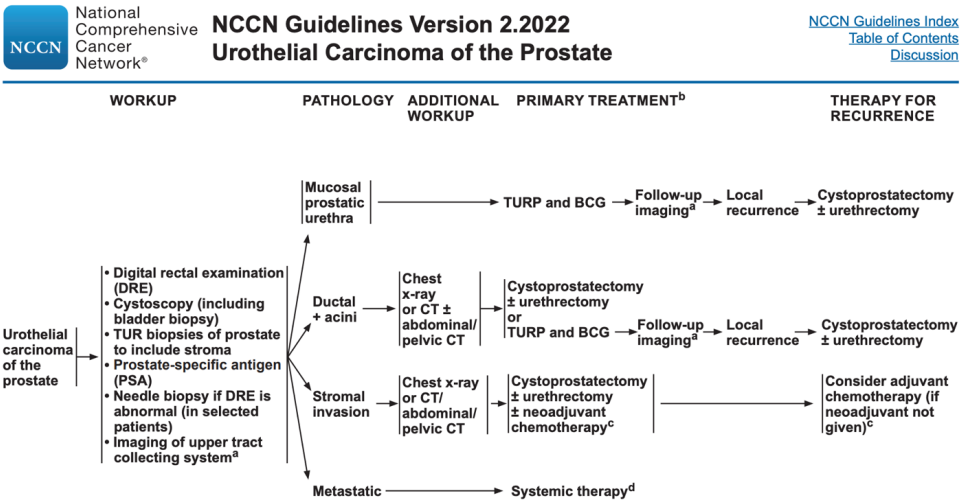

Figure 4: SECTION UCP-1 NCCN Guideline Version 2.2022 Urothelial Carcinoma of the Prostate

7.2 Segmental Urethrectomy

Segmental urethrectomy with primary re-anastomosis can be used to excise malignant strictures of the bulbar and penile urethra <2 cm in length which are clinically limited to the corpus spongiosum.

Longer segments of urethra can be excised but flaps and/or graft techniques are usually required to reconstruct the urethra afterwards. MRI can be very helpful in delineating extent of disease (T2-spongiosum versus T3 invasion into the corpora cavernosum) to aid in ensuring negative margins with resection.

7.3 Penectomy and Perineal Urethrostomy

Historically, tumors invading the corpora cavernosa (T3) required penectomy. However, for tumors of the distal penile urethra, partial penectomy may be possible.[26] Locally advanced tumors of the proximal penile urethra and bulbar urethra generally are managed with total penectomy with perineal urethrostomy.

7.4 Total Penectomy with Prostatectomy and Bladder Neck Closure

Bulky adenocarcinomas or squamous cell carcinomas of the bulbar and membranous urethra can be very challenging to manage. Often, after resection, there is not enough urethral length to allow a perineal urethrostomy or there is no remaining urinary sphincter to allow for continence. Additionally, the prostate may be involved and require resection. In this situation, one can consider bladder neck closure and either an incontinent ileal vesicostomy or Mitrofanoff-type channel. This is contraindicated in urothelial carcinomas given the risk of local recurrence within bladder and need for ongoing cystoscopic surveillance which is challenging to perform through either an ileal chimney or catheterizable channel.

7.5 Cystoprostatectomy

Invasive urothelial carcinomas of the prostatic/membranous urethra are usually best treated with radical cystoprostatectomy with total urethrectomy. Neoadjuvant or adjuvant cisplatin-based chemotherapy should be strongly considered.[17,22,27]

7.6 Radiation therapy

Neoadjuvant radiotherapy can be used to downstage very large urethral tumors, particularly those locally invading the pubic rami. Adjuvant radiation can be used to treat patients with bulky tumors and positive margins at surgical resection. Chemoradiation therapy is an acceptable multimodal treatment especially for patients with squamous cell histology. [19,20,28,29,30,31,32]

However, as a primary therapy, radiation therapy is associated with poor local control. 5-year overall survival for anterior urethral tumors is reported at 0-25% and only anecdotal survivors for posterior tumors. Complications associated with primary XRT include stricture, edema, necrosis, and fistula.

8. Treatment of Female Urethral Cancer

The treatment of urethral cancer in woman depends on tumor histology, stage, grade, and location. For patients with locally advanced tumors, multimodality therapy is preferred based on small retrospective series. Although there are no randomized trials to guide treatment, patients with locally advanced urothelial carcinoma of the urethra are typically treated with Cisplatin-based neoadjuvant chemotherapy followed by surgery with curative intent.[17,22,27] Patients with squamous cell carcinoma can be treated with either chemo-radiation therapy or neoadjuvant chemotherapy followed by surgical consolidation. **Triple therapy (chemoradiation therapy followed by surgery) can be used for bulky yet localized urethral cancer (rare T4N0M0--typically squamous) with direct extension into the pubis or genitourinary diaphragm**.[19,20,21,22]

8.1 Transurethral Resection (TUR)

As with men, TUR is the treatment of choice for all non-invasive tumors in women. It is diagnostic, yielding histology and staging data. **Women are at higher risk of post-TUR incontinence** and great care is needed to prevent this complication.

8.2 Partial Urethrectomy and Diverticulectomy

Partial urethrectomy in the female is often difficult given the short length of the female urethra (~4cm) with risk to the urinary sphincter mechanism. Nevertheless, resection of the distal urethra is sometimes possible. Post-resection closure usually requires a vaginal flap. Patients should be counselled that recurrences are common. Tumors occurring in urethral diverticula can sometimes be managed with diverticulectomy and local excision of the surrounding tissues and vaginal wall.

8.3 Complete Urethrectomy with Bladder Neck Closure

Occasionally, there is insufficient urethra remaining after urethrectomy to allow for continence. In

such circumstances, bladder neck closure with an ileal vesicostomy or Mitrofanoff channel can be considered. **This approach needs to allow for surveillance cystoscopy in patients with urothelial carcinoma, and therefore is rarely performed.**

8.4 Cystectomy

Large invasive tumors, especially urothelial carcinoma, are best treated with radical cystectomy and en bloc urethrectomy. Neoadjuvant (preferred especially for urothelial carcinoma) or adjuvant chemotherapy should be considered.[17,22,27] Often an anterior strip of vagina is excised to ensure complete tumor resection.

8.5 Radiation therapy

External beam radiation therapy and brachytherapy have been applied with some success in women. This modality is generally reserved for **distal tumors and can be associated with fistula formation or delayed urethral stenosis**. Neoadjuvant radiation therapy can be used to downsize tumors prior to surgical resection and intraoperative radiation can be used in cases where a positive surgical margin is probable. **Chemo-radiation is an option especially in cases of non-urothelial invasive carcinoma (squamous/adeno carcinoma) of the female urethra**.[20]

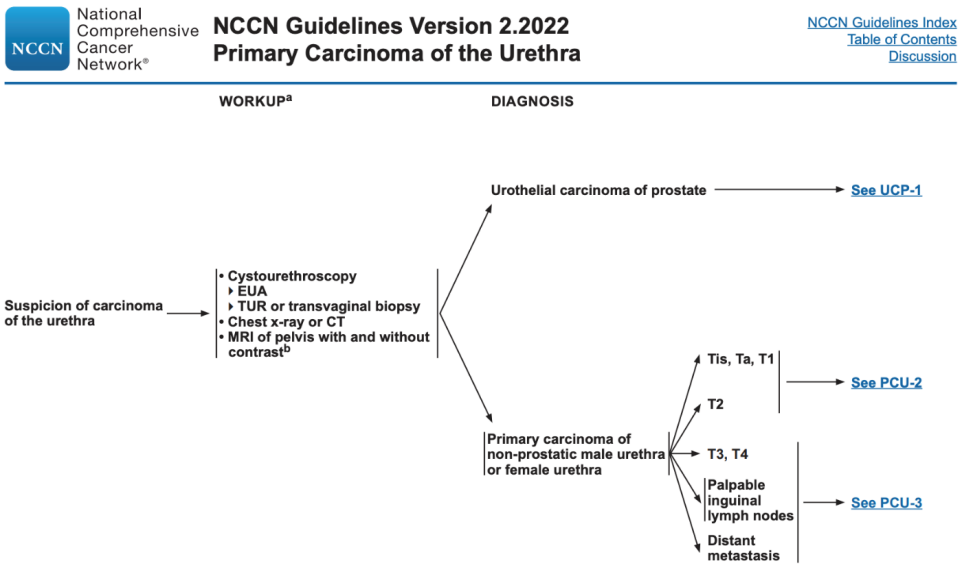

Figure 5: ALGORITHM NCCN Guideline Version 2.2022 PRIMARY CARCINOMA OF THE URETHRA.

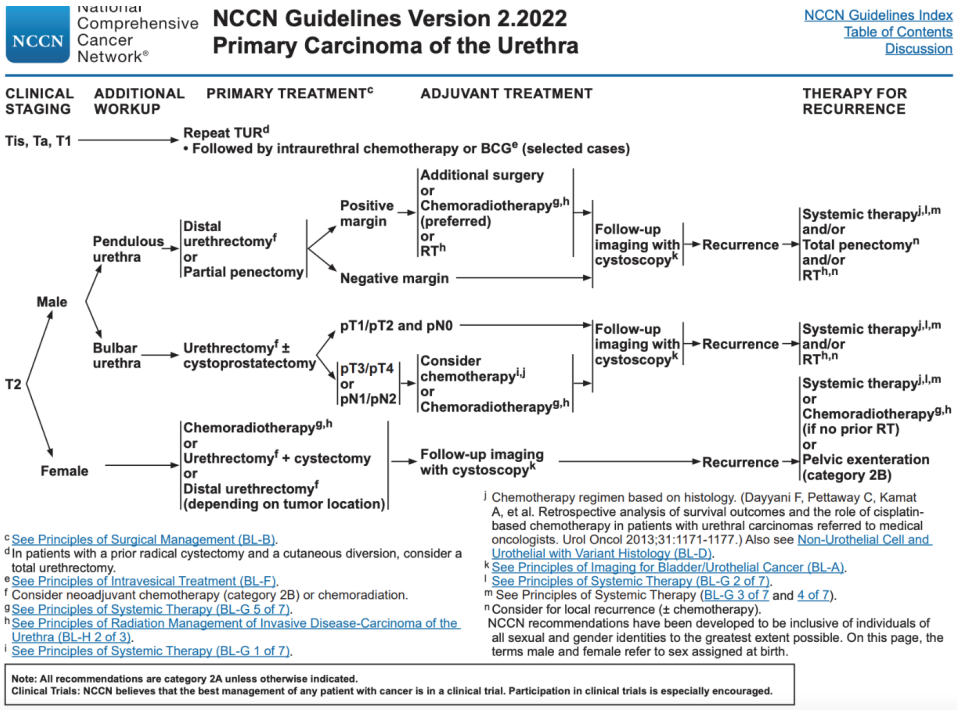

Figure 6: ALGORITHM SECTION PCU-2 NCCN Guideline Version 2.2022 PRIMARY CARCINOMA OF THE URETHRA.

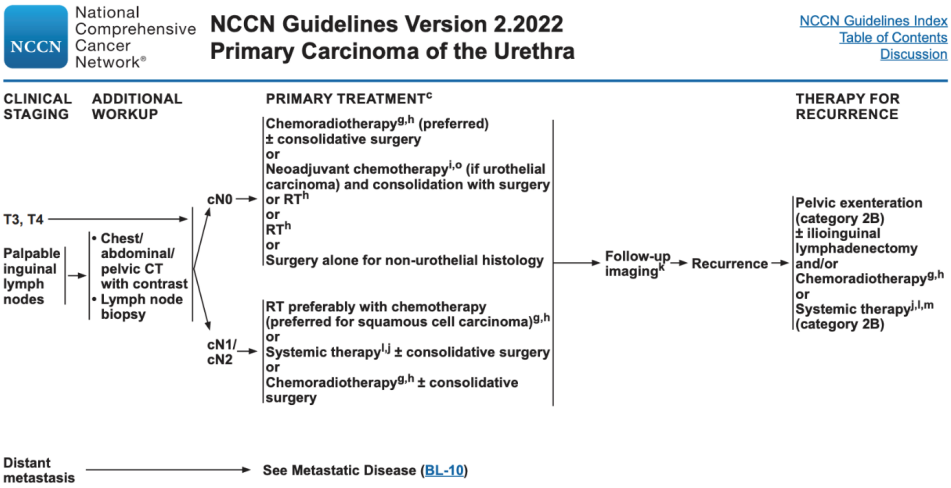

Figure 7: ALGORITHM SECTION PCU-3 NCCN Guideline Version 2.2022 PRIMARY CARCINOMA OF THE URETHRA.

9. Other Treatment Issues

9.1 Lymphadenectomy

Contrary to the management of the cN0 inguinal nodes in penile cancer, management of the cN0 inguinal lymph nodes in primary anterior urethral cancer is not based on pT status of the primary tumor. **All patients undergoing cystectomy or cystoprostatectomy (posterior/proximalurethral carcinomas) should undergo bilateral pelvic lymphadenectomy since the risk of nodal involvement is high.** Patients with **palpable or enlarged inguinal nodes on imaging should undergo percutaneous lymph node biopsy** (**Figure 7**). Despite the limited number of published

series, **systemic therapy** along with consolidative radiation or surgery is recommended.

Unlike in penile cancer, the benefit of prophylactic inguinal lymph node dissection (regardless of pT status) in patients with cN0 squamous cell of the anterior (male) or distal (female) urethra is not supported in the literature. The incidence of pathologic node positivity in the setting of clinical negative inguinal nodes appears to be less than 10%.[33] All patients at risk for inguinal metastases not undergoing inguinal lymphadenectomy should have their inguinal regions examined and imaged regularly during surveillance visits.

9.2 Chemotherapy

(see **Table 5**)

A recent analysis of the National Cancer Database supports the use of neoadjuvant chemotherapy in men with urethral urothelial carcinoma.[34] **Chemotherapy is indicated for patients with locally advanced T3/T4 disease and in those with nodal or systemic metastases** .[17,22,27] The specific regimen utilized is selected according to the histology of the primary tumor. Chemotherapy is also utilized in combination chemoradiation therapy, which may be used to downstage locally advanced tumors prior to surgery or occasionally as a curative therapy in women. Perioperative chemotherapy may provide a survival advantage. [35] The role of neoadjuvant chemotherapy with or without radiation therapy is expanding and recent data suggests a survival benefit for urothelial tumors, those with locally advanced and clinically node positive tumors. [36]

Table 5. Main Chemotherapy Regimens Used for Urethral Cancer

Regimen	Agents	Mechanism	Main Toxicities
Urothelial carcinoma			
MVAC	Methotrexate	*Antimetabolite (purine analog)* • folic acid analog, inhibits dihydrofolate reductase (DNA synthesis)	• **Myelosuppression** • **Mucositis** • Nausea/vomiting • Nephrotoxicity • Alopecia
	Vinblastine	*Plant derivative: Vinca alkaloid* • inhibits tubulin and microtubule (spindle formation)	• **Myelosuppression**
	Doxorubicin (Adriamycin)	*Antitumor antibiotic (anthracycline)* • inhibits topoisomerase II (double strand DNA breaks) • DNA intercalation (unwinds DNA) • free radical formation	• **Cardiotoxicity** • Myelosuppression • Alopecia • Mucositis

	Cisplatin	*Alkalating agent* • crosslinks DNA (inhibits DNA synthesis)	• **Peripheral neuropathy** • **Nephrotoxicity** • Ototoxicity (high frequency) • Nausea/vomiting
GC	Gemcitabine	*Antimetabolite (pyrimidine analog)* • cytidine analog, inhibits DNA synthesis	• **Myelosuppression** • Nausea/vomiting
	Cisplatin	**see above**	
Squamous cell carcinoma			
PMB	Cisplatin	**see above**	
	Methotrexate	**see above**	
	Bleomycin	*Antitumor antibiotic* • binds to iron and DNA (double strand DNA breaks)	• **Pulmonary fibrosis** • Skin hyperpigmentation & thickening • Mucositis
TPF	Paclitaxel	*Plant derivative: Taxane* • inhibits microtubule depolymerization	• **Myelosuppression** • Nausea/vomiting • Alopecia • Peripheral neuropathy
	Cisplatin	**see above**	

	5-FU	*Antimetabolite (pyrimidine analog)* • uracil analog, inhibits thymidylate synthesis	• **Myelosuppression** • **Hand/foot syndrome** • Mucositis • Cardiotoxicity • Ocular toxicity
VBM	Vincristine	*Plant derivative: Vinca alkaloid* • inhibits tubulin (spindle formation)	• **Peripheral neuropathy** • SIADH
	Bleomycin	**see above**	
	Methotrexate	**see above**	
TIP	Paclitaxel	**see above**	
	Ifosphamide	*Alkylating agent* • crosslinks DNA (inhibits DNA synthesis)	• **Hemorrhagic cystitis** • **Encephalopathy** • Myelosuppression • Bladder cancer • SIADH
	Cisplatin	**see above**	
Adenocarcinoma			
	5-FU	**see above**	
		Purine & pyrimidine precursor • rescues normal	

FOLFOX	Folinic acid (Leucovorin)	cells from methotrexate (allows higher doses) • inhibits thymidylate synthase (enhances 5-FU effect)	• Allergic reactions
	Oxaliplatin	*Alkalating agent* • crosslinks DNA (inhibits DNA synthesis)	• **Peripheral neuropathy** • Mucositis • Nausea/vomiting
FOLFIRI	5-FU	**see above**	
	Folinic acid (Leucovorin)	**see above**	
	Irinotecan	*Synthetic alkaloid* • Topoisomerase I inhibitor (prevents DNA unwinding)	• **Myelosuppression** • **Diarrhea**
	Cetuximab	*Chimeric (mouse/human) antibody* • blocks EGFR	• **Rash** • Allergic reactions • Photosensitivity

10. Prognosis

The prognosis for urethral cancer is stage-dependent, with 5-year overall survival of 80% for stage I, 50% for stage II, 30% for stage III, and 10% for stage IV. Poor prognostic factors include (i) tumors of the proximal urethra, (ii) stage T2 or higher, (iii) lymph node involvement, and (iv) advanced age. In both men and woman, a more proximal location and higher stage portend a worse prognosis. Women have inferior survival compared to men.[10,37] Individuals with concomitant bladder cancer, variant histologies[38] and black patients also have worse survival. New[7,39] nomograms have been recently published to estimate overall survival and cancer-specific survival.[40] Overall survival may be associated with treatment at high volume centers.[41]

11. Radical Cystectomy and Urethral Recurrence

Approximately 25% of radical cystectomy specimens performed for urothelial carcinoma will have some degree of prostatic involvement. However, most patients do not require urethrectomy (distal to the prostate) and **only those male patients with clear clinical evidence of urethral cancer distal to the prostatic urethra should undergo radical urethrectomy at the time of cystectomy**. Frozen section of the urethra at surgery is about 85% sensitive and 95% specific for detecting urethral cancer. [42] The remainder should undergo surveillance for urethral recurrence, generally with urethral washes for cytology. Urethral recurrences occur in 5-10% of male cystectomy patients a median of 18 months post-cystectomy. **Risk factors include (i) multifocal bladder tumors (ii) CIS, (iii) prostatic urethral invasion (men) (iv) bladder neck invasion (women) and (v) positive urethral margins.**

The 2020 AUA/ASCO/ASTRO/SUO Guideline for the treatment of non-metastatic muscle-invasive bladder cancer states an expert opinion that "following radical cystectomy in patients with a retained urethra, clinicians should monitor the urethral remnant for recurrence".

Following radical cystectomy, the 2022 NCCN recommendations recommend urine cytology every 6-12 months for the first two years with urethral wash considered for high-risk patients (positive urethral margin, multifocal CIS, and prostatic urethral invasion). Beyond two years, cytology should be obtained as clinically indicated.[43]

There may be advantages to a prophylactic urethrectomy in patients with an ileal conduit. Factors that increase recurrence include history of TURBT for NMIBC, tumor grade, stage, and multifocality, as well as BMI. These covariates are included in a recently published nomogram for urethral recurrence after RC. [44] In addition, a systematic review and meta-analysis found prostatic urethral involvement and or prostatic stromal involvement also increased urethral recurrence.[45] These factors should prompt discussion of urethral management.

Post-cystectomy male urethral recurrence in patients with a non-orthotopic urinary diversion (i.e. ileal conduit) can be managed with perineal urethrectomy alone (video below). Locally advanced recurrences (rare T3/T4) should be managed with systemic therapy prior to surgical extirpation of the

urethra as per the management of a primary urethral tumor.[17,22,46,27]

In patients with an orthotopic neobladder with high grade urethral recurrence, preservation of the urethra and thus the orthotopic diversion is desirable. Intraurethral/neobladder BCG is an acceptable option for patients with **CIS without concomitant papillary tumor**.[47] Localized high grade *papillary* recurrence or invasive disease (T1), are treated with urethrectomy and conversion to alternative urinary diversion.[46,47]

See **Treatment of Non-Metastatic Muscle-Invasive Bladder Cancer: AUA/ASCO/ASTRO/SUO Guideline (2020)**
See **Core Curriculum Anatomy: Perineal Incision**

References: [49,36,7,50,3,51,52,53,15,54,55,56,35,57,58,59,60,61,11,19,20,33,21,62]

Videos

Perineal Urethrectomy

Presentations

Primary Urethral Carcinoma

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