

Cancer Association of South Africa (CANSA)

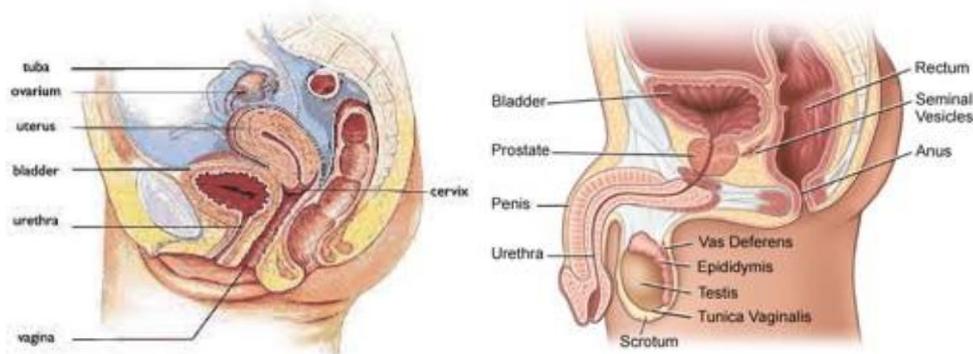


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Fact Sheet on Cancer of the Urethra

Introduction

The urethra is a tube that connects the urinary bladder to the urinary meatus for the removal of urine from the body. In males the urethra travels through the prostate and penis, and carries semen as well as urine. In females, the urethra is shorter and emerges above the vaginal opening at the external urethral orifice.



[Picture Credit: Female Urethra]

[Picture Credit: Male Urethra]

Cancer of the Urethra

Urethral cancer is a rare type of cancer affecting the male or female urethra that comprises approximately 1 to 2 percent of all urological cancers. Urethral cancer is the only urological cancer that affects women more frequently than men. The exact cause of urethral cancer is not known. However, chronic inflammation and infection have been identified as factors that may increase the risk for developing this condition. Many men with urethral cancer have previously been treated for urethral stricture disease or sexually transmitted infections (STIs). Many women with urethral cancer have previously been treated for urethral caruncle (a deep red growth on the mucous membrane of the urinary meatus in women), urethral diverticulum or chronic urinary tract infection. In both men and women the presence of human papilloma virus (HPV) has been linked to urethral cancer. It is often associated with invasive bladder cancer. It tends to spread rapidly to surrounding

Researched and Authored by Prof Michael C Herbst

[D Litt et Phil (Health Studies); D N Ed; M Art et Scien; B A Cur; Dip Occupational Health; Dip Genetic Counselling; Dip Audiometry and Noise Measurement; Diagnostic Radiographer; Medical Ethicist.]

Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]

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tissues (the vagina and bladder for women; the penile area, prostate, and regional lymph nodes for men), and is often advanced at the time of diagnosis.

There are different types of cancer of the urethra that begin in cells that line the urethra. These cancers are named for the types of cells that become malignant (cancerous):

- Squamous cell carcinoma is the most common type of urethral cancer. It forms in cells in the part of the urethra near the bladder in women, and in the lining of the urethra in the penis in men.
- Transitional cell carcinoma forms in the area near the urethral opening in women, and in the part of the urethra that goes through the prostate gland in men.
- Adenocarcinoma forms in the glands that are around the urethra in both men and women.

Zhang, M., Adeniran, A.J., Vikram, R., Tamboli, P., Pettaway, C., Bondaruk, J., Liu, J., Baggerly, K. & Czerniak, B. 2018.

“Primary carcinomas of the urethra are rare and poorly understood lesions; hence, their clinical and pathologic spectrum is not completely defined. We analyzed a series of 130 primary urethral tumors and classified 106 of them as primary urethral carcinomas. The age at diagnosis of patients with primary urethral carcinomas ranged from 42 to 97 years (mean, 69.4 years; median, 70 years). There were 73 male and 33 female patients with a ratio of 2.2:1. In male patients, the tumors most frequently developed in the bulbous-membranous segment of the urethra. In female patients, the entire length of the urethra was typically involved. Microscopically, they were poorly differentiated carcinomas with hybrid squamous and urothelial features and developed from precursor intraepithelial conditions such as dysplasia and carcinoma in situ, which were frequently present in the adjacent urethral mucosa. High-risk human papilloma virus infection could be documented in 31.6% of these tumors. Follow-up information was available for 95 patients. Twenty-three patients died of the disease with a mean and median survival of 39 and 21 months, respectively. Urethral carcinomas are aggressive tumors with a high propensity for regional and distant metastases with mean and median survival of 39 and 21 months, respectively. Our observations have important implications for the management of patients with primary carcinoma of the urethra by defining them as a unique entity linked to human papilloma virus infection.”

Dell’Atti, L. & Galosi, A.B. 2018.

“Female urethra adenocarcinoma (FUA) is a rare aggressive tumor that occurs in Skene ducts and glands. It is associated with a relatively poor prognosis. The aim of this review was to evaluate FUA in terms of epidemiology, risk factors, diagnosis, natural history of disease, modalities of treatment, and outcomes. These tumors are usually large masses, which typically spread through the lymphatic system. Patients present with vague symptoms similar to urinary tract infections. Cystourethroscopy permits visualization of the urethral tumor and allows biopsies to be performed to remove samples for histologic examination. Magnetic resonance imaging is recommended for tumor staging. Local, superficial, and distal urethral tumors may be treated by partial resection with preservation of the urethra. Radical urethrectomy with wide, comprehensive resection of the paraurethral tissues and anterior vaginal wall may offer superior local control for this disease. Advanced FUA and lymph node positivity are associated with poor prognosis for all survival outcomes (recurrence-free, cancer-specific, and overall survival). Multimodal therapy including surgery, chemotherapy, and radiotherapy is required in the modern management of FUA, although the specific role and combination of each treatment is less clearly determined. Wide resection after chemotherapy and/or radiotherapy is associated with the best local control, but it reduces quality of life.”

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Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]

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Incidence of Cancer of the Urethra in South Africa

The National Cancer Registry (2017) does not provide information regarding the incidence of Cancer of the Urethra in South Africa.

Risk Factors for Cancer of the Urethra

Risk factors for cancer of the urethra include the following:

- Having a history of bladder cancer
- Having conditions that cause chronic inflammation in the urethra, including:
 - Sexually transmitted infections (STIs)
 - Frequent urinary tract infections (UTIs)
 - Human Papilloma Virus infection (HPV)
- Being 60 years of age or older
- Being a white female

Signs and Symptoms of Cancer of the Urethra

Early cancer of the urethra often does not produce symptoms. As the disease progresses, symptoms include the following:

- Blood in the urine (haematuria)
- Diminished urine stream and straining to void (caused by urethral stricture)
- Frequent urination and increased night time urination (nocturia)
- Hardening of tissue in the perineum, labia, or penis
- Itching
- Incontinence
- Pain during or after sexual intercourse (dyspareunia)
- Painful urination (dysuria)
- Recurrent urinary tract infection
- Urethral discharge and swelling

Advanced cases of urethral cancer may produce swollen lymph nodes in the groin.

Diagnosis and Staging of Cancer of the Urethra

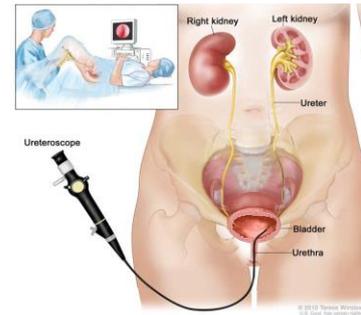
After urethral cancer has been diagnosed, tests are done to find out if cancer cells have spread within the urethra or to other parts of the body.

The process used to find out if cancer has spread within the urethra or to other parts of the body is called staging. The information gathered from the staging process determines the stage of the disease. It is important to know the stage in order to plan treatment. The following procedures may be used in the staging process:

- Chest X-Ray: An X-ray of the organs and bones inside the chest. An X-ray is a type of energy beam that can go through the body and onto film, making a picture of areas inside the body
- CT Scan (CAT scan) of the pelvis and abdomen: A procedure that makes a series of detailed pictures of the pelvis and abdomen, taken from different angles. The pictures are made by a computer linked to an X-ray machine. A dye may be injected into a vein or swallowed to help the organs or tissues show up more clearly. This procedure is also called computed tomography, computerised tomography, or computerised axial tomography
- MRI (magnetic resonance imaging): A procedure that uses a magnet, radio waves, and a computer to make a series of detailed pictures of the urethra, nearby lymph nodes, and other soft tissue and bones in the pelvis. A substance called gadolinium is injected into the patient through a vein. The gadolinium collects around the cancer cells so they show up brighter in the picture. This procedure is also called nuclear magnetic resonance imaging (NMRI)
- Blood chemistry studies: A procedure in which a blood sample is checked to measure the amounts of certain substances released into the blood by organs and tissues in the body. An unusual (higher or lower than normal) amount of a substance can be a sign of disease in the organ or tissue that produces it
- Complete Blood Count (CBC): A procedure in which a sample of blood is drawn and checked for the following:
 - The number of red blood cells, white blood cells, and platelets
 - The amount of haemoglobin (the protein that carries oxygen) in the red blood cells
 - The portion of the blood sample made up of red blood cells
- Physical examination and health history: An examination of the body to check general signs of health, including checking for signs of disease, such as lumps or anything else that seems unusual. A history of the patient's health habits and past illnesses and treatments will also be taken
- Pelvic examination: An examination of the vagina, cervix, uterus, fallopian tubes, ovaries, and rectum in the female. The doctor inserts one or two lubricated, gloved fingers of one hand into the vagina and places the other hand over the lower abdomen to feel the size, shape, and position of the uterus and ovaries. A speculum is also inserted into the vagina and the doctor looks at the vagina and cervix for signs of disease
- Digital rectal exam: An examination of the rectum in a male. The doctor inserts a lubricated, gloved finger into the lower part of the rectum to feel for lumps or anything else that seems unusual
- Urine cytology: Examination of urine under a microscope to check for abnormal cells
- Urinalysis: A test to check the colour of urine and its contents, such as sugar, protein, blood, and white blood cells. If white blood cells (a sign of infection) are found, a urine culture is usually done to find out what type of infection it is
- Ureteroscopy: A procedure to look inside the ureter and renal pelvis to check for abnormal areas. A ureteroscope is a thin, tube-like instrument with a light and a lens for viewing. The ureteroscope is inserted through the urethra into the bladder, ureter, and renal pelvis. A tool may be inserted through the ureteroscope to take tissue samples to be checked under a microscope for signs of disease

[Picture Credit: Ureteroscope]

- Biopsy: The removal of cell or tissue samples from the urethra, bladder, and, sometimes, the prostate gland. The samples are viewed under a microscope by a pathologist to check for signs of cancer.



Three ways that cancer spreads in the body are:

- Through tissue. Cancer invades the surrounding normal tissue.
- Through the lymph system. Cancer invades the lymph system and travels through the lymph vessels to other places in the body.
- Through the blood. Cancer invades the veins and capillaries and travels through the blood to other places in the body.

When cancer cells break away from the primary (original) tumour and travel through the lymph or blood to other places in the body, another (secondary) tumour may form. This process is called metastasis. The secondary (metastatic) tumour is the same type of cancer as the primary tumour. For example, if breast cancer spreads to the bones, the cancer cells in the bones are actually breast cancer cells. The disease is metastatic breast cancer, not bone cancer.

Urethral cancer is staged and treated based on the part of the urethra that is affected and how deeply the tumour has spread into tissue around the urethra. Urethral cancer can be described as anterior or posterior urethral cancer.

Anterior urethral cancer - in anterior urethral cancer, the tumours are not deep and they affect the part of the urethra that is closest to the outside of the body.

Posterior urethral cancer - in posterior urethral cancer, the tumours are deep and affect the part of the urethra closest to the bladder. In women, the entire urethra may be affected. In men, the prostate gland may be affected.

Galgano, S.J., Sivils, C., Selph, J.P., Sanyal, R., Lockhart, M.E. & Zarzour, J.G. 2020.

“Urethral pathology is common in clinical practice and important to recognize. It is essential to recognize urethral pathology on imaging and to understand how to best image the urethra. In this way, the radiologist can provide the urologist with the necessary information prior to intervention. Basic knowledge of commonly performed urethral surgeries can help the radiologist understand the expected appearance of the post-treatment urethra and common postoperative complications.”

Treatment of Cancer of the Urethra

The following treatment is used in cases of cancer of the urethra:

Surgery - In the female, most tumours present with bleeding or distal urethral mass. Distal urethral or anterior lesions usually present early and are diagnosed while at low stage. These tumours have been successfully managed with local excision, transurethral resection, partial urethrectomy, and

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[D Litt et Phil (Health Studies); D N Ed; M Art et Scien; B A Cur; Dip Occupational Health; Dip Genetic Counselling; Dip Audiometry and Noise Measurement; Diagnostic Radiographer; Medical Ethicist.]

Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]

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fulguration or ablation with either neodymium: YAG or CO₂ laser techniques. In rare instances, higher stage local lesions may be managed with total urethrectomy and preservation of the bladder with interposition of a catheterisable segment or with the Mitrofanoff procedure (catheterisable urinary stoma).

More proximal lesions present later and at higher stage than distal lesions. Progressive obstructive symptoms are the hallmark of proximal or 'posterior' urethral lesions. For superficial tumours, transurethral resection or laser surgery may be appropriate. Advanced or extensive lesions, and those which involve the bladder or vagina, may necessitate cystectomy or anterior exenteration with urinary diversion. Local recurrence in such high-stage disease occurs frequently.

In advanced disease, metastases to the lymph nodes are present in 50% of cases. Inguinal node dissection should be performed in the presence of palpably enlarged nodes, and pelvic node dissection should be performed when proximal involvement of the urethra is identified. There does not appear to be any therapeutic advantage to prophylactic node dissection when the inguinal nodes are not enlarged.

In the male patient low-grade, low-stage tumours of the urethra may lend themselves to transurethral resection or laser fulguration, but such lesions are rare. Excisional biopsy may be feasible, and biopsy prior to laser fulguration is essential to assess histopathology and tumour depth.

Selected lesions of the distal urethra may lend themselves to partial penectomy (removal of the penis through surgery). Tumours must not involve the corpus spongiosum or the corpora cavernosa, and must be amenable to a 2-cm margin. More advanced or more proximal lesions may require a total penectomy with creation of a perineal urethrostomy (artificial opening for urine to pass through). Proximal cancers may necessitate an anterior exenteration with radical cystoprostatourethrectomy and urinary diversion.

Inguinal and pelvic lymphadenopathy portends metastatic disease. Careful serial palpation of the groins as well as interval pelvic CT evaluations are essential in the follow-up of definitive treatment of a urethral primary. Inguinal node dissection should be performed in the presence of clinically positive groin nodes. This has been curative in many cases. In several small series, 5-year survival following inguinal node dissection ranged from 12% to 66%. Pelvic node dissection has also proven curative in an occasional case and is worthwhile, although the prognosis in pelvic nodal disease is much worse than with inguinal node involvement. In the absence of inguinal adenopathy, inguinal lymphadenectomy is probably not warranted.

Mano, R., Vertosick, E.A., Sarcona, J., Sjoberg, D.D., Benfante, N.E., Donahue, T.F., Herr, H.W., Donat, S.M., Bochner, B.H., Dalbagni, G. & Goh, A.C. 2020.

Objectives: To evaluate treatment patterns and associated outcomes of patients with urethral cancer.

Patients and methods: After obtaining institutional review board approval we identified 165 patients treated for primary urethral cancer between 1956 and 2017. Treatment included monotherapy (surgery or radiation), dual therapy (surgery+radiation, surgery+chemotherapy, or chemotherapy+radiation) or triple therapy (surgery+radiation+chemotherapy). Rates of different treatments were described by treatment year. The association between treatment type and outcomes was evaluated with multivariable Cox regression models, adjusting for disease characteristics.

Results: The study cohort included 74 men and 91 women, with a median age of 61 years. Common histologies were squamous cell (36%), urothelial (27%) and adenocarcinoma (25%). At presentation,

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[D Litt et Phil (Health Studies); D N Ed; M Art et Scien; B A Cur; Dip Occupational Health; Dip Genetic Counselling; Dip Audiometry and Noise Measurement; Diagnostic Radiographer; Medical Ethicist.]

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72% of patients had invasive disease, 24% had nodal involvement, and 5% had metastases. Treatment included monotherapy (57%), dual therapy (21%), and triple therapy (10%). The use of monotherapy decreased over time, while rates of dual therapy remained consistent, and rates of triple therapy increased. The median follow-up was 4.7 years. Estimated 5-year local recurrence-free, disease-specific and overall survival were 51%, 48% and 41%, respectively. Monotherapy was associated with decreased local recurrence-free survival after adjusting for stage, histology, sex and year of treatment ($P = 0.017$). There was no evidence that treatment type was associated with distant recurrence, cancer-specific or overall survival.

Conclusions: We found preliminary evidence that multimodal therapy, more commonly used in recent years, was of benefit in patients with primary urethral cancer. This finding should be confirmed in further studies involving multiple centres because of the low incidence of the disease.

Khalil, M.I., Alliston, J.T., Bauer-Erickson, J.J., Davis, R., Bissada, N.K. & Kamel, M.H. 2019.

Purpose: The impact of radical surgery for urothelial carcinoma is significant on patient's quality of life. Organ-sparing surgery (OSS) can provide comparable oncological outcomes and with improved quality of life. In this review, we summarize the indications, techniques and outcomes of OSS for these tumors.

Methods: PubMed[®] was searched for relevant articles. Keywords used were: for upper tract urothelial carcinoma (UTUC): endoscopic, ureteroscopic/percutaneous management, laser ablation; for urothelial bladder cancer: bladder preservation, trimodal therapy, muscle invasive bladder cancer (MIBC); for urethral cancer: urethra/penile-sparing, urethral carcinoma.

Results: Kidney-sparing surgery is an option in patients with low-risk UTUC with better renal function preservation and comparable oncological control to radical nephroureterectomy. In select patients with MIBC, trimodal therapy has better quality of life and comparable oncological control to radical cystectomy. In distal male urethral cancer, penile conserving surgery is feasible and offers acceptable survival outcomes. In female urethral cancer, organ preservation can be achieved, in addition to OSS, through radiation.

Conclusions: In the appropriately selected patient, OSS in upper tract, bladder and urethral carcinoma has comparable oncological outcomes to radical surgery and with the additional benefit of improved quality of life.

Keywords: Bladder preservation; Muscle invasive bladder cancer; Penile sparing; Percutaneous management; Trimodal therapy; Upper tract urothelial cancer; Ureteroscopic management; Urethra sparing; Urethral carcinoma.

Castiglione, F., Alnajjar, H.M., Christodoulidou, M., Albersen, M., Parnham, A., Freeman, A., Jameson, C., Mitra, A., Nigam, R., Malone, P., Muneer, A. & Trauma and Reconstructive Urology Working Party of the European Association of Urology Young Academic Urologists. 2019.

BACKGROUND: Primary squamous cell carcinoma (SCC) of the male proximal urethra is an aggressive and rare urogenital malignancy.

OBJECTIVE: To review the surgical management and outcomes for male proximal urethral SCCs within a single centre and to suggest an algorithm for the surgical management of these rare tumours.

DESIGN, SETTING, AND PARTICIPANTS: This was a retrospective study of patients undergoing surgery for male proximal urethral SCC within a single tertiary academic centre managing rare genital tumours. Ten patients with a histological diagnosis of proximal urethral SCC were identified from an institutional database over a period of 10 yr with a median follow-up of 22.5 mo (standard deviation ± 25.77 mo).

OUTCOME MEASUREMENTS AND STATISTICAL ANALYSIS: Pathological staging, surgical treatment, and neoadjuvant and adjuvant treatment were recorded. Complications according to the Clavien-Dindo classification and overall survival rates were recorded. Kaplan-Meier curves were used for overall survival.

RESULTS AND LIMITATIONS: A total of 10 patients were identified of whom eight underwent panurethrectomy and radical prostatectomy. Radical inguinal lymphadenectomy was performed in five patients, which confirmed bilateral metastatic disease. Perioperative complications were reported in six patients (Clavien I and II). Within 6 mo of surgery, 90% of patients developed distant metastatic disease. Nine patients died of urethra cancer during the follow-up. One patient is still on follow-up. The median overall follow-up was 13.92 mo (range: 5-91 mo). At 5 yr, cancer-specific/overall survival was 10%. A limitation of this study is the retrospective design, which is unavoidable for such a rare disease.

CONCLUSIONS: Radical surgery allows local disease control, but despite neo/adjuvant treatment, proximal urethral SCC is associated with poor survival outcomes and progression to distant metastatic disease within 6 mo.

PATIENT SUMMARY: Proximal urethral squamous cell carcinoma is a rare cancer in men which is often detected late. Patients often present with problems such as voiding, urethral bleeding, or a palpable mass. Aggressive surgery allows local control, but despite this the overall survival is poor. Adjuvant and neoadjuvant radiochemotherapy can improve survival. Multicentric randomised trials are needed to identify the correct treatment modality.

Wertz, R.P., Riedinger, C.B., Fantus, R.J., Smith, Z.L., Packiam, V.T., Adamsky, M.A., Smith, N. & Steinberg, G.D. 2018.

INTRODUCTION: Urethral squamous cell cancer is a rare disease with limited clinical recommendations regarding management of the inguinal lymph nodes. Despite the similarities to penile cancer in terms of squamous cell carcinoma (SCC) histology and lymphatic drainage, there is not enough evidence to recommend for or against a prophylactic inguinal lymph node dissection (ILND) in patients with clinically negative groins and a primary tumor stage of T1b or higher. The objective of the study was to identify the rate of prophylactic inguinal lymph node dissection, node positive rate, and overall survival in patients with clinical T1 to T4 stage. The patients were separated into clinical N stage and the rates of node positivity were compared. We hypothesize that the node positivity rate would be similar to that observed in penile cancer of similar clinical T and N stage and provide evidence for prophylactic inguinal lymph node dissection in urethral squamous cancer. We also sought to determine the value of ILND in clinically node positive (cN+) and clinically node negative (cN-) patients.

METHODS: The National Cancer Database was queried for all cases of primary urethral cancer in men from 2004 to 2014. Patients with other cancer diagnoses, metastasis, nonsquamous histology, female patients, and patients with a history of radiation therapy were excluded. Male patients with urethral squamous cell cancer of the anterior urethra with T1 or higher T stage were included in this study. All-cause mortality was compared using multivariable Cox regression controlling for covariates.

RESULTS: The study included 725 men with urethral SCC with T1 or higher clinical T stage. The median age was 63 years (33-83 interquartile range). Of the 725 men, 536 men did not receive an ILND and 189 (26%) underwent ILND. Patients who received LND had significantly higher clinical T and clinical N stage. There was no difference in age, sex, or histology between those with ILND versus no ILND. In patients with T1 to T4 and clinical N0, the ILND rate was 21.8% (89/396). The lymph node positive rate in patients with N0 and T1 to T4 primary tumor was 9%. In patients with clinically node positive disease (N1/N2), the overall ILND rate was 76%. The lymph node positive rate for patients with clinical

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nodal disease was 84%. On multivariable analysis cox regression, lymph node positivity was associated with worse overall survival when controlling for T stage, clinical N stage, and age (HR 1.56, 95% 1.3-1.9, P = 0.000). On multivariable analysis after controlling for T stage, sex, and age, having an ILND was associated with improved OS in patients with clinical N1 or N2 disease (HR 0.46, 95% 0.28-0.78 P = 0.002).

CONCLUSION: The node positivity rate in patients with T1 to T4 and N0 is 9%, much lower than reported in penile cancer with a high-risk primary tumor but clinically negative groins. This argues against routine prophylactic inguinal ILND in patients with urethral SCC who are clinically N0, perhaps suggesting different biological behavior of urethral SCC compared to penile SCC. Performing a lymph node dissection in patients with clinically N1 or N2 disease is associated with improved OS.

Radiation Therapy - Radiation therapy, administered as both external beam radiation and brachytherapy, has been used for definitive treatment of both localised and advanced tumours. It has also been used to downsize tumours before definitive surgical intervention. Results have been mixed, with 5-year survivals averaging approximately 35% in advanced disease. Side effects and complications, including oedema, fistulae, and damage to the bowel, are commonplace.

Chemotherapy and Combined Therapy - The rarity of these tumours has precluded much meaningful clinical research in chemotherapeutic treatment, or in chemotherapy combined with radiation or surgery. Combination chemotherapy in conjunction with radiation and surgery has produced promising outcomes in squamous carcinomas of the head and neck, anus, and penis, and may be expected to demonstrate similar benefit in squamous cancers of the urethra. However, multinational, multi-institutional trials are required to provide clinical data to assess the efficacy of any such treatment regimens.

About Clinical Trials

Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

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Male Urethra

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MedicineNet.com

http://www.medicinenet.com/urethral_cancer/page3.htm#stages_of_urethral_cancer

National Cancer Institute

<http://www.cancer.gov/about-cancer/treatment/clinical-trials/what-are-trials>

NCBI

<http://www.ncbi.nlm.nih.gov/books/NBK13861/>

UCLA Health

<http://urology.ucla.edu/body.cfm?id=478&ref=36&action=detail>

Ureteroscope

<http://www.siteman.wustl.edu/CancerDetails.aspx?mid=131&id=659&xml=CDR343585.xml>

Urology Care Foundation

<http://www.urologyhealth.org/urology/index.cfm?article=65>

WebMD

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