Cancer Association of South Africa (CANSA)

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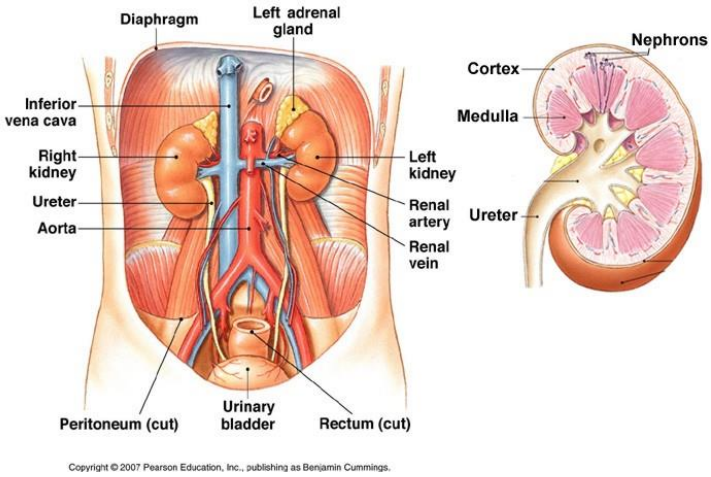
Fact Sheet
on
Ureteral Cancer

Introduction

In human anatomy, the ureters are tubes consisting of smooth muscle fibres that propel urine from the kidneys to the urinary bladder. In the adult, the ureters are usually 25 to 30 cm long and ~3 to 4 mm in diameter. Histologically, the ureter contains transitional epithelium and an additional smooth muscle layer in the more distal one-third to assist with peristalsis.



[Picture Credit: Ureters]

In humans, the ureters arise from the pelvis of each kidney, and descend on top of the psoas major muscle to reach the brim of the pelvis. Here, they cross in front of the common iliac arteries. They then pass down along the sides of the pelvis, and finally curve forward and enter the bladder from its left and right sides at the back of the bladder. At the entrance to the bladder, the ureters are surrounded by valves known as ureterovesical valves, which prevent the backflow of urine into the ureters. In females, the ureters pass through the mesometrium (the mesentery of the uterus) and under the uterine arteries on their way to the urinary bladder. (Wikipedia).

[Picture Credit: Ureteral Cancer]

Ureteral Cancer

Ureteral cancer is cancer of a ureter or both ureters, the muscular tube(s) that propel urine from the kidneys to the urinary bladder. It is also known as ureter cancer, renal pelvic cancer, and rarely ureteric cancer or uretal cancer. Cancer in this location is rare. Ureteral cancer is usually transitional cell carcinoma. Most patients with this condition are older (above the age of 60) and the disease is much more common in men (by a ratio of 3 to 1). However, the incidence is increasing, probably as a result of the increase of smoking among women (Froedtert & Medical College of Wisconsin).

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Incidence of Ureteral Cancer in South Africa
The National Cancer Registry (2013) does not provide any information regarding the incidence of ureteral cancer in South Africa.

Types of Ureteral Cancer
Renal cell carcinoma (RCC) is the most common type of kidney and ureter cancer in adults (85%). In RCC, cancerous (malignant) cells develop in the lining of the kidney's tubules and grow into a mass.

Transitional Cell Cancer of the Renal Pelvis and/or Ureter - about 6% to 7% of kidney and ureter cancer does not arise in the kidney itself, but in the renal pelvis, the point where the kidney joins the tube that carries urine from the kidney to the bladder (ureter). These tumours are called transitional cell carcinomas (TCC) and are made up of cancer cells different from those that characterise Renal Cell Carcinoma.
(SEER Training Modules).

Causes of Ureteral Cancer
The disease appears to be caused by carcinogens excreted in the urine. Inhaled tobacco is the most common source of these carcinogens, but occupational exposure to certain industrial chemicals can also play a role. In addition, there may be a link between vitamin D deficiency and incidence of ureteral cancer.

People who have been exposed to certain chemicals used in dye factories and chemical industries are also at a slightly increased risk.

People who have kidney damage from long-term use of certain painkillers may also have a higher risk of developing cancer in the renal pelvis. This risk is highest in people who were overexposed to painkillers containing phenacetin. Although the use of phenacetin as a painkillers has now been discontinued, phenacetin may be added to some illegal recreational drugs, such as cocaine, so regular users could still be at risk.

People with a rare condition called Lynch syndrome, also known as hereditary non-polyposis colorectal cancer (HNPCC), have an increased risk of developing TCC of the renal pelvis and ureter.

Ureter and renal pelvis cancer, like other cancers, is not infectious and cannot be passed on to other people. It is not caused by an inherited faulty gene, so other members of one's family are not likely to develop it.
(MacMillan Cancer Support; Froedtert & Medical College of Wisconsin).

Symptoms of Ureteral Cancer
The most common symptom of ureteral cancer is visible (or microscopic) blood in the urine. Occasionally, bladder irritability and frequent urination can be symptoms of these malignancies. People who notice blood in the urine or other symptoms should be evaluated by a physician immediately, because outcomes are correlated with the length of time

between symptom onset and treatment. Ureteral cancer arises in the cells that line these organs (Froedtert & Medical College of Wisconsin).

Diagnosis of Ureteral Cancer

To diagnose or rule out transitional cell carcinoma, the doctor will ask about medical history and symptoms, perform a physical examination and order blood tests, urine tests and radiologic imaging studies such as a CT scan or MRI.

If transitional cell carcinoma is suspected, the doctor may recommend a ureteroscopy in order to determine the best way to surgically manage the disease. During a ureteroscopy, a thin, flexible tube is passed through the urethral opening and threaded up through the bladder into the ureters. Fibre optic cable within the tube allows doctors to view any lesions in the ureteral or renal pelvic wall. In this way, doctors can count the lesions and determine their precise location. During ureteroscopy, a biopsy of the lesions may also be taken for further examination by a pathologist, who can confirm the grade of the cancer. X-rays, radiologic imaging and urine cytology (examining the size and shape of cells found in the urine) may also be used in diagnosing transitional cell carcinoma.
(NYU Langone Medical Center).

Staging of Ureteral Cancer

Transitional cell carcinoma of the ureter is staged using the TNM System and is very similar to staging of TCC of the bladder and to staging of TCC of the renal pelvis.

T

Ta : non-invasive papillary tumour
Tis : in situ (non-invasive flat)
T1 : through lamina propria into sub-epithelial connective tissues
T2 : into muscularis propria
T3 : invasion into periureteric fat
T4 : direct invasion into adjacent organs / structures

N

Nodal staging is the same for TCC of any part of the urinary tract.
N0 : no nodal involvement
N1 : single node involved < 2cm
N2

- single node 2 - 5cm OR
- multiple nodes all < 5cm

N3 : one or more nodes > 5cm

M

M0 : no metastases
M1 : metastases identified

Staging groups

Individual TNM stages can then be grouped:
stage 0 : Ta or Tis, N0, M0

stage I : T1, N0, M0
stage II : T2(a or b), N0, M0
stage III : T3(a or b) or T4a, N0, M0
stage IV

- T4b, any N, any M
- N1-3, any T, any M (Radiopaedia).

Treatment of Ureteral Cancer

Surgery is the primary treatment option for caner of the ureter. Treatment depends on the type, size, stage and location of the lesion. Removal of the entire kidney and ureter is the most common procedure. However, surgeons may use nephron-sparing procedures to save kidney function. These include the use of delicate telescopes to target the ureteral cancer tumours without removing the kidney.

If the ureteral cancer tumour is large, it may be possible to remove the affected portion of the ureter without removing the kidney itself.

For a tumour in the middle of the ureter, surgeons remove the tumour and rebuild the ureter. When the tumour is located in the bottom third, surgeons may remove that section of the ureter. The rest is reconnected to the bladder. This procedure is called a ureteroneocystomy, or reimplantation.

If the entire kidney and ureter need to be removed, surgeons often can do this laparoscopically (minimally-invasive) with better results.

If the tumour is located in the upper third of the ureter, a nephroereterectomy is often performed, removing the entire kidney and remainder of the ureter.
(Fox Chase Cancer Center).

About Clinical Trials

Clinical trials are research studies that involve people. These studies test new ways to prevent, detect, diagnose, or treat diseases. People who take part in cancer clinical trials have an opportunity to contribute to scientists' knowledge about cancer and to help in the development of improved cancer treatments. They also receive state-of-the-art care from cancer experts.

<u>Types of Clinical Trials</u>

Cancer clinical trials differ according to their primary purpose. They include the following types:

Treatment - these trials test the effectiveness of new treatments or new ways of using current treatments in people who have cancer. The treatments tested may include new drugs or new combinations of currently used drugs, new surgery or radiation therapy techniques, and vaccines or other treatments that stimulate a person's immune system to fight cancer. Combinations of different treatment types may also be tested in these trials.

Prevention - these trials test new interventions that may lower the risk of developing certain types of cancer. Most cancer prevention trials involve healthy people who have not had cancer; however, they often only include people who have a higher than average risk of developing a specific type of cancer. Some cancer prevention trials involve people who have had cancer in the past; these trials test interventions that may help prevent the return (recurrence) of the original cancer or reduce the chance of developing a new type of cancer

Screening - these trials test new ways of finding cancer early. When cancer is found early, it may be easier to treat and there may be a better chance of long-term survival. Cancer screening trials usually involve people who do not have any signs or symptoms of cancer. However, participation in these trials is often limited to people who have a higher than average risk of developing a certain type of cancer because they have a family history of that type of cancer or they have a history of exposure to cancer-causing substances (e.g., cigarette smoke).

Diagnostic - these trials study new tests or procedures that may help identify, or diagnose, cancer more accurately. Diagnostic trials usually involve people who have some signs or symptoms of cancer.

Quality of life or supportive care - these trials focus on the comfort and quality of life of cancer patients and cancer survivors. New ways to decrease the number or severity of side effects of cancer or its treatment are often studied in these trials. How a specific type of cancer or its treatment affects a person's everyday life may also be studied.

Where Clinical Trials are Conducted

Cancer clinical trials take place in cities and towns in doctors' offices, cancer centres and other medical centres, community hospitals and clinics. A single trial may take place at one or two specialised medical centres only or at hundreds of offices, hospitals, and centres.

Each clinical trial is managed by a research team that can include doctors, nurses, research assistants, data analysts, and other specialists. The research team works closely with other health professionals, including other doctors and nurses, laboratory technicians, pharmacists, dieticians, and social workers, to provide medical and supportive care to people who take part in a clinical trial.

Research Team

The research team closely monitors the health of people taking part in the clinical trial and gives them specific instructions when necessary. To ensure the reliability of the trial's results, it is important for the participants to follow the research team's instructions. The instructions may include keeping logs or answering questionnaires. The research team may also seek to contact the participants regularly after the trial ends to get updates on their health.

Clinical Trial Protocol

Every clinical trial has a protocol, or action plan, that describes what will be done in the trial, how the trial will be conducted, and why each part of the trial is necessary. The protocol also includes guidelines for who can and cannot participate in the trial. These guidelines, called eligibility criteria, describe the characteristics that all interested people must have before they can take part in the trial. Eligibility criteria can include age, sex, medical history, and

current health status. Eligibility criteria for cancer treatment trials often include the type and stage of cancer, as well as the type(s) of cancer treatment already received.

Enrolling people who have similar characteristics helps ensure that the outcome of a trial is due to the intervention being tested and not to other factors. In this way, eligibility criteria help researchers obtain the most accurate and meaningful results possible.

National and International Regulations

National and international regulations and policies have been developed to help ensure that research involving people is conducted according to strict scientific and ethical principles. In these regulations and policies, people who participate in research are usually referred to as "human subjects."

Informed Consent

Informed consent is a process through which people learn the important facts about a clinical trial to help them decide whether or not to take part in it, and continue to learn new information about the trial that helps them decide whether or not to continue participating in it.

During the first part of the informed consent process, people are given detailed information about a trial, including information about the purpose of the trial, the tests and other procedures that will be required, and the possible benefits and harms of taking part in the trial. Besides talking with a doctor or nurse, potential trial participants are given a form, called an informed consent form, that provides information about the trial in writing. People who agree to take part in the trial are asked to sign the form. However, signing this form does not mean that a person must remain in the trial. Anyone can choose to leave a trial at any time—either before it starts or at any time during the trial or during the follow-up period. It is important for people who decide to leave a trial to get information from the research team about how to leave the trial safely.

The informed consent process continues throughout a trial. If new benefits, risks, or side effects are discovered during the course of a trial, the researchers must inform the participants so they can decide whether or not they want to continue to take part in the trial. In some cases, participants who want to continue to take part in a trial may be asked to sign a new informed consent form.

New interventions are often studied in a stepwise fashion, with each step representing a different "phase" in the clinical research process. The following phases are used for cancer treatment trials:

Phases of a Clinical Trial

Phase 0. These trials represent the earliest step in testing new treatments in humans. In a phase 0 trial, a very small dose of a chemical or biologic agent is given to a small number of people (approximately 10-15) to gather preliminary information about how the agent is processed by the body (pharmacokinetics) and how the agent affects the body (pharmacodynamics). Because the agents are given in such small amounts, no information is obtained about their safety or effectiveness in treating cancer. Phase 0 trials are also called micro-dosing studies, exploratory Investigational New Drug (IND) trials, or early phase

I trials. The people who take part in these trials usually have advanced disease, and no known, effective treatment options are available to them.

Phase I (also called phase 1). These trials are conducted mainly to evaluate the safety of chemical or biologic agents or other types of interventions (e.g., a new radiation therapy technique). They help determine the maximum dose that can be given safely (also known as the maximum tolerated dose) and whether an intervention causes harmful side effects. Phase I trials enrol small numbers of people (20 or more) who have advanced cancer that cannot be treated effectively with standard (usual) treatments or for which no standard treatment exists. Although evaluating the effectiveness of interventions is not a primary goal of these trials, doctors do look for evidence that the interventions might be useful as treatments.

Phase II (also called phase 2). These trials test the effectiveness of interventions in people who have a specific type of cancer or related cancers. They also continue to look at the safety of interventions. Phase II trials usually enrol fewer than 100 people but may include as many as 300. The people who participate in phase II trials may or may not have been treated previously with standard therapy for their type of cancer. If a person has been treated previously, their eligibility to participate in a specific trial may depend on the type and amount of prior treatment they received. Although phase II trials can give some indication of whether or not an intervention works, they are almost never designed to show whether an intervention is better than standard therapy.

Phase III (also called phase 3). These trials compare the effectiveness of a new intervention, or new use of an existing intervention, with the current standard of care (usual treatment) for a particular type of cancer. Phase III trials also examine how the side effects of the new intervention compare with those of the usual treatment. If the new intervention is more effective than the usual treatment and/or is easier to tolerate, it may become the new standard of care.

Phase III trials usually involve large groups of people (100 to several thousand), who are randomly assigned to one of two treatment groups, or “trial arms”: (1) a control group, in which everyone in the group receives usual treatment for their type of cancer, or 2) an investigational or experimental group, in which everyone in the group receives the new intervention or new use of an existing intervention. The trial participants are assigned to their individual groups by random assignment, or randomisation. Randomisation helps ensure that the groups have similar characteristics. This balance is necessary so the researchers can have confidence that any differences they observe in how the two groups respond to the treatments they receive are due to the treatments and not to other differences between the groups.

Randomisation is usually done by a computer program to ensure that human choices do not influence the assignment to groups. The trial participants cannot request to be in a particular group, and the researchers cannot influence how people are assigned to the groups. Usually, neither the participants nor their doctors know what treatment the participants are receiving.

People who participate in phase III trials may or may not have been treated previously. If they have been treated previously, their eligibility to participate in a specific trial may depend on the type and the amount of prior treatment they received.

In most cases, an intervention will move into phase III testing only after it has shown promise in phase I and phase II trials.

Phase IV (also called phase 4). These trials further evaluate the effectiveness and long-term safety of drugs or other interventions. They usually take place after a drug or intervention has been approved by the medicine regulatory office for standard use. Several hundred to several thousand people may take part in a phase IV trial. These trials are also known as post-marketing surveillance trials. They are generally sponsored by drug companies.

Sometimes clinical trial phases may be combined (e.g., phase I/II or phase II/III trials) to minimize the risks to participants and/or to allow faster development of a new intervention.

Although treatment trials are always assigned a phase, other clinical trials (e.g., screening, prevention, diagnostic, and quality-of-life trials) may not be labelled this way.

Use of Placebos

The use of placebos as comparison or "control" interventions in cancer treatment trials is rare. If a placebo is used by itself, it is because no standard treatment exists. In this case, a trial would compare the effects of a new treatment with the effects of a placebo. More often, however, placebos are given along with a standard treatment. For example, a trial might compare the effects of a standard treatment plus a new treatment with the effects of the same standard treatment plus a placebo.

Possible benefits of taking part in a clinical trial

The benefits of participating in a clinical trial include the following:

- Trial participants have access to promising new interventions that are generally not available outside of a clinical trial.
- The intervention being studied may be more effective than standard therapy. If it is more effective, trial participants may be the first to benefit from it.
- Trial participants receive regular and careful medical attention from a research team that includes doctors, nurses, and other health professionals.
- The results of the trial may help other people who need cancer treatment in the future.
- Trial participants are helping scientists learn more about cancer (e.g., how it grows, how it acts, and what influences its growth and spread).

Potential harms associated with taking part in a clinical trial

The potential harms of participating in a clinical trial include the following:

- The new intervention being studied may not be better than standard therapy, or it may have harmful side effects that doctors do not expect or that are worse than those associated with standard therapy.

- Trial participants may be required to make more visits to the doctor than they would if they were not in a clinical trial and/or may need to travel farther for those visits.

Correlative research studies, and how they are related to clinical trials

In addition to answering questions about the effectiveness of new interventions, clinical trials provide the opportunity for additional research. These additional research studies, called correlative or ancillary studies, may use blood, tumour, or other tissue specimens (also known as 'biospecimens') obtained from trial participants before, during, or after treatment. For example, the molecular characteristics of tumour specimens collected during a trial might be analysed to see if there is a relationship between the presence of a certain gene mutation or the amount of a specific protein and how trial participants responded to the treatment they received. Information obtained from these types of studies could lead to more accurate predictions about how individual patients will respond to certain cancer treatments, improved ways of finding cancer earlier, new methods of identifying people who have an increased risk of cancer, and new approaches to try to prevent cancer.

Clinical trial participants must give their permission before biospecimens obtained from them can be used for research purposes.

When a clinical trial is over

After a clinical trial is completed, the researchers look carefully at the data collected during the trial to understand the meaning of the findings and to plan further research. After a phase I or phase II trial, the researchers decide whether or not to move on to the next phase or stop testing the intervention because it was not safe or effective. When a phase III trial is completed, the researchers analyse the data to determine whether the results have medical importance and, if so, whether the tested intervention could become the new standard of care.

The results of clinical trials are often published in peer-reviewed scientific journals. Peer review is a process by which cancer research experts not associated with a trial review the study report before it is published to make sure that the data are sound, the data analysis was performed correctly, and the conclusions are appropriate. If the results are particularly important, they may be reported by the media and discussed at a scientific meeting and by patient advocacy groups before they are published in a journal. Once a new intervention has proven safe and effective in a clinical trial, it may become a new standard of care.
(National Cancer Institute).

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