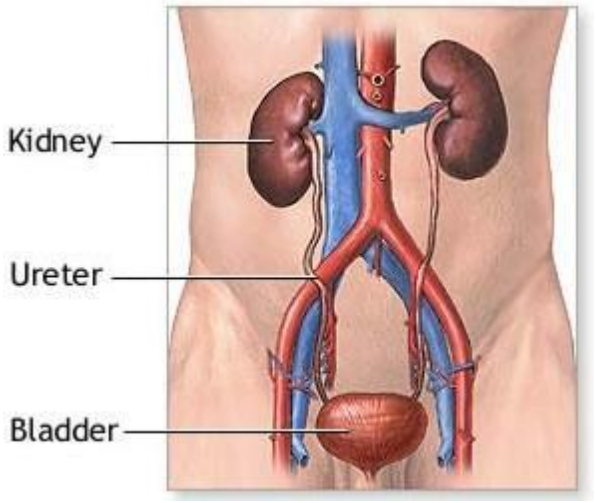
# Cancer Association of South Africa (CANSA)

Fact Sheet
on
Kidney Cancer

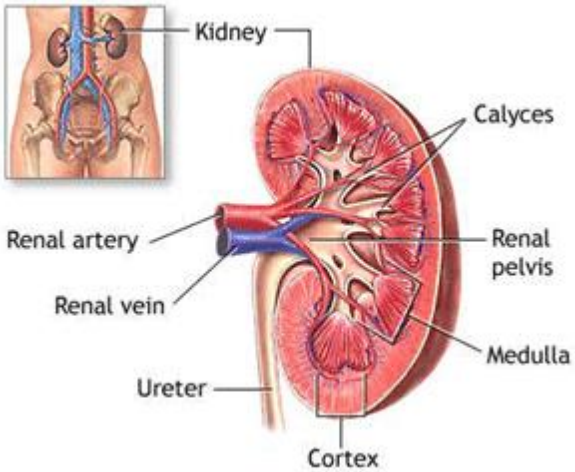
**Introduction**

The kidneys are two organs that serve several essential regulatory roles in man. They form an essential part of the urinary system and also serve homeostatic functions such as the regulation of electrolytes, maintenance of acid–base balance and regulation of blood pressure (by maintaining salt and water balance). They serve the body as a natural filter of the blood and remove wastes which are diverted to the urinary bladder. In the process of producing urine, the kidneys excrete wastes such as urea and ammonia. They are also responsible for the reabsorption of water, glucose, and amino acids. The kidneys also produce hormones including calcitriol, erythropoietin, and the enzyme renin. Many of the kidney's functions are accomplished by relatively simple mechanisms of filtration, reabsorption, and secretion, which take place in the nephron. Filtration, which takes place at the renal corpuscle, is the process by which cells and large proteins are filtered from the blood to make an ultrafiltrate that eventually becomes urine (WebMD).




[Picture Credit: Urinary Tract Anatomy].

Located at the back of the abdominal cavity in the retroperitoneum, the kidneys receive blood from the paired renal arteries, and drain into the paired renal veins. Each kidney excretes urine into a ureter, itself a paired structure that empties into the urinary bladder.




[Picture credit:: Urinary Tract Anatomy].

**Cancer of the Kidneys**

Kidney cancer is the uncontrolled growth of abnormal cells in the kidneys. Cancerous cells are also called malignant cells.

Each person diagnosed with kidney cancer goes through the shock of being told they have the disease. It is a difficult experience.

Feelings of shock, loneliness, alienation, fear, frustration, anger, and hurt are natural parts of any life-threatening illness. It is okay to have these feelings, to cry, and to be upset. After the shock of diagnosis, it's time to start healing. One should not let one's emotions and cancer diagnosis destroy one's home life or relations with the important people in one's life. They may also be hurting inside, fearing for their loved and as well as themselves. When cancer strikes, it hits the whole family (Kidney Cancer Association).

Some patients are diagnosed before the cancer has metastasised (spread) to other parts of the body, while others have metastatic disease when their cancer is initially diagnosed. Surgery may be the first course of treatment. If surgery is done first, additional treatment may be recommended to delay the cancer's return, or to treat metastatic disease.

**Possible Early Signs and Symptoms of Kidney Cancer**

Early kidney cancers do not usually cause any signs or symptoms, but larger ones might. Some possible signs and symptoms of kidney cancer include:

- Blood in the urine (haematuria)
- Low back pain on one side (not caused by injury)
- A mass (lump) on the side or lower back
- Fatigue (tiredness)
- Loss of appetite
- Weight loss not caused by dieting
- Fever that is not caused by an infection and that doesn't go away
- Anaemia (low red blood cell counts)

These signs and symptoms can be caused by kidney cancer (or another type of cancer), but more often they are caused by other, benign, diseases. For example, blood in the urine is most often caused by a bladder or urinary tract infection or a kidney stone. Still, if one has any of these symptoms, see a doctor so that the cause can be found and treated, if needed. (American Cancer Society).

**Incidence of Kidney Cancer in South Africa**

According to the National Cancer Registry (2012) the following number of Kidney Cancer cases was histologically diagnosed in South Africa during 2012:

| Group - Males 2012 | Actual No of Cases | Estimated Lifetime Risk | Percentage of All Cancers |
|---|---|---|---|
| All males | 329 | 1:432 | 1,03% |
| Asian males | 10 | 1:376 | 1,58% |
| Black males | 92 | 1:1 305 | 0,93% |
| Coloured males | 49 | 1:287 | 1,28% |
| White males | 178 | 1:160 | 1,01% |

| Group - Females 2012 | Actual No of Cases | Estimated Lifetime Risk | Percentage of All Cancers |
|---|---|---|---|
| All females | 233 | 1:838 | 0,74% |
| Asian females | 11 | 1:628 | 1,52% |
| Black females | 107 | 1:1 637 | 0,78% |
| Coloured females | 28 | 1:638 | 0,75% |
| White females | 87 | 1:325 | 0,64% |

The frequency of histologically diagnosed cases of Kidney Cancer in South Africa for 2012 was as follows (National Cancer Registry, 2012):

| Group - Males 2012 | 0 – 19 Years | 20 – 29 Years | 30 – 39 Years | 40 – 49 Years | 50 – 59 Years | 60 – 69 Years | 70 – 79 Years | 80+ Years |
|---|---|---|---|---|---|---|---|---|
| All males | 48 | 1 | 15 | 41 | 67 | 89 | 58 | 8 |
| Asian males | 0 | 0 | 1 | 0 | 2 | 5 | 2 | 0 |
| Black males | 35 | 1 | 6 | 12 | 17 | 11 | 9 | 1 |
| Coloured males | 3 | 0 | 2 | 12 | 10 | 15 | 6 | 1 |
| White males | 9 | 0 | 6 | 17 | 38 | 58 | 41 | 8 |

| Group - Females 2012 | 0 – 19 Years | 20 – 29 Years | 30 – 39 Years | 40 – 49 Years | 50 – 59 Years | 60 – 69 Years | 70 – 79 Years | 80+ Years |
|---|---|---|---|---|---|---|---|---|
| All females | 50 | 3 | 19 | 29 | 47 | 51 | 29 | 4 |
| Asian females | 3 | 0 | 2 | 1 | 2 | 3 | 0 | 0 |
| Black females | 37 | 2 | 11 | 17 | 19 | 15 | 4 | 1 |
| Coloured females | 4 | 0 | 3 | 6 | 5 | 6 | 2 | 0 |
| White females | 3 | 1 | 3 | 5 | 21 | 27 | 21 | 3 |

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females', however, always reflect the correct totals.

**Risk Factors for Kidney Cancer**

A risk factor is anything that affects one's chance of getting a disease such as cancer. Different cancers have different risk factors. For example, unprotected exposure to strong sunlight is a risk factor for skin cancer. Having a risk factor, or even several risk factors, does not mean that you will get the disease. Several risk factors that may make one more likely to develop kidney cancer have been identified.

***Lifestyle- and Work-related Risk Factors***

- Smoking
  - Smoking increases the risk of developing renal cell carcinoma. Smoking has been shown to double the risk of kidney cancer and contributes to as many as one-third of the cases. The increased risk seems to be related to how much one smokes. The risk increases the longer one smokes and decreases after one quits, although it takes years to reach the same risk level as someone who has never smoked.

- Obesity
  - People who are very overweight have a higher risk of developing renal cell cancer. Some doctors think obesity is a factor in about 2 out of 10 people who get this cancer. Obesity may cause changes in certain hormones that can lead to renal cell carcinoma.

- Workplace exposures
  - Many studies have suggested that workplace exposure to certain substances increases the risk for renal cell carcinoma. Some of these are petroleum products, asbestos, cadmium (a type of metal), some herbicides, benzene, and organic solvents, particularly trichloroethylene.

(National Institutes for Health; Mayo clinic; Columbia University Medical Centre)

***Genetic and Hereditary Risk Factors***
Genetic factors have been linked to an increased risk of kidney cancer. Some people inherit a tendency to develop certain types of cancer. It is important that people who have hereditary causes of renal cell cancer see their doctors frequently, particularly if they have already had a renal cell cancer diagnosed. Some doctors recommend regular imaging tests (such as CT scans) for these people.

People who have the conditions listed here have a much higher risk for getting kidney cancer, although they account for only a small portion of cases overall:

- von Hippel-Lindau (VHL) disease
  - People with this hereditary disorder often develop several kinds of tumours and cysts (fluid-filled sacs) in different parts of the body. They have an increased risk for developing clear cell renal cell carcinoma, especially at a younger age. They may also have benign tumours in their eyes, brain, spinal cord, pancreas and other organs; and a type of adrenal gland tumour called pheochromocytoma. This condition is caused by mutations (changes) in the VHL gene.

- Hereditary papillary renal cell carcinoma
  - People with this condition have inherited a tendency to develop one or more papillary renal cell carcinomas, but they do not have tumours in other parts of the body, as is the case with the other inherited conditions listed here. This disorder is linked to changes in many genes, most often the MET gene.

- Hereditary leiomyoma-renal cell carcinoma
  - People with this syndrome develop smooth muscle tumours called leiomyomas or fibroids of the skin and uterus (in women) and have a higher risk for developing papillary renal cell cancers. It has been linked to changes in the fumarate hydratase (FH) gene.

- Birt-Hogg-Dube (BHD) syndrome
  - People with this syndrome, which is characterised by the development of small benign skin tumours, have an increased risk of developing different kinds of kidney tumours, including renal cell cancers and oncocytomas. They
  - may also have benign or malignant tumours of several other tissues. The gene linked to BHD is officially known as folliculin (FLCN).

- Hereditary renal oncocytoma
  - Some people inherit the tendency to develop a kidney tumour called oncocytoma, which has a very low potential for being malignant.

(National Institutes for Health; Mayo clinic; Columbia University Medical Centre)

**Other risk factors**
Other risk factors include:

- Family history of kidney cancer

People with a strong family history of renal cell cancer (without one of the known inherited conditions listed previously) also have a 2 to 4 times higher chance of developing this cancer. This risk is highest in brothers or sisters of those with the cancer. It is not clear whether this is due to shared genes or something that both people were exposed to in the environment - or both.

- High blood pressure

The risk of kidney cancer is higher in people with high blood pressure. Some studies have suggested that certain medicines used to treat high blood pressure may raise the risk of kidney cancer, but it is hard to tell if it is the condition or the medicine (or both) that may be the cause of the increased risk.

- Certain medicines

Phenacetin, once a popular non-prescription pain reliever, has been linked to renal cell cancer in the past. Because this medicine has not been available for over 20 years, this no longer appears to be a major risk factor.

Over-The-Counter Pain Relievers**:** many over the counter pain relievers are somewhat toxic to the kidney. These non-steroidal anti-inflammatory drugs include aspirin, ibuprofen, and naproxen. Trade names for ibuprofen and naproxen include Motrin, Advil, and Aleve. Long term use of acetaminophen (Tylenol) has also been associated with kidney failure.

- Diuretics

Some studies have suggested that diuretics (water pills) may be linked to a small increase in the risk of renal cell carcinoma. It is not clear whether the cause is the drugs or the high blood pressure it treats.

- Advanced kidney disease

People with advanced kidney disease, especially those needing dialysis, have a higher risk of renal cell carcinoma. Dialysis is a treatment used to remove toxins from your body if the kidneys do not work properly.

- Sex

Renal cell carcinoma is about twice as common in men as in women. Men are more likely to be smokers and are more likely to be exposed to cancer-causing chemicals at work, which may account for some of the difference.

- Physical activity

An active lifestyle has many positive healthy benefits including decreasing high blood pressure, strengthening bones, helping to maintain a healthy weight, and reducing the risk of kidney cancer. It is important to discuss an exercise or physical activity regimen with your doctor - most physicians suggest getting at least 30 minutes a day of exercise.

- Alcohol consumption

Alcohol use is a cause of cancer. Any level of alcohol consumption increases the risk of developing an alcohol-related cancer; the level of risk increases in line with the level of consumption. There is *convincing* evidence that alcohol use increases the risk of cancers of the mouth, pharynx, larynx, oesophagus, kidney, bowel (in men) and breast (in women), and *probable* evidence that it increases the risk of bowel cancer (in women) and liver cancer.

- Age

According to the international literature, the risk of renal cell carcinoma significantly increases with age, most kidney cancers occur in people over 45 years of age; with the highest incidences between the ages of 55 and 84. Kidney cancer is mostly a disease seen in adults aged over 55, and is rare in children (Kidney Health Australia). In South Africa, according to the National Cancer Registry of 2004, there is a high incidence of kidney cancer in the 0 to 9 year age group with a peak in the 45 to 69 year age group in both males and females.

- Dialysis

People who receive long-term dialysis for treatment of chronic renal failure are at greater risk of developing kidney cancer, possibly because renal failure depresses the immune system. People who have a kidney transplant and receive immunosuppressant drugs also are more likely to develop kidney cancer.

- Radiation

In some cases, exposure to radiation may increase the risk of kidney cancer.
(American Cancer Society; Kidney Cancer Association; National Institutes of Health; Columbia University Medical Center; Kidney Cancer Institute; Cancer Council, New South Wales; National Institutes for Health; Mayo clinic; Columbia University Medical Centre)

**Diagnosis of Kidney Cancer**

Early kidney cancer does not usually cause any signs or symptoms. Most kidney tumours are found incidentally — during an evaluation with radiologic imaging studies for other nonspecific abdominal complaints (gallbladder pain, for example), or during follow-up for other previously treated malignancies. These 'incidental cancers' are often found early, before any symptoms have occurred. Because such cancers are usually detected before they have spread, patients with incidental kidney tumours are often cured of their disease, commonly by surgery alone. As many as 30 percent of kidney masses represent a benign condition (Memorial Sloan-Kettering Cancer Centre).

Some of the earliest signs and symptoms of kidney cancer include:

- Blood in the urine (haematuria)
- Low back pain on one side (not caused by injury)
- A mass (lump) on the side or lower back
- Fatigue (tiredness)
- Weight loss not caused by dieting
- Fever that is not caused by an infection and that does not go away after a few weeks
- Swelling of the ankles and legs (oedema)

None of these symptoms are positively indicative of kidney cancer. For example, blood in the urine may be a sign of kidney, bladder or prostate cancer, but can also be an indication of a bladder infection or a kidney stone (American Cancer Society).

The following tests and procedures are used to diagnose kidney cancer:

Blood and urine tests - tests of blood and urine may give the doctor clues about what is causing the signs and symptoms (Mayo Clinic).

Urinary aquaporin-I (AQP-1) and adipose differentiation-related protein (ADFP) as biomarkers of kidney cancer. This is a new process for:

- early and non-invasive detection of renal cancer
- population screening for renal cancer
- post-treatment surveillance for recurrence of renal cancer
- progression, regression or time-course of disease in untreated, partially treated, and definitively treated patients with renal cancer

The process is non-invasive, using readily available biological fluids such as urine and possibly blood (Kharasch).

Imaging tests - imaging tests allow a doctor to visualise a kidney tumour or abnormality. Imaging tests might include ultrasound, computerised tomography (CT) or magnetic resonance imaging (MRI).

Removing a sample of kidney tissue (biopsy) - in some selected cases, the doctor may recommend a procedure to remove a small sample of cells (biopsy) from a suspicious area of a kidney. Because surgery is usually the first line treatment for kidney cancer and a kidney biopsy carries the risk of a "false-negative," doctors usually forgo kidney biopsy. Kidney biopsy is typically reserved for cases that are most likely to be noncancerous or for people who can't undergo an operation (Mayo Clinic).

Fine needle aspiration (FNA) - are sometimes used to obtain a biopsy of the kidney. This involves the insertion of a long, thin needle into the kidney to take a tiny sample of tissue for examination under a microscope. With modern biopsy methods, there is virtually no risk of 'spreading cancer' (MD Anderson Cancer Center).

Cystoscopy and retrograde pyelography - if a doctor suspects that a kidney tumour is arising from the collecting system in the kidney, he/she may examine the patient using cystoscopy and retrograde pyelography. Using a cystoscope (an instrument consisting of a slender tube with a lens and light that is placed into the kidney through the urethra), the doctor can pass a small catheter into the opening of the ureter (the tube that carries urine form the kidney to the bladder), inject dye, and take X-ray pictures of the entire collecting system of the affected kidney to check for possible cancers.

Intravenous Pyelogram (IVP) – the doctor performs this examination by injecting a dye into the bloodstream, which travels to the kidneys, ureters, and bladder to more clearly outline these organs on x-ray. IVP has been largely replaced by CT scans because the CT scan creates a computer enhanced reconstruction of the entire urinary tract and more accurately identifies small tumours (Columbia University Medical Centre).

**Types of Kidney Cancer**

Renal Cell Carcinoma (RCC) **-** Renal Cell Carcinoma (RCC) is the most common type of kidney cancer, accounting for approximately 85% of all malignant kidney tumours. In RCC, cancerous (malignant) cells develop in the lining of the kidney tubules and grow into a mass called a tumour. Like many other cancers, the growth begins small and grows larger over time. RCC typically grows as a single mass. However, there are cases where a kidney may contain more than one tumour, or tumours are found in both kidneys at the same time.

***Types of Renal Cell Carcinoma (RCC)***

There are five main types of renal cell carcinoma that are identified by examining the tumour under a microscope: clear cell, papillary, chromophobe, collecting duct and 'unclassified'.

Clear Cell RCC - Clear Cell RCC is the most common form of renal cell carcinoma, accounting for about 80% of people with kidney cancer. When viewed under a microscope, the individual cells that make up *clear cell* renal cell carcinoma appear very pale or clear.

Papillary RCC - Papillary RCC is the second most common type - about 10% to 15% of people have this form. These cancers form little finger-like projections (called papillae).

Chromophobe RCC - The third most common form of renal carcinoma is chromophobe RCC, accounting for about 5% of cases. Like clear cell carcinoma, the cells of these cancers are also pale, but are much larger and have certain other distinctive features.

Collecting Duct RCC - The rarest form of RCC is collecting duct renal carcinoma. The major characteristic of collecting duct RCC is that the cancer cells can form irregular tubes.

Unclassified RCC - About 5% of renal cancers are *unclassified* because their appearance does not fit into any of the other categories.

Recent data suggests that clear cell RCC has a slightly worse prognosis as compared to papillary or chromophobe cell RCC. However, the majority of low stage tumours, regardless of cell type, can be cured with surgical resection. Oncocytoma is usually a benign lesion with an extremely low chance of spreading. Spindle cell types, or sarcomas, tend to grow and spread more quickly than the other kinds of renal cell carcinoma. It can be associated with any of the subtypes mentioned, and this subtype is a sign of a poor prognosis.

***Other Types of Cancerous Kidney Tumours***

RCC accounts for about 90% of malignant kidney tumours. Less common types of cancerous tumours include transitional cell carcinomas, Wilms tumours and renal sarcomas.

Transitional Cell Carcinoma: About 5% to 10% of all kidney tumours are transitional cell carcinomas, also known as *urothelial carcinomas*. Transitional cell carcinomas begin in the renal pelvis (the junction of ureter and kidney). Under the microscope, transitional cell carcinomas look like bladder cancer cells and act very much like bladder cancer. Studies have shown that, like bladder cancer, these cancers are linked to cigarette smoking and occupational exposures to certain cancer-causing chemicals.

The signs and symptoms of transitional cell carcinoma are typically the same as with renal cell carcinoma - blood in the urine and, sometimes, back pain.

Transitional cell carcinomas are usually treated by surgically removing the entire kidney and the ureter, as well as the section of the bladder where the ureter is attached. Chemotherapy and radiation therapy are often used in addition to surgery, depending on how much cancer is found. As with RCC, with early stage transitional cell carinomas, there are several treatments. If a patient has early transitional cell carcinoma, there are several treatment options available. There are different ways to surgically treat early disease. Newer surgical techniques are also being studied. Patients should talk with their surgeon and be aware of their options and the benefits and risks of those options.

About 90% of transitional cell carcinomas of the kidney are curable if they are found early enough. The chances for cure drop dramatically if the tumour has grown into the ureter wall, or if it has a more aggressive (high-grade) appearance when viewed under the microscope.

Wilms Tumour - About 5% to 6% of all kidney cancers are Wilms' tumours. This type of cancer is almost always found in children and is extremely rare among adults. It has a female predominance and a higher incidence in black children. Seventy eight per cent of children are diagnosed at 1 - 5 years of age, with a peak incidence at 3 - 4 years. Wilms' tumour usually occurs sporadically, but in 1% of cases it is familial.

Renal Sarcoma - Renal sarcomas are a rare type of kidney cancer (less than 1% of all kidney tumours) that begins within the kidney's connective tissue.

***Benign (Non-Cancerous) Kidney Tumours***

Some types of kidney tumours (including renal cell adenomas, renal oncocytomas and angiomyolipomas) do not usually spread (metastasize) to other parts of the body, although they can still grow and cause problems.

Renal Adenoma - Renal adenomas are very small, slow growing, benign tumours that, under a microscope, look a lot like low-grade renal cell carcinomas. In rare cases, tumours first thought to be renal adenomas may turn out to be small renal cell carcinomas.

Oncocytoma **-** Oncocytomas are a type of benign kidney tumour that can sometimes grow quite large. Because oncocytomas do not normally metastasize to other organs, removing the kidney can often produce a cure.

Angiomyolipoma - Angiomyolipomas are another rare benign kidney tumour. They often develop in people with tuberous sclerosis (a disease charachterized by several bumps on the skin, seizures, mental retardation, and cysts in the kidneys, liver and pancreas).
(UCLA Health System)

**Stages of Kidney Cancer**

A staging system is a standardised way in which the cancer care team describes the extent of the cancer. The most commonly used staging system is that of the American Joint Committee on Cancer (AJCC), sometimes also known as the TNM system. The TNM system describes 3 key pieces of information:

**T** indicates the size of the main (primary) **tumour** and whether it has grown into nearby areas.

**N** describes the extent of spread to nearby (regional) lymph **nodes**. Lymph nodes are small bean-shaped collections of immune system cells that are important in fighting infections.

**M** indicates whether the cancer has spread (**metastasized**) to other organs of the body. (The most common sites of spread are to the lungs, bones, liver, and distant lymph nodes.)

Numbers or letters appear after T, N, and M to provide more details about each of these factors. The numbers 0 through 4 indicate increasing severity. The letter X means 'cannot be assessed because the information is not available'.

- ***T categories for kidney cancer***
  - TX**:** The primary tumour cannot be assessed (information not available).

- T0**:** No evidence of a primary tumour.
- T1**:** The tumour is only in the kidney and is 7 cm T1a**:** The tumour is 4 cm across or smaller and is only in the kidney.
- T1b**:** The tumour is larger than 4 cm but not larger than 7 cm across and is only in the kidney.
- T2**:** The tumour is larger than 7 cm across but is still only in the kidney.
- T2a**:** The tumour is more than 7 cm but not more than 10 cm across and is only in the kidney
- T2b**:** The tumour is more than 10 cm across and is only in the kidney
- T3**:** The tumour is growing into a major vein or into tissue around the kidney, but it is not growing into the adrenal gland (on top of the kidney) or beyond Gerota's fascia (the fibrous layer that surrounds the kidney and nearby fatty tissue).
- T3a**:** The tumour is growing into the main vein leading out of the kidney (renal vein) or into fatty tissue around the kidney
- T3b**:** The tumour is growing into the part of the large vein leading into the heart (vena cava) that is within the abdomen.
- T3c**:** The tumour has grown into the part of the vena cava that is within the chest or it is growing into the wall of that blood vessel (the vena cava).
- T4**:** The tumour has spread beyond Gerota's fascia (fibrous layer that surrounds the kidney and nearby fatty tissue). The tumour may have grown into the adrenal gland (on top of the kidney).

- ***N categories for kidney cancer***
  - NX**:** Regional (nearby) lymph nodes cannot be assessed (information not available).
  - N0**:** No spread to nearby lymph nodes.
  - N1**:** Tumour has spread to nearby lymph nodes.

- ***M categories for kidney cancer***
  - M0**:** There is no spread to distant lymph nodes or other organs.
  - M1**:** Distant metastasis is present; includes spread to distant lymph nodes and/or to other organs (such as the lungs, bones, or brain) (American Cancer Association).

**Stage grouping**

Once the **T**, **N**, and **M** categories have been assigned, this information is combined to assign an overall stage of I, II, III, or IV. The stages identify cancers that have a similar prognosis and thus are treated in a similar way. Patients with lower stage numbers tend to have a better prognosis.

- ***Stage I: T1, N0, M0***
  - The tumour is 7 cm across or smaller and is only in the kidney (T1). There is no spread to lymph nodes (N0) or distant organs (M0).

- ***Stage II: T2, N0, M0***
  - The tumour is larger than 7 cm across but is still only in the kidney (T2). There is no spread to lymph nodes (N0) or distant organs (M0).

- ***Stage III*:** Either of the following:
  - T3, N0, M0**:** The tumour is growing into a major vein (like the renal vein or the vena cava) or into tissue around the kidney, but it is not growing into the adrenal gland or beyond Gerota's fascia (T3). There is no spread to lymph nodes (N0) or distant organs (M0).

  - T1 to T3, N1, M0**:** The main tumour can be any size and may be outside the kidney, but it has not spread beyond Gerota's fascia. The cancer has spread to nearby lymph nodes (N1) but has not spread to distant lymph nodes or other organs (M0).

- **Stage IV:** Either of the following:
  - T4, any N, M0**:** The main tumour is growing beyond Gerota's fascia and may be growing into the adrenal gland on top of the kidney (T4). It may or may not have spread to nearby lymph nodes (any N). It has not spread to distant lymph nodes or other organs (M0).

  - Any T, Any N, M1**:** The main tumour can be any size and may have grown outside the kidney (any T). It may or may not have spread to nearby lymph nodes (any N). It has spread to distant lymph nodes and/or other organs (M1) (American Cancer Association; National Cancer Institute).

**How Kidney Cancer Spreads Through the Body**
In the event of kidney cancer spreading to other parts of the body, it would most probably spread as indicated below:

| **Cancer Type:** | **Main Sites of Metastasis (Spread)** |
|---|---|
| Bladder | Bone, liver, lung |
| Breast | Bone, brain, liver, lung |
| Colon | Liver, lung |
| Colorectal | Liver, lung, peritoneum (lining of abdomen) |
| Kidney | Adrenal gland, bone, brain, liver, lung |
| Lung | Adrenal gland, bone, brain, liver, other lung |
| Melanoma | Bone, brain, liver, lung, skin, muscle |
| Ovary | Liver, lung, peritoneum (lining of abdomen) |
| Pancreas | Liver, lung, peritoneum (lining of abdomen) |
| Prostate | Adrenal gland, bone, liver, lung |
| Stomach | Liver, lung, peritoneum (lining of abdomen), ovaries |
| Thyroid | Bone, liver, lung |
| Uterus | Boner, liver, lung, peritoneum (lining of abdomen), vagina |
| Non-melanoma skin cancer | Very rare: lymph nodes, lung, bone (if in head/neck region) |

(National Cancer Institute)

**Treatment of Kidney Cancer**
Common treatment options for people with kidney cancer are surgery, targeted therapy, and biological therapy. A patient may receive more than one type of treatment.

Treatment depends mainly on the following:

- The size of the tumour
- Whether the tumour has invaded tissues outside the kidney

- Whether the tumour has spread to other parts of the body
- Age and general health

At any stage of disease, supportive care is available to control pain and other symptoms, to relieve the side effects of treatment and to ease emotional concerns. For example, some people with kidney cancer may need to have radiation therapy to relieve pain or certain other problems.

***Surgery***

Surgery is the most common treatment for people with kidney cancer. The type of surgery depends on the size and stage of the cancer, whether the patient has two kidneys, and whether cancer was found in both kidneys.

The patient and his/her surgeon can talk about the types of surgery and which may be right:

Removing all of the kidney (radical nephrectomy): The surgeon removes the entire kidney along with the adrenal gland and some tissue around the kidney. Some lymph nodes in the area may also be removed.

Removing part of the kidney (partial nephrectomy): The surgeon removes only the part of the kidney that contains the tumour. People with a kidney tumour that is smaller than a tennis ball may choose this type of surgery.

There are two approaches for removing the kidney. The surgeon may remove the tumour by making a large incision into the body (open surgery). Or the surgeon may remove the tumour by making small incisions (laparoscopic surgery). The surgeon sees inside the abdomen with a thin, lighted tube (a laparoscope) placed inside a small incision. Sometimes a robot is used. The surgeon uses handles below a computer display to control the robot's arms.

The surgeon may use other methods of destroying the cancer in the kidney. For people who have a tumour smaller than 4cm and who can't have surgery to remove part of the kidney because of other health problems, the surgeon may suggest:

Cryosurgery: The surgeon inserts a tool through a small incision or directly through the skin into the tumour. The tool freezes and kills the kidney tumour.

Radiofrequency ablation: The surgeon inserts a special probe directly through the skin or through a small incision into the tumour. The probe contains tiny electrodes that kill the kidney cancer cells with heat.

It takes time to heal after surgery, and the time needed to recover is different for each person. It is common to feel weak or tired for a while.

Pain or discomfort may be felt for the first few days. Medicine can help control the pain. Before surgery, there should be discussions about a plan for pain relief with the doctor or nurse. After surgery, the doctor can adjust the plan if the patient needs more pain control.
The health care team will watch for signs of bleeding, infection, or other problems. They will keep track of how much fluid the patient takes in and how much urine passes out of his/her body.

If one kidney is removed, the remaining kidney is usually able to do the work of both kidneys. However, if the remaining kidney is not doing a good job cleaning the blood, the patient may need dialysis. Some people may need a transplant with a healthy kidney from a donor.

***Arterial Embolisation for Kidney Cancer***

Arterial embolisation for kidney cancer is a treatment that may be used when surgery to remove the tumour is not an option. This treatment is meant to shrink the tumour and relieve the symptoms of kidney cancer by blocking the flow of blood to the tumour. After undergoing an arterial embolization for kidney cancer, some people may experience back pain or develop a fever. Other side effects of arterial embolization can include nausea and vomiting.

***Targeted Therapy***

People with kidney cancer that has spread may receive a type of drug called targeted therapy. Many kinds of targeted therapy are used for kidney cancer. This treatment may shrink a kidney tumour or slow its growth.

Usually, the targeted therapy is taken by mouth. Patients may feel very tired while taking targeted therapy for kidney cancer. Other side effects may include diarrhoea, nausea, vomiting, sores on the lips or in the mouth and high blood pressure.

***Biological Therapy***

People with kidney cancer that has spread may receive biological therapy. Biological therapy for kidney cancer is a treatment that may improve the body's natural defence (the immune system response) against cancer. The treatments used for kidney cancer can slow the growth of tumours or shrink them. The biological therapy is injected intravenously or under the skin. The treatment may be given at the hospital or a doctor's office.

Other drugs may be given at the same time to prevent side effects. The side effects differ with the biological therapy used, and from person to person. Biological therapy commonly causes a rash or swelling. Patients may feel very tired during treatment. The treatment may also cause a headache, muscle aches, a fever, or weakness.

Nivolumab (Opdivo) has now become available in South Africa for the treatment of Renal Cell Carcinoma. Opdivo is supplied in either a 40 mg/4 mL single-use vial or a 100 mg/10 mL single-use vial. The recommended dose of Opdivo is 3 mg/kg by intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.

A single dose of Nivolumab (Opdivo) for a male patient weighing 85kg will be 255mg of Opdivo at a price of ±R372/mg = ±R94 860,00. This dosage is repeated every two weeks.

Opdivo should be stored under refrigeration at $2^{o}$C to $8^{o}$C and protected from light by storing in the original package until use.
(Reconsult).

***Radiotherapy***

Renal-cell carcinoma is considered to be radio-resistant, but it was recently found that this notion might be wrong. During Recent research De Meerleer, *et al*. (2014) found that if given in a few (even single) fractions, but at a high fraction dose, steriotactic body radiotherapy becomes increasingly important in the management of renal-cell carcinoma, both in primary settings and in treatment of oligometastatic disease.

There is an established biological rationale for the radio-sensitivity of renal-cell carcinoma to stereotactic body radiotherapy based on the ceramide pathway, which is activated only when a high dose per fraction is given. Apart from the direct effect of stereotactic body radiotherapy on renal-cell carcinoma, stereotactic body radiotherapy can also induce an abscopal effect (an abscopal effect is a phenomenon in the treatment of metastatic cancer where localised irradiation of a tumour causes not only a shrinking of the irradiated tumour but also a shrinking of tumours far from the irradiated area), This effect, caused by immunological processes, might be enhanced when targeted drugs and stereotactic body radiotherapy are combined. Therefore, rigorous, prospective randomised trials involving a multidisciplinary scientific panel are needed urgently, according to De Meerleer, *et al*.

***Second Opinion***

Before starting treatment, patients may want a second opinion about the diagnosis, stage of cancer, and treatment plan. Some people worry that the doctor will be offended if they ask for a second opinion. Usually the opposite is true. Most doctors welcome a second opinion.

If a patient gets a second opinion, the second doctor may agree with the first doctor's diagnosis and treatment plan. Or the second doctor may suggest another approach. Either way, the patient has more information and perhaps a greater sense of control. Patients can also feel more confident about the decisions they make, knowing that they have looked at all of their options.

It may take some time and effort to gather the medical records and see another doctor. In most cases, it's not a problem to take several weeks to get a second opinion. The delay in starting treatment usually will not make treatment less effective. To make sure, patients should discuss this delay with their doctor.
(National Cancer Institute).

## RENAL CELL CARCINOMA TREATMENT REGIMENS

**Clinical Trials:** The NCCN recommends cancer patient participation in clinical trials as the gold standard for treatment.

Cancer therapy selection, dosing, administration, and the management of related adverse events can be a complex process that should be handled by an experienced healthcare team. Clinicians must choose and verify treatment options based on the individual patient; drug dose modifications and supportive care interventions should be administered accordingly. The cancer treatment regimens below may include both U.S. Food and Drug Administration-approved and unapproved indications/regimens. These regimens are only provided to supplement the latest treatment strategies.

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**General treatment notes:**[1]

- Targeted therapy using tyrosine kinase inhibitors and anti-vascular endothelial growth factor antibodies is now widely used as first- and second-line treatments in renal cell carcinoma (RCC). To date, seven such agents have been approved by the FDA for the treatment of advanced RCC: axitinib, bevacizumab with or without interferon (IFN), everolimus, pazopanib, sorafinib, sunitinib, and temsirolimus.
- Prior to targeted therapies, systemic treatment options were limited to cytokine therapy, notably IL-2 and interferon-α-2A (IFN-α-2a).

## First-line Therapy for Patients with Predominantly Clear Cell Histology[1]

**Note:** All recommendations are Category 2A unless otherwise indicated.

(Revised 3/2016)


| REGIMEN | DOSING |
|---|---|
| **Sunitinib (Category 1)**[2,3] | Sunitinib 50mg orally daily with or without food for 4 weeks, followed by 2 weeks off. |
| **Temsirolimus (Category 1: poor-prognosis patients; Category 2B: selected patients of other risk groups)**[4,5] | Temsirolimus 25mg IV over 30–60 minutes once weekly until disease progression or unacceptable toxicity. |
| **Bevacizumab + IFN-α(Category 1)**[6-8] | Bevacizumab 10mg/kg IV every 2 weeks + IFN-α. |
| **Pazopanib (Category 1)**[9,10] | Pazopanib 800mg orally once daily without food. |
| **High-dose IL-2 (for selected patients with excellent performance status and normal organ function)**[11,12‡] | **Days 1–5 and 15–19:** IL-2 600,000 IU/kg IV every 8 hours (max 14 doses).<br>Repeat cycle every 4 weeks for max 3 cycles. |
| **Axitinib**[13,14*] | Axitinib 5mg orally every 12 hours. |
| **Sorafenib**[15†] | Sorafenib 400mg orally twice daily without food. |
| **Subsequent Therapy for Patients with Predominantly Clear Cell Carcinoma**[1] | |
| **High-dose IL-2**[11,12‡] | **Days 1–5 and 15–19:** IL-2 600,000 IU/kg IV every 8 hours (max 14 doses).<br>Repeat cycle every 4 weeks for max 3 cycles. |
| **After Tyrosine Kinase Inhibitor Therapy** | |
| **Axitinib (Category 1)**[13,14*] | Axitinib 5mg orally every 12 hours. |
| **Cabozantinib (Category 1)**[16§] | Cabozantinib 60mg orally once daily without food until disease progression or unacceptable toxicity. |
| **Nivolumab (Category 1)**[17,18] | Nivolumab 3mg/kg IV every 2 weeks until disease progression or unacceptable toxicity. |
| **Everolimus (Category 1)**[19,20] | Everolimus 10mg orally once daily with or without food. |
| **Sorafenib**[21-24] | Sorafenib 400mg orally twice daily without food. |
| **Sunitinib**[2,25,26] | Sunitinib 50mg orally daily with or without food for 4 weeks, followed by 2 weeks off. |
| **Pazopanib**[9,10] | Pazopanib 800mg orally once daily without food. |
| **Temsirolimus (Category 2B)**[27,28] | Temsirolimus 25mg IV over 30-60 minutes weekly until disease progression or unacceptable toxicity. |

# RENAL CELL CARCINOMA TREATMENT REGIMENS

**Clinical Trials:** The NCCN recommends cancer patient participation in clinical trials as the gold standard for treatment.

Cancer therapy selection, dosing, administration, and the management of related adverse events can be a complex process that should be handled by an experienced healthcare team. Clinicians must choose and verify treatment options based on the individual patient; drug dose modifications and supportive care interventions should be administered accordingly. The cancer treatment regimens below may include both U.S. Food and Drug Administration-approved and unapproved indications/regimens. These regimens are only provided to supplement the latest treatment strategies.

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**General treatment notes:**[1]

- Targeted therapy using tyrosine kinase inhibitors and anti-vascular endothelial growth factor antibodies is now widely used as first- and second-line treatments in renal cell carcinoma (RCC). To date, seven such agents have been approved by the FDA for the treatment of advanced RCC: axitinib, bevacizumab with or without interferon (IFN), everolimus, pazopanib, sorafinib, sunitinib, and temsirolimus.
- Prior to targeted therapies, systemic treatment options were limited to cytokine therapy, notably IL-2 and interferon-α-2A (IFN-α-2a).

| First-line Therapy for Patients with Predominantly Clear Cell Histology[1] | |
|---|---|
| **Note:** All recommendations are Category 2A unless otherwise indicated. | |
| **Bevacizumab (Category 2B)**[29] | Bevacizumab 10mg/kg IV every 2 weeks. |
| **After Cytokine Therapy** | |
| **Axitinib (Category 1)**[13,14*] | Axitinib 5mg orally every 12 hours. |
| **Sorafenib (Category 1)**[21-24] | Sorafenib 400mg orally twice daily without food. |
| **Sunitinib (Category 1)**[2,25,26] | Sunitinib 50mg orally daily with or without food for 4 weeks, followed by 2 weeks off. |
| **Pazopanib (Category 1)**[9,10] | Pazopanib 800mg orally once daily without food. |
| **Temsirolimus**[27,28] | Temsirolimus 25mg IV over 30-60 minutes weekly until disease progression or unacceptable toxicity. |
| **Bevacizumab**[29] | Bevacizumab 10mg/kg IV every 2 weeks. |

| Systemic Therapy for Patients with Non-Clear Cell Histology[1] | |
|---|---|
| **Temsirolimus (Category 1: poor-prognosis patients; Category 2A: selected patients of other risk groups)**[27,28] | Temsirolimus 25mg IV over 30–60 minutes weekly until disease progression or unacceptable toxicity. |
| **Sorafenib**[21-24] | Sorafenib 400mg orally twice daily without food. |
| **Sunitinib**[2,25,26] | Sunitinib 50mg orally daily with or without food for 4 weeks, followed by 2 weeks off. |
| **Pazopanib**[9,10] | Pazopanib 800mg orally once daily without food. |
| **Axitinib**[13,14*] | Axitinib 5mg orally every 12 hours. |
| **Everolimus**[19,20] | Everolimus 10mg orally once daily with or without food. |
| **Bevacizumab**[29] | Bevacizumab 10mg/kg IV every 2 weeks. |
| **Erlotinib**[30¶] | Erlotinib 150mg orally once daily without food. |

* May increase to 7mg every 12 hours after 2 weeks based on criteria; may increase to 10mg every 12 hours after 2 weeks

## RENAL CELL CARCINOMA TREATMENT REGIMENS

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**General treatment notes:**[1]

- Targeted therapy using tyrosine kinase inhibitors and anti-vascular endothelial growth factor antibodies is now widely used as first- and second-line treatments in renal cell carcinoma (RCC). To date, seven such agents have been approved by the FDA for the treatment of advanced RCC: axitinib, bevacizumab with or without interferon (IFN), everolimus, pazopanib, sorafinib, sunitinib, and temsirolimus.
- Prior to targeted therapies, systemic treatment options were limited to cytokine therapy, notably IL-2 and interferon-α-2A (IFN-α-2a).

### First-line Therapy for Patients with Predominantly Clear Cell Histology[1]

**Note:** All recommendations are Category 2A unless otherwise indicated.

based on criteria.

† Patients who progressed were dose-escalated to 600 mg twice daily.

‡ Treatments divided into 60-day courses, with each IV treatment course consisting of 2 cycles of therapy, separated by approximately 7–10 days of rest with no other therapy during the remainder of the 60 days.

§ Cabozantinib has not yet been approved by the FDA in RCC, but it received breakthrough designation for this indication in August 2015. The NCCN recommendation is based on data from phase III trials, which suggest that eligible patients should preferentially receive cabozantinib over everolimus.

¶ Erlotinib is used off-label for RCC. The NCCN guidelines include it as an optional first-line therapy for patients with relapsed or medically unresectable stage IV non-clear cell carcinoma.

(Cancer Therapy Advisor).

**Side Effects of Treatment**

Because treatment may damage healthy cells and tissues, unwanted side effects are common. These side effects depend mainly on the type and extent of the treatment. Side effects may not be the same for each person, and they may change from one treatment session to the next. Before treatment starts, the health care team will explain possible side effects and suggest ways to help the patient manage them.

*Surgery* - It takes time to heal after surgery, and the time needed to recover is different for each person. Patients are often uncomfortable during the first few days. However, medicine can usually control their pain. Before surgery, patients should discuss the plan for pain relief with the doctor or nurse. After surgery, the doctor can adjust the plan if more pain relief is needed.

It is common to feel tired or weak for a while. The health care team watches the patient for signs of kidney problems by monitoring the amount of fluid the patient takes in and the amount of urine produced. They also watch for signs of bleeding, infection, or other problems requiring immediate treatment. Lab tests help the health care team monitor for signs of problems.

If one kidney is removed, the remaining kidney generally is able to perform the work of both kidneys. However, if the remaining kidney is not working well or if both kidneys are removed, dialysis is needed to clean the blood. For a few patients, kidney transplantation may be an option. For this procedure, the transplant surgeon replaces the patient's kidney with a healthy kidney from a donor.

*Arterial Embolisation* - After arterial embolization, some patients have back pain or develop a fever. Other side effects are nausea and vomiting. These problems soon go away.

*Radiation Therapy* - The side effects of radiation therapy depend mainly on the amount of radiation given and the part of the body that is treated. Patients are likely to become very tired during radiation therapy, especially in the later weeks of treatment. Resting is important, but doctors usually advise patients to try to stay as active as they can.

Radiation therapy to the kidney and nearby areas may cause nausea, vomiting, diarrhoea, or urinary discomfort. Radiation therapy also may cause a decrease in the number of healthy white blood cells, which help protect the body against infection. In addition, the skin in the treated area may sometimes become red, dry, and tender. Although the side effects of radiation therapy can be distressing, the doctor can usually treat or control them.

*Biological Therapy* - Biological therapy may cause flu-like symptoms, such as chills, fever, muscle aches, weakness, loss of appetite, nausea, vomiting, and diarrhoea. Patients also may get a skin rash. These problems can be severe, but they go away after treatment stops.

*Chemotherapy* - Kidney cancer does not respond well to chemotherapy drugs.

The side effects of chemotherapy depend mainly on the specific drugs and the amount received at one time. In general anticancer drugs affect cells that divide rapidly, especially:

*Blood cells*: These cells fight infection, help the blood to clot, and carry oxygen to all parts of the body. When drugs affect blood cells, patients are more likely to get infections, may bruise or bleed easily, and may feel very weak and tired.

*Cells in hair roots*: Chemotherapy can cause hair loss. The hair grows back, but sometimes the new hair is somewhat different in colour and texture.

*Cells that line the digestive tract*: Chemotherapy can cause poor appetite, nausea and vomiting, diarrhoea, or mouth and lip sores. Many of these side effects can be controlled with drugs (Rosswell Park Cancer Institute).

**Reducing the Risk for Kidney Cancer**

Taking steps to improve one's health may help reduce the risk of kidney cancer. To reduce the risk:

- Quit smoking. If smoking, quit. Many options for quitting exist, including support programs, medications and nicotine replacement products. Contact CANSA to join CANSA's e-KickButt programme
- Eat at least five portions of vegetables and fresh fruit (in season). A variety of fruits and vegetables helps ensure getting all the nutrients one needs. Replace some snacks and side dishes with fruits and vegetables – this may help one lose weight as well
- Maintain a healthy weight. Work to maintain a healthy weight. If overweight or obese, reduce the number of calories consumed each day and try to exercise most days of the week
- Control high blood pressure
- Reduce or avoid exposure to environmental toxins (Mayo Clinic).

**Complications of Kidney Cancer**

Complications that have been mentioned in various sources for Kidney Cancer includes:

- Metastases (cancer that has spread) to:
  - Lungs
  - Bones
  - Brain
- Paraneoplastic syndrome
- Blood clots
- Congestive heart failure
- Polycythaemia
- Pyrexia (fever) of unknown origin
- AA amyloidosis
- Renal cysts
- Malignant hepatopathy
- Haematuria
- Cutaneous metastasis
- Renal enlargement

(Right Diagnosis).

**Follow-up Care**

After surgery for early or locally advanced kidney cancer, the patient will have regular check-ups. The first appointment is usually 4 to 6 weeks after going home from hospital. This is to make sure the patient is recovering well from the operation. After this, if the risk of cancer coming back is thought to be low, they patient may only need follow up for 5 years. They might have a chest X-ray every 3 months for the first 2 years, and then every 6 months until they reach 5 years.

If the risk of cancer coming back is higher patients are usually ordered to undergo regular CT scans for the first 3 years. Things that increase the risk of the cancer coming back include:

- Having a tumour larger than 5cm across
- Changes in the tumour cells called sarcomatoid de-differentiation
- Tumour cells at the edge of the tissue that the surgeon removed – doctors call this a positive margin
- Raised levels in the blood of a chemical called alkaline phosphatase
- Raised levels in the blood of a chemical called lactate dehydrogenase

If all is well after 3 years, the patient is advised to have X-rays every 6 months. But this follow up may continue for life to check for any sign of the cancer coming back.

After surgery for kidney cancer, the more time that passes with no sign of it, the smaller the risk of the cancer ever coming back. But there is still a small risk, even after 10 years.

***What happens at follow-up appointments***

The treating doctor will conduct a physical examination and may order one or more of the following tests

- Blood tests
- Chest X-ray
- CT scan
- Ultrasound scan

***Follow-up after cryotherapy or radiofrequency ablation***

In the event of a small kidney cancer treated by cryotherapy or radiofrequency ablation, the patient will be advised to attend appointments and scans every 3 to 6 months. These are to see whether the cancer has come back or is growing.

***Appointments during biological therapy treatment for advanced kidney cancer***

In the case of advanced cancer and while on treatment with biological therapy, the patient will be advised to attend regular appointments and scans every 3 to 6 months. The scans check how well the treatment is working.

***Between appointments***

Patients who have any concerns or who are worried or notice any new symptoms between appointments, must contact their doctor as soon as possible (CancerHelp UK).

**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.

Types of Clinical Trials

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).

**Medical Disclaimer**

This Fact Sheet is intended to provide general information only and, as such, should not be considered as a substitute for advice, medically or otherwise, covering any specific situation. Users should seek appropriate advice before taking or refraining from taking any action in reliance on any information contained in this Fact Sheet. So far as permissible by law, the Cancer Association of South Africa (CANSA) does not accept any liability to any person (or his/her dependants/estate/heirs) relating to the use of any information contained in this Fact Sheet.

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