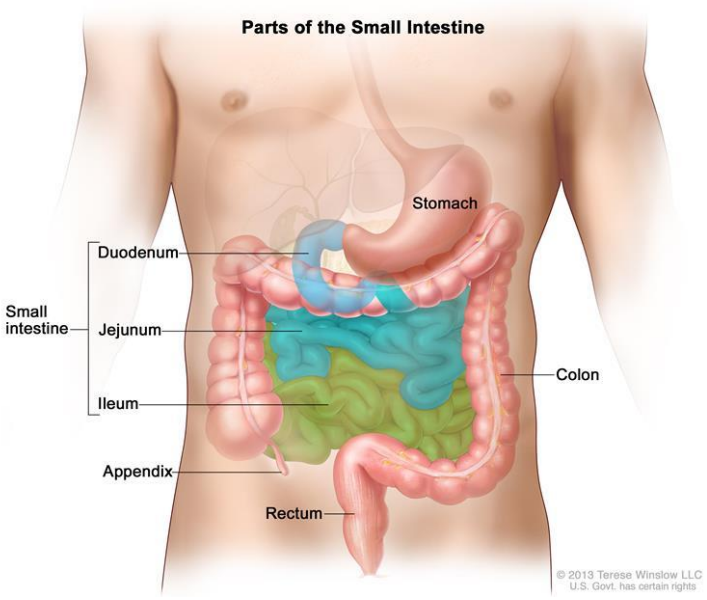
Cancer Association of South Africa (CANSA)

Research • Educate • Support

Fact Sheet
on
Cancer of the Small Intestine

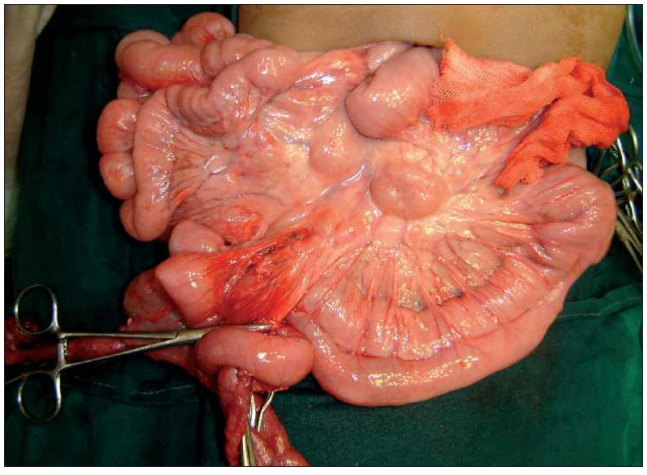
Introduction

The small intestine is a long, highly convoluted tube in the digestive system that absorbs about 90% of the nutrients from the food that is consumed. It is given the name “small intestine” because it is only about 2,5cm in diameter, making it less than half the diameter of the large intestine. The small intestine is, however, more than twice the length of the large intestine and usually measures about 6 metres in length.



[Picture Credit: Small Intestine]

The small intestine winds throughout the abdominal cavity inferior to the stomach. Its many folds help it to pack all of its length into such a small body cavity.



A thin membrane known as the mesentery extends from the posterior body wall of the abdominal cavity to surround the small intestine and anchor it in place. Blood vessels, nerves, and lymphatic vessels pass through the mesentery to support the tissues of the small intestine and transport nutrients from food in the intestines to the rest of the body.

[Picture Credit: Mesentery]

The small intestine can be divided into 3 major regions:

- The **duodenum** is the first section of intestine that connects to the pyloric sphincter of the stomach. It is the shortest region of the small intestine, measuring only about

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25cm in length. Partially digested food, or *chyme*, from the stomach is mixed with bile from the liver and pancreatic juice from the pancreas to complete its digestion in the duodenum.

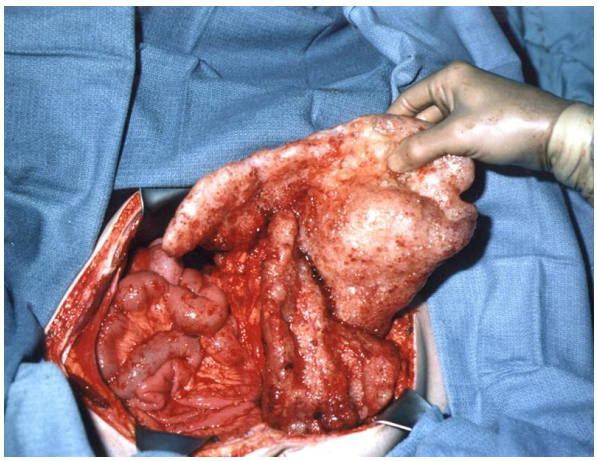
- The **jejunum** is the middle section of the small intestine that serves as the primary site of nutrient absorption. It measures around 1 metre in length.

- The **ileum** is the final section of the small intestine that empties into the large intestine via the ileocecal sphincter. The ileum makes up the rest of the small intestine and completes the absorption of nutrients that were missed in the jejunum.

(InnerBody).

Cancer of the Small Intestine

The small intestine is part of the body's digestive system, which also includes the oesophagus, stomach, and large intestine (colon). Small intestine cancer is a rare disease in which malignant (cancer) cells form in the tissues of the small intestine.



[Picture Credit: Small Intestine Cancer]

The digestive system removes and processes nutrients (vitamins, minerals, carbohydrates, fats, proteins, and water) from foods and helps pass waste material out of the body. The small intestine is a long tube that connects the stomach to the large intestine. It folds many times to fit inside the abdominal cavity.

The types of cancer found in the small intestine are adenocarcinoma, sarcoma, carcinoid tumours, gastrointestinal stromal tumour, and lymphoma.
(National Cancer Institute).

Incidence of Cancer of the Small Intestine in South Africa

According to the National Cancer Registry (2012) the following number of small intestine 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	78	1:1 924	0,21%
Asian males	3	1:3 742	0,50%
Black males	30	1:3 155	0,26%
Coloured males	15	1:1 099	0,35%
White males	29	1:997	0,15%

Group - Females 2012	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	62	1:3 391	0,16%
Asian females	2	1:2 634	0,20%
Black females	30	1:5 107	0,18%
Coloured females	7	1:2 651	0,18%
White females	22	1:1 678	0,14%

The frequency of histologically diagnosed cases of small intestine 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	0	1	6	11	19	22	12	2
Asian males	0	0	0	1	1	0	1	0
Black males	0	0	2	2	10	7	2	1
Coloured males	0	0	2	3	3	3	2	0
White males	0	0	1	2	4	12	7	0

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	0	1	3	7	13	15	16	7
Asian females	0	0	0	1	0	1	0	0
Black females	0	1	1	5	8	7	3	0
Coloured females	0	0	0	0	2	1	4	0
White females	0	0	2	1	2	4	8	4

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.

Signs and Symptoms of Cancer of the Small Intestine

One should see one's doctor if one notices any of the following signs, which could be caused by small intestine cancer or sometimes something else:

- Pain or cramps in the middle of the abdomen
- Losing weight for no known reason
- Weakness or fatigue (sometimes as a result of anaemia)
- A noticeable lump in the abdomen
- Blood or tarry stools (from bleeding tumours)

Abdominal pain accompanied by nausea and vomiting may be signs of an intestinal obstruction. In this case, one may require immediate medical attention. Often, surgery is necessary to remove the blockage. In rare cases, the tumour may cause a perforation in the intestinal wall, causing the contents to spill out into the abdominal cavity. This, too, will cause severe pain and vomiting.

Small intestine cancer symptoms may be signs of other conditions or gastrointestinal diseases. Often, however, small tumours may not cause any apparent symptoms. Sometimes the cancer may be found by chance during another unrelated procedure or surgery.

Slow growing types of cancer, like carcinoid tumours, may take years to find and diagnose. (WebMD; Cancer Treatment Centers of America).

Risk Factors for Cancer of the Small Intestine
Malignant small intestine tumours occur in a small number relative to the frequency of tumours in other parts of the GI tract.

There are many suggested reasons for this:

- It has been proposed that the liquid nature of the small intestinal contents may be less irritating to the mucosa, the innermost lining of the small bowel.

- Rapid transit time in the small bowel may reduce exposure of the intestinal wall to cancer-inducing agents found in the intestinal contents.

- Other factors that might limit the presence or impact of potential cancer-inducing agents include the following:

    - A low bacterial count
    - A large lymphoid tissue component in the wall of the small intestine
    - An alkaline pH inside the small intestine
    - The presence of the enzyme benzpyrene hydroxylase which protects the body against polycyclic hydrocarbons (a known carcinogen) that may be present in the gut content

- Adenocarcinoma of the small bowel is associated with the following underlying conditions:

    - Crohn's disease - An inflammatory disease of the small intestine. Crohn disease usually occurs in the lower part of the small intestine, called the ileum. The inflammation extends deep into the lining of the affected organ, causing pain and making the intestines empty frequently, resulting in diarrhoea.
    - Celiac disease – Gluten intolerance
    - Familial polyposis syndromes - A group of inherited diseases in which small growths develop in the intestinal tract. In the case of familial adenomatous polyposis, while most polyps and later cancers appear in the large intestine, cancers arising in the small intestine do occur and are often found at the beginning of the small intestine in the duodenum.

- Cancer is more common in the large bowel than in the small bowel. Risk factors in the general population for small intestine cancer include the following:

    - Alcohol abuse
    - Consumption of salted or smoked meats and fish
    - Heavy sugar intake

- Risk factors for developing cancer of the small intestine in Crohn's disease include the following:

    - Male sex
    - Long duration of disease
    - Associated fistulous disease: A fistula is an abnormal connection that passes from one surface to another, such as from the colon to the skin.
    - Surgical removal of part of the bowel

- The risk of developing small intestinal cancer is 6 times greater for people with Crohn disease compared to the general population.

- Lymphoma of the small intestine is associated with celiac disease but is also strongly associated with weakened immune systems such as occurs with Aids.

(eMedicineHealth).

Diagnosis of Small Intestine Cancer

Procedures that make pictures of the small intestine and the area around it help diagnose small intestine cancer and show how far the cancer has spread. The process used to find out if cancer cells have spread within and around the small intestine is called staging.

In order to plan treatment, it is important to know the type of small intestine cancer and whether the tumour can be removed by surgery. Tests and procedures to detect, diagnose, and stage small intestine cancer are usually done at the same time. The following tests and procedures may be used:

- **Physical examination and history**: An exam of the body to check general signs of health, including checking for signs of disease, such as lumps or anything else that seems unusual. A history of the patient's health habits and past illnesses and treatments will also be taken.
- **Blood chemistry studies**: A procedure in which a blood sample is checked to measure the amounts of certain substances released into the blood by organs and tissues in the body. An unusual (higher or lower than normal) amount of a substance can be a sign of disease.
- **Liver function test**: A procedure in which a blood sample is checked to measure the amounts of certain substances released into the blood by the liver. A higher than normal amount of a substance can be a sign of liver disease that may be caused by small intestine cancer.
- **Endoscopy**: A procedure to look at organs and tissues inside the body to check for abnormal areas. There are different types of endoscopy:
    - **Upper endoscopy**: A procedure to look at the inside of the oesophagus, stomach, and duodenum (first part of the small intestine, near the stomach). An endoscope is inserted through the mouth and into the oesophagus, stomach, and duodenum. An endoscope is a thin, tube-like instrument with a light and a lens for viewing. It may also have a tool to remove tissue samples, which are checked under a microscope for signs of cancer.
    - **Capsule endoscopy**: A procedure to look at the inside of the small intestine. A capsule that is about the size of a large pill and contains a light and a tiny wireless camera is swallowed by the patient. The capsule travels through the digestive tract, including the small intestine, and sends many pictures of the inside of the digestive tract to a recorder that is worn around the waist or over the shoulder. The pictures are sent from the recorder to a computer and viewed by the doctor who checks for signs of cancer. The capsule passes out of the body during a bowel movement.
    - **Double balloon endoscopy**: A procedure to look at the inside of the small intestine. A special instrument made up of two tubes (one inside the other) is inserted through the mouth or rectum and into the small intestine. The inside tube (an endoscope with a light and lens for viewing) is moved through part of the small intestine and a balloon at the end of it is inflated to keep the endoscope in place. Next, the outer tube is moved through the small intestine to reach the end of the endoscope, and a balloon at the end of the outer tube is inflated to keep it in place.

Then, the balloon at the end of the endoscope is deflated and the endoscope is moved through the next part of the small intestine. These steps are repeated many times as the tubes move through the small intestine. The doctor is able to see the inside of the small intestine through the endoscope and use a tool to remove samples of abnormal tissue. The tissue samples are checked under a microscope for signs of cancer. This procedure may be done if the results of a capsule endoscopy are abnormal. This procedure is also called double balloon enteroscopy.

- **Laparotomy**: A surgical procedure in which an incision (cut) is made in the wall of the abdomen to check the inside of the abdomen for signs of disease. The size of the incision depends on the reason the laparotomy is being done. Sometimes organs or lymph nodes are removed or tissue samples are taken and checked under a microscope for signs of disease.
- **Biopsy**: The removal of cells or tissues so they can be viewed under a microscope to check for signs of cancer. This may be done during an endoscopy or laparotomy. The sample is checked by a pathologist to see if it contains cancer cells.
- **Upper GI series with small bowel follow-through**: A series of X-rays of the oesophagus, stomach, and small bowel. The patient drinks a liquid that contains barium (a silver-white metallic compound). The liquid coats the oesophagus, stomach, and small bowel. X-rays are taken at different times as the barium travels through the upper GI tract and small bowel.
- **CT scan (CAT scan)**: A procedure that makes a series of detailed pictures of areas inside the body, taken from different angles. The pictures are made by a computer linked to an x-ray machine. A dye may be injected into a vein or swallowed to help the organs or tissues show up more clearly. This procedure is also called computed tomography, computerized tomography, or computerized axial tomography.
- **MRI (magnetic resonance imaging)**: A procedure that uses a magnet, radio waves, and a computer to make a series of detailed pictures of areas inside the body. This procedure is also called nuclear magnetic resonance imaging (NMRI).

(National Cancer Institute).

Staging of Cancer of the Small Intestine

Staging is a way of describing where the cancer is located, if or where it has spread, and whether it is affecting other parts of the body. Doctors use diagnostic tests to find out the cancer's stage, so staging may not be complete until all the tests are finished. Knowing the stage helps the doctor to decide what kind of treatment is best and can help predict a patient's prognosis, which is the chance of recovery. There are different stage descriptions for different types of cancers.

<u>TNM staging system</u>

One tool that doctors use to describe the stage is the TNM system. Doctors use the results from diagnostic tests and scans to answer these questions:

- **Tumour (T)**: How large is the primary tumour? Where is it located?
- **Node (N)**: Has the tumour spread to the lymph nodes? If so, where and how many?
- **Metastasis (M)**: Has the cancer metastasized to other parts of the body? If so, where and how much?

The results are combined to determine the stage of cancer for each person. There are five stages: stage 0 (zero) and stages I through IV (one through four). The stage provides a

common way of describing the cancer, so doctors can work together to plan the best treatments.

Tumour (**T**)
Using the TNM system, the "T" plus a letter or number (0 to 4) is used to describe the location of the small bowel tumour. Some stages are also divided into smaller groups that help describe the tumour even in more detail. This helps the doctor develop the best treatment plan for each patient. Specific tumour stage information is listed below.

TX: The primary tumour cannot be evaluated.
T0: There is no evidence of a primary tumour.
Tis: This refers to carcinoma (cancer) in situ. Cancer in situ is very early cancer in which cancer cells are found only in 1 small area and have not spread.
T1a: There is a tumour in the lamina propria, the innermost layer of the small bowel.
T1b: There is a tumour in the submucosa, the next deepest layer of the small bowel.
T2: The tumour is in the muscularis propria, the third layer of the small bowel.
T3: The tumour has grown through the muscularis propria and into the subserosa, a thin layer of connective tissue beneath the outer layer of some parts of the large intestine, or into tissues surrounding the small bowel.
T4: The tumour has invaded other organs or has grown through the lining of the abdominal cavity, the space between the abdomen and the spine that holds several organs, called the visceral peritoneum.

Node (**N**)
The “N” in the TNM staging system stands for lymph nodes, the tiny, bean-shaped organs that help fight infection. Lymph nodes near the small bowel are called regional lymph nodes. Lymph nodes in other parts of the body are called distant lymph nodes.

NX: The regional lymph nodes cannot be evaluated.
N0 (N plus zero): There is no regional lymph node metastasis.
N1: Cancer has spread to 1 to 3 regional lymph nodes.
N2: Cancer has spread to 4 to 6 regional lymph nodes.
N3: Cancer has spread to 7 or more regional lymph nodes.

Metastasis (**M**)
The “M” in the TNM system indicates whether the cancer has spread to other parts of the body, called distant metastasis.

MX: Distant metastasis cannot be evaluated.
M0: The disease has not metastasized.
M1: There is distant metastasis, meaning the cancer has spread to other parts of the body beyond the small bowel.

Cancer stage grouping for small bowel adenocarcinoma
Doctors assign the stage of the cancer by combining the T, N, and M classifications.

Stage 0: This refers to cancer in situ. The cancer is found in only 1 place and has not spread (Tis, N0, M0).
Stage I: The cancer has grown through the inner layers of the small bowel. It has not spread into nearby tissue or lymph nodes (T1 or T2, N0, M0).

Stage IIA: The cancer has spread through the wall of the small bowel, and it may have spread to nearby tissue. It has not spread to the nearby lymph nodes (T3, N0, M0).
Stage IIB: The cancer has invaded nearby structures outside of the small bowel, but it has not spread to the nearby lymph nodes (T4, N0, M0).
Stage IIIA: The cancer has spread to 1 to 3 regional lymph nodes. It may or may not have grown through the inner lining or into the muscle layers of the small bowel, but it has not spread to other parts of the body (any T, N1, M0).
Stage IIIB: The cancer has spread to 4 or more regional lymph nodes. It may or may not have grown through the inner lining or into the muscle layers of the small bowel, but it has not spread to other parts of the body (any T, N2, M0).
Stage IV: The cancer has spread to other parts of the body, such as the liver or lungs (any T, any N, M1).

Recurrent: Recurrent cancer is cancer that has come back after treatment. The disease may return in the colon, rectum, or another part of the body. If the cancer does return, there will be another round of tests to learn about the extent of the recurrence. These tests and scans are often similar to those done at the time of the original diagnosis.

Grade (**G**)
Doctors also describe this type of cancer by its grade (G), which describes how much cancer cells look like healthy cells when viewed under a microscope. The doctor compares the cancerous tissue with healthy tissue. Healthy tissue usually contains many different types of cells grouped together. If the cancer looks similar to healthy tissue and contains different cell groupings, it is called differentiated or a low-grade tumour. If the cancerous tissue looks very different from healthy tissue, it is called poorly differentiated or a high-grade tumour. The cancer's grade may help the doctor predict how quickly the cancer will spread. In general, the lower the tumour's grade, the better the prognosis.

GX: The tumour grade cannot be identified.
G1: The cells look more like normal tissue cells (well differentiated).
G2: The cells are somewhat different (moderately differentiated).
G3: The cells look very unlike normal cells (poorly differentiated).
G4: The cells barely resemble normal cells (undifferentiated).
(Cancer.Net).

Treatment of Cancer of the Small Intestine
Different types of treatments are available for patients with cancer of the small intestine. Some treatments are standard (the currently used treatment), and some are being tested in clinical trials. A treatment clinical trial is a research study meant to help improve current treatments or obtain information on new treatments for patients with cancer. When clinical trials show that a new treatment is better than the standard treatment, the new treatment may become the standard treatment. Patients may want to think about taking part in a clinical trial. Some clinical trials are open only to patients who have not started treatment.

Three types of standard treatment are used:

Surgery - surgery is the most common treatment of small intestine cancer. One of the following types of surgery may be done:

- Resection: Surgery to remove part or all of an organ that contains cancer. The resection may include the small intestine and nearby organs (if the cancer has spread). The doctor may remove the section of the small intestine that contains cancer and perform an anastomosis (joining the cut ends of the intestine together). The doctor will usually remove lymph nodes near the small intestine and examine them under a microscope to see whether they contain cancer.
- Bypass: Surgery to allow food in the small intestine to go around (bypass) a tumour that is blocking the intestine but cannot be removed.

Even if the doctor removes all the cancer that can be seen at the time of the surgery, some patients may be given radiation therapy after surgery to kill any cancer cells that are left. Treatment given after the surgery, to lower the risk that the cancer will come back, is called adjuvant therapy.

Radiation therapy - radiation therapy is a cancer treatment that uses high-energy X-rays or other types of radiation to kill cancer cells or keep them from growing. There are two types of radiation therapy. External radiation therapy uses a machine outside the body to send radiation toward the cancer. Internal radiation therapy uses a radioactive substance sealed in needles, seeds, wires, or catheters that are placed directly into or near the cancer. The way the radiation therapy is given depends on the type and stage of the cancer being treated.

Chemotherapy - chemotherapy is a cancer treatment that uses drugs to stop the growth of cancer cells, either by killing the cells or by stopping them from dividing. When chemotherapy is taken by mouth or injected into a vein or muscle, the drugs enter the bloodstream and can reach cancer cells throughout the body (systemic chemotherapy). When chemotherapy is placed directly into the spinal column, an organ, or a body cavity such as the abdomen, the drugs mainly affect cancer cells in those areas (regional chemotherapy). The way the chemotherapy is given depends on the type and stage of the cancer being treated.

New types of treatment are being tested in clinical trials - below describes treatments that are being studied in clinical trials. It may not mention every new treatment being studied. Information about clinical trials is available from the NCI Web site.

Biologic therapy - biologic therapy is a treatment that uses the patient's immune system to fight cancer. Substances made by the body or made in a laboratory are used to boost, direct, or restore the body's natural defenses against cancer. This type of cancer treatment is also called biotherapy or immunotherapy.

Radiation therapy with radiosensitizers - radiosensitizers are drugs that make tumour cells more sensitive to radiation therapy. Combining radiation therapy with radiosensitizers may kill more tumour cells.

Patients may want to think about taking part in a clinical trial - for some patients, taking part in a clinical trial may be the best treatment choice. Clinical trials are part of the cancer

research process. Clinical trials are done to find out if new cancer treatments are safe and effective or better than the standard treatment.

Many of today's standard treatments for cancer are based on earlier clinical trials. Patients who take part in a clinical trial may receive the standard treatment or be among the first to receive a new treatment.

Patients who take part in clinical trials also help improve the way cancer will be treated in the future. Even when clinical trials do not lead to effective new treatments, they often answer important questions and help move research forward.

Follow-up tests may be needed - some of the tests that were done to diagnose the cancer or to find out the stage of the cancer may be repeated. Some tests will be repeated in order to see how well the treatment is working. Decisions about whether to continue, change, or stop treatment may be based on the results of these tests. This is sometimes called re-staging.

Some of the tests will continue to be done from time to time after treatment has ended. The results of these tests can show if your condition has changed or if the cancer has recurred (come back). These tests are sometimes called follow-up tests or check-ups.

Treatment Options for Small Intestine Cancer

For some types or stages of cancer, there may not be any trials listed. Check with your doctor for clinical trials that are not listed here but may be right for you.

Small Intestine Adenocarcinoma - when possible, treatment of small intestine adenocarcinoma will be surgery to remove the tumour and some of the normal tissue around it.

Treatment of small intestine adenocarcinoma that cannot be removed by surgery may include the following:

- Surgery to bypass the tumour.
- Radiation therapy as palliative therapy to relieve symptoms and improve the patient's quality of life.
- A clinical trial of radiation therapy with radiosensitizers, with or without chemotherapy.
- A clinical trial of new anticancer drugs.
- A clinical trial of biologic therapy.

Small Intestine Leiomyosarcoma - when possible, treatment of small intestine leiomyosarcoma will be surgery to remove the tumour and some of the normal tissue around it.

Treatment of small intestine leiomyosarcoma that cannot be removed by surgery may include the following:

- Surgery (to bypass the tumour) and radiation therapy.
- Surgery, radiation therapy, or chemotherapy as palliative therapy to relieve symptoms and improve the patient's quality of life.
- A clinical trial of new anticancer drugs.

- A clinical trial of biologic therapy.

Recurrent Small Intestine Cancer - treatment of recurrent small intestine cancer that has spread to other parts of the body is usually a clinical trial of new anticancer drugs or biologic therapy.

Treatment of locally recurrent small intestine cancer may include the following:

- Surgery
- Radiation therapy or chemotherapy as palliative therapy to relieve symptoms and improve the patient's quality of life.
- A clinical trial of radiation therapy with radiosensitizers, with or without chemotherapy

(Cleveland Clinic).

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.

<u>Use of Placebos</u>

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 condition or situation. Readers of this document should seek appropriate medical advice prior to taking or refraining from taking any action resulting from the contents of this Fact Sheet. As far as permissible by South African law, the Cancer Association of South Africa (CASNA) accepts no responsibility or liability to any person (or his/her dependants/estate/heirs) as a result of using any information contained in this Fact Sheet.

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