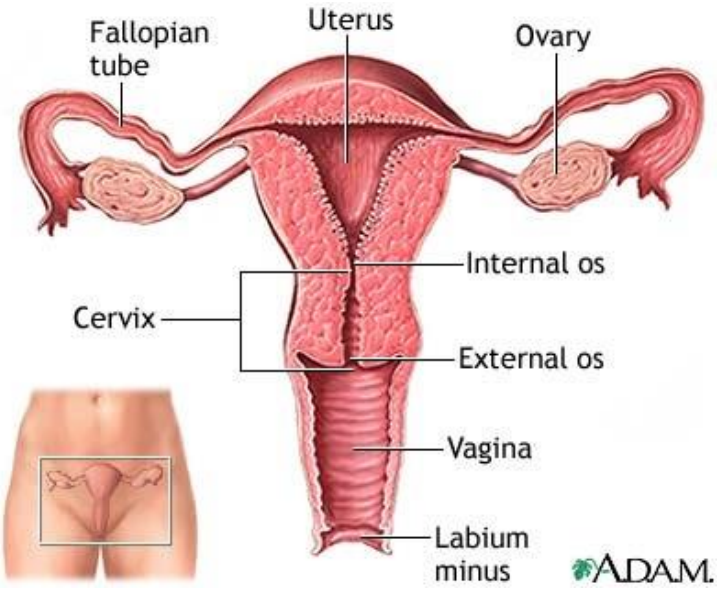
Cancer Association of South Africa (CANSA)

Research • Educate • Support

Fact Sheet on Cancer of the Uterus

Introduction

The uterus (from Latin 'uterus', plural *uteri*) or womb is a major female hormone-responsive reproductive sex organ of most mammals including humans.



[Picture Credit: Uterus]

In humans one end of the cervix opens into the vagina, while the other is connected to one or both fallopian tubes. The foetus develops completely within the uterus during gestation. Humans and other higher primates such as chimpanzees, along with horses, usually have a single completely fused uterus. In English, the term *uterus* is used consistently within the medical and related professions, while the Germanic-derived term *womb* is more common in everyday usage.

Cancer of the Uterus

In this Fact Sheet cancer of the uterus will refer to endometrial cancer or uterine cancer unless indicated otherwise. Endometrial cancer is a disease in which malignant (cancer) cells form in the tissues of the endometrium. The endometrium is the lining of the uterus, the hollow, muscular organ in a woman's pelvis. Cancer of the endometrium is different from cancer of the muscle of the uterus, which is called sarcoma of the uterus.

Cancer is a disease in which cells in the body grow out of control. Cancer is always named for the part of the body where it starts, even if it spreads to other body parts later. When cancer starts in the uterus, it is called uterine cancer. The uterus is the pear-shaped organ in a woman's pelvis (the area below your stomach and in between your hip bones). The uterus, also called the womb, is where the baby grows when a woman is pregnant. The most common type of uterine cancer is also called endometrial cancer because it forms in the lining of the uterus, called the endometrium.

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When uterine cancer is found early, treatment is most effective.
(Centers for Disease Control and Prevention).

Incidence of Cancer of the Uterus in South Africa

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

Group - Females 2012	No of Cases	Lifetime Risk	Percentage of All Cancers
All females	1 199	1:147	3,10%
Asian females	74	1:76	6,85%
Black females	714	1:160	4,32%
Coloured females	129	1:125	3,09%
White females	282	1:130	1,77%

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

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	2	7	15	55	206	425	333	141
Asian females	0	2	1	6	15	28	12	6
Black females	2	4	7	21	93	258	200	83
Coloured females	0	0	1	3	32	40	34	13
White females	0	0	5	25	60	85	66	28

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.

Causes of Cancer of the Uterus

Doctors don't know what causes endometrial cancer. What's known is that something occurs to create a genetic mutation within cells in the endometrium — the lining of the uterus.

The genetic mutation turns normal, healthy cells into abnormal cells. Healthy cells grow and multiply at a set rate, eventually dying at a set time. Abnormal cells grow and multiply out of control, and they don't die at a set time. The accumulating abnormal cells form a mass (tumour). Cancer cells invade nearby tissues and can separate from an initial tumour to spread elsewhere in the body (Mayo Clinic).

Although the exact cause of endometrial cancer is unknown, increased levels of estrogen appear to play a role. Estrogen helps stimulate the buildup of the lining of the uterus. Studies have shown that high levels of estrogen in animals result in excessive endometrial growth and cancer.

Most cases of endometrial cancer occur between the ages of 60 and 70 years, but a few cases may occur before age 40.

The following increases the risk of endometrial cancer:

- diabetes
- oestrogen replacement therapy without the use of progesterone

- history of endometrial polyps
- infertility (inability to become pregnant)
- infrequent periods
- Tamoxifen, a drug for breast cancer treatment
- never being pregnant
- obesity
- polycystic ovarian syndrome (PCOS)
- starting menstruation at an early age (before age 12)
- starting menopause after age 50

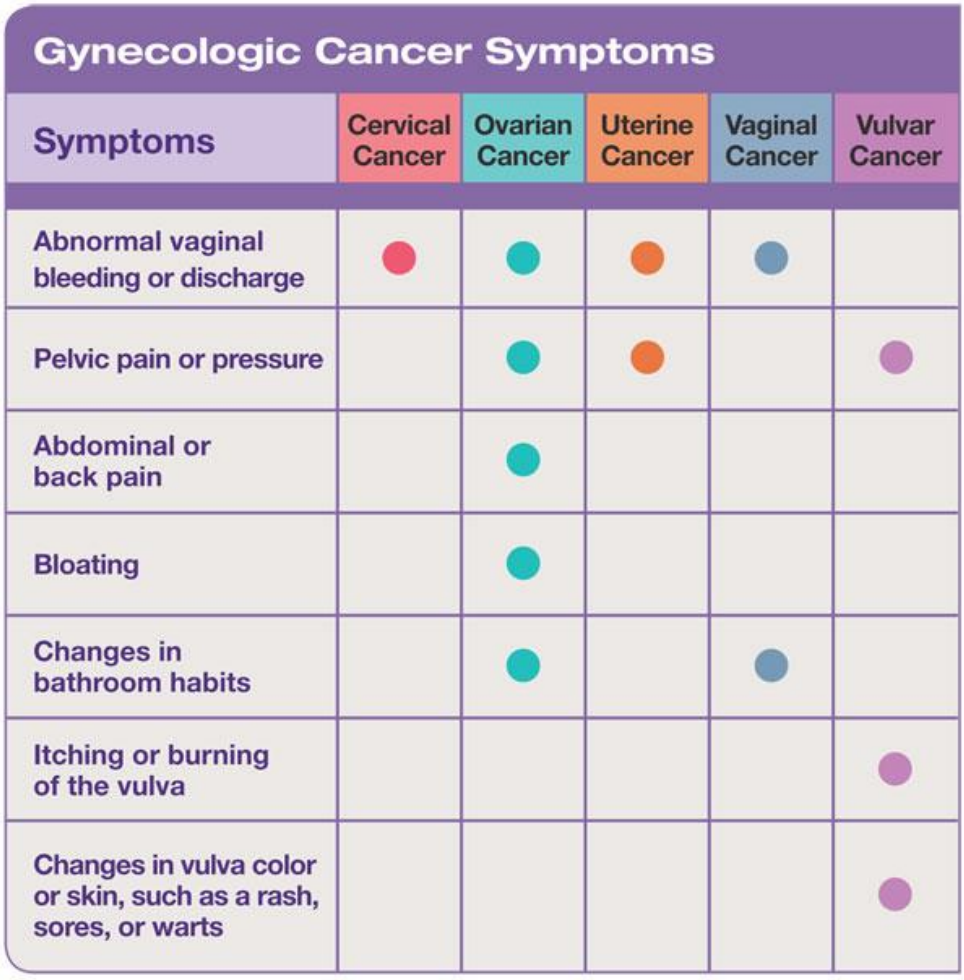
Associated conditions include the following:

- colon or breast cancer
- gallbladder disease
- high blood pressure
- polycystic ovarian disease

(PubMed Health).

Sign and Symptoms of Cancer of the Uterus

Cancer of the uterus may cause abnormal vaginal discharge or bleeding. Abnormal bleeding is mostly associated with high volumes or when it happens, such as after someone has gone through menopause, between periods, or any other bleeding that is longer or heavier than is normal. It may also cause other symptoms, such as pain or a feeling of pressure in the pelvis (Centers for Disease Control and Prevention)



Diagnosis of Cancer of the Uterus
If a doctor suspects that someone may have cancer of the uterus, the first step will be to do a biopsy. The doctor will decide the best way to do the biopsy. Methods include:

Endometrial biopsy: A thin, flexible tube is inserted through the cervix and into the uterus. Using suction, a small amount of tissue is removed through the tube.

Dilation and curettage (D&C): If an endometrial biopsy does not provide enough tissue or if a uterine cancer diagnosis is not definite, a D&C may be done. The cervix is dilated (enlarged) with a series of increasingly larger metal rods. A tool called a curette then is used to take cells from the uterus lining.

Hysteroscopy**:** A thin, telescope-like device with a light (hysteroscope) is put into the uterus through the vagina. The doctor then looks at the uterus and the openings to the fallopian tubes. Small pieces of tissue can be removed. Hysteroscopy may be done with a D&C.
One or more of the following tests may be used to find out if you have uterine cancer and if it has spread. These tests also may be used to find out if treatment is working.

Surgery, which may include:
- hysterectomy: removal of the uterus
- bilateral salpingo-oophorectomy: removal of the uterus, ovaries and Fallopian tubes
- lymph node dissection: removal of lymph nodes in the pelvis and lower abdomen

Imaging tests, which may include:
- ultrasound
- computed axial tomography scans (CT or CAT)
- magnetic resonance imaging scans (MRI)
- positron emission tomography scans (PET)
- chest X-ray
- transvaginal ultrasound exam

  Transvaginal ultrasound is a procedure used to examine the vagina, uterus, fallopian tubes and bladder. An ultrasound transducer (probe) is inserted into the vagina and used to bounce high-energy sound waves (ultrasound) off internal tissues or organs and make echoes. The echoes form a picture of body tissues called a sonogram. The doctor can identify tumours by looking at the sonogram.

Blood tests, which may include:
- complete blood count (CBC) – also known as full blood count (FBC)
- CA 125: Uterine cancers sometimes release this substance into the blood.

  CA 125 test measures levels of CA 125. High levels of CA 125 may indicate that the cancer has spread beyond the uterus or come back after treatment (MD Anderson Cancer Centre; National Cancer Institute).

Staging of Cancer of the Uterus
Knowing the stage helps the doctor to decide what kind of treatment is best and can help predict a woman's prognosis (chance of recovery). There are different stage descriptions for different types of cancer.

The stage provides a common way of describing the cancer, assisting doctors to plan the best treatments. One tool that doctors use to describe the stage is the TNM system. This system judges three factors: the tumour itself, the lymph nodes around the tumour and if the tumour has spread to other parts of the body. 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 Roman numerals are stages used in another widely used staging system from the *Federation Internationale de Gynecologie et d'Obstetrique*, or FIGO. The FIGO system is the standard system used by most doctors to stage uterine cancer.

TNM is an abbreviation for tumour (T), node (N), and metastasis (M). Doctors look at these three factors to determine the stage of cancer:

- how large the primary tumour is and where is it located? **(Tumour, T)**
- whether the tumour has spread to the lymph nodes **(Node, N)**
- whether the cancer metastasised to other parts of the body? **(Metastasis, M)**

Tumour. Using the TNM system, 'T' plus a letter or number (0 to 4) is used to describe the size and location of the tumour. Some stages are also divided into smaller groups that help describe the tumour in even more detail.

TX:	the primary tumour cannot be evaluated due to a lack of information. More tests may be needed
T0 (T plus zero):	there does not seem to be a primary tumour in the uterus
Tis:	this condition is called carcinoma (cancer) in situ, which means that the cancer is found only in the layer of cells lining the uterus and has not spread to deeper tissues of the uterus
T1/FIGO I:	the tumour is found only in the corpus uteri (the body of the uterus).
T1a/FIGO IA:	the tumour is found only in the endometrium has spread to less than one-half of the myometrium
T1b/FIGO IB:	the tumour has spread to one-half or more of the myometrium
T2/FIGO II:	the tumour has spread to the cervical stroma (the connective tissue of the cervix) but has not spread beyond the uterus
T3a/FIGO IIIA:	the tumour involves the serosa (the layer of tissue that covers the outer surface of the uterus) and/or the tissue of the fallopian tubes and ovaries
T3b/FIGO IIIB:	the tumour has spread to the vagina or adjacent organs
T4/FIGO IVA: the	the tumour has spread to the lining of the bladder mucosa (lining of bladder) and/or the bowel mucosa (lining of the bowel)

Node. The 'N' in the TNM staging system stands for lymph nodes, the tiny, bean-shaped organs that help fight infection. Lymph nodes near the uterus 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 spread to regional lymph nodes
N1/FIGO IIIC1:	the cancer has spread to the regional pelvic lymph node(s)

N2/FIGO IIIC2: the cancer has spread to the para-aortic lymph nodes, which are located in the mid and upper abdomen, with or without spread to the regional pelvic lymph nodes

Distant metastasis the 'M' in the TNM system describes whether the cancer has spread to other parts of the body
M0 (M plus zero): the cancer has not metastasized
M1/FIGO IVB: there is distant metastasis

Cancer Stage Grouping
Doctors assign the stage of the cancer by combining the T, N, and M classifications

Stage 0:
The tumour is called carcinoma *in situ*, which means it is very early stage cancer. It is found only in one layer of cells and has not spread (Tis, N0, M0)

Stage I:
The cancer is found only in the uterus or womb and has not spread to other parts of the body (T1, N0, M0)

Stage IA:
The cancer is found only in the endometrium or less than one-half of the myometrium (T1a, N0, M0)

Stage IB:
The tumour has spread to one-half or more of the myometrium (T1b, N0, M0)

Stage II:
The tumour has spread from the uterus to the cervical stroma but not to other parts of the body (T2, N0, M0)

Stage III:
The cancer has spread beyond the uterus, but it is still only in the pelvic area (T3, N0, M0)

Stage IIIA:
The cancer has spread to the serosa of the uterus and/or the tissue of the fallopian tubes and ovaries but not to other parts of the body (T3a, N0, M0)

Stage IIIB:
The tumour has spread to the vagina or next to the uterus (T3b, N0, M0)

Stage IIIC1:
The cancer has spread to the regional pelvic lymph nodes (T1 to T3, N1, M0)

Stage IIIC2:
The cancer has spread to the para-aortic lymph nodes with or without spread to the regional pelvic lymph nodes (T1 to T3, N2, M0)

Stage IVA:
The cancer has spread to the mucosa of the rectum or bladder (T4, any N, M0)

Stage IVB:
The cancer has spread to lymph nodes in the groin area, and/or it has spread to distant organs, such as the bones or lungs (any T, any N, M1)

Grade
In addition to the stage, doctors may also use the term 'grade', which is how similar the tumour is to normal tissue. Tumour grade is determined by examining the tumour tissue under a microscope. In a tumour that resembles healthy tissue, doctors can clearly see different types of cells grouped together (called well-differentiated). In a higher-grade cancer, the cancer cells usually look less like healthy cells, or 'wilder' (called poorly differentiated or undifferentiated). In general, patients with a lower-grade tumour have a better prognosis.

The letter 'G' is used to define a grade for uterine cancer.

GX: the grade cannot be evaluated
G1: the cells are well differentiated
G2: the cells are moderately differentiated
G3: the cells are poorly differentiated
G4: the cells are undifferentiated

Recurrent Uterine Cancer
Recurrent cancer is cancer that comes back after treatment. Uterine cancer may come back in the uterus, pelvis, lymph nodes of the abdomen, or another part of the body. Approximately 70% of recurrent uterine cancer happens within three years of initial treatment. Some symptoms of recurrent cancer are similar to those experienced when the disease was first diagnosed:

- vaginal bleeding or discharge
- pain in the pelvic area, abdomen, or back of the legs
- difficulty or pain when urinating
- weight loss
- chronic cough

If there is a recurrence, the cancer may need to be staged again (called re-staging) using the system above.
(Cancer.net).

Should the cancer of the uterus spread to other parts of the body, it will 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	Bones, 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 Cancer of the Uterus

Uterine cancer is treated by one or a combination of treatments, including surgery, radiation therapy, chemotherapy and hormone therapy. Each treatment option is described below, followed by an outline of treatments based on the stage of the disease. Treatment options and recommendations depend on several factors, including the type and stage of cancer, possible side effects, the patient's preferences and overall health as well as personal considerations such as the woman's age and if she is planning to have children (fertility). Women with uterine cancer may have concerns about if or how their treatment may affect their sexual function and fertility and these topics should be discussed with the health care team before treatment begins.

Surgery - surgery refers the removal of the tumour and surrounding tissue during an operation. It is typically the first treatment used for uterine cancer. A surgical oncologist is a doctor who specialises in treating cancer using surgery. Depending on the extent of the cancer, the surgeon will perform either a simple hysterectomy (removal of the body of the uterus and cervix) or a radical hysterectomy (removal of the uterus, cervix, the upper part of the vagina, and nearby tissues). In addition, the surgeon will remove lymph nodes near the tumour to determine if the cancer has spread beyond the uterus. The surgeon may also perform a bilateral salpingo-oophorectomy (removal of both fallopian tubes and ovaries) for patients who have been through menopause.

A hysterectomy may be performed as a traditional surgery (with one large incision) or by laparoscopy, which uses several smaller incisions. Robotically assisted hysterectomy may also be available. In this type of surgery, a camera and instruments are inserted through small, keyhole incisions. The surgeon then directs the robotic instruments to remove the uterus, cervix, and surrounding tissue. Talk with your doctor about whether your treatment center offers this procedure and how the side effects and results compare to traditional surgery or laparoscopy.

After surgery, the woman may remain in the hospital for several days to a week. Woman who received laparoscopic or robotically assisted surgery often have a shorter hospital stay than women who received traditional surgery. The most common short-term side effects include pain and extreme tiredness. If a woman is experiencing pain, her doctor will prescribe appropriate medicine. Other immediate side effects may include nausea and vomiting, as well as difficulty emptying the bladder and having bowel movements. The woman's diet may be restricted to liquids, followed by a gradual return to solid foods.

After a hysterectomy, a woman can no longer become pregnant. If the ovaries are removed, this ends the body's production of sex hormones, resulting in premature menopause (if the woman has not already gone through menopause). Soon after surgery, the woman is likely to experience menopausal symptoms, including hot flashes and vaginal dryness. Women are encouraged to talk with their doctors about sexual and emotional side effects, reproductive health concerns and ways to address these issues before and after cancer treatment.

Radiation therapy - radiation therapy is the use of high-energy x-rays or other particles to kill cancer cells. A doctor who specializes in giving radiation therapy to treat cancer is called a radiation oncologist. A radiation therapy regimen (schedule) usually consists of a specific number of treatments given over a set period of time. The most common type of radiation treatment is called external-beam radiation therapy, which is radiation given from a machine outside the body.

When radiation treatment is given using implants, it is called internal radiation therapy or brachytherapy. Internal radiation therapy for uterine cancer is given by injecting a small amount of radioactive material directly into the tumour.

Some women with uterine cancer need both radiation therapy and surgery. The radiation therapy is most often given after surgery to destroy any cancer cells remaining in the area. Radiation therapy is rarely given before surgery to shrink the tumour. If a woman cannot have surgery, the doctor may recommend radiation therapy as another option.

Side effects from radiation therapy may include fatigue, mild skin reactions, upset stomach and loose bowel movements. Most side effects usually go away soon after treatment is finished.

Doctors may advise their patients not to have sexual intercourse during radiation therapy. Women may resume normal sexual activity within a few weeks after treatment if they feel ready.

Bracytherapy (a form of radiation therapy where radioactive seeds are inserted) - for women with surgically staged 1A or 1B endometrial adenocarcinoma, use of vaginal brachytherapy (VB) is associated with a reduction in mortality, according to a study recently published in *Cancer* (Cancer Therapy Advisor).

Chemotherapy - chemotherapy is the use of drugs to kill cancer cells, usually by stopping the cancer cells' ability to grow and divide. Systemic chemotherapy is delivered through the bloodstream to reach cancer cells throughout the body. Chemotherapy is given by a medical oncologist, a doctor who specializes in treating cancer with medication. A chemotherapy regimen (schedule) usually consists of a specific number of cycles given over a set period of time. A patient may receive one drug at a time or combinations of different drugs at the same time.

The goal of chemotherapy can be to destroy cancer cells remaining after surgery, slow the tumour's growth, or reduce side effects. Although chemotherapy can be given orally (by mouth), most drugs used to treat uterine cancer are given intravenously (IV). IV chemotherapy is either injected directly into a vein or through a catheter (a thin tube inserted into a vein).

The side effects of chemotherapy depend on the individual, the type of chemotherapy and the dose used, but it can include fatigue, risk of infection, nausea and vomiting, loss of appetite, and diarrhoea. These side effects usually ceases once treatment is finished. Advances in chemotherapy during the last ten years include the development of new drugs for the prevention and treatment of side effects, such as anti-emetics for nausea and vomiting and hormones to prevent low white and red blood cell counts.

Other potential side effects of chemotherapy for uterine cancer include the inability to become pregnant and early menopause. Rarely, some drugs may cause some hearing loss and kidney damage. Patients may be given extra fluid intravenously for kidney protection.

Hormone therapy - hormone therapy is used to slow the growth of uterine cancer cells. Hormone therapy for uterine cancer involves the sex hormone progesterone, given in a pill form. Other hormone therapies are tamoxifen (Nolvadex) and aromatase inhibitors (AIs), such as anastrozole (Arimidex), letrozole (Femara), and exemestane (Aromasin). An AI is a drug that reduces the amount of the hormone estrogen in a woman's body by stopping tissues and organs other than the ovaries from producing it. Hormone therapy may be used for women who cannot have surgery or radiation therapy or in combination with other types of treatment.

Side effects of hormone therapy include fluid retention, increase in appetite and weight gain. Women in their childbearing years may experience changes in their menstrual cycle.

Treatment options by stage

Stage I
- Surgery
- Surgery and radiation therapy
- Hormone therapy
- Surgery, radiation and chemotherapy

Stage II
- Surgery and radiation therapy
- Surgery, radiation and chemotherapy

Stage III
- Surgery and radiation therapy
- Surgery and chemotherapy
- Surgery, radiation and chemotherapy

Stage IV
- Surgery
- Radiation therapy
- Hormone therapy
- Chemotherapy

Palliative/supportive care - cancer and its treatment often cause side effects. In addition to treatment to slow, stop, or eliminate the cancer, an important part of cancer care is relieving

a person's symptoms and side effects. This approach is called palliative or supportive care, and it includes supporting the patient with his or her physical, emotional, and social needs.

Palliative care can help a person at any stage of illness. People often receive treatment for the cancer and treatment to ease side effects at the same time. In fact, patients who receive both often have less severe symptoms, better quality of life, and report they are more satisfied with treatment.

Before treatment, patients should talk with their health care team about the possible side effects of your specific treatment plan and supportive care options.

Recurrent uterine cancer - remission is when cancer cannot be detected in the body and there are no symptoms. This may also be called 'no evidence of disease' or NED.

A remission can be temporary or permanent. This uncertainty leads to many survivors feeling worried or anxious that the cancer will return. While many remissions are permanent, it's important to talk with the doctor about the possibility of the cancer returning. Understanding the risk of recurrence and the treatment options may help the survivor to feel more prepared if the cancer does return.

If the cancer does return after the original treatment, it is called recurrent cancer. It may come back in the same place (called a local recurrence), nearby (regional recurrence), or in another place (distant recurrence).

When this occurs, a cycle of testing will begin again to learn as much as possible about the recurrence. After testing is done the doctor will discuss more treatment options with the patient. Often the treatment plan will include the therapies described above (including hormone therapy, radiation, and chemotherapy) but may be used in a different combination or given at a different pace. The doctor may also suggest clinical trials that are studying new ways to treat this type of recurrent cancer.

Metastatic Uterine Cancer

If cancer has spread to another location in the body, it is called metastatic cancer. Patients with this diagnosis are encouraged to talk with doctors who are experienced in treating this stage of cancer, as there may be different opinions regarding the best treatment plan.

The health care team may recommend a treatment plan that includes radiation therapy, especially for recurrent cancer in the pelvis. Hormone therapy may be used for cancer that has spread to distant parts of the body. A cancer that is high grade or that does not respond to hormone therapy is treated with chemotherapy. Women with stage IV uterine cancer are encouraged to consider participating in clinical trials. Supportive care will also be important to help relieve symptoms and side effects.

For many patients, a diagnosis of metastatic cancer can be very stressful and at times, difficult to bear. Patients and their families are encouraged to talk about the way they are feeling with doctors, nurses, social workers, or other members of the health care team. It may also be helpful to talk with other patients, including through a support group.

If treatment fails - recovery from cancer is not always possible. If treatment is not successful, the disease may be called advanced or terminal cancer.

This diagnosis is stressful and it may be difficult to discuss. However, it is important for the patient to have open and honest conversations with his/her doctor and health care team to express feelings, preferences and concerns. The health care team is there to help and many team members have special skills, experience and knowledge to support patients and their families. Making sure a person is physically comfortable and free from pain is extremely important.
End-of-life care is given toward the end of a person's life. The patient and loved ones are encouraged to think about where a patient would be most comfortable: at home, in the hospital or in another specialised environment. Nursing care and special equipment can make staying at home a workable alternative for many families.

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).

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