What is ovarian cancer?

Let us explain it to you.
The ESMO / Anticancer Fund Guides for Patients are designed to assist patients, their relatives and caregivers to understand the nature of different types of cancer and evaluate the best available treatment choices. The medical information described in the Guides for Patients is based on the ESMO Clinical Practice Guidelines, which are designed to guide medical oncologists in the diagnosis, follow-up and treatment in different cancer types. These guides are produced by the Anticancer Fund in close collaboration with the ESMO Guidelines Working Group and the ESMO Cancer Patient Working Group.

For more information please visit www.esmo.org and www.anticancerfund.org
OVARIAN CANCER: A GUIDE FOR PATIENTS

PATIENT INFORMATION BASED ON ESMO CLINICAL PRACTICE GUIDELINES

This guide for patients has been prepared by the Anticancer Fund as a service to patients, to help patients and their relatives better understand the nature of ovarian cancer and appreciate the best treatment choices available according to the subtype of ovarian cancer. We recommend that patients ask their doctors about what tests or types of treatments are needed for their type and stage of disease. The medical information described in this document is based on the clinical practice guidelines of the European Society for Medical Oncology (ESMO) for the management of ovarian cancer. This guide for patients has been produced in collaboration with ESMO and is disseminated with the permission of ESMO. It has been written by a medical doctor and reviewed by two oncologists from ESMO including the lead author of the clinical practice guidelines for professionals. It has also been reviewed by patient representatives from ESMO’s Cancer Patient Working Group.

More information about the Anticancer Fund: www.anticancerfund.org

More information about the European Society for Medical Oncology: www.esmo.org

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This is the third update of this guide. Updates reflect changes in the successive versions of the ESMO Clinical Practice Guidelines. The update was done by Dr. Gauthier Bouche (Anticancer Fund) and was reviewed by Dr. Svetlana Jezdic (ESMO) and by Pr. Cristiana Sessa (ESMO) and by Ruth Payne (Ovacome UK).
DEFINITION OF OVARIAN CANCER

Ovarian cancer is a cancer that forms in tissues of the ovary. The ovaries are the female reproductive organs in which the egg cells (ova) are formed and female hormones are produced. Ovarian cancers either arise from the cells of the surface of the ovary (the ovarian epithelium*), a form called epithelial ovarian cancer (also referred to here as ovarian carcinoma) or from other tissues within the ovary (non-epithelial ovarian cancer). Both terms refer to a very diverse group of different ovarian cancer subtypes. The most frequent type of ovarian cancer is epithelial, which accounts for approximately 90% of primary ovarian tumours. In the group of uncommon non-epithelial cancer, two subtypes appear more frequently, namely malignant* germ cell tumours and sex cord stromal tumours.

Anatomy of the female reproductive system showing the ovaries, the Fallopian tubes, the uterus and the vagina. The ovaries are the organs where the egg cells are formed and female hormones are produced. Egg cells migrate through the Fallopian tubes to the uterus, where the foetus develops during pregnancy.

IS OVARIAN CANCER FREQUENT?

Ovarian cancer is the seventh most common cancer and cause of cancer deaths in women in the world.

The worldwide incidence* of ovarian cancer shows strong geographical variation. Developing countries have the lowest incidence. In the European Union, it was estimated that, in 2008, a total of 45,300 women were diagnosed with ovarian cancer. The overall probability for a woman in the European Union in developing ovarian cancer during her lifetime lies between 0.64% and 1.6%. Approximately half of the women diagnosed with ovarian cancer are aged 60 or older. However, younger women can be affected, mainly by two rare types of non-epithelial ovarian cancer called germ cell and sex cord-stromal tumours. Germ cell tumours are diagnosed principally in the first two decades of life, whereas sex cord-stromal tumours are more common in adult women (granulosa
adult type has an average age at diagnosis of 50 years, 90% of juvenile type occurs in pre-pubertal girls and Sertoli*-Leydig* occurs mainly in women younger than 40 years).
WHAT CAUSES OVARIAN CANCER?

Today, the cause of ovarian cancer is not well understood. Importantly, the term ovarian cancer refers to a very diverse group of different types of malignant ovarian tumours, and the cause of the different tumour types may not be the same. A number of risk factors for ovarian cancer have been identified. Some of these risk factors are specific for selected subtypes of ovarian cancer. In many cases, however, none of the risk factors are apparently present. A risk factor increases the risk of cancer occurring, but is neither necessary nor sufficient to cause cancer. A risk factor is not a cause in itself.

Some people who have one or more risk factors will never develop ovarian cancer and some people without any of these risk factors may nonetheless develop ovarian cancer.

Up to 90% of all ovarian cancer cases are sporadic ovarian cancer. This means that they are not associated with inherited genetic mutations. The risk of developing a sporadic form of ovarian cancer principally relates to the total number of ovulatory cycles that have taken place in the ovaries during the reproductive years of a woman. An ovulatory cycle is the monthly stimulation of the ovary leading to the release of an egg cell (ovulation). The total number of ovulatory cycles taking place in a woman’s ovaries between menarche and menopause (the so-called reproductive years) constitute the ‘lifetime number of ovulatory cycles’. It is thought that repetitive stimulation of the ovarian tissues during ovulatory cycles increases the risk of damage to the DNA of the cells, which may lead to cancer.

According to this understanding, risk factors for this type of ovarian cancer are:

- **Aging.** It is thought that as a woman grows older, changes in the DNA within the ovarian tissues may accumulate, increasing the risk of developing ovarian cancer. Overall, the incidence of ovarian cancer increases with each age decade. The average age of women diagnosed with ovarian cancer is approximately 60 years. The incidence declines slightly after the age of 80 years.

- **Family history of ovarian cancer or breast cancer** is another important risk factor of developing ovarian cancer. This is explained by the fact that up to 10% of patients with ovarian cancer have inherited a genetic mutation that may cause cancer in the ovary. A genetic mutation is a variation of the normal DNA structure of a gene. Certain mutations produce a faulty gene that may cause cancer. Mutations in cells that are destined to become egg cells or sperm cells (these cells are called germ cells), are transmitted by a parent to his or her off-spring. For epithelial ovarian cancer, certain subtypes are associated with well-known mutations, for example the mutations called BRCA1 and BRCA2. These mutations are also associated with an increased risk of breast cancer. In general, it is assumed that a woman who has one first-degree relative (mother, daughter or sister) with ovarian cancer, runs a three-fold higher risk of developing ovarian cancer. The risk further increases if there is more than one first-degree relative with a history of ovarian cancer.
Jewish women of Ashkenazi ancestry have a particularly high chance of carrying an inherited mutation that predisposes ovarian cancer: amongst all ovarian cancer patients, up to 40% of Ashkenazi Jewish women have the BRCA1 or BRCA2 mutation, whereas in the overall population of women with ovarian cancer this is only 10%.

In general, for women carrying the BRCA1 mutation, the estimated lifetime risk of developing ovarian cancer lies between 26 and 54%, and for those carrying the BRCA2 mutation this risk lies between 10 and 23%.

- **Personal history of breast cancer** prior to the age of 50, or a **family history** (broader than first-degree relatives) of ovarian cancer, breast cancer, endometrial or colon cancer is also associated with a higher risk of developing ovarian cancer.

- The **number of children a woman has given birth to**. Women who have never had children run a 2-fold higher risk of developing ovarian cancer than those who have given birth. The risk of developing ovarian cancer decreases with each live birth; however, beyond the number of 5 live births, the risk does not decrease any further. During pregnancy, ovulation is temporarily halted and the resulting reduction in the lifetime number of ovulatory cycles is thought to reduce the risk of ovarian cancer. In addition, it is thought that pregnancy may help ovaries to shed premalignant* cells.

- **Race**. Caucasian women have a 30 to 40% higher risk of developing ovarian cancer than black or Hispanic women. This racial difference is not understood. It is thought that differences in parity (see below) and frequency of gynaecological surgical interventions (see below) between the races may play a role.

There are factors associated with a reduced risk of developing ovarian cancer, these are:

- **Strong reproductive history**. As explained above, the risk of developing ovarian cancer decreases with the number of times a woman has given live birth, the effect being maximal at 5 births. The reduction in the total number of ovulatory cycles, as well as enhanced shedding of premalignant* cells, is thought to explain the risk reduction.

- **Breastfeeding** has a protective effect on the development of ovarian cancer. This is presumed to relate to the fact that breastfeeding suppresses ovulation, thereby reducing the lifetime number of ovulatory cycles.

- **Combined oral contraceptives** suppress ovulation and therefore exert a protective effect. Long-term use of oral contraceptives reduces the risk of developing ovarian cancer by up to 50%. Moreover, the protection lasts for more than 30 years after the last use of the contraceptive.

- **Gynaecological surgery**. Both tubal ligation* and hysterectomy* are associated with a reduction in the risk of developing ovarian cancer. The reason for this is not well understood, but it is thought that these surgical procedures disrupt the blood supply to the ovaries, thereby also disrupting their function (ovulation), and reducing the lifetime number of ovulatory cycles and the risk of developing ovarian cancer.

- **Oophorectomy**. The surgical removal of the ovaries significantly reduces the risk of developing ovarian cancer.
Some factors have been suspected to be associated with an increased risk of ovarian cancer, but the evidence is inconsistent:

- **Certain fertility drugs** have been suggested to play a role in causing ovarian cancer, but the evidence is conflicting.
- Studies have suggested that **hormone replacement therapy** with **oestrogens** in postmenopausal women, when given for periods longer than 10 years, may be associated with a higher risk for ovarian cancer. This evidence, however, needs to be confirmed. The heightened risk is thought to wane when replacement therapy is interrupted.
- The use of **talcum powder** in the genital area has been suggested to be related to the development of ovarian cancer. Talc may reach the ovaries through the reproductive tract and may irritate the ovarian epithelium. However, the evidence of the relationship between the use of talcum powder and ovarian cancer is inconsistent.
HOW IS OVARIAN CANCER DIAGNOSED?

Ovarian cancer may be suspected during a routine physical check-up, when a clinical examination shows a mass in the pelvis*, or on the basis of specific symptoms.

The main symptoms of ovarian cancer are related to the presence of a mass in the abdomen and may include:

- Pelvic or abdominal discomfort, pressure or pain
- Abdominal fullness or abdominal swelling
- Eating difficulties: early satiety (being rapidly satisfied), dyspepsia* (stomach upset)
- Bowel habit changes, for example constipation
- Changes in voiding pattern, for example increased frequency of voiding
- Pain during sexual intercourse

When disease is advanced, the aforementioned symptoms may be more pronounced, and may also include:

- Nausea (feeling sick) and anorexia (loss of appetite)
- Abdominal distension due to fluid accumulating in the abdominal cavity (ascites*)
- Bowel obstruction due to a mass in the abdomen
- Shortness of breath due to fluid accumulating around the lungs (pleural effusion*)

These symptoms, however, are not specific for ovarian cancer and can also occur in various non-malignant* conditions.

Malignant* ovarian tumours may produce hormonal substances that cause specific symptoms or signs. Such tumours are called functional tumours. This is particularly common for sex cord stromal tumours. Excess production of estradiol* and/or androgens* may cause sexual precocity (premature onset of puberty) in prepubertal girls. Excess estradiol may cause irregular menstrual cycles (menses) in a premenopausal patient, or postmenopausal uterine bleeding in a postmenopausal woman. Excess production of testosterone*, a male hormone, may cause virilization*. Excess production of cortisol* may produce Cushing syndrome*, a condition characterized by weight gain, thinning of the skin and excess hair growth.

Besides asking about the aforementioned symptoms, the doctor will perform a general physical examination and ask for blood tests to evaluate blood cell counts as well as the liver and kidney function. Young prepubescent girls who develop an ovarian tumour may have dysgenetic gonads*, meaning that they have an inborn growth disturbance of the ovaries due to a variation in the chromosomes*. In such patients, a blood test should be performed to identify the number and size of the chromosomes, also called the karyotype*.

If a postmenopausal patient presents symptoms of an ovarian tumour and postmenopausal bleeding, a hysteroscopy* (examination of the interior of the uterus using a small camera) may be indicated to document endometrial hyperplasia*. Endometrial hyperplasia refers to excessive growth of the inner lining of the uterus (the endometrium), which may give rise to abnormal uterine bleeding.
The diagnosis of ovarian cancer is based on the following specific examinations:

- **Clinical examination**
  
  **Clinical pelvic examination***

  As part of the general gynaecological examination, the doctor will perform a bimanual pelvic examination* to evaluate the presence of a mass, as well as its size and its possible fixation to surrounding tissues. During this exam the gynaecologist will palpate the ovaries simultaneously via the abdomen and the vagina.

- **General physical examination**

  In advanced stages of disease doctors will search for signs of the presence of ascites*, bowel obstruction, pleural effusion*, and enlarged lymph nodes* or solid organs (e.g. liver) due to metastases*.

- **Radiological investigation**

  - **Transvaginal ultrasonography***

    The doctor performs an ultrasound examination imaging of the organs in the pelvis* using a probe that is inserted vaginally. This exam is well tolerated. The objective of ultrasound imaging is to detect the presence of a tumour in the ovaries and Fallopian tubes (also called adnexal mass). The objective is also to distinguish, on the basis of how the mass looks, benign* lesions from lesions that require further evaluation (histopathology) for malignancy*. Ultrasound imaging using the transvaginal route allows very good visualization of the adnexall structures.

    A pelvic mass is to be considered suspicious for malignancy* if it shows a solid component (and not only fluid), irregular margins and the presence of many blood vessels. In that case, it is necessary to refer the patient to an experienced ultrasound examiner. Transvaginal ultrasonography may also reveal ascites* (accumulation of fluid in the abdominal cavity) or peritoneal* metastases* (metastases on the peritoneum*, the tissue lining the abdominal cavity), which are also indicative of malignancy.

    Other imaging techniques may provide additional information, but are not routinely necessary in the preoperative evaluation. The goal of imaging in ovarian cancer detection is to distinguish benign* adnexal mass from those requiring further histopathological evaluation for malignancy*.

  - **Magnetic Resonance Imaging* (MRI)**

    MRI examination of the pelvis* may provide additional information on the nature of an ovarian mass, particularly if ultrasonography could not provide evidence on the benign* or malignant* aspect. It is helpful for staging and planning of treatment.
Computed tomography* (CT)
CT features could raise suspicion on certain types of ovarian cancer. It is helpful for staging and planning of treatment.

Positron-emission tomography* – computed tomography* (PET-CT)
PET-CT is an imaging technique that visualizes the anatomy of a tissue as well as the metabolic activity of the cells in that tissue. PET-CT is not recommended for primary cancer detection. It may be useful in the staging of tumours that are metabolically active, meaning that the tumour produces substances that induce changes in the chemical composition of the fluids in the patient’s body. The small cell carcinoma of the ovary is an example of a tumour that may be metabolically active.

**Tumour markers**

Certain types of ovarian cancer produce factors that can be measured using a blood test. These so-called tumour markers may help in establishing the diagnosis of ovarian cancer. It is important to note that unless ovarian tumours produce substances that cause specific symptoms or signs of disease, they are not often recognized. Therefore, cancer antigen 125 (CA125) is a tumour marker usually measured in the primary assessment of a suspicious adnexal mass, and other tumour markers are used if there is a suspicion of a certain type of non-epithelial ovarian cancer. Some tumour markers may also be used during or after treatment to monitor response to treatment and/or to monitor recurrence* of tumour disease (see chapter ‘What happens after the treatment’). Whether or not the tumour marker is clinically useful depends on many tumour- and patient-specific factors, and needs to be carefully determined for each individual patient.

It is important to note that, although tumour markers may be helpful, the diagnosis of ovarian cancer is essentially based on imaging and histopathology.

**CA125** - The doctor usually asks to determine the blood level of the protein* CA125. Most ovarian cancer cells produce CA125 at higher levels than non-malignant cells do. Combining the results of ultrasonography* and CA125 level is more accurate for the diagnosis of primary ovarian cancer than transvaginal ultrasound alone. It is important to note that whereas an elevated level of CA125 may support the diagnosis, it is by itself not diagnostic. Elevated CA125 levels can also be found in various benign* conditions such as menstruation, benign* cysts*, uterine fibroids*, pelvic inflammatory disease*, adenomyosis*, endometriosis* and peritoneal* inflammation.

Non-epithelial ovarian cancers are rare and may generate difficulty in establishing diagnosis. Review of tumour markers* and clinical findings may indicate some of these tumours.

If younger women present symptoms of pelvic mass, their age should raise suspicion for germ cell tumours. Elevated levels of proteins* called human chorionic gonadotropin* (hCG), α-fetoprotein* (AFP) and lactate dehydrogenase* (LDH) may be found in patients with these tumours. Otherwise these markers* are measured in the blood when a diagnosis of such tumour type is already established.

In androgen*- and cortisol*-secreting ovarian tumours that present signs of virilization* or Cushing syndrome*, these substances may be measured and useful, especially in follow-up.

**Estradiol** and **testosterone** are reproductive hormones that may be measured and may be useful in the follow up of granulosa cell tumours* (estradiol) and Sertoli*-Leydig* cell tumours (testosterone).
Inhibin* is a hormone secreted by granulosa cell tumours* and may be measured as a marker* for the disease.

Neuron-specific enolase (abbreviated NSE) is a protein* that may be elevated in some ovarian neuro-endocrine* tumours.

- Histopathological examination

This is the laboratory investigation of the tumour cells and is performed on tissue from the ovarian tumour. The histopathological information will confirm the diagnosis of ovarian cancer and will reveal the specific characteristics of the tumour, allowing the doctor to determine the histological type* of ovarian cancer according to the established criteria of the World Health Organization (WHO).

Histopathological examination is also performed on tissues from other organs, such as from the pelvis* or the abdomen to which the ovarian tumour has spread, or may have spread. This is part of a process called surgical staging. Staging means that the doctor defines the extent to which the ovarian tumour has invaded other organs. In ovarian cancer, staging involves a laparotomy*. This is a surgical procedure in which the surgeon makes an incision in the abdominal wall to inspect the abdominal cavity and organs, and to perform resections or biopsies* from (potentially) affected organs.

The histological type* of the tumour and the stage of the disease provide very important information on the cancer. The histological types are explained in ‘What is important to know to define the optimal treatment’ section of this document.
WHAT IS IT IMPORTANT TO KNOW TO DEFINE THE OPTIMAL TREATMENT?

Doctors will need to consider many aspects of both the patient and the cancer in order to decide on the best treatment. In some patients, this information can be used to predict the risk of recurrence* of the cancer.

**Relevant information about the patient**

- Age
- Reproductive history and menopausal* status in adult women
- Pubescent status in pre-adolescent girls
- Family history of ovarian cancer, breast cancer or other cancer
- Personal medical history, previous illnesses and treatments
- General well-being and specific physical complaints
- Results of the clinical examination
- Results of laboratory tests on blood counts, kidney and liver function
- Results of possible other specific laboratory tests, such as initial value of tumour markers* that might be important for monitoring response to treatment.

**Relevant information about the cancer**

Information about the cancer that is important to direct the treatment include the stage of the cancer, the histological type* and the grade of the tumour; in selected tumour types the gene expression profile of the tumour cells may be relevant.

**STAGING**

Determining the stage of the cancer means that doctors assess the extension of the cancer and the prognosis* of the patient. The lower the stage, the better the prognosis. The size of the tumour and invasion* of nearby tissue, the involvement of lymph nodes*, and the absence or presence of metastasis* are taken into account for determining the stage of the disease. The stage is fundamental in order to make the right decision about the treatment.

In ovarian cancer, staging is complete when the following examinations are performed: clinical examination, radiological investigations, a surgical exploration of the abdomen (called surgical staging), and the histopathological examination of tissue from the primary tumour and from biopsies* from possibly affected other organs.

A critical element of the staging procedure in ovarian cancer is performing laparotomy* under general anaesthesia*. This so-called ‘surgical staging procedure’ allows the surgeon to visually determine the presence and the spread of the ovarian cancer, and to obtain tissues from the tumour (and from other possibly affected abdominal organs) for histopathological examination. In addition to its use for staging, the laparotomy* is also the first step (and in some cases the final step) in the treatment, since it allows the surgeon to remove the primary tumour and visibly affected organs.

Surgical staging is performed according to guidelines issued by the
International Federation of Gynaecology and Obstetrics (abbreviated: FIGO). The surgeon performs an incision in the abdominal wall, and carefully examines the abdominal cavity and all abdominal organs for the presence of a primary tumour and the possible spread of the tumour to other organs. Supported by the findings from clinical and radiological examinations, this will enable the surgeon to determine the stage of the disease.

The surgeon will remove the tumour and selected organs, and will perform biopsy* sampling (surgical removal of small pieces of tissue for histopathological examination) of other organs to which the cancer may have spread. The exact protocol of necessary interventions depends on the stage of the disease as diagnosed during the procedure. The spread of the disease (through histopathological examination of tissues and biopsies) can be assessed and affected tissues may be removed by these interventions. The interventions during surgical staging may include:

- a total abdominal hysterectomy* (resection of the uterus) and bilateral salpingo-oophorectomy* (resection of the ovaries and Fallopian tubes), a complete or selected lymphadenectomy (resection of lymph nodes*) of pelvic and para-aortic lymph nodes* (lymph nodes in the pelvis* and alongside the main artery called aorta), a partial or complete omentectomy (resection of the omentum*, a large fold of the peritoneum* that lines the bowel), and resection of any other organ to which the tumour has spread.
- Biopsy* sampling from the peritoneum (tissue that lines the abdominal cavity) of the diaphragm, the pelvis* and the spaces between the abdomen and the large bowel (called paracolic gutters*)
- washing of the abdominal cavity with salt-water to detect presence of malignant* cells (also called peritoneal* washing*)
- for selected tumour types, resection of the appendix* (appendectomy)

In selected cases, the surgical staging procedure can be performed using a laparoscopy* rather than a laparotomy*. Whether or not this is possible needs to be evaluated for each patient individually.

The table below presents the different stages for ovarian cancer according to the guidelines of the International Federation of Gynaecology and Obstetrics (FIGO)¹. The definitions are somewhat technical. Therefore, it is recommended to ask doctors for more detailed explanations.

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¹ It should be noted that a new FIGO classification, with only minor modifications, is proposed for use from January 2014 on. However, decisions about treatment still rely on the previous classification. This will change progressively in the coming years but has no consequence on the treatment recommendations indicated in his guide.
### STAGE DEFINITION

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Stage I</td>
<td>The tumour is confined to the ovaries</td>
</tr>
<tr>
<td>Stage IA</td>
<td>The tumour is confined to the interior of one ovary: there is no tumour on the outer side of the ovary and the capsule surrounding the ovary is intact. There are no ascites* containing malignant* cells.</td>
</tr>
<tr>
<td>Stage IB</td>
<td>There is tumour growth in both ovaries but the tumours are confined to the interior of the ovaries. There is no tumour on the outer sides of the ovaries and the capsules surrounding the ovaries are intact. There are no ascites* containing malignant* cells.</td>
</tr>
</tbody>
</table>
| Stage IC | There is tumour growth in one or both ovaries (stage IA or stage IB), and there is one or more of the following elements:  
- tumour growth on the outer side of one or both ovaries  
- tumour growth through the capsule of one or both ovaries, or rupture of the capsule during the operation  
- ascites* with malignant* cells  
- peritoneal* washing* fluid showing the presence of malignant cells |
| Stage II | The tumour involves one or both ovaries and has extended beyond the ovaries, into the pelvic organs |
| Stage IIA | The tumour involves one or both ovaries and has extended to the uterus and/or the Fallopian tubes |
| Stage IIB | The tumour involves one or both ovaries and has extended to pelvic tissues other than the uterus and the Fallopian tubes. |
| Stage IIC | The tumour involves one or both ovaries and has extended to the uterus or Fallopian tubes (stage IIA) or other pelvic organs (stage IIB). In addition, there is one or more of the following:  
- tumour growth on the outer side of one or both ovaries  
- tumour growth through the capsule of one or both ovaries  
- ascites* with malignant* cells  
- peritoneal* washing* fluid showing the presence of malignant cells. |

### CATEGORY

- early disease
- Advanced disease
### Stage III
The tumour involves one or both ovaries. To the naked eye, the tumour growth seems limited to the pelvis*, but histopathological examination shows that it has extended beyond the pelvis to one or more of the following:
- the peritoneum* outside the pelvis
- the lymph nodes* in the region of the pelvis
- the surface layers of the liver
- small bowel or omentum*.

### Stage IIIA
The tumour involves one or both ovaries. To the naked eye, the tumour growth seems limited to the pelvis*, but histopathological examination shows tumour growth - at the microscopic level - in the small bowel or the mesentery*, or in the peritoneal* membranes outside the pelvis (including the omentum*). There is no tumour spreading to lymph nodes*.

### Stage IIIB
The tumour involves one or both ovaries. Histopathological examination of biopsies* from the peritoneal* membranes outside the pelvis* shows metastases* smaller than 2 cm in diameter. There is no tumour spreading into the lymph nodes*.

### Stage IIIC
The tumour involves one or both ovaries. The tumour growth has caused metastasis* in the peritoneal* membranes larger than 2 cm in diameter and/or has spread into the lymph nodes* of the pelvis*.

### Stage IV
The tumour involves one or both ovaries and has caused
- liver metastasis* in the deep liver tissues (parenchymal metastasis)
- metastasis in organs at a distance of the pelvis*
- fluid around the lungs (pleural effusion*) containing malignant* cells
RESULTS OF THE EXAMINATION OF THE TUMOUR TISSUE

The surgical specimen of the tumour is examined in the laboratory by a pathologist*. This examination is called histopathology and will provide information on the histological type* and the grade of the tumour. The histopathological investigation of the tumour tissue provides critical information on the cancer. The results of the examination of the tumour tissue thus include the histological type, and the grade.

Some tumours produce characteristic proteins* that can be identified in tumour tissue using a special laboratory method called immunohistochemistry*. In selected forms of ovarian cancer, this additional investigation on the surgical specimen of the tumour may help in identifying the histological type of the tumour.

- **Histological type**

The histological type of a tumour refers to the type of cells that compose the tumour. The histological type is defined according to established criteria of the World Health Organization (WHO).

Approximately 90% of malignant* ovarian tumours arise from the epithelium* of the ovary or from the epithelium of the outer end of the Fallopian tube. These tumours are referred to as’ epithelial ovarian cancer’ or ‘ovarian carcinomas’.

About 10% of ovarian cancers derive from other ovarian tissues other than the epithelium. These tumours are referred to as ‘non-epithelial ovarian cancer’.

Both epithelial ovarian cancer and non-epithelial ovarian cancer constitute a mixed group of different types of tumours. These two groups are discussed separately below.

If a malignant tumour of ovarian type is found in the peritoneum*, it is considered a primary ovarian tumour.

**OVARIAN CARCINOMA or EPITHELIAL OVARIAN CANCER**

Amongst ovarian carcinomas, several histological types* are recognized, each representing distinct entities with distinct process of development (carcinogenesis). Every histological type is classified in one of three categories that reflect the prognosis*:

- **Benign** tumours are composed of non-malignant cells. Benign tumours may grow larger, but do not spread to other parts of the body.

- **Malignant** tumours are composed of cancer cells. Malignant tumours grow in an unlimited manner, and may invade and destroy the surrounding tissue. They may also spread to other parts of the body (metastases*).

- **Borderline tumours** are composed of cells that are neither considered benign*, nor malignant*, but rather show a low malignant potential. These lesions are also known as **tumours of intermediate malignancy***, **tumours of low malignant potential**, and **atypical proliferative tumours**. Borderline tumours are usually **serous carcinomas**, less frequently **mucinous carcinomas** and rarely **endometrioid carcinomas**.

The six major histological types* of epithelial ovarian cancer are described below. The definition of these tumours and their different subtypes is very specialized and technical; it is therefore recommended to consult your doctor for more information.
- **Serous carcinomas** account for approximately 80-85% of all ovarian carcinomas in Western countries. Most *serous carcinomas* are high-grade; low-grade *serous carcinomas* are rare. Up to 95% of patients with FIGO stage III-IV disease have *serous carcinomas*, while serous carcinomas of FIGO stage I are very uncommon. Low-grade and high-grade *serous carcinomas* are considered distinct types of tumours.

- **Endometrioid carcinomas** account for approximately 10% of all *ovarian carcinomas*. Most carcinomas of this type are FIGO stage I or II.

- **Clear-cell carcinomas** make up approximately 5% of all *ovarian carcinomas*. They are common in Japanese women only. Most carcinomas of this type are FIGO stage I or II, and they are the most common tumour amongst FIGO stage I tumours.

- **Mucinous carcinomas** consist of two subgroups. The *intestinal-type mucinous tumour* is the most common. The *endocervical-type* (seromucinous or Mullerian) *mucinous tumour* is usually a borderline tumour*, and is similar to the *borderline serous tumours*.

- **Transitional cell carcinomas** are common, and most are high-grade tumours with histological features similar to those seen in *serous carcinomas*.

- **Squamous carcinomas**

In addition to these six major histological types*, other ovarian carcinomas include:

- **Undifferentiated carcinomas** that behave similarly to high-grade *serous carcinomas*.

**NON-EPITHELIAL OVARIAN CANCER**

Non-epithelial ovarian cancer also consists of a mixed group of malignant* tumours. Characteristically, these are all uncommon tumours. Six major histopathological types, often with several distinct subtypes are recognized. A comprehensive overview of the classification is given below. The definition of these tumours, in particular the different subtypes, is very specialized and technical; it is therefore recommended to consult doctors for more information.

- **Germ cell tumours** arise from the egg cells within the ovary. Overall, germ cell tumours constitute only 5% of all ovarian tumours, but they make up more than 75% of all the malignant* ovarian tumours that are diagnosed in pre-adolescent girls. Several different types of *germ cell tumours* are recognized. Since the distinction between these subtypes is very technical, it is recommended to ask doctors for more information.

  The so-called *dermoid* cyst*(or mature cystic teratoma*) is a subtype of *germ cell tumours* that may account for 20% of all ovarian tumours, and is usually benign*.

- **Sex cord stromal tumours** arise from the ovarian stroma (the soft tissue that forms the supportive structure of the ovary) or from the sex cords (the structures that during development of the reproductive organs give rise to specific cell types such as Leydig cells*, Sertoli cells*, granulosa cells* and thecal cells*). *Sex cord stromal tumours* make up 5% of all ovarian tumours and 7% of all ovarian malignant* tumours. They occur mostly in women of adult age. These tumours usually produce hormonal substances, producing distinct clinical symptoms such as virilization*, or endometrial hyperplasia* which may cause irregular menses or postmenopausal bleeding.

  Several types of *sex cord stromal tumours* are recognized. The distinction between these subtypes is very technical and it is recommended to ask doctors for more information.
The most common type of malignant* tumour in the group of sex cord stromal tumours is the granulosa cell tumour*. These tumours can occur in adults but are most frequent in juveniles, namely in females younger than 20 years of age. In this age group they often present with signs of sexual precocity (premature onset of puberty).

Immunohistochemistry* may help in the differentiating these tumours from other types of ovarian cancer since these tumours typically show tissue expression of the proteins* CD99* and melanA* (in the adult form) and α-inhibin* and calretinin* (in the adult and juvenile forms).

The Sertoli cell*, Leydig cell* and Sertoli-Leydig cell tumours form a subtype of sex cord stromal tumours that may typically produce male hormones. The Leydig cell tumour (also called hilus cell tumour) is always benign* and typically presents virilization* due to secretion of androgen*. The Sertoli-Leydig cell tumour also presents itself in younger patients and may also produce hormones. Also in these tumours, immunohistochemistry* may help in their identification since they typically show expression of the specific proteins* α-inhibin and low molecular weight cytokeratin.

- Carcinosarcomas* make up 2 to 4% of all ovarian tumours. Typically these tumours consist of malignant* cells arising from the ovarian epithelium* as well as from the ovarian stroma.

- Small cell and neuro-endocrine* tumours of the ovary characteristically consist of cells that are smaller than normal cells. Neuro-endocrine tumours of the ovary consist of cells that typically occur in endocrine and nervous systems*.

This category of tumours, which also consists of different subtypes, makes up approximately 1% of all ovarian cancers and each subtype has a characteristic clinical presentation. These tumours are rare but most of them are very aggressive, in particular when they are diagnosed beyond FIGO stage I. The distinction between the different subtypes is very technical, and it is recommended to consult their doctor for more information.

- Squamous cell carcinoma arising within a dermoid* cyst*/teratoma* is a malignant* tumour that arises within a dermoid cyst: this so-called ‘malignant transformation’ is uncommon and occurs in only 1 to 2% of dermoid cysts. These tumours typically occur in postmenopausal women and are usually diagnosed in a later stage when the large tumour size causes discomfort or when twisting of the tumour (called torsion) causes pain. The diagnosis is also often made when a patient undergoes surgery for a presumed dermoid cyst.

- Struma ovarii malignum (or strumal carcinoid) is a malignant* tumour that arises within a teratoma* and that consists of more than 50% of tissue that is typically found in the thyroid gland*. Struma ovarii malignum is very uncommon and is usually diagnosed as an incidental finding in 50- to 60-year old women. It rarely produces metastases*. Very rarely, the ovarian tumour represents a metastasis from a primary thyroid malignant tumour, and this possibility should therefore be investigated in patients presenting strumal carcinoid.

- Grade

The so-called grade of a malignant* tumour reflects the presence of atypical characteristics of the cells and/or the atypical architecture of the tumour. The grade is considered to provide information on the rate at which the tumour will grow and the degree to which it will be invasive*.

For ovarian cancer, numerous grading systems can be used. The grading system may differ according to the histological type* of the tumour. A number (usually from 1 to 3) or an adjective (low or high) is attributed to the grade. A general rule is that the lower the grade is, the better the prognosis* is.
**WHAT ARE THE TREATMENT OPTIONS?**

The planning of the treatment for the patient involves a multidisciplinary team* of medical professionals. This usually implies a meeting of different specialists, called multidisciplinary opinion* or tumour board review. In this meeting, the treatment planning will be discussed according to the relevant information mentioned before.

The treatment will usually combine surgery, and systemic chemotherapy*, which acts on the cancer cells wherever they are located in the body.

The extent of the treatment will depend on the stage of the cancer, on the characteristics of the tumour and on the risks for the patient. The treatments listed below have their benefits, their risks and their contraindications*. It is recommended that patients ask their doctors about the expected benefits and risks of every treatment in order to be informed about the consequences of the treatment. For some treatments, several possibilities are available and the choice should be discussed according to the balance between benefits and risks.

In general, the treatment of ovarian cancer follows a standard treatment plan. This is given below. However, ovarian cancer represents a very diverse group of tumours and for selected subtypes of non-epithelial ovarian cancer, the recommended treatment varies.

It should be noted that most non-epithelial cancers are very rare tumours, and the treatment options given below are regimens based on the current clinical experience in a limited number of cases.

Apart from the standard treatment, it is possible to participate in a clinical trial* at all stages of the disease. In a clinical trial, new treatments or strategies are proposed with the intent to learn more about the possible benefits and risks. If a patient wants to participate in a clinical trial, it is recommended to discuss ongoing clinical trial(s) with the doctor.

**STANDARD TREATMENT PLAN FOR OVARIAN CANCER**

Treatment plan for early disease (FIGO stage I and IIA)

At these stages, the tumour is confined to the ovaries (stage I) or to the ovaries, the uterus and/or the Fallopian tubes (stage IIA).

Since there is no extension beyond the pelvis*, the main goal of the treatment is to surgically remove the tumour as well as the organs to which the tumour has spread, if that were the case. For patients with selected risk profiles, however, additional treatment (called adjuvant* chemotherapy*) is recommended since it lowers the risk of the tumour to progressing and/or returning.

**Surgical resection of the tumour and the affected organs during surgical staging**

Surgical resection of the tumour and the organs affected by the tumour constitute the first (and in selected cases the definitive) step in the treatment of early ovarian cancer. The surgical resection takes place during the surgical staging procedure, a critical element of the diagnostic work-up for ovarian cancer (see chapter on ‘Staging’). By means of a laparotomy* under general anesthesia*, the surgeon visually determines the presence and the spread of the ovarian cancer; in other words, the surgeon will determine the ‘stage’ of the cancer. Depending on the stage, the surgeon*

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Ovarian cancer: a guide for patients - Information based on ESMO Clinical Practice Guidelines - v.2014.1

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will then perform a standardized protocol of resections and biopsy* sampling. This not only provides tissues for histopathological examination, but thus also constitutes the local treatment of the tumour. In the case where surgical staging shows **early ovarian cancer**, the surgeon will perform

- a total abdominal hysterectomy* (resection of the uterus)
- bilateral salpingo-oophorectomy* (resection of the ovaries and Fallopian tubes on both sides)
- omentectomy (resection of a large fold of the tissue that lines the bowel)

In addition, as part of the staging procedure, the entire abdominal cavity is evaluated and includes

- assessment of the pelvic and para-aortic* retroperitoneum (the space behind the tissue that lines the abdominal cavity in the region of the pelvis* and the aorta)
- biopsy* sampling of the peritoneum* (the tissue that lines the abdominal cavity)
- peritoneal* washing* (salt-water is used to wash the abdominal cavity and then examined for the presence of malignant* cells)

In selected patients, so-called fertility-sparing surgery can be performed. This means that one ovary and Fallopian tube, as well as the uterus, are preserved. Fertility-sparing surgery may be considered in patients who wish to preserve the ability to conceive and bear children, provided comprehensive surgical staging is performed, the preserved organs are healthy, and the patient is appropriately counseled. Fertility-sparing surgery may be considered as the only treatment for certain types of ovarian cancer, such as germ cell tumours.

**Adjuvant* Chemotherapy***

In patients with stage I ovarian cancer, grade is the strongest indicator for the risk of recurrence*.

- Low risk: stage IA and IB, grade 1
- Medium risk: stage IA and IB, grade 2
- High risk: stage IA grade 3, stage IC all grade 1, 2 or 3; stage IB grade 2 or 3, and clear cell histology

Other clinical factors that determine the risk of recurrence are:

- the occurrence of tumour rupture before surgery or during surgery
- the presence of a tumour on both ovaries
- age at time when tumour presents itself.

Therefore for those patients in whom surgical staging and histopathological examination of the tumour tissue indicate the presence of intermediate-risk or high-risk early disease, it is recommended to give 6 cycles of chemotherapy* with carboplatin*, given intravenously*. Adjuvant* chemotherapy may reduce the risk of recurrence and/or progression.

**Treatment plan for advanced disease (FIGO stages IIB to IIIC)**

At **these stages**, the tumour has extended into pelvic tissues other than the uterus and Fallopian tubes; the tumour has extended into upper abdominal tissues and/or has caused distant metastasis*. The tumour has spread significantly and it is difficult or impossible to surgically remove all tumour growth. Therefore, the goal of the initial treatment for these patients is to maximally remove tumour
tissue through surgery, and to subsequently target remaining tumour cells using chemotherapy*. Chemotherapy is given through a vein and therefore acts systemically on the tumour cells. More and more, part of the chemotherapy is administered before surgery to reduce the extent of the tumour, thus allowing maximal removal of the tumour during surgery.

**Debulking surgery**

As for all patients suspected of ovarian cancer, a laparotomy* is performed for comprehensive surgical staging (see chapter on ‘Staging’). If surgical staging shows and/or confirms **advanced disease**, the initial surgical intervention aims to remove the bulk of the tumour, meaning that the surgeon will try to surgically remove all visible tumour. This procedure is also referred to as maximal (or optimal) cytoreduction.

The extent of the surgical interventions in this procedure, and the likelihood that the surgeon can achieve optimal cytoreduction, depends on the stage of the individual patient. The goal of this procedure is to remove as much as possible of the primary tumour mass, and the term optimal cytoreduction refers to the absence of residual disease (no tumour left).

Standard elements of the procedure are a total abdominal hysterectomy*, bilateral salpingo-oophorectomy*, omentectomy, lymphadenectomy and peritoneal* washing; the procedure may further include (partial) resections of the peritoneum*, liver, spleen, stomach, gallbladder, pancreas, bowel and urinary bladder.

If optimal cytoreduction is not possible, and the patient subsequently either responds or shows stable disease under chemotherapy*, so-called ‘interval debulking* surgery’ should be considered. This means that after three cycles of chemotherapy, patients undergo debulking surgery, which is followed by another three cycles of chemotherapy. This strategy is becoming more widely accepted and more frequently offered to patients, especially when there is extensive tumour dissemination.

**Chemotherapy**

After primary surgical tumour reduction, the standard treatment for patients with advanced ovarian cancer is platinum-based therapy*, in particular a combination of carboplatin* and paclitaxel*, given intravenously* in six cycles. Some patients with extensive tumour dissemination may receive 3 cycles before surgery in order to decrease the extent of the tumour, then undergo surgery and afterwards receive the remaining 3 chemotherapy cycles. For patients who develop an allergy to or do not tolerate paclitaxel, the combination of docetaxel and carboplatin or of pegylated liposomal doxorubicin* and carboplatin can be considered an alternative.

In the USA, it has been suggested that intraperitoneal chemotherapy - the administration of chemotherapy through a surgically implanted flexible tube that allows passage of fluids into the abdomen – should be offered to patients with very limited or no residual disease after surgery. However, a combination of intraperitoneal and intravenous* chemotherapy cannot be considered as standard of care in Europe.

**Targeted therapy**

Bevacizumab* is an antibody* that binds to vascular endothelial growth factor* (VEGF), a growth factor for blood vessels. Ovarian cancer cells produce high amounts of VEGF, which stimulates the formation of new blood vessels in and around the tumour. Blocking VEGF using bevacizumab therefore may prevent this from occurring.
Adding bevacizumab to chemotherapy could be recommended as initial treatment to patients with either stage III cancer and residual tumour of more than 1 cm after debulking* surgery, or stage IV cancer. It should be given with paclitaxel and carboplatin and for one year.

**Treatment plan for metastatic* disease (FIGO stage IV)**

Approximately 15% of patients with ovarian cancer are diagnosed at stage IV (metastatic) disease. As explained in the section of treatment of advanced disease, the treatment outcome at this stage depends also on residual disease after surgery of primary tumour mass, which is followed by chemotherapy* consisting of six cycles of platinum-paclitaxel*. For patients who develop an allergy to or do not tolerate paclitaxel, the combination of docetaxel and carboplatin or of pegylated liposomal doxorubicin* and carboplatin can be considered alternatives. A drug called bevacizumab* could be added to chemotherapy as described in the previous section on advanced disease.

**SPECIFIC ASPECTS IN THE TREATMENT OF SELECTED NON-EPITHELIAL OVARIAN CANCER TYPES**

**Germ cell tumours**

About two thirds of germ cell tumours are diagnosed in stage I: in these patients, fertility-sparing surgery is generally recommended and the complete procedure of surgical staging is not indicated. The high efficacy of the therapies that can be used later in case a germ cell tumour comes back is the main reason for such practice. Adjuvant* treatment for low-risk stage I tumours is not recommended.

In advanced disease, debulking* surgery is performed, followed by Bleomycin*, Etoposide* and cisPlatin (BEP) chemotherapy*. This chemotherapy is administered over a 3-week period (called a cycle). The optimal duration is not clearly defined but 3 cycles of BEP are generally used for patients whose disease has been completely surgically removed. For patients whose disease could not be fully surgically removed, 4 to 5 cycles of BEP regimen (from fourth cycle without bleomycin to reduce the risk of lung toxicity) seem appropriate. Since germ cell tumours are sensitive to chemotherapy, surgery can be fertility-sparing, also in advanced disease. In older, postmenopausal women, however, the treatment follows the standard treatment plan.

For endodermal sinus tumours, a specific subtype of germ cell tumour that grows more aggressively, adjuvant* chemotherapy* is recommended, except for stage IA patients, whose treatment may be followed by monitoring α-fetoprotein* (AFP) levels in the blood.

**Sex cord stromal tumours**

In young patients with a sex cord stromal tumour who seem to have localized disease, fertility-sparing surgery can be considered and full staging is not recommended.

Most of these tumours are diagnosed at stage I and for these patients adjuvant* therapy is not recommended. Some doctors suggest adjuvant therapy with a platinum-based chemotherapy for patients with a stage IC and high grade (grade 3) cancer. The most commonly used regimen is the BEP (Bleomycin*, Etoposide* and cisPlatin) combination but several other combinations of drugs can also be used.
For higher-risk granulosa cell tumours*, adjuvant chemotherapy* with bleomycin*, etoposide and cisplatin or with carboplatin and paclitaxel is indicated.

For Sertoli-Leydig cell tumours, adjuvant chemotherapy should be considered for those patients with stage I and either high grade (grade 3) or heterologous elements reported by the pathologist.

The treatment of advanced disease follows the general treatment guidelines of ovarian cancer. Debulking* surgery, whenever feasible, remains the most effective treatment of metastatic or recurrent granulosa cell tumours. Platinum-based chemotherapy is currently used for patients with advanced stage.

**Carcinosarcoma**

All carcinosarcomas are high-grade, even when diagnosed in stage I. Therefore, adjuvant* chemotherapy* is recommended, with carboplatin* and paclitaxel*. In older patients with a poor general health status, monotherapy with carboplatin may be considered.

**Small-cell and neuro-endocrine** tumours

Standard surgical principles apply. However, for young patients with an isolated ovarian tumour, fertility-sparing surgery may be considered in combination with adjuvant* chemotherapy*. Chemotherapy usually consists of platinum and etoposide*.

**Struma ovarii malignum**

Surgical treatment with hysterectomy* and bilateral salpingo-oophorectomy* is recommended in postmenopausal women and in premenopausal women who no longer have the wish to conceive and bear children. For younger women who do wish to preserve fertility, fertility-sparing surgery may be considered on the condition that there is no spread of the tumour through the capsule of the ovary, and that there is no associated mature cystic teratoma*. More aggressive surgery is indicated for patients in whom the tumour has clearly spread. Adjuvant* therapy is not recommended.

When surgery for struma ovarii malignum is completed, a radio-iodine* whole body scan should be considered. This is an imaging procedure that allows visualizing the presence of thyroid tissue* anywhere in the body. Radioactive iodine*, which is administered intravenously*, is taken up by functional thyroid tissue. This procedure can thus be used to detect residual tumour tissue postoperatively and during follow-up. Prior to the scan, the thyroid gland* is surgically removed (thyroidectomy), to prevent that the majority, if not all, of the iodine is taken up by the thyroid gland rather than by the tumour tissue.

**Squamous cell carcinoma arising within dermoid** cyst*/teratoma*

If the tumour is confined to the ovary and has not ruptured through the capsule of the ovary, treatment is limited and may consist of salpingo-oophorectomy* only. For more advanced disease, standard surgical staging should be performed. If the tumour is not totally removed by primary surgery, repeat surgery is not advised. Adjuvant* chemotherapy* is indicated with platinum-based regimens*; combination therapy with bleomycin*, etoposide* and cisplatin, or with carboplatin* and paclitaxel*.
WHAT ARE THE POSSIBLE SIDE EFFECTS OF THE TREATMENTS?

Surgery

General risks and side effects

Some risks are common for every surgical intervention performed under general anaesthesia*. These complications are unusual and include deep vein thrombosis*, heart or breathing problems, bleeding, infection, or reaction to the anaesthesia. These are prevented by thorough medical evaluation before surgery and appropriate management.

The ovaries, Fallopian tubes and uterus are located in the pelvis* together with lymph nodes*, the bladder, major blood vessels and parts of the bowel. During the surgical intervention, mainly depending on the extent of tumour spread, some of these structures may become damaged. Accurate preoperative staging and imaging will help to minimize such risk.

When lymph nodes in the pelvis* and along the aorta are removed, it can damage or block the lymph system resulting in lymphedema, a condition where lymph fluid accumulates in the legs and makes them swell. This may occur soon after the intervention but also later.

Loss of reproductive function

The standard treatment plan for ovarian cancer involves the surgical removal of both ovaries and Fallopian tubes and of the uterus. As a result, following treatment, ovarian cancer patients will no longer be able to conceive and bear children. Patients will be appropriately counselled and referred to specialized support providers.

In selected patients, fertility-sparing surgery can be performed, meaning that one ovary and Fallopian tube, as well as the uterus, are preserved. Fertility-sparing surgery may be considered in patients who wish to preserve the ability to conceive and bear children, provided comprehensive surgical staging is performed, the preserved organs are healthy, and the patient is appropriately counselled.

The loss of ovarian function following resection of both ovaries also results in the loss of female hormone production. In women of reproductive age, this will lead to loss of menstruation and appearance of menopausal* symptoms. Whether or not hormone replacement therapy* is indicated or contra-indicated* should be carefully evaluated since this will depend on the type of ovarian cancer, the medical condition of the individual patient and the patient’s preference.

Loss of abdominal organs

In patients with advanced stage ovarian cancer, debulking*surgery may include the surgical removal of various abdominal organs affected by the tumour.

The loss of parts of the bowel, part of the liver and loss of the gallbladder may result in gastrointestinal problems. Surgical diversion* of the bowel (ileostomy* or colostomy*) may be necessary to ensure collection and/or evacuation of stool.
Removal of the spleen leads to increased susceptibility for certain infections, and postoperatively, vaccination and preventive antibiotic treatment should be considered.

The loss of urinary bladder function (the storage and evacuation of urine) is less frequent and the need for a surgical diversion* is rare.

Chemotherapy*

The side effects of chemotherapy are very frequent. They will depend on the drug(s) administered and on the dosing and will vary in type and extent for each patient. For patients who have suffered from other medical problems in the past, some precautions should be taken and/or adaptation of the treatment should be made. Combinations of different drugs usually lead to more side effects than the use of a single drug. For some side effects, there are means to prevent or limit them, and this should be discussed beforehand with doctors and nurses.

Listed below are the general side effects that are known to occur with the chemotherapy drugs most commonly used for the treatment of ovarian cancer. The nature, frequency and severity of the side effects vary for each chemotherapeutic drug.

The most frequent side effects are:

- Hair loss or hair thinning (except for carboplatin* for which it is rare)
- Decreased blood cell counts, which may lead to anaemia*, bleeding and bruising, and infections
- Tiredness
- Feeling sick or actual vomiting

Other side effects that may occur frequently include:

- Mouth sores or ulcers
- Loss of taste or changed taste (metallic)
- Diarrhoea
- Numbness or tingling in fingers and toes (peripheral neuropathy*)
- Aches and pains in joints and muscles
- Mild allergic reactions with rash, red face, fever or chills
- Inflammation of the skin around the insertion of the drip
- Skin reactions with reddening, darkening or thickening

Occasional side effects include:

- Changes in liver function
- Inflammation of the lungs causing cough, shortness of breath, and chest pain (bleomycin*)
- Constipation
- Blurred vision
- Severe allergic reaction
- Low blood pressure (possibly causing dizziness)
- Slowing heart rate
- Abdominal pain
• **Headache**

Finally, for women that have received fertility-sparing surgery, it should be noted that some chemotherapeutic* drugs may affect the remaining ovary and cause infertility. Also some chemotherapeutic drugs may damage a developing baby in the womb, and/or may have a harmful effect on a baby if it is being breastfed because they can pass into the breast milk.

Apart from these, each drug can also have different unwanted effects. The most common ones are listed below, although not everyone will have side effects, or experience them to the same extent.

Paclitaxel* can cause peripheral neuropathy* which is dependent upon the dose administered, the duration of the infusion, and the schedule of administration. Symptoms which may present themselves include numbness, paraesthesia* and burning pain in the hands and legs, as if burning gloves and burning stockings were worn. Symptoms are often symmetrical, and usually start in the feet and legs. Patients commonly report the simultaneous onset of symptoms in toes and fingers, but asymmetric occurrences have been described too. Facial involvement is less common. Although mild symptoms have been reported to improve or resolve completely within several months after discontinuation of therapy, the symptoms and deficits have been reported to persist longer in patients who develop severe neuropathy.

Carboplatin* given with paclitaxel* increases the risk of neuropathy*.

Cisplatin* may lead to hearing loss, and to kidney damage. The kidney function is examined in the blood before starting the treatment. To prevent damage it is very important to drink a lot of water during the treatment.

Severe side effects that can occur when using topotecan* include severe allergic reactions, blue or unusually pale skin or nails, fever, chills, or persistent sore throat, painful or burning urination, persistent or severe cough, persistent or severe pain, redness, or swelling at the injection site, persistent or severe stomach pain or cramps, persistent or severe tiredness or weakness, shortness of breath, unusual or unexplained bruising or bleeding, and yellowing of the eyes or skin.

Common side effects of bleomycin* are chills, confusion, dark bands in nails, hair loss, itching, loss of appetite, redness, darkening, or tenderness of the skin, sore mouth, tiredness, and weight loss. The dose of bleomycin that can be administered is limited because of the possibility of development of pulmonary fibrosis, leading to shortness of breath, when it should be reported to your doctor. Hypersensitivity to bleomycin has also been recognised, but it is not dose dependent and usually occurs within hours of administration.

Administration of the drug ifosfamide* should be accompanied by a drug protecting the urinary tract. Medical advice should be sought if blood appears in the urine, or the urine is dark; if coma or confusion are induced, or if lower amount of urine is produced. The drug can also cause yellowing of the skin or eyes.
Bevacizumab*

The most common side effects of bevacizumab* are hypertension, generalized weakness, pain, abdominal pain, nausea and vomiting, poor appetite, constipation, upper respiratory infection, low white blood cell count (which can increase risk for infection), proteinuria, nose bleed, diarrhoea, hair loss, mouth sores and headache.

There are also rare but serious complications of bevacizumab* therapy which include
- gastrointestinal perforation;
- fistula formation;
- wound healing complications;
- severe bleeding;
- hypertensive crisis (severe high blood pressure);
- nephrotic syndrome - a condition marked by very high levels of protein in the urine (proteinuria), low levels of protein in the blood, swelling, especially around the eyes, feet and hands; this syndrome is caused by damage to the tiny blood vessels in the kidney that filter waste and excess water from the blood and send them to the bladder as urine.
WHAT HAPPENS AFTER THE TREATMENT?

It is not unusual for cancer patients to experience treatment-related symptoms after the treatment has been completed.

- Patients may experience anxiety, sleeping difficulty or depression, and may need psychological support.
- During and after treatment, nutrition may become problematic due to reduced appetite, nausea and general malaise
- Difficulties with concentration and memory are not uncommon side effects of intravenous* chemotherapy*.

Follow-up with doctors

After completion of treatment the doctor will propose a follow-up that aims to:

- detect and prevent adverse effects of the treatment
- detect possible recurrence* and direct appropriate treatment
- provide medical information, psychological support and referral to specialized support providers to optimize returning to normal daily life.

Because of the heterogeneity of the different types of ovarian cancer, there is not one single and generally accepted follow-up protocol for patients.

The follow-up protocol for epithelial ovarian cancer includes taking a history of the patients general physical health and symptoms related to disease and physical examination including bimanual pelvic examination* every 3 months for 2 years, every 4 months during the third year and every 6 months during years 4 and 5. Measurement of CA125 is useful in follow-up of responders after completion of chemotherapy*, since it has been shown to be predictive of ovarian cancer recurrence. Progression or recurrence* of disease based on serum CA125 is defined on the basis of progressive serial elevation of serum CA125. Elevated values must be confirmed by two separate measurements obtained at least 1 week apart. If CA125 rises, chemotherapy can be delayed until signs or symptoms of tumour recurrence present themselves. However, it is important to note that potentially resectable recurrence can be signalled by a CA125 rise, therefore informed choices should be offered.

CT* scan should be performed if there is clinical or CA125 evidence for progressive disease. PET*-CT seems to be superior to CT in detecting more tumour sites, especially in lymph nodes, peritoneal* and subcapsular* liver disease.

Specificities in follow-up of patients with non-epithelial ovarian cancer

Typically, follow-up is the same as for epithelial ovarian carcinoma, although in some cases it may vary. Follow-up visits must include taking a history of the patients general physical health and symptoms related to disease, physical examination with pelvic examination* and tumour markers every 3 months for the first 2 years, then every 6 months during the third, fourth and fifth year. A pelvic ultrasound* should be carried out every 6 months in those patients who have undergone fertility-sparing surgery, whereas a CT-scan* of the abdomen and pelvis is usually carried out according to clinical indication. Approximately 75% of germ cell tumour recurrences occur within the first year after initial treatment. Conversely, the indolent nature of sex cord stromal tumours with the tendency for late recurrence (the median time to recurrence is approximately 4 to 6 years)
requires long-term follow-up. Several reports describe recurrences occurring >20 years (up to 37 years) after diagnosis.

Many granulosa cell tumours\* are slow-growing tumours, and could recur after many years, often up to 20 years after diagnosis. Measurement of estradiol\*, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and inhibin\* is used, but they are most reliable in postmenopausal patients and in patients in whom both ovaries have been removed.

In patients with ovarian neuro-endocrine* tumours, a scan with octreotide (octreoscan) is performed postoperatively to detect tumour cells that might be persisting elsewhere in the body (see also paragraph ‘How is ovarian cancer diagnosed’). A radio-actively labelled drug called octreotide is administered intravenously*; the drug attaches to the neuro-endocrine* tumour cells in the patient’s body, and this technique thus allows for testing and specifically visualizing neuro-endocrine tumour cells anywhere in the body. Standard work-up also includes GUT hormone analysis*.

In patients treated for a germ cell tumour, measurement of hCG*, AFP* and LDH* may help in detecting recurrence* of the disease. MRI* has been used more often than CT to avoid radiation in this usually young group of patients.

In patients with struma ovarii malignum, clinical examination and thyroid hormone replacement* in doses that fully suppress thyroid-stimulating hormone (TSH) is needed. Serial measurement of thyroglobulin* (Tg) level has replaced whole body radio-iodine* scintigraphy. Follow-up is lifelong, principally to monitor thyroid function and Tg.

The recommended follow-up for patients treated for squamous cell carcinoma arising within dermoid* cysts* is 5 years, with clinical and imaging examinations.

**Returning to normal life**

Returning to a normal daily life may be difficult knowing that the cancer may come back.

Follow-up visits with the doctor provide an opportunity for the patient to obtain medical information, psychological support and referral to specialized support providers. Additional expert psychological advice may be valuable, and some patients may find support in patient groups or patient-targeted information media. Dieticians may provide advice on adequate nutrition. Social workers may help in finding resources to ensure successful rehabilitation.

Concerns can emerge regarding a possible risk for the patient’s relatives. In most cases, the risk is very low for relatives since 90% of ovarian cancers are not linked to any inherited gene mutation*. However, patients with cancer linked to an inherited mutation, and patients who are concerned about this possibility should discuss with their doctor what is recommended for their relatives.

**What if the cancer comes back?**

When the cancer returns, it is called ‘recurrence*’. The treatment decision will depend on the type of ovarian cancer, the timing and the nature of the recurrence, the extent to which the patient received and responded to prior chemotherapy*, and the general health status of the patient. These factors should be carefully determined for each individual patient.

In addition, particular attention should be given to side effects of the treatment, which may become more important when treatment intensifies. In particular, patients receiving a repeated regimen of
platinum/paclitaxel* combination chemotherapy within one year after completing the first one, run a significant risk of developing toxic side effects within the nervous system*.

As part of a personalized treatment plan, the doctor will at all times discuss the realistic treatment options for the individual patient. Where possible, the patient’s own preference should be respected in directing the treatment choice.

Depending on the individual situation, the treatment for recurring epithelial ovarian cancer may include the following approaches:

- **Surgical resection of the recurring tumour.**

  This may be considered in patients that have responded well to previous chemotherapy treatment, particularly those who develop an isolated recurrence long after the treatment has finished, and otherwise have a good general health status. Surgical intervention may be needed to relieve symptoms from, for example, bowel obstruction caused by the tumour.

- **Chemotherapy**

  The choice of the type of chemotherapy depends on the time between the last dose of the platinum-based chemotherapy administered the first time and the time of disease recurrence. The four categories defined according to this time interval are described below, together with the treatment options for each situation.

  The disease is considered **platinum-refractory** when the tumour progresses during chemotherapy or within 4 weeks after the last dose, and **platinum-resistant** when a recurrence develops less than 6 months after the last dose. The treatment plan for these patients should be focused on providing individualised supportive care, which should aim to maintain and/or improve quality of life and control symptoms. Drugs that can be used are paclitaxel, topotecan, pegylated liposomal doxorubicin* and gemcitabine. As no treatment has proven to be superior to another, the choice of the treatment should be based on the patient’s needs after discussion of the expected side effects and the convenience of drug administration. There is no benefit of combining several drugs at a time.

  The disease is considered **partially platinum-sensitive** when a recurrence develops between 6 and 12 months after the last dose and **platinum-sensitive** when a recurrence develops more than 12 months after the last dose. These patients have a high probability of responding again to platinum-containing* chemotherapy. The preferred regimen is the combination of carboplatin with paclitaxel but other combinations can be proposed after discussion of the expected side effects and the convenience of drug administration. In particular, the combination of carboplatin and pegylated liposomal doxorubicin* showed lower rates of long-lasting side effects. Patients with partially platinum-sensitive disease may also benefit from being treated with a combination of trabectedin* and pegylated liposomal doxorubicin.

- **Targeted therapy***

  At time of recurrence, bevacizumab* can be recommended to patients with platinum-sensitive disease if they did not receive bevacizumab before. The benefit of bevacizumab at time of recurrence for patients with platinum-refractory disease is unclear.

  The treatment of recurrence of non-epithelial cancers should be evaluated for each individual subtype. Recommendations for specific situations include:

  - For small cell cancers, treatment of recurrence is ifosfamide*-based (vincristine*, ifosfamide, carboplatin* and etoposide* or VICE). In patients with poor general health
status, chemotherapy* with cyclophosphamide, doxorubicin*, vincristine* and etoposide (CAVE) is an option.

- In patients with **Germ cell tumour**, previously treated with platinum, who had a recurrence more than 6 months after the end of the chemotherapy, ifosfamide/platinum (IP) with or without paclitaxel should be considered. Further active chemotherapy regimens include: vinblastine, ifosfamide, and cisplatin (VeIP), or cisplatin, vinblastine and bleomycin (PVB). Patients who had a recurrence less than 6 months after the end of the platinum-based chemotherapy may receive vincristine, actinomycin D and cyclophosphamide (VAC), or paclitaxel and gemcitabine. It is unclear if a new debulking* surgery might be beneficial. It may have some benefits in some patients, particularly in those with immature teratoma and a growing teratoma syndrome.

- In patients with carcinosarcoma* of the ovary, ifosfamide* has shown activity in recurrent disease.

- In patients with sex cord and stromal tumours, carboplatin* and paclitaxel* have shown activity as second line chemotherapy. The utility of chemotherapy in patients with persistent Sertoli-Leydig tumours is not clear, but some improvements in patients have been reported. Since granulosa cell tumours express steroid hormone receptors, hormone therapy has been considered. Indeed, some patients treated with gonadotropin-releasing hormone agonists, tamoxifen, progestins or aromatase inhibitors have shown to benefit from these therapies.

- In patients with squamous cell carcinoma rising within a dermoid* cyst*/teratoma, pelvic radiation is used in case of isolated pelvic recurrence.
DEFINITIONS OF MEDICAL TERMS

5-fluorouracil
A drug used to treat symptoms of cancer of the colon, breast, stomach, and pancreas. It is also used in a cream to treat certain skin conditions. 5-fluorouracil stops cells from making DNA* and it may kill cancer cells. It is a type of antimetabolite. Also called 5-FU and fluorouracil.

α-fetoprotein (AFP)
A protein normally produced by a foetus. AFP levels are usually undetectable in the blood of healthy adult men or women (who are not pregnant). An elevated level of AFP suggests the presence of either a primary liver cancer or germ cell tumour.

Adenomyosis
Medical condition in which endometrial tissue which composes the normal lining of the uterus and should only be found there, is also found within the muscle of the uterus, causing pain and discomfort, and sometimes excessive bleeding during menses.

Adjuvant therapy
An adjuvant therapy in cancer treatment is a therapy that helps another therapy to reach its ultimate goal, that is, it reinforces its effect. For example radio or/and chemotherapy help a surgery to accomplish its goal of eliminating a cancerous tumour.

Androgen
A type of hormone that promotes the development and maintenance of male sex characteristics.

Anaemia
Condition characterized by the shortage of red blood cells* or haemoglobin, the iron that contains the haemoglobin carries oxygen from the lungs to the whole body; this process is diminished in this condition.

Anaesthesia
Reversible state of loss of awareness in which the patient feels no pain, has no normal reflexes, and responds less to stress. Anaesthesia is induced artificially by the employment of certain substances known as anaesthetics. It can be complete or partial and allows patients to undergo surgery.

Appendix
A small, fingerlike pouch that sticks out from the cecum (the first part of the large intestine near the end of the small intestine).

Ascites
Abnormal buildup of fluid in the abdomen that may cause swelling. In late-stage cancer, tumour cells may be found in the fluid in the abdomen. Ascites also occurs in patients with liver disease.

Benign
Not cancerous. Benign tumours may grow larger, but do not spread to other parts of the body. Also called nonmalignant.

Bevacizumab
Bevacizumab is a monoclonal antibody* that has been designed to recognize and attach itself to a specific structure (called an antigen) that is found in certain cells in the body or is circulating in the body. Bevacizumab has been designed to attach to vascular endothelial growth factor (VEGF*), a protein that circulates in the blood and makes blood vessels grow. By attaching to VEGF, bevacizumab stops it having an effect. As a result, the cancer cells cannot develop their own blood supply and are starved of oxygen and nutrients, helping to slow down the growth of tumours.

**Bilateral salpingo-oophorectomy**
Surgery to remove both ovaries and both fallopian tubes.

**Biopsy**
The removal of cells or tissues* for examination by a pathologist*. The pathologist may study the tissue* under a microscope or perform other tests on the cells or tissue*. There are many different types of biopsy procedures. The most common types include: (1) incisional biopsy, in which only a sample of tissue* is removed; (2) excisional biopsy, in which an entire lump or suspicious area is removed; and (3) needle biopsy, in which a sample of tissue or fluid is removed with a needle. When a wide needle is used, the procedure is called a core biopsy. When a thin needle is used, the procedure is called a fine-needle aspiration biopsy.

**Bleomycin**
The active ingredient in a drug that is used to treat many types of cancer and is being studied in the treatment of other types of cancer. It comes from the bacterium Streptomyces verticillus. Bleomycin damages DNA and may kill rapidly growing cancer cells. It is a type of antineoplastic antibiotic.

**Borderline tumour / Ovarian borderline malignant tumour**
A condition in which cells that may become cancerous form in the thin layer of tissue that covers an ovary. In this condition, tumour cells rarely spread outside of the ovary. Also called ovarian low malignant potential tumour.

**Calretinin proteins**
Proteins which are dependent on vitamin D and bind to calcium. They exist abundantly in neurons. Calretinin is also present in steroid producing cells, such as some ovarian cells. Measuring its level of expression in ovarian tissue can help making the exact diagnosis of some ovarian tumours.

**Carboplatin**
A drug that is used to treat advanced ovarian cancer that has never been treated, or symptoms of ovarian cancer that have come back after treatment with other anticancer drugs. It is also used with other drugs to treat advanced, metastatic*, or recurrent* non-small cell lung cancer and is being studied in the treatment of other types of cancer. Carboplatin is a form of the anticancer drug cisplatin* and causes fewer side effects in patients. It attaches to DNA* in cells and may kill cancer cells. It is a type of platinum compound.

**Carcinosarcoma**
A malignant* tumour that is a mixture of carcinoma (cancer of epithelial tissue, which is skin and tissue* that lines or covers the internal organs) and sarcoma* (cancer of connective tissue*, such as bone, cartilage and fat).

**CD99 proteins**
Proteins present in almost all human tissues and highly expressed in some cancers. Measuring its level of expression in ovarian tissue can help making the exact diagnosis of some ovarian tumours.

Chemotherapy
A type of cancer treatment using drugs that kill cancer cells and/or limit their growth. These drugs are usually administered to the patient by slow infusion into a vein but can also be administered orally, by direct infusion to the limb or by infusion to the liver, according to cancer location.

Chromosome
An organized structure which encodes genes which are the body's code for characteristics such as hair color or gender. Human cells have 23 pairs of chromosomes (total of 46 chromosomes). Cancer or leukemia cells often have a chromosomal abnormality which is a change to their chromosomes, such as a chromosomal duplication or an extra chromosome (47 chromosomes) or have a chromosomal deletion or a loss of a chromosome (45 chromosomes). A chromosomal or genetic inversion is when no extra chromosomes are added or deleted, but instead a portion is backwards.

Cisplatin
A drug used to treat many types of cancer. Cisplatin contains the metal platinum. It kills cancer cells by damaging their DNA* and stopping them from dividing. Cisplatin is a type of alkylating agent.

Clinical trial
A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease. Also called clinical study.

Colostomy
An opening into the colon from the outside of the body. A colostomy provides a new path for waste material to leave the body after part of the colon has been removed.

Computed tomography (CT-scan)
A form of radiography in which body organs are scanned with X-rays and the results are synthesised by a computer to generate images of parts of the body. Also called CT scan.

Contraindication
Condition or symptom that prevents the administration of a given treatment or procedure to the patient. Contraindications are either absolute, meaning the treatment should never be given to patients with this condition or symptom, or relative, meaning that the risk can be outweighed by the benefits in some patients with this condition or symptom.

Cortisol
A hormone made by the adrenal cortex (the outer layer of the adrenal gland). It helps the body use glucose, protein, and fats. Cortisol made in the laboratory is called hydrocortisone. It is used to treat many conditions, including inflammation, allergies, and some cancers. Cortisol is a type of glucocorticoid hormone.

Cushing syndrome
A condition in which there is too much cortisol* in the body. Cushing syndrome may be caused by taking too many steroid drugs or by certain types of tumors. Tumors that make adrenocorticotropic hormone (ACTH) cause the adrenal gland to make too much cortisol*. Symptoms of Cushing syndrome include a round face, thin arms and legs, severe fatigue and muscle weakness, high blood pressure, high blood sugar, purple or pink stretch marks on the skin, and weight gain, especially in the abdomen.

**Cyst**
A sac or capsule in the body. It may be filled with fluid or other material.

**Debulking surgery**
Surgical removal of as much of a tumor as possible. Debulking may increase the chance that chemotherapy or radiation therapy will kill all the tumor cells. It may also be done to relieve symptoms or help the patient live longer. Also called tumor debulking.

**Deep vein thrombosis**
The formation of a blood clot in a deep vein of the leg or lower pelvis*. Symptoms may include pain, swelling, warmth, and redness in the affected area. Also called DVT.

**Dermoid cyst**
A type of benign (non-cancerous) germ cell tumour (type of tumour that begins in the cells that give rise to sperm or eggs) that often contains several different types of tissue such as hair, muscle, and bone. Also called mature teratoma*.

**DNA**
Abbreviation for deoxyribonucleic acid. DNA serves as the carrier of genetic information.

**Docetaxel**
Docetaxel belongs to the group of anticancer medicines known as the taxanes*. Docetaxel blocks the ability of cells to destroy the internal ‘skeleton’ that allows them to divide and multiply. With the skeleton still in place, the cells cannot divide and they eventually die. Docetaxel also affects non-cancer cells such as blood cells, which can cause side effects.

**Doxorubicin**
A drug that is used to treat many types of cancer and is being studied in the treatment of other types of cancer. Doxorubicin comes from the bacterium Streptomyces peucetius. It damages DNA* and may kill cancer cells. It is a type of anthracycline* antitumour antibiotic. Also called Adriamycin PFS, Adriamycin RDF, doxorubicin hydrochloride, hydroxydaunorubicin, and Rubex.

**Dysgenetic gonad/ Gonadal dysgenesis**
Abnormal development of a gonad (ovary or testicle). Men with gonadal dysgenesis have a greater risk of developing testicular cancer. Gonadal dysgenesis is usually part of a genetic syndrome.

**Dyspepsia**
Dyspepsia is also known as upset stomach. It is a condition that mainly involves chronic or recurrent pain in the upper abdomen, together with bloating, heartburn or nausea. Dyspepsia is a common problem, but in rare cases it can be a first symptom of cancer.

**Endometriosis**
A benign condition in which tissue that looks like endometrial tissue grows in abnormal places in the abdomen

**Epithelium**
The term "epithelium" refers to cells that line hollow organs and glands and those that make up the outer surface of the body. Epithelial cells help to protect or enclose organs. Most produce mucus or other secretions.

**Estradiol**
Estradiol is a sex hormone. Generally, it is considered a female sex hormone, but it is also found in men. Estradiol has many uses, e.g., it is important for breast development and the growth of female reproductive organs.

**Estrogen**
A type of hormone made by the body that helps develop and maintain female sex characteristics and the growth of long bones. Estrogens can also be made in the laboratory. They may be used as a type of birth control and to treat symptoms of menopause*, menstrual disorders, osteoporosis and other conditions.

**Etoposide**
A drug used to treat testicular and small cell lung cancers. It is also being studied in the treatment of several other types of cancer. Etoposide blocks certain enzymes needed for cell division and DNA repair, and it may kill cancer cells. It is a type of podophyllotoxin derivative and a type of topoisomerase inhibitor.

**Fertility drug**
Medication used to enhance the capability of producing offspring. In women these drugs stimulate ovulation.

**Gemcitabine**
The active ingredient in a drug that is used to treat pancreatic cancer that is advanced or has spread. It is also used with other drugs to treat breast cancer that has spread, advanced ovarian cancer, and non-small cell lung cancer that is advanced or has spread. It is also being studied in the treatment of other types of cancer. Gemcitabine blocks the cell from making DNA and may kill cancer cells. It is a type of antimetabolite.

**Germ cell**
Germ cells are cells that are responsible for reproduction; they include both egg cells and sperm cells.

**Granulosa cells**
Oestrogen-secreting cells that are part of the lining tissue of the follicles of the ovaries. They supply nutrients to the egg cell (oocyte) involved in reproduction.

**GUT (hormone analysis)**
Group of hormones produced in the stomach, pancreas and intestines, also called GUT hormones.

**Histological type**
The category in which a tumour is grouped, considering the characteristics of its cells and other structures under the microscope.

**Hormone replacement therapy**
A therapy where hormones are given to relieve certain symptoms, e.g. menopausal symptoms.

**Human chorionic gonadotropin (hCG)**
A hormone found in the blood and urine during pregnancy. It may also be found in higher than normal amounts in patients with some types of cancer, including testicular, ovarian, liver, stomach, and lung cancers, and in other disorders. Measuring the amount of beta-human chorionic gonadotropin in the blood or urine of cancer patients may help to diagnose cancer and find out how well cancer treatment is working. Beta-human chorionic gonadotropin is a type of tumour marker. Also called beta-hCG.

**Hyperplasia**
An abnormal increase in the number of normal cells in an organ or tissue.

**Hysterectomy**
Surgical procedure to remove the uterus and, sometimes, the cervix. If both the uterus and the cervix are removed, it is called total or simple hysterectomy. If only the uterus is removed, then it is called partial or supracervical hysterectomy. Radical hysterectomy is the removal of the uterus, cervix, and part of the vagina. The ovaries, fallopian tubes, and nearby lymph nodes* may also be removed.

**Hysteroscopy**
Examination of the uterine cavity through the cervix, with a thin tube called endoscope. This procedure can be used in the diagnosis of diseases of the uterine cavity as well as support for a surgical intervention.

**Ifosfamide**
A drug that is used with other drugs to treat germ cell testicular cancer that did not respond to previous treatment with other drugs. It is also being studied in the treatment of other types of cancer. Ifosfamide attaches to DNA in cells and may kill cancer cells. It is a type of alkylating agent and a type of antimetabolite.

**Ileostomy**
An opening into the ileum, part of the small intestine, from the outside of the body. An ileostomy provides a new path for waste material to leave the body after part of the intestine has been removed.

**Immunohistochemistry**
A technique used to identify specific molecules in different kinds of tissue. The tissue is treated with antibodies that bind the specific molecule. These are made visible under a microscope by using a color reaction, a radioisotope, colloidal gold, or a fluorescent dye. Immunohistochemistry is used to help diagnose diseases, such as cancer, and to detect the presence of microorganisms. It is also used in basic research to understand how cells grow and differentiate (become more specialized).

**Incidence**
The number of new cases of a disease diagnosed each year.

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Inhibin
Hormone that belongs to the family of transforming growth factor beta (TGFβ) hormones produced principally by the ovaries. It down-regulates FSH synthesis and inhibits FSH secretion and it has tumour suppressor activity.
Inhibin consists of two subunits, alpha and either beta A or beta B (inhibin A and B). Inhibin and free alpha subunit are known products of two ovarian tumours, so that they might be used as markers of the disease.

Intravenous
Into or within a vein. Intravenous usually refers to a way of giving a drug or other substance through a needle or tube inserted into a vein. Also called IV.

Invasive
Cancer that has spread beyond the layer of tissue in which it developed and is growing into surrounding, healthy tissues.

Karyotype
It is the set (number and appearance) of the chromosomes or genetic material of a cell.

Lactate dehydrogenase (LDH)
One of a group of enzymes found in the blood and other body tissues and involved in energy production in cells. An increased amount of lactate dehydrogenase in the blood may be a sign of tissue damage and some types of cancer or other diseases. Also called lactic acid dehydrogenase and LDH.

Laparoscopy
An operation where surgical instruments are introduced in the abdomen or in the pelvis through small incisions and with the help of a camera. A type of keyhole surgery.

Laparotomy
A surgical incision made in the wall of the abdomen.

Leydig cells
Type of cells that are part of the structure of the tubules of the testicles. They produce testosterone in the presence of luteinizing hormone (LH).

Lymphadenectomy
A surgical procedure in which the lymph nodes are removed and a sample of tissue is checked under a microscope for signs of cancer. For a regional lymph node dissection, some of the lymph nodes in the tumour area are removed; for a radical lymph node dissection, most or all of the lymph nodes in the tumour area are removed. Also called lymph node dissection.
A rounded mass of lymphatic tissue* that is surrounded by a capsule of connective tissue. Lymph nodes filter lymph (lymphatic fluid), and they store lymphocytes (white blood cells). They are located along lymphatic vessels. Also called lymph gland.

**Magnetic Resonance Imaging (MRI)**
An imaging technique that is used in medicine. It uses magnetic resonance. Sometimes a fluid is injected that enhances the contrast between different tissues* to make structures more clearly visible.

**Malignant/ Malignancy**
Malignant is used to describe a severe and progressively worsening disease. A malignant tumour is synonym for cancer.

**Marker**
A diagnostic indication that a disease may develop.

**MelanA proteins**
A protein found on normal melanocytes (cells that make the pigment melanin) in the skin and in the retina. It is also found on most melanomas (cancers that begin in melanocytes). Vaccines using pieces of the Melan-A protein are being studied for their ability to boost the immune response to cancer cells in patients with melanoma. Also called MART-1 antigen and Melanoma Antigen Recognized by T cells 1.

**Menarche**
First menstrual cycle (period) in a woman’s life. Usually occurring during puberty.

**Menopause**
The time of life when a woman’s ovaries stop producing hormones and menstrual periods stop. Natural menopause usually occurs around age 50. A woman is said to be in menopause when she hasn’t had a period for 12 months in a row. Symptoms of menopause include hot flashes, mood swings, night sweats, vaginal dryness, trouble concentrating, and infertility.

**Mesentery/mesenteric membrane**
The peritoneal* membrane that attaches the intestines to the abdominal wall near the back.

**Metastasis**
The spread of cancer from one part of the body to another. A tumour formed by cells that have spread is called a metastatic tumour or a metastasis. The metastatic tumour contains cells that are like those in the original tumour.

**Monoclonal antibody**
Monoclonal antibodies are antibodies that are exactly the same because they are produced by clones of the same parent cell.

**Multidisciplinary opinion/team**
A treatment planning approach in which a number of doctors who are experts in different specialties (disciplines) review and discuss the medical condition and treatment options of a patient. In cancer treatment, a multidisciplinary opinion may include that of a medical oncologist (who provides cancer treatment with drugs), a surgical oncologist (who provides cancer treatment with surgery), and a
radiation oncologist (who provides cancer treatment with radiation). Also called tumour board review.

**Mutation**
A change in the sequence of base pairs in the DNA* that makes up a gene. Mutations in a gene do not necessarily change the gene permanently.

**Nervous system**
The organized network of nerve tissue in the body. It includes the central nervous system (the brain and spinal cord), the peripheral nervous system (nerves that extend from the spinal cord to the rest of the body), and other nerve tissue.

**Neuro-endocrine (tumours)**
Having to do with the interactions between the nervous system and the endocrine system. Neuroendocrine describes certain cells that release hormones into the blood in response to stimulation of the nervous system.

**Omentum**
A fold of the peritoneum* (the thin tissue that lines the abdomen) that surrounds the stomach and other organs in the abdomen.

**Paclitaxel**
A drug used to treat breast cancer, ovarian cancer, and AIDS-related Kaposi sarcoma*. It is also used together with another drug to treat non-small cell lung cancer. Paclitaxel is also being studied in the treatment of other types of cancer. It blocks cell growth by stopping cell division and may kill cancer cells. It is a type of antimitotic agent.

**Palliative (therapy)**
Treatment given to relieve the symptoms and reduce the suffering caused by cancer and other life-threatening diseases. Palliative cancer therapies are given together with other cancer treatments, from the time of diagnosis, through treatment, survivorship, recurrent* or advanced disease, and at the end of life.

**Para-aortic lymph nodes**
Lymph node* group that is located right in front of the lumbar vertebrae, near the aorta.

**Paracolic gutters**
The spaces between the ascending and descending colon (lateral parts of the colon) and the abdominal wall.

**Paresthesia**
An abnormal touch sensation, such as burning or prickling, that occurs without an outside stimulus.

**Pathologist**
A doctor specialized in histopathology; the study of diseased cells and tissues using a microscope.

**Pegylated liposomal doxorubicin**
A form of the anticancer drug doxorubicin that is contained in very tiny, fat-like particles. It may have fewer side effects and work better than doxorubicin. It is also called liposomal doxorubicin.
Liposomal doxorubicin hydrochloride. It is used to treat ovarian cancer, AIDS-related Kaposi sarcoma, and multiple myeloma in patients whose disease has not gotten better after treatment with other anticancer drugs. It may be used together with other anticancer drugs. It is also being studied in the treatment of other types of cancer. Liposomal doxorubicin hydrochloride is a type of anthracycline antitumor antibiotic.

**Pelvic/Gynaecological examination**
A physical examination in which the health care professional will feel for lumps or changes in the shape of the vagina, cervix, uterus, fallopian tubes, ovaries, and rectum. The health care professional will also use a speculum* to open the vagina to look at the cervix and take samples for a Pap test*.

**Pelvic inflammatory disease**
A condition in which the female reproductive organs are inflamed. It may affect the uterus, fallopian tubes, ovaries, and certain ligaments. Pelvic inflammatory disease is usually caused by a bacterial infection. It may cause infertility and an increased risk of an ectopic pregnancy (pregnancy in the fallopian tubes).

**Pelvis**
The lower part of the abdomen, located between the hip bones.

**Peripheral neuropathy**
A nerve problem that causes pain, numbness, tingling, swelling, or muscle weakness in different parts of the body. It usually begins in the hands or feet and gets worse over time. Peripheral neuropathy may be caused by physical injury, infection, toxic substances, disease (such as cancer, diabetes, kidney failure, or malnutrition), or drugs, including anticancer drugs. Also called neuropathy.

**Peritoneal**
Having to do with the parietal peritoneum (the tissue that lines the abdominal wall and pelvic cavity) and visceral peritoneum (the tissue that covers most of the organs in the abdomen, including the intestines). Intra peritoneal chemotherapy – treatment given into the peritoneum.

**Peritoneal washing**
Procedure performed during surgery where salt solution is introduced into the peritoneal* cavity and then removed by suction. The fluid removed is then analysed in the laboratory to look for cancer cells.

**Peritoneum**
The tissue that lines the abdominal wall and covers most of the organs in the abdomen.

**Platinum-based therapy/ regimens**
Treatment that uses drugs that are derived from the element platinum. It includes cisplatin*, carboplatin and oxaliplatin.

**Pleural effusion**
An abnormal collection of fluid between the thin layers of tissue (pleura) lining the lung and the wall of the chest cavity.

**Positron-emission tomography (PET)**
A procedure in which a small amount of radioactive glucose (sugar) is injected into a vein, and a scanner is used to make detailed, computerized pictures of areas inside the body where the glucose...
is used. Because cancer cells often use more glucose than normal cells, the pictures can be used to find cancer cells in the body. Also called PET scan.

Pre-malignant
A term used to describe a condition that may (or is likely to) become cancer. Also called precancerous.

Prognosis
The likely outcome or course of a disease; the chance of recovery or recurrence*.

Protein
Essential nutrients that are made of amino acids. They are essential for the functioning of many organisms including the human body. They are responsible for transport and communication between cells, for chemical changes and they also maintain the structure of cells.

Radioactive iodine
A radioactive form of iodine, often used for imaging tests or to treat an overactive thyroid, thyroid cancer, and certain other cancers. For imaging tests, the patient takes a small dose of radioactive iodine that collects in thyroid cells and certain kinds of tumours and can be detected by a scanner. To treat thyroid cancer, the patient takes a large dose of radioactive iodine, which kills thyroid cells. Radioactive iodine is also used in internal radiation therapy for prostate cancer, intraocular (eye) melanoma, and carcinoid tumours. Radioactive iodine is given orally as a liquid or in capsules, by infusion, or sealed in seeds, which are placed in or near the tumour to kill cancer cells.

Recurrence
Cancer or disease (usually auto-immune) that has come back, usually after a period of time during which the cancer or disease was not present or could not be detected. This may happen in the same location as the original (primary) tumour or to another location in the body. Also called recurrent cancer or disease.

Sertoli cells
Cells of support located in the testes. Sertoli cells arise from the sex cord, which is the embryonic structure later developing into testes in males and ovaries in females.

Subcapsular (liver disease)
Area beneath the external membrane that covers up the liver. It refers to the pathologies developed in that area.

Surgical diversion (digestive and urinary)
Re-routing of the urinary or digestive stream surgically created. It might involve the creation of an opening in the abdomen to which the contents of the urinary or digestive system will be released to be collected in a bag outside the body.

Targeted therapy
A type of treatment that uses drugs or other substances, such as monoclonal antibodies*, to identify and attack specific cancer cells. Targeted therapy may have fewer side effects than other types of cancer treatments.
Teratoma
A type of germ cell tumour that may contain several different types of tissue, such as hair, muscle, and bone. Teratomas occur most often in the ovaries in women, the testicles in men, and the tailbone in children. Not all teratomas are malignant.

Testosterone
A hormone made mainly in the testes (part of the male reproductive system). It is needed to develop and maintain male sex characteristics, such as facial hair, deep voice, and muscle growth. Testosterone can also be made in the laboratory and is used to treat certain medical conditions.

Thecal cells
Cells forming an outer layer of the developing ovarian follicle (an ovarian follicle contains an egg or ovum, which is fundamental for female reproduction). Theca cells contribute to hormone production associated with reproduction.

Thyroglobulin (Tg)
The form that the thyroid hormone takes when stored in the cells of the thyroid. If the thyroid has been removed, thyroglobulin should not show up on a blood test. Doctors measure the thyroglobulin level in the blood to detect thyroid cancer cells that remain in the body after treatment.

Thyroid gland/tissue
A gland located beneath the larynx (voice box) that makes thyroid hormone and calcitonin. The thyroid gland helps regulate growth and metabolism. Also called the thyroid.

Topotecan
Topotecan is an anticancer medicine that belongs to the group ‘topoisomerase inhibitors’. It blocks an enzyme called topoisomerase I, which is involved in the division of DNA*. When the enzyme is blocked, the DNA strands break. This prevents the cancer cells from dividing and they eventually die.

Trabectedin
A drug used to treat patients with ovarian cancer that has relapsed and is sensitive to medicines containing platinum. It is used in combination with pegylated liposomal doxorubicin* (another anticancer medicine). It is also used to treat patients with advanced soft-tissue sarcoma, a type of cancer that develops from the soft, supporting tissues of the body, when treatment with anthracyclines and ifosfamide (other anticancer medicines) have stopped working, or in patients who cannot be given these medicines

Tubal ligation
An operation to tie the fallopian tubes closed. This procedure prevents pregnancy by blocking the passage of eggs from the ovaries to the uterus.

Ultrasonography
A procedure in which high-energy sound waves are bounced off internal tissues or organs and make echoes. The echo patterns are shown on the screen of an ultrasound machine, forming a picture of body tissues called a sonogram. Also called ultrasound.
Uterine fibroid
Noncancerous (benign*) tumours that develop in the wall of the uterus.

Vascular endothelial growth factor (VEGF)
A substance made by cells that stimulates new blood vessel formation.

Vincristine
The active ingredient in a drug used to treat acute leukemia. It is used in combination with other drugs to treat Hodgkin disease, non-Hodgkin lymphoma, rhabdomyosarcoma, neuroblastoma, and Wilms tumour. Vincristine is also being studied in the treatment of other types of cancer. It blocks cell growth by stopping cell division. It is a type of vinca alkaloid and a type of antimitotic agent.

Virilization
Development of male secondary sexual characteristics, such as deepened voice, increase in body and facial hair, a decrease in breast size, an enlargement of the clitoris, and "male-pattern" baldness.