ENDOMETRIAL CANCER: A GUIDE FOR PATIENTS PATIENT INFORMATION BASED ON ESMO CLINICAL PRACTICE GUIDELINES

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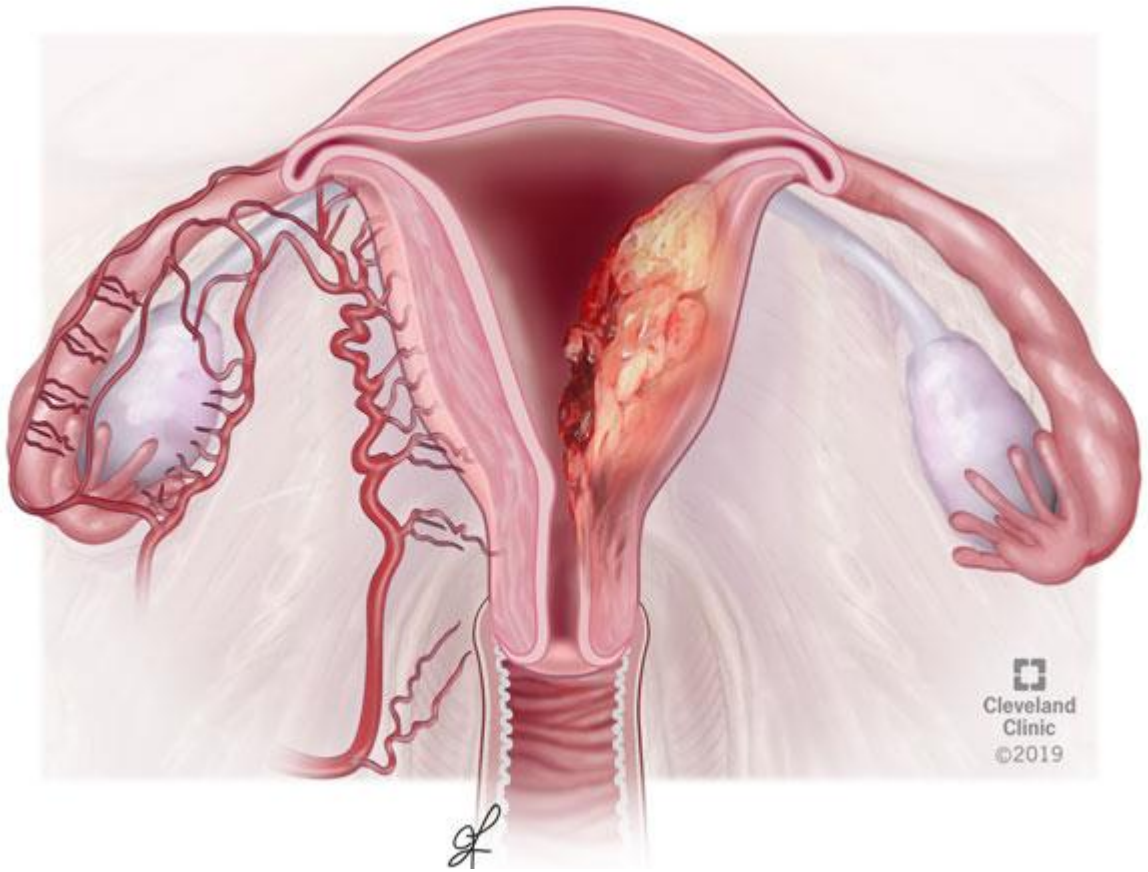


- **DEFINITION OF ENDOMETRIAL CANCER**
- This definition comes from and is used with the permission of the National Cancer Institute (NCI) of the United States of America. Cancer that forms in the tissue* lining the uterus (the small, hollow, pear-shaped organ in a woman's pelvis in which a fetus develops). Most endometrial cancers are adenocarcinomas* (cancers that begin in cells that make and release mucus and other fluids).
- Important note regarding other types of cancer of the uterus
- **Cervical cancer** Cervical cancer is a cancer forming in the cervix of the uterus, unlike endometrial cancer which forms in the corpus of the uterus. Diagnosis and treatment of this type of cancer is different from endometrial cancer.
- **Uterine sarcoma*** Uterine sarcoma* is another type of cancer forming in the corpus of the uterus. It forms in the muscle of the uterus (myometrium) or in other tissues* in the uterus. Although the treatment of uterine sarcoma* and endometrial cancer have some similarities, the information presented here is valid for endometrial cancer but not for uterine sarcoma*.
- **Uterine carcinosarcoma*** Uterine carcinosarcoma is a type of cancer forming in the corpus of the uterus. It is now acknowledged that carcinosarcoma may be a type of aggressive endometrial cancer. The information provided on endometrial cancer is therefore also valid for uterine carcinosarcoma

IS ENDOMETRIAL CANCER FREQUENT?

- Endometrial cancer is the most common cancer of the organs of the female reproductive system. In Europe, 1 to 2 in every 100 women will develop endometrial cancer at some point in their life. In the European Union, over 88,000 women are diagnosed with an endometrial cancer each year. This number is increasing in the majority of European countries. It is the seventh most common cause of death from cancer in women in Western Europe. Endometrial cancer usually occurs in women over the age of 50 and thus after menopause, but up to 25% of cases may occur before the menopause. At diagnosis, about 75% of women have a cancer confined to the uterus (stage I). For these women, the prognosis* is good and the 5-year survival rate is 90%.

WHAT CAUSES ENDOMETRIAL CANCER?

- Today, it is not clear why endometrial cancer occurs. Some risk factors have been identified. A risk factor increases the risk that cancer occurs, but is neither a necessary nor sufficient to cause cancer. A risk factor is not a cause in itself. Some women with these risks factors will never develop endometrial cancer and some women without any of these risk factors will develop endometrial cancer. The majority of endometrial cancers need estrogens* to grow. Without estrogens they stop growing or grow more slowly. This is why, with a few exceptions, the factors increasing the risk of endometrial cancer are linked to estrogens.

- **The main risk factors of endometrial cancer are**: Aging: the risk of endometrial cancer increases as women get older. Genes: women with hereditary nonpolyposis colon cancer syndrome, also known as HNPCC or Lynch syndrome, have a high risk of developing colon and endometrial cancer. One in 2 women with this syndrome will develop an endometrial cancer at some point in their life. This syndrome is an inherited disorder due to a mutation of a gene. It accounts for up to 5% of endometrial cancers.
- Family history of endometrial cancer: having a first-degree relative (mother, sister, or daughter) who had endometrial cancer increases the risk of having endometrial cancer.
- Personal history of breast or ovarian cancer: o Having had a breast cancer or an ovarian cancer increases the risk of developing endometrial cancer. o For women with a personal history of breast cancer, the risk also increases if the patient has been treated with tamoxifen*.
- Tamoxifen is an anti-estrogen substance and a decrease in the risk should be expected, but tamoxifen also has a stimulating effect on the endometrium that can support the development or growth of endometrial cancer. On the whole, for women with breast cancer where tamoxifen is indicated, the benefit of taking tamoxifen outweighs the risk of developing endometrial cancer.
- Personal history of certain gynaecological diseases: o Polycystic ovarian syndrome: this syndrome leads to a higher level of estrogens* and a lower level of progesterone* than usual and consequently increases the risk of developing endometrial cancer.
- Endometrial hyperplasia: endometrial hyperplasia is a proliferation of cells of the endometrium. The cells are normal but may become cancerous later. The risk of cancer is very low for simple or mild hyperplasia but is high for atypical hyperplasia Exposure to estrogen *without, or with insufficient amount of progesterone*, for example: o There is sometimes a natural imbalance in some women. o The use or intake of external estrogens, especially hormone therapies that contain only estrogens and no progesterone* after the menopause. Overweight and obesity: being overweight or obese increases the risk of endometrial cancer because it modifies the level of estrogens* and their effects.

- Diabetes: women with diabetes are at an increased risk of developing endometrial cancer because it modifies the level of estrogens* and their effects.
- Hypertension*: it has been suggested that hypertension is associated with a higher risk of endometrial cancer, but the mechanism of this possible association is not yet clear.
- Geographic factors: women living in North America or in Europe are at increased risk of developing endometrial cancer.
- No pregnancy: women who have never been pregnant are at a higher risk of developing endometrial cancer. On the other hand, women who have had one child or more are at a lower risk of developing endometrial cancer. This is especially the case for women with 5 or more children.
- Total number of menstrual cycles: having more menstrual cycles in a lifetime increases the risk of developing endometrial cancer, again for hormonal reasons.

HOW IS ENDOMETRIAL CANCER DIAGNOSED?

- In contrast to cervical cancer, no systematic screening1 for endometrial cancer is recommended. Cervical cancer screening (cervical smear usually taken every 3 years) performed during gynaecological examination aims to detect cervical cancer and not endometrial cancer.
- Cervical cancer is the cancer of the cervix, the lowest and narrow part of the uterus that leads to the vagina as shown on the picture presented in the definition. Nevertheless, some cervical smear tests may detect endometrial cancer even if this is not their goal.
- The most frequent sign of endometrial cancer is vaginal bleeding. After menopause, there should not be vaginal bleeding, the presence of vaginal bleeding is therefore not normal. Vaginal bleeding after menopause should alert women to consult their doctor. Before menopause, vaginal bleeding between menstrual periods or unusually heavy vaginal bleeding during menstrual periods, should also alert women to consult their doctor.

- Endometrial cancer is not the single and most frequent cause of such vaginal bleeding and doctors will recommend further examination.
- The diagnosis of endometrial cancer is based on the three following examinations:
- 1. Clinical examination*. This includes gynaecological examination to assess the location and volume of the tumor and if it has extended to other organs in the pelvis.
- 2. Radiological examination. This includes ultrasound examination of the uterus. A probe is introduced into the vagina in order to be closer to the uterus, thus allowing for a better examination. This is called trans-vaginal ultrasound. During this examination, the thickness of the endometrium is measured. If the thickness is more than 3 to 4 mm, a sample of the endometrium should be taken (biopsy*). Additional investigations such as chest X-ray*, abdominal ultrasound and abdominal CT-scan* may be performed to exclude metastasis*. If it is suspected that the cancer has spread to the cervix of the uterus, a Magnetic Resonance Imaging* (MRI) should be requested.
- 3. Histopathological* examination. This is the laboratory examination of the tumor cells by dissecting a sample from the tumor (a biopsy*). This laboratory examination is performed by a pathologist who will confirm the diagnosis of endometrial cancer and will give more

WHAT IS IT IMPORTANT TO KNOW TO GET 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. Relevant information about the patient
- Personal medical history
- History of cancer in relatives, especially breast and ovarian cancer
- Status regarding menopause
- Results from the clinical examination* by the doctor
- General well-being
- Before the operation, a preoperative evaluation will be performed to assess the risks of the anaesthesia* and the risks of the operation.
- A preoperative evaluation consists of specific questions and physical examination*. It also usually requires a chest X-ray* and blood tests to assess the white blood cells, the red blood cells, the platelets, and the functioning of the liver and kidneys. Some additional examinations may be necessary according to the medical history of the patient. Relevant information about the cancer

- Results of the biopsy* The biopsy performed with the special device introduced into the uterus during the gynaecological examination will be examined in the laboratory. This examination of the biopsy is called histopathology*.
- A second histopathological examination will be performed later by examination of the tumor and the lymph nodes* after their surgical removal. Before surgery, results of the examination of the biopsy* should include: o
- Histological type* Histological type is based on the type of cells that the tumor is composed of. Endometrial cancers form in the endometrium, the tissue* lining the uterine cavity. The main histological type of endometrial cancer are endometrioid carcinoma (80%), papillary serous carcinoma* (5%-10%) and clear cell carcinoma* (about 1%).
- Endometrioid carcinomas are composed of cells that resemble the normal endometrium and can be associated with or preceded by the abnormal multiplication of normal cells of the endometrium, a phenomenon called endometrial hyperplasia.
- Papillary serous carcinomas (also called serous carcinomas) are composed of cells that are different from the normal endometrium and share similarities with the most frequent form of cancer of the ovary or ovarian tube. o
- Grade Grade is based on how different from normal endometrial cells tumor cells look and on how quickly they grow. For endometrial cancer, the grade will be between 1 and 3. The lower the grade, the better the prognosis*. When the histological type is endometrioid

- Based on the histological type*, the grade and the gene expression profile*, doctors sometimes divide endometrial cancer into two types.
- Type I endometrial cancers are typically endometrioid carcinomas and grade 1 or 2 cancers. They are thought to be caused by excess of estrogen*. They are usually less aggressive and are less likely to spread to other tissues* than type II endometrial cancers.
- Type II endometrial cancers are usually papillary serous carcinomas*, clear cell carcinomas* or carcinosarcomas* and grade 3 cancers. They also have different mutations of their genes and express different proteins than type I endometrial cancers.
- They don't seem to be caused by an excess of estrogen*. Cells from these tumors do not usually have estrogen and progesterone* receptors. Clear cell carcinomas never present with such hormone receptors. Because they are more likely to grow and spread outside the uterus, doctors tend to use more aggressive treatment to treat patients with type II cancers.
- Staging* Doctors use staging* to assess the extension of the cancer and the prognosis* of the patient. For endometrial cancer, the staging* system from the International Federation of Gynecology and Obstetrics (FIGO) is commonly used. This FIGO staging* system is based on the spread of the tumour from its initial location in the endometrium to other tissues* or organs.
- The stage is fundamental for the decision regarding treatment. The more advanced the stage, the worse the prognosis*. For endometrial cancer, the stage is defined after the patient has been operated on, based on what the surgeon actually observed during the operation and on the results of the laboratory analysis of the removed tumor.
- The staging* is thus surgical and pathological. The pathologist will assess the depth of invasion of the tumor in the muscle of the uterus, its spread to the cervix, its size and location, its extension to the fallopian tubes and ovaries, its grade, its histological type* and the lymphovascular space invasion. If lymph nodes* have been removed during surgery, the pathologist will check for the presence of cancer cells in these lymph nodes. The table below presents the different stages of endometrial cancer. The definitions may be technical, so it is recommended to ask doctors for more detailed explanations.

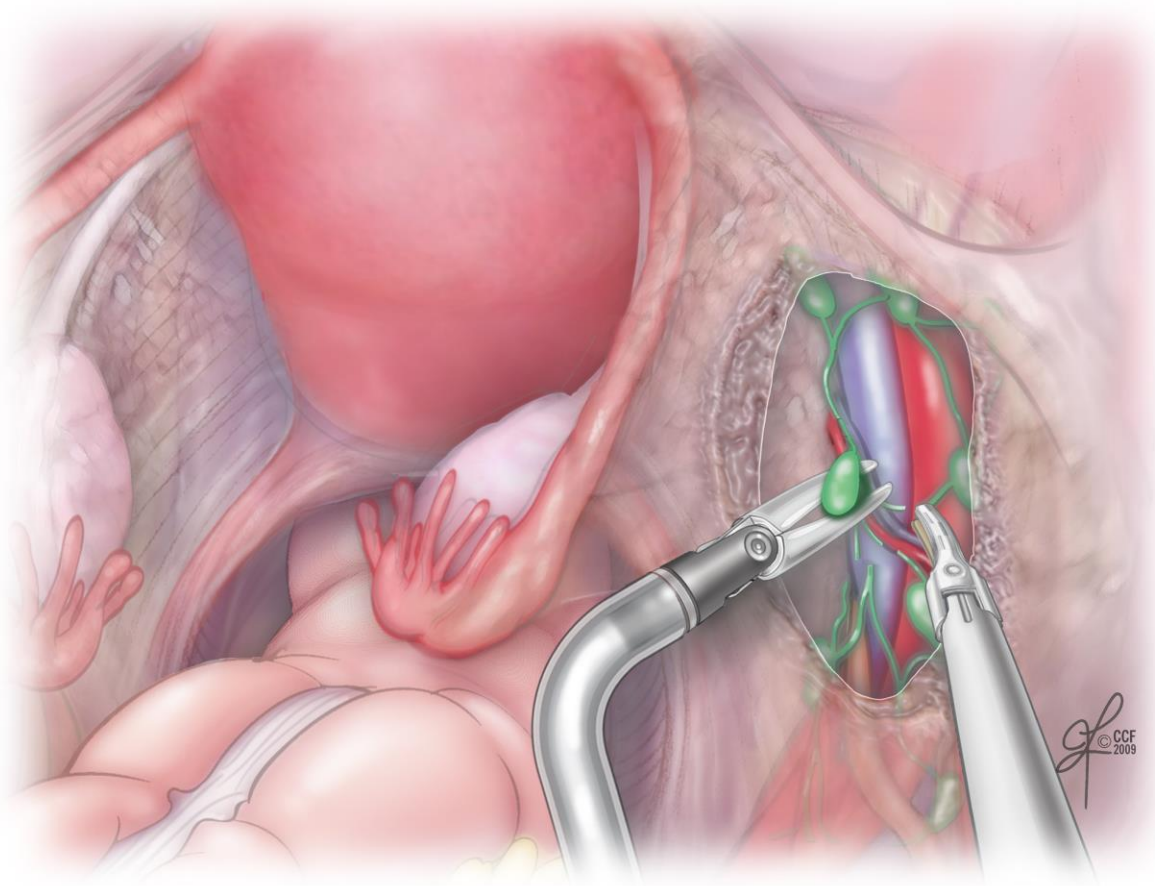
Stage Definition
Stage I The tumor is found in the uterus but has not spread outside the uterus.
Stage I is divided into stages IA and IB according to the thickness of the tumor in
the uterus.
Stage IA The tumor is either limited to the endometrium or has invaded less than 50% of the thickness of
the muscle of the uterus.
Stage IB The tumor has invaded more than 50% of the thickness of the muscle of the uterus.
Stage II The tumor is found in the uterus and has spread to the cervix.
Since 2009, stage II endometrial cancer is not divided into stage IIA and IIB
anymore.
Stage III The tumor has spread beyond the uterus and cervix to other part(s) of the
female genital organ (vagina, ovary, fallopian tube or tissues* around the
uterus) or to lymph nodes* in this area. Stage III is divided into stages IIIA, IIIB,
IIIC1 and IIIC2 based on the organs to which the tumor has spread.
Stage IIIA The tumor has invaded the outer membrane of the uterus (called the serosa) or the fallopian
tube(s) or to the ovaries.
Stage IIIB The tumor has invaded the vagina or the parametrium, the tissue surrounding the cervix.
Stage IIIC1 Tumor cells are found in pelvic* lymph nodes*.
Stage IIIC2 Tumor cells are found in para-aortic* lymph nodes*.
Stage IV The tumor has spread to the bladder or the bowel or to other organs in the body
(metastasis*). Stage IV is divided into stages IVA and IVB.
Stage IVA The tumor has invaded the bladder or the bowel mucosa.
Stage IVB Tumor cells are found in lymph nodes* in the groin or in the abdomen or in distant organs such as
the liver or the lungs.
Note: the stages presented in this table are based on the 2009-FIGO staging* system. Another FIGO staging* system was
used before 2009. Consequently, all data and evidence for management of endometrial cancers are available on the basis of
the old staging* system and unfortunately do not fully apply to the current staging* system.

- Evaluation of the risk of recurrence* in stage I cancers
- Most women are diagnosed with stage I cancer and treatment by surgery at this stage is very effective. For these women, it is essential to evaluate the risk of recurrence, or, in other words, the risk that the cancer could come back. Evaluating the risk of recurrence allows doctors to decide on the best treatment to reduce this risk as much as possible without over treating by some therapies that would not reduce the risk but could alter the quality of life.
- It is known today that the risk of recurrence is increased when the cancer presents some of the following characteristics:
- histological types* other than endometrioid, grade 3, stage IB, lymphovascular space invasion and tumor diameter larger than 2 cm. In this regard, stage I cancers are subdivided into
- three risk categories:
- Women whose cancers do not present any of the abovementioned characteristics, i.e. whose cancers are stage IA tumors, less than 2 cm, of the endometrioid type with grade 1 or 2 and no lymphovacular invasion are considered at low risk of recurrence.
- Women whose cancers are either stage IA tumors of the endometrioid type with grade 3, or stage IB tumors of the endometrioid type with grade 1 or 2 are considered at intermediate risk of recurrence

- **WHAT ARE THE TREATMENT OPTIONS?**

- The cornerstone of treatment is surgery.
- Radiotherapy* and chemotherapy* used after surgery are called adjuvant* therapies, meaning that they are used in addition to surgery. Treatments listed below have their benefits, their risks and their contraindications.
- It is recommended to ask doctors about the expected benefits and risks of every treatment in order to be informed of the consequences of the treatment. For some patients, several treatment possibilities are available and the choice should be discussed according to the balance between expected benefits and risks.
- Surgery A preoperative evaluation is performed for every patient. Surgery might not be feasible in 5-10% of patients with endometrial cancer due to medical contraindications and the risk posed by anaesthesia*. This is usually because of conditions such as obesity, diabetes and cardiac diseases.
- For patients considered operable, the goal of the surgery is to stage the disease and to remove the uterus containing the tumor. Staging* the disease Surgery will allow for staging* of the disease. This is done by examination of the tumor to evaluate its size, location and to check whether tumor cells can be found in the cervix, in the ovarian tubes, in the ovaries, in the lymph nodes* or elsewhere in the pelvis and in the abdomen. During the operation, surgeons inspect and palpate other abdominal organs (liver, diaphragm, omentum*, peritoneal* surfaces). Surgeons also put liquid in the abdominal cavity, remove it by suction and send it to the laboratory to search for cancer cells. This is called peritoneal washing. All tissues* removed during the operation are sent to the laboratory to be examined by the pathologist (histopathological* examination

- **Removing the tumor**
- The uterus containing the tumor will be removed The operation involves removing the uterus, the two ovarian tubes and the two ovaries. Removal of the uterus is called hysterectomy* and removal of both ovarian tubes and both ovaries is called bilateral salpingo-oophorectomy*, or bilateral salpingo-ovariectomy.
- For patients with stage I, stage II and stage III cancer, this operation can be performed by making an incision to the lower abdomen (laparotomy*), or by a technique called laparoscopically assisted vaginal hysterectomy*.
- This technique uses a video camera to project and enlarge the image on a television screen in order to guide the removal of the uterus, the ovarian tubes and the ovaries through the vagina.
- This latter technique seems to provide equivalent results in terms of quality of the removal of the tumor and survival, and compared to laparotomy* has been showed to reduce the length of hospital stay, reduces the use of pain killers, lowers the rate of complication after surgery and improves quality of life.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- The standard surgical approach for stage I endometrial cancer consists of removal of uterus, ovaries, and ovarian tubes with or without lymph nodes* removal. Many surgeons suggest removal of lymph nodes* in patients with intermediate and high risk stage I endometrial cancer (stage IA grade 3 and stage IB).
- The surgical approach for stage II endometrial cancer consists of removal of uterus, ovaries, ovarian tubes, and pelvic* lymph nodes* with or without removal of paraaortic* lymph nodes.
- For patients with stage III and stage IV cancers, the goal of the surgery is to remove as much of the primary tumor as possible. This is called debulking or cytoreductive surgery. Several lymph nodes* in the pelvis and along the aorta* may be removed Removal of lymph nodes* in the pelvic* area and along the aorta* may be performed. This practice varies between hospitals.
- Even if the removal of lymph nodes* helps doctors to be more accurate in defining the stage of the cancer, there is no evidence that it has any added value in treating the cancer and ensuring that it does not come back. Removal of the lymph nodes* increases the risk of lymphoedema, a condition where lymph fluid accumulates in the legs. However, it is part of the staging* procedure and helps to identify patients who may need adjuvant* therapies.
- Many surgeons suggest that lymph nodes should be removed for all patients operated on, with the exception of patients with a stage IA and grade 1 or 2 tumor.

- **Adjuvant therapy**
- An adjuvant therapy is a therapy given in addition to surgery. There is no definitive data supporting the routine use of adjuvant treatment for patients with disease confined to the uterus (localized endometrial cancers).
- For all stages, there is still controversy and lack of clear evidence of what the best options are. It is recommended that the decision for treatment of endometrial cancer should be based on discussion in an inter-disciplinary team of medical professionals. This meeting of different specialists is called a multidisciplinary meeting* or tumor board review. In this meeting, the planning of treatment is discussed according to the relevant information mentioned above.
- Adjuvant treatment for stage I cancer The options for patients with stage I cancer include:
- Observation*, which consists of medical consultations on a regular basis that includes history-taking (a review of the patient's medical history), a physical and a vaginal examination*. Further examinations such as a radiological examination, blood tests and an examination under anaesthesia* can be undertaken if signs or symptoms are noticed.
- Adjuvant vaginal brachytherapy*, which is an internal type of radiotherapy* where the source of radiation is placed in the vagina.

- **Adjuvant pelvic radiotherapy**, which is an external type of radiotherapy* where radiations are produced by an external source and then directed to the pelvis.
- Adjuvant chemotherapy*, which is the use of anticancer drugs to kill cancer cells or limit their growth. It is not clear which combination of drugs are the most effective but they should include one drug containing platinum (cisplatin* and carboplatin* are platinum containing drugs used in the treatment of endometrial cancer).
- For patients with stage I cancers, the choice of the treatment after surgery mainly depends on the risk of recurrence. For patients with low risk of recurrence* (stage IA and grade 1-2 tumor), observation* is recommended.
- For patients with intermediate risk of recurrence (either stage IB and grade 1-2 tumors, or stage IA and grade 3 tumors):
- □ Observation* is also an option, but vaginal brachytherapy* can be proposed.
- □ Adjuvant pelvic* radiotherapy and chemotherapy* can be discussed when the patient is more than 60 years old, when a lymphovascular space invasion was found during the histological examination or when the tumor is large. For patients with high risk of recurrence (stage IB and grade 3 tumors):
- □ Adjuvant pelvic* radiotherapy* is recommended □ Adjuvant chemotherapy* can be discussed when the patient is more than 60 years old, when a lymphovascular space invasion was found during the histological examination or when the tumor is large.

- **Adjuvant treatment for stage II cancer**
- The options for patients with stage II cancer include:
- □ Adjuvant vaginal brachytherapy*, which is an internal type of radiotherapy* where the source of radiation is placed in the vagina.
- □ Adjuvant pelvic* radiotherapy*, which is an external type of radiotherapy* where radiations are produced by an external source and then directed to the pelvis.
- □ Adjuvant chemotherapy*, which is the use of anticancer drugs to kill cancer cells or limit their growth. It is not clear which combination of drugs are the most effective but they should include one drug containing platinum (cisplatin* and carboplatin* are platinum containing drugs used in the treatment of endometrial cancer).
- **Vaginal brachytherapy*** can only be used in patients with grade 1-2 tumors with no lymphovascular invasion, and for which lymph nodes* were removed and were free of tumor cells according to the histological examination. When the lymph nodes* have not been checked for tumor cells during the surgery, both pelvic* radiotherapy* and vaginal brachytherapy* are recommended.

- Adjuvant chemotherapy* may be considered alone or together with pelvic* radiotherapy*. The use of adjuvant chemotherapy may reduce the risk of extra-pelvic recurrence* (spread of cancer outside
- the pelvis known as “metastasis*”). It is not clear which combination of drugs are the most effective but they should include one drug containing platinum (cisplatin* and carboplatin* are platinum containing drugs used in the treatment of endometrial cancer).

- **Treatment of advanced disease (stage III and IV)** The treatment of advanced endometrial cancer usually includes combination of surgery, radiotherapy*, and chemotherapy*.
- In 5-10% of patients with advanced endometrial cancer, it will not be possible to perform surgery due to medical contraindications. These patients may be treated with external radiotherapy* (radiations produced by an external source and then directed to the tumor) and/or internal radiotherapy* called brachytherapy* (involves placing a source of radiation in the cavity of the uterus and/or vagina), and additionally by systemic treatment*.
- Adjuvant* treatment for stage III cancer The adjuvant options for patients with operated stage III cancer include:
- □ Adjuvant vaginal brachytherapy*
- □ Adjuvant pelvic radiotherapy*
- □ Adjuvant chemotherapy*

- Historically, pelvic* radiotherapy* and vaginal brachytherapy* were recommended after surgery for stage III patients. Now, there is growing evidence that chemotherapy* should be administered to patients with stage III disease instead of or in addition to radiotherapy. The optimal treatment should be discussed with doctors.
- Adjuvant chemotherapy* should include one platinum containing drug (cisplatin* and carboplatin* are platinum containing drugs used in the treatment of endometrial cancer). It should be noted that adjuvant radiotherapy*, both internal and external, protects against local tumor re-growth (in the pelvis).
- Chemotherapy*protects against the spread of the disease outside the pelvis.

- Treatment for stage IV endometrial cancer For patients with stage IV disease, the goal of the treatment after cytoreductive surgery is to act on cancer cells that are left in the body, in the pelvis or elsewhere (metastasis*).
- Postoperative radiotherapy* has effect locally in order to prevent tumor recurrence in the pelvis. A systemic treatment* acts on cancer cells all over the body and not only locally.
- Systemic treatment* may consist of chemotherapy* or hormonal therapyChemotherapy* drugs include platinum-based compounds, anthracyclines*, and taxanes*. Paclitaxel*-based combination regimens are preferred for first-line chemotherapy in patients with advanced endometrial cancer, because they have been shown to be more effective and better tolerated.
- The use of hormonal therapy is recommended for endometrioid histologies only. It involves the use of drugs containing the hormone progesterone*. Tamoxifen* and aromatase* inhibitors are two other drugs that are also being used. Therapies administered to patients with advanced endometrial cancer should be individualized to the needs, prognosis* and health status of each patient.

- Specificities of therapy* for papillary serous* and clear cell* tumors Papillary serous* and clear cell carcinomas* are cancers that are more aggressive, but less frequent than endometrioid carcinomas.
- They require complete staging with removal of uterus, ovaries, ovarian tubes, pelvic* and para-aortic* lymph nodes*, as well as removal of appendix*, biopsy* and removal of abdominal lining. Platinum-based adjuvant* chemotherapy* should be proposed for early (stage I and II) disease.
- Platinum-based chemotherapy is recommended in patients with stage III or IV disease. The same chemotherapy regimens usually employed for epithelial ovarian cancer can be considered in patients with advanced, or recurrent, papillary serous or clear cell uterine cancer. Papillary serous endometrial carcinomas are not considered as hormone responsive.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF THE TREATMENTS?

- Surgery 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.
- The female reproductive organs are located in the pelvis together with the lower urinary tract and the lower digestive tract. During the surgical intervention, the urinary tract and the intestines may be damaged. When lymph nodes* in the pelvis and along the aorta* are removed, it can damage or block the lymph system resulting in lymphoedema, a condition where lymph fluid accumulates in the legs and makes them swell. It can occur right after the intervention, but also later.
- Having a hysterectomy* also increases the risk of urinary incontinence and vaginal prolapse years after the surgical intervention, because it can damage or weaken the supporting pelvic* floor muscles. Women operated on before the menopause will experience symptoms of menopause quickly after the operation because of the removal of the ovaries. Hot flashes, mood swings, night sweats, vaginal dryness and trouble concentrating are frequent. Side effects can be relieved and advice should be provided by the specialists in oncology.

- **Side effects of adjuvant therapies**
- The most frequent side effects of adjuvant therapies are usually reversible after treatment. Some strategies are available to prevent or relieve a certain range of these side-effects. This should be discussed upfront with doctors.
- Pelvic radiotherapy* Side effects of external radiotherapy* to treat endometrial cancer are mainly due to the irradiation of the organs surrounding the uterus. Effects of radiation on the urinary tract include painful urination, bladder spasms resulting in an urgent need to urinate, presence of blood in the urine, urinary tract obstruction, and ulceration or necrosis of the mucous membrane lining the bladder. Effects of radiation on the lower digestive tract include rectal discomfort, diarrhea, mucus and blood rectal discharge, and, rarely, perforation of the intestines. Vaginal narrowing is another possible late effect of pelvic* radiotherapy*.
- Treatment options for these post-radiation reactions should be advised by the oncologist. Modern techniques of external radiotherapy* such as Intensity Modulated Radiotherapy* (IMRT) are intended to reduce its toxicity.

- **Intravaginal brachytherapy*** The aforementioned side effects of external radiotherapy* can also appear with intravaginal brachytherapy*, but less frequently, since this type of radiotherapy* is better targeted.
- Vaginadryness is frequent during and after the treatment. Vaginal narrowing and dryness can also occur and can result in long-term sexual dysfunction. In young women radiation stops the ovarian function and this may result in further vaginal dryness and sexual dysfunction.
- It may also result in a higher risk for osteoporosis and/or insufficiency fractures of pelvic* bones. Women must be under the care of a specialist for these problems.

- Chemotherapy*
- Side effects of chemotherapy* are very frequent. They will depend on the drug(s) administered, on the doses and on individual factors. If you have suffered from other problems (such as heart 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.
- The most frequent side effects of the drugs used for chemotherapy* in endometrial cancer are hair loss and decreased blood cell count. Decreased blood cell count can result in anaemia, bleeding and infections. Once the chemotherapy* is over, the hair grows back and the blood cell count returns to normal.

Other frequent side effects include:

 allergic reactions, such as flushing and rash

 nerve problems affecting the hands and/or feet (peripheral neuropathy*), which can cause tingling feelings in the skin, numbness and/or pain

 temporary loss of or changes in your eyesight

 ringing in the ears or changes in your hearing

 low blood pressure

 nausea, vomiting and diarrhea

 inflammation of areas such as the lining of the mouth

 loss of sense of taste

 lack of appetite

 slow heart beat

 dehydration

 mild changes in nail and skin which soon disappear painful swelling and inflammation where the injection is given

 muscle or joint pain seizures tiredness

Other less frequent, but more serious side effects can occur. These include especially, stroke, myocardial infarction and damage to the function of the kidneys and liver. Any of these symptoms should be reported to a doctor

- **WHAT HAPPENS AFTER THE TREATMENT**?
- Follow-up* with doctors After the treatment has been completed, doctors will propose a follow-up* program consisting of consultations on a regular basis which aim to:
- □ detect possible recurrence* at an early stage
- □ evaluate treatment-related complications and manage them
- □ provide psychological support and information to enhance your return to normal life
- □ implement a surveillance schedule because there is an increased risk of breast, ovarian and colon cancer. This increased risk to develop other cancers is not true for every woman, but some women may be at increased risk, mainly because of some genetic factors and sometimes because of the treatments received. Patients should undergo follow-up* visits every 3–4 months with physical and gynecological examination for the first 2 years, and then with a 6 month interval until 5 years. Further investigations can be performed, if clinically indicated.

- Return to normal life It can be hard to live with the idea that the cancer can come back. From what is known today, no specific way of decreasing the risk of recurrence* after completion of the adjuvant* treatment can be recommended.
- As a consequence of the cancer itself and of the treatment, return to normal life may not be easy for some people. Questions related to body image, sexuality, fatigue, work, emotions or lifestyle may be of concern to you. Discussing these questions with relatives, friends or doctors may be helpful. Support from ex-patients' groups or telephone information services and helplines is available in many countries.
- What if the cancer comes back? If the cancer comes back, it is called a recurrence* and the treatment depends on the extent of the recurrence*. If the cancer comes back, it is usually within the first 3 years following the initial treatment. The extension of the recurrence* should be fully evaluated by physical examination*, radiological examinations and blood tests. The majority of recurrences* for patients for whom the initial tumor was limited to the uterus, arise in the pelvis. The treatment options will depend on the extension of the recurrence*. Discussion of treatment options should be done in a multidisciplinary* meeting.

- If cancer comes back as a pelvic* recurrence*, surgery, radiotherapy* and chemotherapy* are the options.
- If the recurrent tumor is located next to solid organs in the pelvis (central recurrence), it should be removed by surgery whenever possible or treated with radiotherapy.
- If the recurrence occurs in lymph nodes* located in the pelvis (regional recurrence), radiotherapy is the preferred option, with, if possible, chemotherapy. Radiotherapy* can only be considered for the treatment of the recurrence* if it was not given before. In fact, there is a maximal dose of radiotherapy that can be delivered and any previous radiotherapy has usually reached this maximal dose. However, external radiotherapy* can be given if only internal (brachytherapy*) was given before and vice versa.
- A paclitaxel*-based combination regimen is preferred for first-line chemotherapy of recurrent disease. Endometrial cancer recurring after first-line chemotherapy is to a large degree resistant to chemotherapy. Chemotherapy drugs showing a clinical benefit and good tolerance in such situations are paclitaxel, and a combination of weekly topotecan* and docetaxel*.

- If cancer comes back as a recurrence with metastasis
- options are chemotherapy* and hormonal therapy.
- Chemotherapy* can be proposed and considered after discussion in a multidisciplinary* meeting and discussion with the patient. Decisions should be taken after considering the expected benefits and side effects of chemotherapy*. A paclitaxel*-based combination regimen is preferred as a first-line chemotherapy regimen. Endometrial cancer recurring after first-line chemotherapy is to a large degree resistant to chemotherapy.
- Chemotherapy drugs showing a clinical benefit and good tolerance in such situations are paclitaxel, and a combination of weekly topotecan* and docetaxel*. Side effects of chemotherapy* are very frequent. These side effects have been described previously in the chapter, entitled ‘What are the treatment options’. The main predictors of a good response in the treatment of metastatic* disease if the tumor is welldifferentiated*, a long disease-free interval and the location and extent of extrapelvic (particularly pulmonary) metastases.
- Hormone therapy can be proposed to patients with grade 1 tumors and positive progesterone* receptor status. A progestin (medroxyprogesterone acetate or megestrol), a type of drug that has the same effect as progesterone, or tamoxifen*, which counteracts the action of estrogens*, can be used. Side effects of hormone therapy are less frequent than those of radiotherapy* and chemotherapy*. Build-up of fluid causing swelling of the ankles, increase in appetite, and weight gain are the most common side effects of progestins. Other less frequent but more serious side effects can occur. R Risk of blood clots (including clots in the lungs), stroke and heart attack increase significantly. Any symptoms should be reported to your doctor.