

BREAST CANCER: A GUIDE FOR PATIENTS

PATIENT INFORMATION BASED ON ESMO CLINICAL PRACTICE GUIDELINES

This guide for patients has been prepared by Reliable Cancer Therapies (RCT) as a service to patients, to help patients and their relatives better understand the nature of breast cancer and appreciate the best treatment choices available according to the subtype of breast 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 primary breast cancer and for the management of locally recurrent or metastatic breast 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 Reliable Cancer Therapies: www.reliablecancertherapies.com

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

For words marked with an asterisk, a definition is provided at the end of the document.

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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.

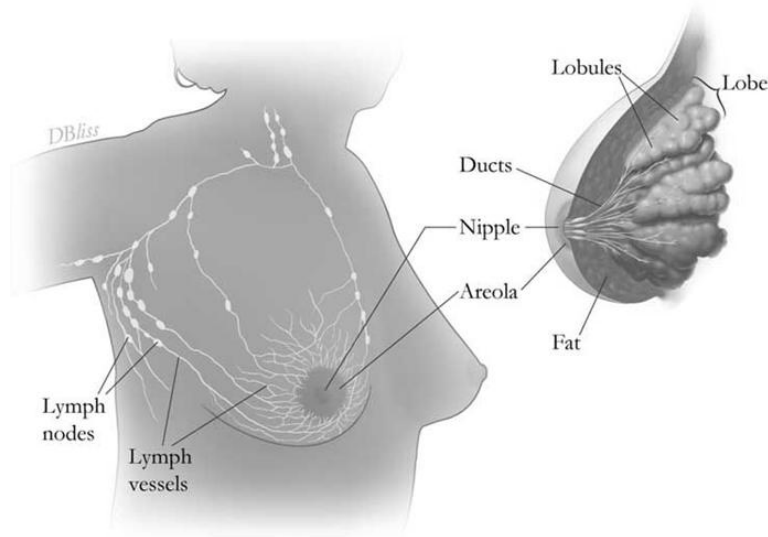
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The third update was done by Dr. Gauthier Bouche (RCT) and was reviewed by Dr. Svetlana Jezdic (ESMO). Pr. Gabriella Kornek (ESMO's Cancer Patient Working Group) and Pr. Raphael Catane (ESMO's Cancer Patient Working Group) approved the changes included in this update.

DEFINITION OF BREAST 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 tissues of the breast, usually the ducts (tubes that carry milk to the nipple) or lobules (glands that make milk). It occurs in both men and women, although male breast cancer is rare.



Anatomy of the breast, showing lymph nodes and lymph vessels

IS BREAST CANCER FREQUENT?

Breast cancer is the most common of all cancers in women and is the leading cause of death from cancer in European women. It is estimated that one in every 9 European women will develop breast cancer at some point in her life but this estimates varies by country. In the European Union, about 332,000 women were diagnosed with breast cancer in 2008.

Breast cancer occurs more frequently in older women but 1 in 4 breast cancers is diagnosed in women under the age of 50. Less than 5% of all breast cancers are diagnosed in women younger than 35.

In most Western countries, fewer and fewer women have died of breast cancer in recent years (especially in younger age groups) because of improved treatment and earlier detection.

Breast cancer can also occur in men, but is rare, accounting for less than 1% of all breast cancers. Every year, one out of 100,000 men is diagnosed with breast cancer.¹

There are different types of breast cancer, which will be explained in this guide.

¹Even if the management of breast cancer in men shares some elements with the management of breast cancer in women, the explanations given in this summary do not fully apply to men. Frequency and risk factors for men are different than for women, as well as some treatments. To get more information on the management of breast cancer in men we advise you to look [here](#).

WHAT CAUSES BREAST CANCER?

Today, it is not clear why breast cancer occurs. Some risk factors* have been identified. A risk factor* increases the risk that cancer occurs, but is neither necessary, nor sufficient, to cause cancer by itself.

Some women with these risks factors will never develop breast cancer and some women without any of these risk factors* will develop breast cancer.

The majority of breast cancers need estrogens to grow. Without estrogens they stop growing or grow more slowly. This is why, with a few exceptions, risk factors* for breast cancer are linked to estrogens.

The main risk factors* for breast cancer in women are:

- **Aging:** the risk of breast cancer increases as women get older.
- **Genes:** mutations of certain genes that are inherited from the mother or the father increase the risk of breast cancer. Current knowledge suggests that these abnormal genes cause less than 10 percent of breast cancers.
- **Family history of breast cancer:** having a first-degree relative (mother, sister, daughter, brother and father) who had breast cancer increases the risk of developing breast cancer, especially if this relative was under 45 years of age at the time of the diagnosis. When multiple family members have been affected by breast and/or ovarian cancer at a young age, a genetic predisposition must be suspected. *BRCA1* and *BRCA2* are the 2 main genes involved in familial forms of breast cancer. The lifetime risk of breast cancer in a *BRCA1* mutation carrier is 80–85%, with a 60% chance that the cancer will be bilateral. The risk of both subsequent breast cancer occurrence and mortality is reduced by prophylactic surgery*. Careful genetic assessment and psychological counselling are mandatory before undertaking such surgery.
- **Personal history of breast cancer:** having had breast cancer increases the risk of having breast cancer in a different part of the breast or in the other breast.
- **Lifetime exposure to estrogen and progesterone:**
 - Women whose menstrual periods began before the age of 12 and ended after the age of 55 are at an increased risk of developing breast cancer.
 - Women who have not had children or had their first child after the age of 30 are at an increased risk of developing breast cancer.
- **History of certain benign* breast conditions:** the risk of breast cancer occurring is particularly high for women with two conditions called atypical lobular hyperplasia* and atypical ductal hyperplasia*.
- **Geographic and social factors:** women living in western countries and women with a higher level of education are at an increased risk of developing breast cancer.
- **Use of medications containing estrogens and progesterone:**
 - Use of the oral contraceptive pill, especially before the first pregnancy, increases the risk of breast cancer. If a woman has not taken the oral contraceptive pill for a period of 10 years, the increased risk of breast cancer from such medication is no longer present.



- Use of hormone replacement therapy after the menopause* increases the risk of developing breast cancer. A higher risk of breast cancer has been confirmed for hormone replacement therapy combining estrogen and progesterone, and to a lesser extent for hormone replacement therapy with estrogen alone. The increased risk of breast cancer is present in current or recent users. Among users who stopped hormone replacement therapy at least five years ago, the risk is no greater than that for someone who has never received hormone replacement therapy.
- **Radiotherapy* of the breast during childhood or adolescence:** having received radiotherapy in childhood or adolescence (usually for the treatment of lymphomas*) increases the risk of developing breast cancer in adulthood.
- **Overweight and obesity:** being overweight or obese increases the risk of developing breast cancer, especially after menopause*. This is probably due to the production of estrogens in fat tissues - the main source of estrogens after menopause*.
- **Alcohol consumption and smoking:** the risk of breast cancer increases with alcohol consumption and with smoking, but the mechanisms are unclear.

Other factors have been suspected to be associated with an increased risk of breast cancer, but the evidence is inconsistent. Unfortunately, the factors that have the highest influence on the risk of developing breast cancer like age, genes, personal and familial history of breast cancer and history of atypical hyperplasia* cannot be changed.

HOW IS BREAST CANCER DIAGNOSED?

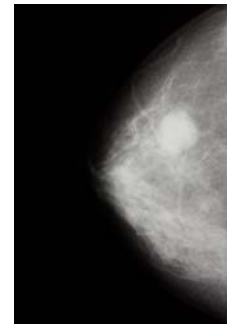
Breast cancer can be suspected under different circumstances. The main circumstances are a positive screening mammography*, the discovery by palpation* of a mass in the breast, any modification of the skin of the breast noticed by the patient or her doctor, or any fluid leaking from the nipple of one single breast.

The diagnosis of breast cancer is based on the three following examinations:

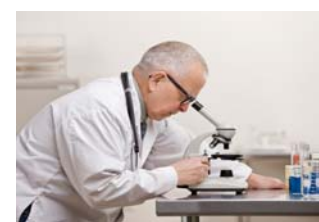
1. **Clinical examination***. The physical examination of the breasts and neighbouring lymph nodes* includes inspection and palpation*.



2. **Radiological examination***. This includes conducting an X-ray*, (mammography*), and an ultrasound* examination of the breasts and neighbouring lymph nodes*. Magnetic resonance imaging* (MRI) of the breast may be needed in some patients, especially young women with dense breast tissue, women with *BRCA* gene mutations, and women with silicone gel implants. MRI can also be considered when tumor cells have been found in a suspicious lymph node in the armpit but no tumor can be seen in the breast on mammography, or when several tumors are suspected. Additional investigations such as chest X-ray*, abdominal ultrasound* and bone scintigraphy* may be performed to exclude distant spread of the disease, also known as metastasis*.



3. **Histopathological* examination**. This is the laboratory examination of the breast and tumor tissue after removing a sample from the tumor. This is called a biopsy*. This laboratory examination will confirm the diagnosis of breast cancer and will give more information on the characteristics of the cancer. The biopsy* is obtained manually by the doctor with a needle, often with the help of ultrasound* to guide the needle into the tumor. Once the needle is introduced into the tumor, a sample is removed. Depending on the needle used, this is called either a fine needle aspiration or a core biopsy*. A second histopathological examination will be performed later when examining the tumor and the lymph nodes* removed by surgery.



COMMON MISCONCEPTIONS ABOUT BREAST CANCER TREATMENT

According to Prof. Martine Piccart, expert in breast cancer treatment:

- Breast cancer does not develop within days or weeks! There is always time to seek a second opinion about treatment options.
- The multidisciplinary consultation before starting treatment is very important and should not be underestimated. The treating physician and the general practitioner should be provided with the written report of this consultation.
- The importance of the pathological examination of the tumor is often underestimated. The entire treatment strategy depends on a carefully conducted, well standardized pathological examination in a well-experienced laboratory. Asking for a second, independent pathological examination is a good idea if the testing has been done in a laboratory with limited experience in breast cancer diagnosis.
- Access to new agents or strategies in the context of well-designed and carefully conducted clinical trials has more benefits than risks at all stages of the disease. Patients should ask their doctors which clinical trials are relevant for them.
- Pregnancies after breast cancer are possible, especially if the ovaries are not damaged by the use of certain chemotherapy* drugs which are toxic to them. This needs to be discussed upfront with young women who want to preserve their fertility. For women who become pregnant following completion of breast cancer therapy, neither pregnancy nor subsequent breastfeeding increase the likelihood of relapse*.

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 cancer and ovarian cancer
- Status regarding menopause*, which in some cases requires taking a blood sample to measure the level of some hormones in the blood (estradiol* and FSH*)
- Results from the clinical examination* by the doctor
- General well-being
- Results from blood tests performed to assess the white blood cells*, the red blood cells* and the platelets*, and tests performed to exclude any problems in the liver, the kidneys and the bones.

Relevant information about the cancer

- **Staging***

Doctors use staging* to assess the risks and prognosis* associated with specific characteristics of the patient and the type of cancer involved. The TNM staging* system is commonly used. The combination of size of the tumor (T) and invasion of nearby tissue, involvement of lymph nodes* (N), and metastasis* or spread of the cancer (M) to other organs of the body, will classify the cancer into one of the following stages.

The stage of cancer is fundamental for decisions regarding treatment. The less advanced the stage, the better the prognosis is. Staging* is usually performed twice: after clinical and radiological examination* as well as after surgery. If surgery is performed, staging* may also be influenced by the laboratory examination of the removed tumor and lymph nodes*.

Additional radiological examinations* such as chest X-ray*, abdominal ultrasound* or CT and bone scintigraphy* can be performed to be sure that there is no metastasis* in the lung, the liver and the bones. CT and/or MRI of the brain should only be performed if there are symptoms pointing in that direction. All of these examinations are usually only recommended for stages II or higher (see below). They are also considered for patients for whom a pre-surgery therapy is planned. Conversely, for patients with small tumors and no suspicious lymph nodes* (stage I), there is no reason to do all these exams.

The table below presents the different stages for breast cancer. The definitions are very technical so it is recommended to ask doctors for more detailed explanations.



Stage	Definition
Stage 0	The abnormal cells are still contained in the duct where they initially appeared.
Stage I	The tumor is less than 2 cm in diameter and small clusters of cancer cells may be found in the lymph nodes*. Stage I breast cancer is divided into stages IA and IB.
Stage II	The tumor is either smaller than 2 cm in diameter and has spread to the lymph nodes* in the armpit or the tumor is between 2cm and 5cm in diameter, but has not spread to the lymph nodes in the armpit. Stage II breast cancer is divided into stages IIA and IIB.
Stage III	The tumor maybe of any size, but: <ul style="list-style-type: none"> - has spread either to the chest wall and/or the skin of the breast - has spread to at least 10 lymph nodes* in the armpit or the lymph nodes in the armpit are attached to each other or to other structures - has spread to lymph nodes near the sternum (breastbone). - has spread to lymph nodes below or above the clavicle (collar bone). Stage III breast cancer is divided into stages IIIA, IIIB, and IIIC
Stage IV	Cancer has spread to other organs of the body, most often the bones, lungs, liver, or brain. Such distant tumor deposits are called metastases*.

- **Results of the biopsy***

Tumor obtained by biopsy* will be examined in the laboratory. The method and the result of such an examination are called histopathology*. A second histopathological examination is performed on the tissues obtained by surgical removal of the tumor and the lymph nodes*. This is very important to confirm the results of the biopsy* and to provide further information on the cancer. Results of the examination of the biopsy* should include:

- **Histological type***

Assignment of histological type is based on the type of cells that compose the tumor. Breast cancers form in tissues of the breast, usually the ducts or the lobules. The main histological types of breast cancer are ductal carcinomas* and lobular carcinomas*. The histopathological examination will also classify the cancer as invasive* or non-invasive*. Non-invasive* cancers are also called cancer *in situ*

- **Grade***

Assignment of grade* is based on the heterogeneity of tumor cells, the architectural structure of the tissue they form and the frequency of mitosis* (cell division) of tumor cells. A well differentiated tumor (grade 1) has low heterogeneity of cells, preserved architectural structure and few mitoses. An undifferentiated tumor (grade 3) has high heterogeneity, loss of architecture and many mitoses. A moderately differentiated tumor (grade 2) is in between grade 1 and grade 3. The lower the grade*, the better the prognosis*.

When systemic treatment is planned before surgery, the biopsy results should include hormone receptor* status and HER2* status. When no systemic treatment is planned before surgery, these can be determined in the tumor (and/or the lymph nodes*) after their removal by surgery.

- **Hormone receptor* status for estrogen and progesterone**

Tumor cells can present receptors to estrogen and receptors to progesterone on their surface or inside the cell. Cells of some tumors present a high level of receptors. This



means that their growth and multiplication are stimulated by hormones. Tumors with a high level of estrogen receptors (ER+)* and/or progesterone receptors* (PR+) have a better prognosis* than tumors lacking estrogen receptors (ER-) and/or lacking progesterone receptors (PR-).

- **HER2* status**

HER2* is a cell surface protein* present in about 20% of breast cancer cases. HER2 is involved in the growth and migration of cells*. HER2* status of tumor tissue can be analysed by various tests in the laboratory: by Immunohistochemistry* (IHC), by Fluorescence In Situ Hybridization* (FISH) or by Chromogenic In Situ Hybridization* (CISH). A cancer is HER2* positive when the result of the IHC test is 3+ or the result of a FISH or CISH test is positive as stated in the pathology report. Otherwise, the HER2* status is negative. Before anti-HER2 directed therapy was available, HER2* positive cancers had more aggressive behaviour than other cancers.

- **Multigene expression profiles***

The quantification of the expression of distinct sets of genes expressed by the tumor can also be performed on the biopsy*. Such multigene signature analyses are not routinely performed, but can help to predict the risk of recurrence* and the likelihood of benefit from chemotherapy*.

- **Ki-67 labelling index**

Ki-67 is a protein* found in the nucleus* of cells when they are dividing but not when they rest. Ki-67 labelling index indicates the percentage of cells in which Ki-67 can be found. Analysing the proportion of dividing cells is a method to determine the level of proliferation* of the tumor. Highly proliferating tumors grow faster and have a worse prognosis than slowly proliferating tumors, but at the same time highly proliferating tumors are more sensitive to chemotherapy*.

It is important to know that tests used to define hormone receptor* status and HER2* status may give an incorrect result. No test used to assess HER2 status today is 100% reliable. Moreover, it is also possible that the piece of tissue examined classifies the tumor as HER2 negative but examination of another piece of the tumor would have classified it as HER2 positive. That is why, whenever possible, these analyses should be performed on both the biopsy* material and on the tumor tissue removed by surgery.

Another very important part of the histopathological examination after tumor removal by surgery is to check whether the tumor has been completely removed. This is done by analyzing if the microscopic edges of the tumor are surrounded completely by normal tissue. It is reported either as negative margins* of resection, (meaning that it is very likely that the whole tumor has been removed) or as positive margins* of resection (meaning that it is very likely that the tumor has not been removed completely).

- **Hormone responsiveness**

Based on the analysis of the biopsy and/or of the tumor removed by surgery, tumors are classified into three groups according to their hormonal receptor status:

- Hormone responsive* (ER+ and/or PR+) when estrogen or progesterone receptors* have been detected on cancer cells.
- Hormone non-responsive (ER- and PR-) when no estrogen and no progesterone receptors have been detected on cancer cells.
- A third in-between group with uncertain hormone responsiveness*.



Based on this analysis the decision is made whether to add hormone treatment. A hormonal treatment will usually stop or slow the growth of hormone responsive* tumors because these tumors need hormones to grow, but will have no effect on the growth of hormone non-responsive tumors.

- **Intrinsic subtypes of breast cancer**

The combination of the results regarding hormone receptor status, HER2 status and Ki-67 labelling index is used to classify breast cancer in 5 subtypes. This is also important in order to know which therapies are most likely to be effective. The 5 subtypes are presented in the table below. This classification is rather technical and it is recommended to ask a doctor for a more detailed explanation.

Subtype of breast cancer	Hormone receptor status	HER2 status	Ki-67 status
Luminal A	ER+ and/or PR+	HER2 negative	Low (<14%)
Luminal B HER2 negative	ER+ and/or PR+	HER2 negative	High
Luminal B HER2 positive	ER+ and/or PR+	HER2 positive	Any
HER2 positive non-luminal	ER- and PR-	HER2 positive	Any
Triple negative	ER- and PR-	HER2 negative	Any

WHAT ARE THE TREATMENT OPTIONS?

Planning of the treatment involves an inter-disciplinary team of medical professionals. This usually implies a meeting of different specialists, called multidisciplinary opinion* or tumor board. In this meeting, the planning of treatment will be discussed based on the relevant information summarized above.



The treatment will usually combine intervention methods that:

- act on the cancer locally, such as surgery or radiotherapy*
- act on cancer cells all over the body with systemic therapy* such as chemotherapy*, hormone therapy *and/or HER2-directed therapy.

The extent of the treatment will depend on the characteristics of the tumor cells and on the stage of the cancer, as well as on the age, the menopausal status and the co-morbidity of the patient.

Treatments listed below have their benefits, their risks and their contraindications. It is recommended to ask an oncologist about the expected benefits and risks of every treatment in order to be informed of the consequences of the treatment. For some treatments, several options are available. The choice should be discussed according to the balance between benefits and risks.

Treatment plan for non-invasive* cancer (Stage 0)

A non-invasive cancer has not spread outside the duct (ductal carcinoma in situ). Treatment options include the following two possibilities of local therapies.*

- Either the tumor or a part of the breast is removed, but not the whole breast. This is called breast-conserving surgery. This is usually followed by whole breast irradiation except in patients with very low risk of recurrence where radiation may be omitted. Additional irradiation (called a *boost*) of the area from which the tumor has been removed can be considered for patients who have a high risk of local recurrence, for instance in very young patients.
- Or the whole breast is removed by mastectomy, without muscles and skin surrounding the breast. When mastectomy is performed, additional radiation treatment is not necessary for non-invasive cancer.

In addition, treatment with tamoxifen*, a drug which counteracts the action of estrogens on the breast, can be considered if the tumor is estrogen receptor positive*, since it lowers the risk of recurrence, i.e. that the cancer comes back in the breast. Tamoxifen also lowers the risk of developing contralateral breast cancer, i.e. cancer in the opposite breast.

Lobular neoplasia*, which was formerly called lobular carcinoma in situ, is now regarded as a risk factor for future development of breast cancer in both breasts. It therefore requires a discussion with the doctor whether to pursue a surveillance strategy by close follow-up and/or a treatment strategy.

Treatment plan for invasive* cancer (Stage I to III)

An invasive cancer has spread outside the duct (invasive ductal carcinoma) or outside the lobule (invasive lobular carcinoma). The treatment will target the cancer locally as well as cancer cells potentially spread in the body.*

In most cases, the treatment will consist of surgery, radiotherapy* and systemic therapy*. Treating cancer cells that have spread to other parts of the body can be done with the help of hormone therapy, chemotherapy* or HER2-directed therapy.

For tumors of more than 2 cm in diameter, systemic therapy* is sometimes preferred as the first treatment since shrinkage of the tumor with drugs can facilitate local therapy and might permit breast conservation. Surgery is preceded by chemotherapy* for most cases of stage IIIA and IIIB cancers. This is called neo-adjuvant* chemotherapy. It is also indicated to reduce tumor size so as to permit breast-conserving surgery. Trastuzumab* is added in cases with HER2*-positive tumors.

Surgery

The surgery will be performed under general anaesthesia*. The surgeon will remove the tumor and some lymph nodes* during the same operation by one of two methods.

- Removal of the tumor or a part of the breast including the tumor, but not the whole breast. This is called breast-conserving surgery.
- Removal of the whole breast but not muscles and skin surrounding the breast. This is called total mastectomy.



The choice between breast-conserving surgery and total mastectomy depends on the characteristics of the tumor, on the size of the breast and on the patient's preference. Some patients require a mastectomy because of tumor size, multiple locations of the tumor(s) in the breast or other reasons. This has to be discussed with doctors. Currently in Western Europe, breast-conserving surgery can be performed in 2 out of 3 women with breast cancer.

For some patients, a treatment is given before surgery (neo-adjuvant) with the intent of reducing the size of the tumor and allowing for breast-conserving surgery. Once the neo-adjuvant treatment has produced its effect, the doctor will ask for an MRI to check whether it will indeed be possible to conserve the breast without decreasing the chances of cure. In some cases, the complete removal of the breast will still be necessary.

For women requiring mastectomy, a breast reconstruction may be recommended. This reconstruction can be immediate or delayed (for medical reasons or for personal preference). It is not necessary that patients should wait 2 years after mastectomy before being offered reconstruction. It is also not true that reconstruction of the affected sites makes detection of recurrence* of cancer more difficult.

One or several lymph nodes* in the armpit will also be removed

This removal is very important to know whether the cancer has spread to lymph nodes, but it has a limited effect in treating the cancer. Two types of surgery of the lymph nodes can be performed:

- The surgeon performs a sentinel lymph node* biopsy*. After injection of a marker near the tumor, the marker will naturally be led to lymphatic vessels and then to lymph nodes. With the help of a probe, the surgeon will be able to identify in which lymph node(s) the marker is located. He/she will remove the lymph node(s) to check if cancer cells are present. A rapid examination of the lymph nodes will be made while the patient is still in surgery. If cancer cells are found in the lymph node(s), the surgeon will usually perform an axillary dissection* (see below). For patients with tumors of less than 5 cm in diameter, axillary dissection might not be necessary if the examination shows that only 1 or 2 sentinel lymph nodes contain cancer cells.
- The surgeon performs an axillary dissection*. The surgeon makes an incision under the arm and removes the axillary soft tissue where lymph nodes are located. These lymph nodes will be checked for the presence of cancer cells.

Sentinel lymph node* biopsy* causes less arm swelling (lymphedema) and shoulder stiffness than axillary dissection*. Sentinel lymph node biopsy is recommended in stage I and stage II breast cancer, unless involved lymph nodes can be detected preoperatively on physical examination or by ultrasound*. In higher stages, an axillary dissection will be performed.

Laboratory examination of the tumor and lymph nodes* removed by surgery

Once the tumor and lymph nodes have been removed, they will be examined in the laboratory to:

- Confirm the results of the biopsy* regarding histological type*, grade*, hormone receptor* status, HER2* status and possibly multigene expression profile*.
- Measure the size of the tumor and see if it has spread to surrounding tissues.
- Check whether cancer cells have entered lymphatic vessels or blood vessels, which would make it more likely that they have spread outside of the breast.
- Check whether the whole tumor has been removed and margins are free of tumor tissue*.
- Check whether cancer cells have spread to the lymph nodes and count the number of lymph nodes affected.

Second surgery

Some patients may be operated on a second time. The two main reasons are:

- The margins* of resection were positive; the tumor is not completely surrounded by normal tissue. The new operation should remove the rest of the tumor.
- After a more thorough examination of the lymph node(s)* from the sentinel lymph node biopsy*, it turns out that they contain cancer cells. An axillary dissection* will usually be performed. For patients with tumors of less than 5 cm in diameter, axillary dissection might not be necessary if the examination shows that only 1 or 2 sentinel lymph nodes contain cancer cells.

Adjuvant therapy

An adjuvant therapy* is a therapy given in addition to surgery. For patients with stage I to III breast cancer, possible adjuvant therapies are radiotherapy*, chemotherapy*, hormone therapy and targeted therapy*. In this setting, radiotherapy is a local treatment whereas chemotherapy, hormone therapy and targeted therapy can reach cancer cells that may have spread to other parts of the body. These latter treatments are called systemic therapies.

Radiotherapy*

Radiotherapy is the use of radiation to kill cancer cells. Generally, cancer cells are less capable of recovery from radiation damage than normal cells.

Radiotherapy is recommended for almost all invasive* breast cancers. A limited number of patients may not benefit from radiotherapy, which could therefore be omitted. This concerns patients of more than 70 years of age who have a tumor of less than 2 cm in diameter that is hormone-responsive. In addition, one should be sure that the whole tumor has been removed by surgery with negative margins.

Radiotherapy in breast cancer aims to destroy cancer cells locally using high-energy radiation produced by a radiotherapy device.

- **After breast-conserving surgery radiotherapy is strongly recommended for all patients:** radiotherapy of the whole breast, followed by additional irradiation (called a *boost*) of the area from which the tumor has been removed.
- **After mastectomy radiotherapy** is recommended or should be considered for patients with large tumors and/or for whom cancer cells have been found in axillary lymph nodes. The radiotherapy will target the chest wall and sometimes the regional lymph node areas as well. When there is a clear and extensive spread of cancer cells to the lymph nodes over the collar bone or behind the breastbone (sternum), the field of irradiation can be extended to include these areas.

The dose of radiation to be delivered is between 45 and 50 Grays (Gy). A Gray is the unit used to measure the quantity of radiation delivered in radiotherapy. This total dose is divided into fractions. Each fraction is given during one session of radiotherapy. Typically for breast cancer, 25 to 28 fractions are planned, but a shorter treatment using 16 fractions has shown the same efficacy without increased side effects. When a boost is planned, an additional 10 to 16 Gy is administered in fractions of 2 Gy. The goal of giving the treatment in fractions is to lower the risk of significant damages to normal tissues and to increase the probability of long-term tumor control.

In order to shorten the time of treatment duration and to avoid the patient having to come between 16 and 35 times to the radiotherapy unit, attempts have been made to deliver radiotherapy during surgery. This has been called accelerated partial breast irradiation. Research is ongoing but preliminary results suggest that this could be considered for patients of at least 50 years of age, with a single tumor of less than 3 cm in diameter and resection margins of more than 2 mm, and no spread to the lymph nodes*. In addition, the tumor should have specific histological characteristics (non-lobular histology without any intraductal component and no lymphovascular invasion). This type of radiotherapy requires specific devices that are not available in many centres because research is still on-going.



Systemic therapy*

The goal of systemic therapy* is to act on cancer cells that might have reached other parts of the body.

The characteristics of the tumor tissue identified by laboratory examination of the biopsy* and of surgically removed tumor are essential to decide which therapy or combination of therapies is most appropriate. These tumor characteristics include tumor size, histological type*, grade*, margins* of resection, number of lymph nodes* involved, hormone receptor* status, HER2* status and, if available, multigene expression profile*. Age, menopausal status and medical conditions of the patient are the patient factors important for making an informed decision regarding adjuvant systemic treatment.

For each individual, the choice must take into account the potential benefits, the possible side effects and the patient's preference.

Three types of treatment can be used for systemic therapy*: hormonal therapy, chemotherapy* and HER2-directed therapy.

Tumors are classified into three groups according to hormonal receptor status: hormone responsive* (ER+ and/or PR+), hormone non-responsive (ER- and PR-) and a third in-between group with uncertain hormone responsiveness*. A hormonal treatment will usually stop or slow the growth of hormone responsive* tumors because these tumors need hormones to grow, but will have no effect on the growth of hormone non-responsive tumors.

- Patients with hormone responsive* tumors may receive either hormone therapy alone or a combination of hormone therapy and chemotherapy*.
- Patients with tumors of uncertain hormone responsiveness* may receive a combination of hormone therapy and chemotherapy.
- Patients with hormone non-responsive tumors should receive chemotherapy, but no hormone therapy.

Hormone therapy

This therapy consists of one or possibly a combination of two of the following treatments:

- A drug called tamoxifen* which counteracts the action of estrogens on the breast and is active in both premenopausal and in postmenopausal patients
- A drug from the aromatase inhibitor* family like anastrozole, exemestane or letrozole which inhibit the production of estrogens in post-menopausal women
- A drug from the gonadotropin*-releasing hormone analogues family that lower the level of estrogens in pre-menopausal women
- Ovariectomy - the removal of the ovaries in premenopausal women

The choice of hormone therapy is based on the menopausal status of the patient.

For patients in whom menopause has not yet begun (pre-menopausal patients), tamoxifen* alone for 5 years, or the combination of a bilateral ovariectomy or a drug from the gonadotropin*-releasing

hormone analogue family plus tamoxifen for 5 years, are the usual treatments. Tamoxifen should not be used simultaneously with chemotherapy.

For patients after their menopause (post-menopausal patients), aromatase inhibitors* for 5 years is preferred for women at higher risk, but for patients treated with tamoxifen, a switch after 2-3 years to aromatase inhibitor for 2-3 years could be considered. Patients treated with aromatase inhibitors are at higher risk of developing osteoporosis*. This should be counteracted by sufficient intake of calcium and vitamin D*. Other examinations such as measurement of bone mineral density and treatments such as bisphosphonates* are available to deal with osteoporosis.

Tamoxifen slightly increases the risk of blood clots and should be stopped if a surgical intervention is planned. It also doubles the risk of developing endometrial cancer (a cancer of the uterus).

Chemotherapy*

Chemotherapy for early-stage breast cancer consists of combining two or three anti-cancer drugs, which are given according to a precise protocol. For breast cancer, the treatment is generally given for 4 to 8 cycles, a cycle being a time period of 2 to 4 weeks with a precise dosage, duration and sequence of drugs including a resting period before a new cycle is started.

It is not clear which combination of drugs is best, but it is recommended that it contains doxorubicin* or epirubicin*, which are anti-cancer drugs from the anthracycline family*. Assessment of heart function is important before therapy with anthracyclines. However, regimens without any anthracycline have been shown to be as effective, for instance the combination of docetaxel* and cyclophosphamide*. Treatments are often named with acronyms using the initial letter of each drug name (e.g. FEC, stands for the combination of Fluorouracil, Epirubicin and Cyclophosphamide). For frail or elderly patients the CMF (Cyclophosphamide, Methotrexate and Fluorouracil) regimen may still be appropriate.

Another option, especially for women in whom tumor cells have spread to the lymph nodes, is to combine an anthracycline* (doxorubicin* or epirubicin*) with a taxane* drug (paclitaxel*), preferably given in sequence rather than in combined fashion.

HER2*-directed therapy

HER2-directed systemic treatments are used for HER2* positive cancers, i.e. when the result of the laboratory examination reports that the IHC* test is “3+” or the FISH* or CISH test is “positive”. Trastuzumab is* a drug effective in patients with HER2* positive tumors, regardless of the size of the tumor and of its hormonal status. In the studies performed to evaluate its efficacy as an adjuvant therapy, trastuzumab was always given in combination with chemotherapy. It is not clear, whether the adjuvant use of trastuzumab without chemotherapy has a positive effect. *

The standard recommended duration of adjuvant treatment with trastuzumab is 1 year. Results from studies comparing this standard duration to shorter or to longer durations are pending.

Trastuzumab can be given together with paclitaxel* or carboplatin* but should not be given together with doxorubicin* or epirubicin*. The latter two drugs and trastuzumab are both toxic to the heart. Trastuzumab cannot be given to patients whose heart function is abnormal. If there is doubt about the heart function, it should be assessed before trastuzumab treatment.

Treatment plan for metastatic cancer (Stage IV)

A metastatic breast cancer is one that has spread to other parts of the body. The most frequent locations of metastases in breast cancer are bone, the liver, the lungs and the brain. Since tumor cells have spread to other parts of the body, systemic therapy* is the mainstay of treatment. About 5% of women with breast cancer have metastases at the time of diagnosis.*

For the treatment of patients with metastatic breast cancer:

- The main treatment goal is to maintain or improve quality of life. Patients should be offered appropriate psychological, social and supportive care.
- The realistic treatment goals should be discussed with the patient and her family and the patient should be encouraged to actively participate in all decisions. The patient's preferences should always be taken into account, including preferences relating to the practicalities of the treatment (for instance, oral or intravenous*).

In many hospitals, specialist breast nurses can provide crucial support to patients and should be available to all patients.

Surgery and radiotherapy*

Some patients exhibiting metastases* may benefit from having the primary breast tumor removed by surgery or treated by radiotherapy. In some rare cases, surgery can also be used to treat patients with a single or very few metastases e.g. in the liver, in the lung or in the brain. Radiotherapy is also used in the management of bone and brain metastases.

Systemic therapy*

The goal of systemic therapy* is to simultaneously act on cancer cells in various organs involved in metastases*. Systemic therapy* options are the same as for invasive* cancer without metastasis (hormone therapy, chemotherapy* and HER2-directed therapy) with a few additional targeted biological agents such as bevacizumab* or everolimus*. If chemotherapy is used, its composition and duration should be tailored to the individual patient.

The choice of the systemic therapy* depends on the hormone receptor* status, on the HER2* status, on the urgency of obtaining a response and on prior therapies and their effectiveness.

Hormone therapy

Hormone therapy is the treatment of choice for patients with hormone responsive* (ER+ and/or PR+) metastatic* breast cancer. The choice of the hormone therapy depends on the menopausal status and on previous hormone therapy applied.

- For patients before their menopause
 - If there has been no prior treatment with tamoxifen* or if the use of tamoxifen has been discontinued for more than 12 months, tamoxifen with either gonadotropin*-releasing hormone analogues or an ovariectomy is the preferred option.



- Otherwise, aromatase inhibitors* like anastrozole, exemestane or letrozole in combination with either gonadotropin-releasing hormone analogues or an ovariectomy. Calcium and vitamin D supplements are recommended in addition to this treatment.
- For patients after their menopause
 - If there has been no prior treatment with aromatase inhibitors* like anastrozole, exemestane or letrozole or treatment with them has been discontinued for more than 12 months, they are the preferred option. Calcium and vitamin D* supplements are recommended in addition to this treatment.
 - Otherwise, tamoxifen, fulvestrant*, megestrol* or androgens* can be used.
 - When there are signs that the cancer progresses or comes back despite treatment with anastrozole or letrozole, an option is to use a combination of exemestane and everolimus*. Combining tamoxifen* and everolimus* may also be an option, but cannot yet be proposed in Europe.

Cancers change over time and it is possible that an ER+ cancer becomes ER- or that an ER+ cancer becomes otherwise resistant to hormone therapy.

Patients with clear evidence of resistance to hormone therapy should be offered chemotherapy or participation in clinical trials.

HER2-directed therapy

HER2*-directed therapy, such as trastuzumab* or lapatinib* should be offered early to all patients with HER2* positive metastatic disease, in addition to chemotherapy*, to hormone therapy, or alone. This should be the case in patients who didn't receive such therapy in the adjuvant treatment and who do not have contraindications for it (e.g. heart insufficiency). If the cancer continues to expand and to progress under a trastuzumab treatment, trastuzumab may be continued with a different chemotherapy. Lapatinib*, an oral drug that also targets the HER2* receptor, can be given in combination with the oral chemotherapy drug capecitabine*. The choice of treatment should be discussed with an oncologist. Two new drugs, namely pertuzumab* and ado-trastuzumab emtansine*, may soon be available in Europe for patients with HER2*-positive tumors.

Chemotherapy*

Chemotherapy should be offered to:

- Patients with fast-growing tumors involving vital organs (e.g. extensive liver involvement), where an immediate response to systemic treatment is necessary.
- Patients with cancers that are both hormone non-responsive and HER2* negative. Such cancers are called "triple negative" (ER-, PR- and HER2*-) and for these chemotherapy is the main treatment option.
- Patients with hormone-responsive* cancers that do not respond to hormone therapy, or that have ceased to respond to hormone therapy.

If patients have previously received chemotherapy with anthracyclines* (epirubicin* or doxorubicin*), they should be offered chemotherapy including a taxane* (paclitaxel* or docetaxel*).

Single drug chemotherapy is mostly preferred over a combination of drugs because it is associated with a better quality of life without a decrement in survival duration. Duration of chemotherapy should be tailored to the individual patient. In general, in patients with triple-negative tumors, metastases* may be more frequent and disease progression more rapid. Therefore, the combination with chemotherapy* may be offered.

Continuing chemotherapy after the patient has received 3 different types of regimens is possible for patients who are in good general condition and whose tumor has “responded” (shown shrinkage) to previous chemotherapy.

Other biologic therapies

Bevacizumab* is a drug that is thought to limit the development of new vessels around the tumor. In Europe, it is now available only for patients with metastatic* breast cancer in combination with first-line chemotherapy* (paclitaxel* or capecitabine*). This combination could be considered in selected patients with limited treatment options, but only upon evaluation of possible side effects and expected benefits. Bevacizumab* is not anymore authorized for patients with breast cancer in the USA.

Other therapies

Radiotherapy* can be used as a palliative therapy for the management of bone metastases*, brain metastases or other local tumor masses such as fungating soft tissue* lesions.

Bisphosphonates* should be used for the treatment of hypercalcemia* and when bone metastases are present. The goal is to relieve pain and to prevent consequences of bone metastases, such as fractures. Bisphosphonates* exist in oral or intravenous* forms. They are generally well tolerated, but in rare instances they can induce a complication called osteonecrosis* of the jaw. These are lesions of the upper or lower jaw bones with bone denudation that take a long time to heal. This complication occurs more often in patients with poor dental conditions. It is therefore recommended to have a dental check-up prior to a bisphosphonate* treatment.

Denosumab is a new therapy used for bone metastases. It seems to be slightly more efficacious than bisphosphonates in preventing bone complications, and has also less kidney toxicity. Like bisphosphonates, denosumab can also cause osteonecrosis of the jaw.

Clinical trials

Clinical trials of new drugs are often proposed to patients with metastatic cancer. Participation in clinical trials should be encouraged since they are the only way to make progress in a context where cure remains extremely rare.

Response evaluation

The response to treatment has to be evaluated in order to weigh the benefit of the treatment against the adverse events experienced. This response evaluation is recommended after 2-3 months of



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hormone therapy and after 2- 3 cycles of chemotherapy*. The evaluation relies on clinical and symptom evaluation, assessment of quality of life, blood tests and repeating the initially abnormal radiological examinations* with comparative measurements.

If the balance between benefits and side-effects is not favourable, new treatment options should be discussed between the patient, family and doctors.

For some patients, measuring the blood levels of substances called tumor markers such as CA15.3 or CEA may be done to help in the evaluation of treatment response. A tumor marker decrease would indicate that the treatment is efficacious and an increase would indicate the opposite. However, these tests are not very reliable and their use is usually restricted to patients for whom no radiological tumor assessments are available.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF THE TREATMENT?

Risk and side effects of surgery

Some risks are common for every surgical intervention performed under general anaesthesia*. These complications are rare and include deep vein thrombosis*, heart or breathing problems, bleeding, infection, or reaction to the anaesthesia. Pain right after the operation is frequent, so painkillers will be proposed to prevent and treat it. Shoulder stiffness can also occur, but it does not usually last.

When lymph nodes* in the armpit are removed, it can damage or block the lymph system resulting in lymphedema, a condition where lymph fluid accumulates in the arm and makes it swell. It can occur right after the intervention but also later. The risk is lower when only a sentinel lymph node biopsy is performed. The risk is high when axillary dissection* is followed by radiotherapy, in which case up to 40% of the patients can develop lymphedema.

Side effects can be relieved through the proper consultation and advice provided by the specialists in oncology.

Side effects of radiotherapy*

Most people will have few side effects, and for many people they will be mild. As radiotherapy affects people in different ways, it is difficult to predict exactly how the patient will react to the treatment.

Some strategies are available to prevent or relieve a certain range of these side effects. There are important improvements in radiotherapy machines and severe side effects are now very rare. Most side effects of radiotherapy disappear gradually once the course of treatment is over. For some people however, they may continue for a few weeks.

The main side effect of radiotherapy of breast cancer is redness, soreness or/and itchiness of the skin of the chest after three to four weeks of having external radiotherapy. This usually settles down two to four weeks after the treatment has finished. The area, however, may stay slightly more pigmented than the surrounding skin.

There are some long-term side effects that can take months and sometimes years to develop.

- The skin can feel different or may be more pigmented than before. Red 'spidery' marks (telangiectasia) may appear on the skin because small blood vessels are damaged.
- Swelling in the arm (lymphedema) can occur because lymph nodes* are damaged.
- Radiotherapy itself can cause cancer and a small number of people will develop a second cancer because of the treatment they have had. However, the chance of a second cancer developing is small and the risks of having radiotherapy are out-weighted by the benefits. The risk is not dependent of the dose received and increases with time.

Side effects of 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 breast cancer are hair loss and decreased blood cell count. Decreased blood cell count can result in anaemia*, bleeding and infections. Once the chemotherapy is completed, 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 nails 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 especially include, stroke, myocardial infarction* and damage to the function of the kidneys and liver. Any of these symptoms should be reported to a doctor.

For younger women who have not gone through menopause, some drugs used in chemotherapy can lead to early menopause by stopping the production of hormones by the ovaries. Symptoms of menopause can therefore occur and include no more periods, hot flushes, sweats, mood swings and vaginal dryness. Fertility can be also affected.

Most side effects of chemotherapy can be treated. Therefore it is important to tell the doctor or nurse about any discomfort that you feel.

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.



- Doxorubicin* and epirubicin* (in less extent) can cause damage to the heart muscle, therefore the assessment of heart function is important before therapy with these two drugs. Trastuzumab* can also cause heart damage and should not be given together with doxorubicin or epirubicin. Doxorubicin and epirubicin can make the skin more sensitive to sunlight and cause reddening in areas where the patient has had radiotherapy in the past. The urine may turn red or pink for a few days after treatment. This is not blood and is only due to the color of the medication.
- Capecitabine* can cause soreness of the palms of the hands and soles of the feet. This condition is called palmar - plantar syndrome and may cause tingling, numbness, pain, dryness and possibly peeling of the palms and soles.
- Docetaxel* sometimes causes fluid retention, temporary nail discoloration and an itchy skin rash. Some people also develop the palmar-plantar syndrome mentioned with capecitabine*, or simple numbness and tingling in hands and feet. About one in four patients will suffer from an allergic reaction during the first or second infusion with docetaxel.
- Paclitaxel* can cause a peripheral neuropathy* which is dependent upon the dose administered, the duration of the infusion, and the schedule of administration. With lower doses of paclitaxel or with weekly regimens, neuropathy is less common. Symptoms include numbness, paresthesias and burning pain in a glove-and-stocking distribution. Symptoms are often symmetrical, and usually have their origins distally in the lower extremities. Patients commonly report the simultaneous onset of symptoms in toes and fingers, but asymmetric presentations 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.

Side effects of hormone therapy

Side effects of hormone therapy are very frequent. They will depend on the drug(s) administered but all hormone therapies share the same main side-effects. Tamoxifen* tends to have more side-effects than aromatase inhibitors*.

For pre-menopausal women, the first goal of a hormone therapy is to suppress the function of the ovaries, either by removing them or by the action of a drug (gonadotropin*-releasing hormone analogues). This will lead to symptoms of the menopause such as hot flushes, sweats, mood swings and vaginal dryness. And of course, periods will stop.

The main side effects shared by hormone therapies are listed below and are related to changes in the level or effect of hormones due to the therapy. On the whole, for almost all women, the benefits of hormone therapy outweigh the risks.

- Hot flushes and sweats (very frequent and especially with tamoxifen*)
- Vaginal dryness or discharge
- Muscle and joint pain (especially with aromatase inhibitors*)
- Mood swings
- Fatigue
- Nausea
- Less interest in sex (which can occur for many different reasons related to breast cancer, but changes in hormones due to the therapy can explain this at least partly).



Some other rare, but more serious side effects are possible. Most of the drugs have an effect on the bones and can lead to osteoporosis*. Sufficient intake of calcium and vitamin D* is therefore very important, as can be an assessment of the bone density by radiological examination*.

Tamoxifen* can increase the risk of developing cancers of the body of the uterus for women taking the drug after their menopause. Any vaginal bleeding after the menopause should be reported to a doctor, even if most vaginal bleedings are not due to uterine cancer.

Tamoxifen can also increase the risk of blood clots, usually in the legs (deep vein thrombosis*). Rarely, a piece of the blood clot can become detached (embolize) in the blood flow and may end up in an artery of the lungs (pulmonary embolism) causing chest pain and shortness of breath. Any of these symptoms should be reported to a doctor.

Side effects of targeted* biologic therapies

Trastuzumab*

Side effects of trastuzumab are more limited than side effects of chemotherapy*. Trastuzumab can cause allergic reactions ranging from chills, fever and possibly an itchy rash, feeling sick, breathlessness, wheezing and headaches, to flushes and faintness. Chills, fever, rash, nausea and vomiting are usually due to the infusion itself and tend to happen during the first few infusions before becoming less common.

Trastuzumab can cause harm to the heart, including heart failure. Care should be taken if it is given to patients who already have heart problems or high blood pressure, and all patients need to be monitored during treatment to check their heart.

Trastuzumab should not be used in people who may be hypersensitive to trastuzumab, mouse proteins* or to any of the other ingredients. It must not be used in patients who have serious breathing problems when they are at rest because of their cancer, or who need oxygen therapy*.

One or more of the above side effects may be seen in a patient, but not necessarily all of them in the same patient.

Lapatinib*

Most frequent side effects occurring in more than 30% of patients taking lapatinib in combination with capecitabine are diarrhea and hand-foot syndrome (skin rash, swelling, redness, pain and/or peeling of the skin on the palms of hands and soles of feet). It is usually mild, starts early (usually 2 weeks) after start of the treatment, and may require reductions in drug doses. Anemia may happen, as well as nausea and vomiting, and an increase in the blood level of liver enzymes.

Bevacizumab*

There are 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;
- congestive heart failure in patients who have received bevacizumab* prior treatment with anthracycline*based chemotherapy*, or radiation therapy* to the chest wall.

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, diarrhea, hair loss, mouth sores and headache.

Everolimus*

Although not all of these side effects may occur, if they do occur they may need medical attention. Contact your doctor immediately if any of the following side effects occur:

- swelling of the face, arms, hands, legs, or feet;
- bloody nose;
- Tightness of pain in the chest;
- cough or hoarseness;
- cracked lips;
- decreased weight;
- diarrhea;
- shortness of breath or difficult breathing;
- difficulty with swallowing;
- fever or chills;
- general feeling of discomfort or illness;
- lower back or side pain;
- painful or difficult urination;
- rapid weight gain;
- sores, ulcers, or white spots on the lips, tongue, or inside the mouth;
- swelling or inflammation of the mouth;
- thickening of bronchial secretions;
- and tingling of the hands or feet.



WHAT HAPPENS AFTER ADJUVANT TREATMENT HAS BEEN TERMINATED?



It is not unusual to experience treatment-related symptoms once the adjuvant treatment is completed.

- It is not rare that anxiety, sleeping problems, depression or extreme fatigue are experienced in the post-treatment phase; patients with these symptoms may need psychological support.
- Memory deficiencies, difficulties in concentrating are not uncommon side effects of chemotherapy* and are generally reversible within a few months.
- Young women may have premature menopause* because of the chemotherapy with mood swings, weight gain, hot flushes, joint pain and sleeping problems. The way that these symptoms can be treated should be discussed with their doctor.

Follow-up* with doctors

After the treatment has been completed, doctors will propose a follow-up* program aiming to:

- detect possible recurrence* as soon as possible
- detect possible cancer occurring in the other breast
- evaluate and treat adverse effects of the previous treatment
- provide psychological support and information to enhance returning to normal life

Follow-up* visits with the oncologist should include:

- History-taking (reviewing the patient's medical history), eliciting of symptoms and physical examination
- A mammography* of the breast, if no mastectomy was performed, and of the other breast for all women, is recommended every year. This could be replaced by an MRI examination in particular situations such as in patients with familial breast cancer or women younger than 35. For women who have had breast reconstruction, no mammography* will be done and an MRI examination will be performed.
- No further radiological or blood examination if the patient does not exhibit any symptoms.

It is important to be aware that weight gain affects prognosis* adversely and should be discouraged; if necessary, nutritional counselling is recommended. Regular long-term moderate to strenuous physical activity is associated with a favourable prognosis*; aerobic training and weightlifting does not negatively affect the development of lymphedema*.

Return to normal life

It can be hard to live with the idea that the cancer can come back. Based on what is known today, *avoiding weight gain and engaging in regular physical activity could decrease the risk of recurrence* after completion of the treatment. Regular exercise provides various benefits. It helps one to feel physically and psychologically better and it might also reduce the risk of recurrence*. Weight gain



after completion of treatment should be avoided since it is likely to have a negative effect on the prognosis. Nutrition counseling could be proposed to avoid weight gain and should be recommended for obese patients. For smokers, it is also strongly recommended to quit and this could be done with the help of specialists in smoking cessation.

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 come up. Discussing these questions with relatives, friends or doctors may be helpful. Some people may also want to find support from ex-patients' groups or telephone information services and helplines.

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*. In general, it happens in up to 30% of patients without tumor cells present initially in their lymph nodes* and in up to 70% of those whose tumor has been spread to the lymph nodes* at diagnosis.

If it comes back as a recurrence* in the same area of the breast and lymph nodes* involved the first time, it should be treated like a new cancer. It is always recommended to check for the absence of metastasis* in the lung, liver or bone using radiological examinations*.

Surgery to remove the recurrent tumor completely is recommended, if feasible. After surgery, radiotherapy can also be given and depends on the previous treatment:

- Patients not previously exposed to radiotherapy after the operation should receive radiotherapy to the chest wall and regional lymph node areas.
- Patients previously exposed to radiotherapy should not receive radiotherapy again because it could seriously damage the lungs and the heart. Careful irradiation to limited areas of the chest may be applied.

Is it not clear to what extent the use of chemotherapy*, hormone therapy or HER2*-directed therapy after the local treatment prolongs the life when cancer comes back in the same area of the breast and lymph nodes* involved the first time. The main treatment goal in these patients is palliation, with the aim of maintaining/improving quality of life, and possibly improving survival.

For patients considered to be inoperable at the time of disease recurrence, the first choice is systemic therapy* in order to reduce the size of the tumor and render it operable if possible. The second choice is radiotherapy to the chest wall and regional lymph node areas.

Regarding chemotherapy, many factors including aggressiveness of the tumor, previous treatments received and patients' general well-being and preference have to be considered and discussed before making a treatment decision.

If the cancer recurs as a metastatic cancer, it should be treated as explained in the paragraph "Treatment plan for metastatic cancer (Stage IV)" in the section "What are the treatment options?". In this case and whenever possible, a biopsy* of the metastasis should be made and should undergo a laboratory examination to:



- Confirm that it is a metastasis of the breast cancer and not a metastasis of another cancer or not a metastasis at all.
- See if the characteristics of the cancer, like hormone receptor* status and HER2* status are still the same because cancer characteristics may change over time.

A biopsy of the metastasis may be avoided if the procedure is too risky, if the time that has elapsed between the first diagnosis and the occurrence of the metastasis is short (no more than 2 years), suggesting that the characteristics of the cancer should not have changed, or if the results of the new biopsy will not change the treatment plan.

DEFINITIONS OF DIFFICULT WORDS

Ado-trastuzumab emtansine

An antibody-drug conjugate consisting of the antibody trastuzumab linked to the chemotherapy agent mertansine. It is indicated for the treatment of patients with HER2-positive, metastatic breast cancer; who previously received therapy for metastatic disease (trastuzumab and a taxane, separately or in combination) or for recurrence within the first six months of completing adjuvant therapy.

Anaemia

Condition characterized by the shortage of red blood cells* or hemoglobin, the iron that contains the hemoglobin 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, induced artificially by the employment of certain substances known as anaesthetics. It can be complete or partial and allows patients to undergo surgery.

Androgen

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

Anthracycline (family)

Antibiotic drug used in chemotherapy* to treat a wide range of cancers.

Atypical ductal hyperplasia

A benign* condition in which there are more cells than normal in the lining of breast ducts and the cells look abnormal under a microscope. Having atypical ductal hyperplasia increases the risk of breast cancer. Also called ADH and atypical ductal breast hyperplasia.

Atypical lobular hyperplasia

A benign* (not cancer) condition in which there are more cells than normal in the breast lobules and the cells look abnormal under a microscope. Having atypical lobular hyperplasia increases the risk of breast cancer. Also called ALH and atypical lobular breast hyperplasia.

Aromatase inhibitor

A drug that prevents the formation of estradiol*, a female hormone, by interfering with an aromatase enzyme. Aromatase inhibitors are used as a type of hormone therapy for postmenopausal women who have hormone-dependent breast cancer.

Axillary dissection

Surgery to remove lymph nodes* found in the armpit region. Also called axillary lymph node dissection.

Benign

Not cancerous. Benign tumors 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 recognise 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 tumors.

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.

Bisphosphonate

A drug or substance used to treat hypercalcemia* and bone pain caused by some types of cancer. Forms of bisphosphonates are also used to treat osteoporosis* and for bone imaging. Bisphosphonates inhibit a type of bone cell that breaks down bone. Also called diphosphonate.

Capecitabine

Capecitabine is a cytotoxic medicine that belongs to the group antimetabolites. Capecitabine is a 'prodrug' that is converted to 5-fluorouracil (5-FU) in the body, but more is converted in tumor cells than in normal tissues. It is taken in tablet form, while 5-FU, an analogue of pyrimidine, normally needs to be injected. Pyrimidine is part of the genetic material of cells (DNA and RNA). In the body, 5-FU takes the place of pyrimidine and interferes with the enzymes involved in making new DNA. As a result, it inhibits the growth of tumor cells and eventually kills them.

Carboplatin

A drug that is used to treat advanced ovarian cancer that has never been treated or symptoms of ovarian cancer that has 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. Also called Paraplatin.

Carcinoma

Cancer that begins in the skin or in tissues that line or cover internal organs.

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.

Chromogenic In Situ Hybridization (CISH)

It is a laboratory test in which a labeled complementary DNA or RNA strand made in laboratory is used to localize a specific DNA or RNA sequence in a tissue specimen. DNA and RNA are cellular constituents involved in protein* formation and genetic information transmission. This method is used to identify the characteristics and abnormalities in the DNA that forms part of the chromosomes, even the number of chromosomes.

CISH is an alternative to another test called fluorescent in situ hybridization* (FISH).

Clinical examination

An exam of the body to check for general signs of disease.

CT-scan

A form of radiography in which body organs are scanned with X-rays* and the results are synthesized by a computer to generate images of parts of the body.

Cyclophosphamide

A drug that is used to treat many types of cancer and is being studied in the treatment of other types of cancer. It is also used to treat some types of kidney disease in children. Cyclophosphamide attaches to *DNA* in cells and may kill cancer cells. It is a type of *alkylating agent*. Also called CTX and Cytoxan.

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.

Docetaxel

Docetaxel belongs to the group of anticancer medicines known as the taxanes*. Docetaxel prevents cells from destroying 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* antitumor antibiotic*. Also called Adriamycin PFS, Adriamycin RDF, doxorubicin hydrochloride, hydroxydaunorubicin, and Rubex.

Epirubicin

A drug used together with other drugs to treat early breast cancer that has spread to lymph nodes*. It is also being studied in the treatment of other types of cancer. Epirubicin is a type of anthracycline* antibiotic. Also called Ellence and epirubicin hydrochloride.

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, eg. it is important for breast development and the growth of female reproductive organs.



Estrogen receptor positive

Describes cells that have a receptor protein* that binds the hormone estrogen. Cancer cells that are estrogen receptor positive may need estrogen to grow, and may stop growing or die when treated with substances that block the binding and actions of estrogen. Also called ER+.

Everolimus

Everolimus acts by blocking a *protein* called 'mammalian target of rapamycin' (mTOR). Since mTOR is involved in the control of cell division and the growth of blood vessels, everolimus prevents the division of cancer cells and reduces their blood supply. Everolimus is used to treat patients with:

- breast cancer that is advanced (has started to spread) and hormone-receptor-positive (when the cancer cells have receptors for hormones on their surface) in women who have been through their menopause. It is used together with a medicine called exemestane after other treatments called 'non-steroidal aromatase inhibitors' have failed;
- pancreatic neuroendocrine tumours (tumours of the hormone-producing cells in the pancreas) when the cancer cells are well or moderately differentiated (which means that they have a similar appearance to normal pancreas cells) and the cancer is getting worse. It is used when the cancer is metastatic (has spread to other parts of the body) or when it cannot be surgically removed;
- advanced renal-cell carcinoma (a type of kidney cancer), when the cancer has worsened despite treatment with a type of medicine called a 'VEGF-targeted' medicine.

Fluorescence In Situ Hybridization (FISH)

A technique used by pathologists to identify changes to genes and chromosomes. Unique changes to genes or chromosomes can be detected by FISH and help a pathologist know what type of cancer a patient has.

Follow-up

Monitoring a person's health over time after treatment. This includes keeping track of the health of people who participate in a clinical study or clinical trial for a period of time, both during the study and after the study ends.

FSH

A hormone made in the pituitary gland. In females, it acts on the ovaries to make the follicles and eggs grow. In males, it acts on the testes to make sperm. Also called follicle-stimulating hormone and follitropin.

Fulvestrant

A drug used to treat certain types of breast cancer in postmenopausal women. It is also being studied in the treatment of other types of cancer. Fulvestrant blocks estrogen activity in the body and is a type of antiestrogen.

Gene expression profile

Information about all messenger RNAs that are made in various cell types. A gene expression profile may be used to find and diagnose a disease or condition and to see how well the body responds to treatment. Gene expression profiles may be used in personalized medicine.



Gonadotropin-releasing hormone analogue (family)

It is a man-made product similar to gonadotropin-releasing hormone (GnRH). GnRH is a hormone naturally made by the hypothalamus (part of the brain). GnRH causes the pituitary gland to make hormones involved in reproduction (gonadotropins).

Some GnRH analogues are more potent than GnRH naturally produced in the body in stimulating gonadotropin release.

Grade

A description of a tumor based on how abnormal the cancer cells look under a microscope and how quickly the tumor is likely to grow and spread. Grading systems are different for each type of cancer.

HER2

A protein* involved in normal cell growth. It is found on some types of cancer cells, including breast and ovarian. Cancer cells removed from the body may be tested for the presence of HER2/neu to help decide on the best type of treatment. HER2/neu is a type of receptor tyrosine kinase. Also called c-erbB-2, human EGF receptor 2, and human epidermal growth factor receptor 2.

Histological type

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

Histopathology

The examination and study of tissue and cells using a microscope. Tissue obtained from the body by biopsy or surgery is placed in a fixative and transported to the laboratory. Here, it is cut into thin sections, stained with various dyes and then studied under the microscope. A histopathologist is a doctor interpreting sections of tissue including tumor tissue.

Hormone receptor

A cell protein* that binds a specific hormone. The hormone receptor may be on the surface of the cell or inside the cell. Many changes take place in a cell after a hormone binds to its receptor.

Hormone responsive

In oncology, describes cancer that responds to hormone treatment.

Hypercalcemia

Higher than normal levels of calcium in the blood. Some types of cancer increase the risk of hypercalcemia.

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.

Immunohistochemistry (IHC)

Immunohistochemistry or IHC refers to the process of detecting antigens (e.g. proteins*) in cells of a tissue section by exploiting the principle of antibodies binding specifically to antigens in biological tissues. These antigens are visualized by a marker such as fluorescent dye, enzyme, or colloidal gold. Immunohistochemical staining is widely used in the diagnosis of abnormal cells such as those found in cancerous tumors.

Lapatinib

The active substance in Tyverb[®], lapatinib, belongs to a group of medicines called *protein** kinase inhibitors. These compounds work by blocking *enzymes* known as protein kinases, which can be found in some receptors on the surface of cancer cells including *HER2*. *HER2* is a receptor for epidermal growth factor and is involved in stimulating the cells to divide uncontrollably. By blocking these receptors, Tyverb[®] helps to control cell division. About a quarter of breast cancers express *HER2*.

Lobular neoplasia

A condition in which abnormal cells are found only in the lobules of the breast, but have not spread from the lobules to surrounding tissues as would be seen in an invasive lobular carcinoma. Lobular neoplasia does not become invasive lobular carcinoma very often, but having lobular neoplasia in one breast increases the risk of developing invasive cancer in either breast. Lobular neoplasia was formerly called lobular carcinoma in situ or LCIS.

Lymphedema

A condition in which extra lymph fluid builds up in tissues and causes swelling. It may occur in an arm or leg if lymph vessels are blocked, damaged, or removed by surgery.

Lymph node

A rounded mass of lymphatic tissue that is surrounded by a capsule of connective tissue. Lymph nodes filter lymph and they store lymphocytes. They are located along lymphatic vessels. Also called lymph gland.

Lymphoma

Cancer that begins in cells of the immune system. There are two basic categories of lymphomas. One kind is Hodgkin lymphoma, which is marked by the presence of a type of cell called the Reed-Sternberg cell. The other category is non-Hodgkin lymphoma, which includes a large, diverse group of cancers of immune system cells. Non-Hodgkin lymphomas can be further divided into cancers that have an indolent (slow-growing) course and those that have an aggressive (fast-growing) course. These subtypes behave and respond to treatment differently. Both Hodgkin and non-Hodgkin lymphomas can occur in children and adults, and prognosis* and treatment depend on the stage and the type of cancer.

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.

Mammography

The use of film or a computer to create a picture of the breast.

Margin

The edge or border of the tissue removed in cancer surgery. The margin is described as negative or clean when the pathologist finds no cancer cells at the edge of the tissue, suggesting that all of the cancer has been removed. The margin is described as positive or involved when the pathologist finds cancer cells at the edge of the tissue, suggesting that all of the cancer has not been removed.

Megestrol

A drug used to block estrogen and suppress the effects of *estrogen* and *androgens**. It is used to treat breast and *endometrial* cancer, and is being studied in the treatment of other types of cancer. It is also used to improve appetite in patients with cancer. Megestrol belongs to the group of hormones called *progestins*. Also called Megace.

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.

Metastasis

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

Mitosis

The process by which a single parent cell divides to make two new daughter cells. Each daughter cell receives a complete set of chromosomes from the parent cell. This process allows the body to grow and replace cells.

Multidisciplinary opinion

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 tumor board review.

Myocardial infarction

A myocardial infarction or heart attack is the interruption of blood supply to a part of the heart, causing heart cells to die. If left untreated, a heart attack can cause significant damage to the heart muscle or even death.

Neo-adjuvant therapy

Treatment given as a first step to shrink a tumor before the main treatment, which is usually surgery, is given. Examples of neo-adjuvant therapy include chemotherapy*, radiation therapy, and hormone therapy. It is a type of induction therapy.

Neuropathy

Refers to any disease of the *nervous system*. This includes the brain, the spinal cords and the nerves.

Non-invasive

Cancer that has not spread beyond the layer of tissue in which it developed.

Nucleus

In biology, the structure in a cell that contains the chromosomes. The nucleus has a membrane around it, and is where RNA is made from the DNA in the chromosomes.

Osteonecrosis

A disease where bone tissue dies because the blood supply is impaired.

Osteoporosis

A condition that is marked by a decrease in bone mass and density, causing bones to become fragile.

Oxygen therapy

Treatment in which a storage tank of oxygen or a machine called a compressor is used to give oxygen to people with breathing problems. It may be given through a nose tube, a mask, or a tent. The extra oxygen is breathed in along with normal air. Also called supplemental oxygen therapy.

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. Also called Taxol.

Palpation

The action of touching the breast or other body parts with the fingers, and gently moving the fingers to feel the consistency of the tissue (flesh)

Pertuzumab

An anticancer drug used to treat *HER2*-positive metastatic breast cancer, if the patient did not receive prior anti-*HER2* therapy or chemotherapy for metastatic disease. It should be used together with trastuzumab and docetaxel.

Platelet

Small cell fragments that play a fundamental role in the formation of blood clots. Patients with a low platelet count are at risk of severe bleeding. Patients with a high a count are at risk of thrombosis, the formation of blood clots that can block blood vessels and result in stroke or other severe conditions, and can also be at risk of severe bleeding because of platelet dysfunction.

Prognosis

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

Progesterone receptor positive

Describes cells that have a protein* to which the hormone progesterone will bind. Cancer cells that are progesterone receptor positive need progesterone to grow and will usually stop growing when treated with hormones that block progesterone from binding. Also called PR+.

Proliferation

An increase in the number of cells as a result of cell growth and cell division.

Prophylactic surgery

Mastectomy performed in patients with high risk of developing breast cancer and usually done on both breasts (bilateral).

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.

Radiological examination

Test that uses imaging technology (such as radiography, ultrasound*, computed tomography* and nuclear medicine) to visualize organs, structures and tissues within the body to both diagnose and treat diseases.

Radiotherapy

A therapy in which radiation is used in the treatment of cancer that is always oriented to the specific location of the cancer.

Recurrence

Cancer that has recurred (come back), usually after a period of time during which the cancer could not be detected. The cancer may come back to the same place as the original (primary) tumor or to another place in the body. Also called recurrent cancer.

Red blood cell

The most common type of blood cell. It is the substance that makes the blood appear red. The main function is the transport of oxygen.

Relapse

The return of signs and symptoms of cancer after a period of improvement.

Risk factor

Something that increases the chance of developing a disease. Some examples of risk factors for cancer are age, a family history of certain cancers, use of tobacco products, being exposed to radiation or certain chemicals, infection with certain viruses or bacteria, and certain genetic changes.

Scintigraphy

A procedure that produces pictures (scans) of structures inside the body, including areas where there are cancer cells. Scintigraphy is used to diagnose, stage, and monitor disease. A small amount of a radioactive chemical (radionuclide) is injected into a vein or swallowed. Different radionuclides travel through the blood to different organs. A machine with a special camera moves over the person lying on a table and detects the type of radiation given off by the radionuclides. A computer forms an image of the areas where the radionuclide builds up. These areas may contain cancer cells. Also called radionuclide scanning.

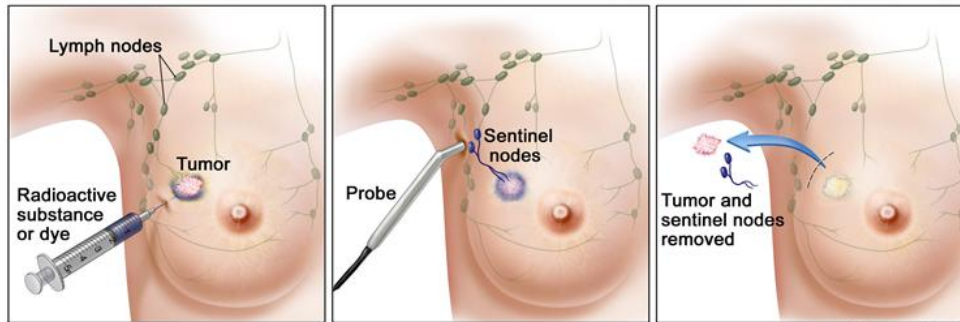


Screening mammography

X-rays* of the breasts taken to check for breast cancer in the absence of signs or symptoms.

Sentinel lymph node biopsy

Removal and examination of the sentinel node(s) (the first lymph node(s)* to which cancer cells are likely to spread from a primary tumor). To identify the sentinel lymph node(s), the surgeon injects a radioactive substance, blue dye, or both, near the tumor. The surgeon then uses a probe to find the sentinel lymph node(s) containing the radioactive substance or looks for the lymph node(s) stained with dye. The surgeon then removes the sentinel node(s) to check for the presence of cancer cells



Sentinel lymph node biopsy of the breast. A radioactive substance and/or blue dye is injected near the tumor (first panel). The injected material is detected visually and/or with a probe that detects radioactivity (middle panel). The sentinel nodes (the first lymph nodes to take up the material) are removed and checked for cancer cells (last panel).

Soft tissue

Refers to muscle, fat, fibrous tissue, blood vessels, or other supporting tissue of the body.

Staging

Performing exams and tests to learn about the extent of the cancer within the body, especially whether the disease has spread from the original site to other parts of the body. It is important to know the stage of the disease in order to plan the best treatment.

Systemic therapy/treatment

Treatment using substances that travel through the bloodstream, reaching and affecting cells all over the body.

Tamoxifen

A drug used to treat certain types of breast cancer in women and men. It is also used to prevent breast cancer in women who have had ductal carcinoma in situ (abnormal cells in the ducts of the breast) and in women who are at a high risk of developing breast cancer. Tamoxifen is also being studied in the treatment of other types of cancer. It blocks the effects of the hormone estrogen in the breast. Tamoxifen is a type of antiestrogen. Also called tamoxifen citrate.

Targeted therapy/treatment

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.

Taxane

A type of drug that blocks cell growth by stopping mitosis* (cell division). Taxanes interfere with microtubules (cellular structures that help move chromosomes during mitosis). They are used to treat cancer. A taxane is a type of mitotic inhibitor and a type of antimicrotubule agent.

Trastuzumab

The active substance in Herceptin®, trastuzumab, is a *monoclonal antibody*. Trastuzumab has been designed to attach to *HER2**. By attaching to *HER2*, trastuzumab activates cells of the *immune system*, which then kill the tumour cells. Trastuzumab also stops *HER2* producing signals that cause the tumour cells to grow. About a quarter of breast cancers and a fifth of gastric cancers overexpress *HER2*.

Triple negative breast cancer

Describes breast cancer cells that do not have estrogen receptors, progesterone receptors, or large amounts of *HER2*/neu protein**. Also called ER-negative PR-negative *HER2*/neu-negative* and ER-PR-*HER2*/neu-*.

Ultrasound

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 ultrasonography.

Vitamin D

A nutrient that the body needs in small amounts to function and stay healthy. Vitamin D helps the body use calcium and phosphorus to make strong bones and teeth. It is fat-soluble (can dissolve in fats and oils) and is found in fatty fish, egg yolks, and dairy products. Skin exposed to sunshine can also make vitamin D. Not enough vitamin D can cause a bone disease called rickets. It is being studied in the prevention and treatment of some types of cancer. Also called cholecalciferol.

White blood cell

Cells of the immune system that are involved in the body's defense against infections.

X-ray

X-rays are a form of radiation used to take images of the inside of objects. In medicine, X-rays are commonly used to take images of the inside of the body.