

Follicular Lymphoma

What is
follicular
lymphoma?

Let us explain
it to you.

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FOLLICULAR LYMPHOMA: A GUIDE FOR PATIENTS

PATIENT INFORMATION BASED ON ESMO CLINICAL PRACTICE GUIDELINES

This guide for patients has been prepared by the Anticancer Fund as a service to patients, to help patients and their relatives better understand the nature of follicular lymphoma and appreciate the best treatment choices available according to the subtype of follicular lymphoma. 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 newly diagnosed and relapsed follicular lymphoma. 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, as well as two oncology nurses from the European Oncology Nursing Society (EONS). It has also been reviewed by patient representatives from ESMO's Cancer Patient Working Group.

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

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

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

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FACT SHEET ABOUT FOLLICULAR LYMPHOMA

Definition of follicular lymphoma

- Follicular lymphoma is a cancer that develops in the white blood cells, lymphatic system and bone marrow.
- Follicular lymphoma is a subtype of Non-Hodgkin Lymphoma (NHL). Cells of the lymphoid tissues in the lymphatic system multiply uncontrollably to eventually result in tumours.

Diagnosis

- Common symptoms of follicular lymphoma are painless swelling of the lymph nodes, fever for no apparent reason, drenching night sweats, fatigue, infections and bleeding. Sometimes the diagnosis in patients occurs with no symptoms as a result of imaging or laboratory tests.
- The number of red blood cells, white blood cells and platelets can be lower than normal and white blood cells could also look larger.
- The diagnosis can only be confirmed with a lymph node* biopsy* (removal of a piece of tissue to be analysed in a laboratory).

Treatment according to the extension of the disease (classified into stages)

- Stage I and stage II follicular lymphomas involve one and two groups of lymph nodes respectively. They are located on the same side of the diaphragm*.
 - When the lesions are smaller than 7.5 cm in diameter, radiotherapy is usually curative.
 - Close monitoring of the patient's condition through watchful waiting is possible instead of using active administration of treatment.
 - In all other cases, treatment with chemotherapy* and rituximab* before radiotherapy* is recommended.
- Stage III follicular lymphomas affect lymph nodes on both sides of the diaphragm* or spread to a nearby organ. Stage IV follicular lymphomas have spread to the bone marrow or other organs. At these stages, an "induction" treatment aiming to reduce the size of the tumour(s) is followed by a "consolidation" treatment to increase the chance of a cure.
 - The induction treatment consists of intensive chemotherapy together with rituximab*. In some cases, the induction treatment can be more or less intensive depending on the features of the disease.
 - The consolidation treatment starts after completion of the induction treatment and consists of rituximab* for 2 years.
- Relapsed disease means that after initial elimination or control of the tumour(s), the disease becomes active again. Depending on the time between completion of treatment and relapse, and on the type of treatment previously administered, various effective options are available. They include chemotherapy, rituximab, radioimmunotherapy* and stem cell transplantation.

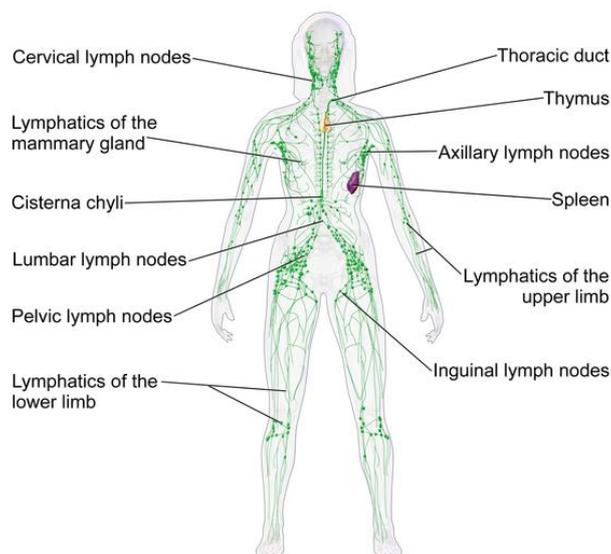
Follow-up

- Consultations are scheduled regularly with the purpose of either detecting a relapse as a transformation into an aggressive form or a new cancer as early as possible. These consultations are more frequent the first few years.
- During this period, blood tests are performed to evaluate anything abnormal.
- Doctors are also vigilant to monitor and if necessary address potential side effects of the therapies administered.

DEFINITION OF FOLLICULAR LYMPHOMA

Follicular lymphoma is a cancer that develops in the white blood cells, lymphatic system and bone marrow. Follicular lymphoma is a well-defined subtype of Non-Hodgkin Lymphoma (NHL)* with cells of the lymphoid tissues in the lymphatic system multiplying uncontrollably to eventually cause tumours to grow. The lymphatic system is constituted of lymph vessels that branch through the body of the veins and arteries* as well as lymph glands or lymph nodes along the lymph vessels. Lymphoid tissue is consisted of several types of system cells that help the body fight infection. Most of the cells in lymphoid tissue are cells called lymphocytes (a type of white blood cells) with two main types of lymphocytes, specifically B- and T-lymphocytes. Different types of lymphoma can develop from each type of lymphocyte, but follicular lymphoma arises in particular from B-lymphocytes. The malignant cells in lymphoma grow in clusters to form nodules. Some organs are also part of the lymphatic system and partially constructed by lymphoid tissue with the spleen, thymus, tonsils and adenoids. The lymphatic system filters blood, lymph (the liquid that circulates in lymph vessels), drains fluid from tissues back to the bloodstream and fights infections. Since lymphoid tissue is found throughout the body, follicular lymphoma can begin in almost any part of the body. The bone marrow may become invaded by lymphocytes* that does not function properly. As the bone marrow also produces platelets to critically stop bleeding and red blood cells to deliver oxygen to all cells in the body, excess accumulation lymphocytes prevents the normal production of red blood cells and platelets. Follicular lymphoma is usually slow-growing.

The Lymphatic System



The Lymphatic System

Photo credit: Bruce Blaus (Creative Commons)

IS FOLLICULAR LYMPHOMA FREQUENT?

Compared to breast cancer in women or prostate cancer in men, NHLs* are not common. But, nevertheless they are the sixth most common cancer in Europe. They account for around 3% of all cancers and follicular lymphomas represent approximately 25% of all NHLs*. In Western Europe, follicular lymphoma is the second most frequent subtype of lymphoma.

The number of patients diagnosed with follicular lymphoma every year has increased from 2-3 cases per 100,000 people in the 1950s, to 5-7 cases per 100,000 people now.

In general, the risk of getting NHL* increases with age. There is a 5-7 fold increase in the number of cases among patients older than 65 years.

WHAT CAUSES FOLLICULAR LYMPHOMA?

Today, the cause of follicular lymphoma is not understood. Some risk factors have been identified. A risk factor increases the risk that cancer occurs, but it is neither necessary nor sufficient to cause cancer. A risk factor is not a cause in itself.

Some people with these risk factors will never develop follicular lymphoma and some people with none of these risk factors will develop it.

Lifestyle, environmental factors and previous medical conditions have been linked to the occurrence of follicular lymphoma, but their influence is not clear yet.

- **Lifestyle factors:**

○ *Diet:* A link between follicular lymphoma and consumption of meat and milk was found, as well as nitrates* and nitrites* frequently present in our diet. Cured meat, food preservatives, and those naturally occurring in some fruits are some sources. Protective effects have been suggested with the consumption of polyunsaturated fatty acids*, vitamin D, fruits and vegetables, among others. The association with obesity is not clear.

○ *Alcohol:* Alcohol intake has been associated with cancer in humans. Wine consumption has been found to increase the risk of developing follicular lymphoma, particularly for drinkers who started before the age of 20 and/or when the alcohol consumption is higher than 19 grams per day (a glass of wine has approximately 14 grams of alcohol).

○ *Smoking:* Current smokers have higher risks of developing follicular lymphoma according to study results in comparison to former smokers. Heavy smokers are also at higher risk.



- **Environmental factors:**

Pesticides allegedly cause a specific genetic mutation that has a role in the development of follicular lymphoma. Yet the specific mutation has been found in healthy individuals that never developed follicular lymphoma. Hair dyes have been linked with follicular lymphoma in some studies. Other chemicals such as solvents with benzene need to be confirmed as risk factors. But their association to follicular lymphoma has already been suggested in different studies. Moderate sun exposure, on the other hand, has been associated with reduced risk.



- **Other medical conditions:**

Conditions with a suppressed immune system are also linked to follicular lymphoma such as HIV/AIDS, autoimmune diseases and medication.

HOW IS FOLLICULAR LYMPHOMA DIAGNOSED?

Patients may be diagnosed on the basis of their symptoms or sometimes in patients with no symptoms as a result of imaging and laboratory tests.

Symptoms and signs of follicular lymphoma may include:

1. **Painless swelling of the lymph nodes** in the neck, arm pits, and/or groin. If follicular lymphoma arises mostly in deep lymph nodes, it might present with compression of some vital organ and causing symptoms. Among others, some include chronic cough, problems to breath, chest pain, abdominal pain or back pain depending on the organ involved.
2. **Fever** for no known reason.
3. Drenching **night sweats**.
4. Undesired or unintentional **weight loss**.
5. **Fatigue**. Fatigue is a common symptom of anaemia*. Patients who are physically active may not notice the effects of being anaemic until it is severe.
6. **Infections**. Due to replacement of an important part of the healthy immune system that protects us from infections and by cancer, patients can experience recurrent infections or infections unusually difficult to treat.
7. **Bleeding**. Rarely a low platelet count resulting from replacement of the normal bone marrow with cancerous cells results in easy bruising, bleeding from the nose or gums, and appearance of small red spots on the skin commonly over the shins and ankles.

Symptoms 2-4 are known as B symptoms, which are taken into account when staging the disease.

Patients with the above symptoms will have a **complete blood count** test, which is a laboratory test done to check the three types of cells made in the bone marrow: 1) white blood cells, 2) red blood cells, and 3) platelets. Occasionally a patient may have a complete blood count done for another reason to show the first indication of a possible lymphoma based on laboratory findings alone. In addition to identifying a low red cell count or platelet count, as part of the white blood cell count the complete blood count may find abnormal cells circulating in the blood. Abnormal white blood cells multiplying at a high rate are larger than the more mature normal white blood cells found in circulation.

If a diagnosis of follicular lymphoma becomes suspected based on symptoms and the white blood cell count, a lymph node biopsy* is performed.

Exact diagnosis of follicular lymphoma can only be based on a **lymph node biopsy***. It involves the removal of a lymph node when the patient may be under anaesthesia (excisional biopsy). The removed lymph node tissue will be examined in the laboratory. This examination is called histopathology* and mainly consists of visually assessing the tissue under a microscope to look for lymphoma cells. In contrast, the removal of only a part of a lymph node using a wide needle (core biopsy) should only be performed in patients without easily accessible lymph nodes due to their position in the body. Of note, the results of the biopsy examination may not be clear since the lymphoma cells could be different from one part of the lymph node to another (known as heterogeneity). The removal of tissue or fluid using a thin needle (fine needle biopsy) is not recommended for a reliable lymphoma diagnosis.



The World Health Organisation (WHO) has classified lymphoma as Grade 1, 2, 3A or 3B. This grade is dependent upon the number of lymphoma cells (called blasts*) seen under the microscope. Grade 3B has the greatest number of blasts and considered to be more aggressive. Therefore, Grade 3B must be treated differently to other types of lymphoma. When possible, additional biopsy material should be stored fresh frozen; this means that additional tests could be performed later into the future if needed.

WHAT IS IMPORTANT TO KNOW TO GET THE OPTIMAL TREATMENT?

Doctors will need to gather different elements to decide what would be the best treatment.



Relevant information about the patient

- General well-being.
- Personal medical history.
- History of cancer in relatives.
- Results from the clinical examination by the doctor. Your doctor will look for enlarged lymph nodes and organs, as well as general appearance of the skin and inside the mouth particularly. The physical examination should be detailed.
- Results of imaging studies* of the body, such as a computed tomography (CT)* scan, includes the neck, chest, abdomen and pelvis. These studies will identify the location and extent of the lymphoma. The scans are critical to stage the lymphoma in one of four stages based on the extent of spread. These stages are described further on the next page. Positron emission tomography (PET)* scan may be useful in confirming a localised form of disease (stage II). PET* results allow doctors to see the locations of cancerous cells since the radiolabeled glucose is concentrated in the cancerous cells and they can be seen in the PET image.
- A complete blood count, routine blood chemistry including lactate deshydrogenase* (LDH) and uric acid, screening tests for human immunodeficiency (HIV) and hepatitis B and C are required. These tests are very important when deciding on the best treatment. If the results of these tests show to be positive, a specific therapy for these conditions is recommended.
- A bone marrow biopsy is a procedure to take a bone marrow sample from the hip to evaluate whether the bone marrow is affected. After the disease diagnosis, the bone marrow biopsy must be done to identify the stage of the disease adequately. It is performed under local anesthesia.
- In addition to clinical examination, others may be performed to assess the risks of complications due to the treatment. For example, to assess the function of the heart, it is recommended to perform an echocardiogram (ultrasound of the heart).
- If severe headaches, problems with vision, sensation, or muscle function are present, an assessment of the cerebrospinal fluid* (the fluid surrounding the brain and spinal cord) may be necessary. This is performed by doing a lumbar puncture (spinal tap) with a fine needle passed into the spine. After anaesthetic is used to numb the area in order to obtain some of this fluid, the next step occurs with the fluid sent to the pathologist for examination under the microscope. A CT scan or magnetic resonance imaging (MRI)* of the head may be necessary if the lumbar puncture does not identify any cancer cells. The CT scan* or MRI* could show an area of lymphoma inside the brain that requires additional treatment specific to that location of tumour.



Relevant information about the cancer

- **Staging**

After the diagnosis of follicular lymphoma, tests must be done to find out if lymphoma cells have spread within the lymph system or to other parts of the body. Staging is the process of determining whether the tumour has spread, and if so, how far. It is extremely important to know the stage of the disease in order to plan the treatment.

The staging system used to describe the spread of follicular lymphoma is called the Ann Arbor Staging System. It uses Roman numerals (I-IV) for different stages.

Stage	Definition
Stage I	The lymphoma is in one group of the body's lymph nodes such as the groin or neck, or in one organ of the lymph system.
Stage II	Two or more groups of lymph nodes, or one organ close to the affected lymph nodes and one or more groups of lymph nodes on the same side of the diaphragm contain lymphoma cells. The diaphragm is the muscle that divides the chest and abdomen. <ul style="list-style-type: none"> ▪ For example, lymphoma might be above the diaphragm in lymph nodes in the neck and arm pits. Or lymphoma might be below the diaphragm in lymph nodes in the groin and abdomen.
Stage III	The lymphoma is in lymph nodes on both sides of the diaphragm. It may have also spread into an organ close to the affected lymph nodes or spleen.
Stage IV	The lymphoma is in stage IV if the lymphoma involves the bone marrow or distant organs.

Follicular lymphoma stages are also noted by the presence or absence of certain findings and/or symptoms of the disease:

- A lymphoma that affects organs or tissues other than the lymph nodes has an "E", for extranodal, added to its staging nomenclature.
- If a nodal mass is at least 7.5 cm of diameter, it translates as a bulky disease.
- If it affects the spleen, an "S" is added.
- If the patient has fever, night sweats, or unexplained weight loss, the letter "B" is added. If none of these is present, an "A" is added.

- **Grade (WHO classification) and other histopathological characteristics**

The grading, as explained previously, could be 1, 2, 3A and 3B to reflect the number of lymphoma cells or blasts under the microscope using maximal magnification. Grade 3B is the highest grade and considered an aggressive lymphoma.

- **Prognosis and risk classification**

A Follicular Lymphoma-specific International Prognostic Index (FLIPI) should be determined for prognostic purposes. FLIPI allows to identify the risk of progression of the disease after treatment and to adapt treatment and follow-up accordingly. The parameters used in the original version FLIPI 1 are > 4 involved nodal sites, age >60 years, elevated LDH* level, stage

III or IV disease and haemoglobin* <12 g/dl. One point is assigned to each of the above characteristics ranging this index score between 0 and 5. For each relevance of index, the 0-1 risk is considered low, the 2 risk as intermediate and the 3-5 risk as high.

Paediatric follicular lymphoma is a variant originally described in children, yet occurs in adults as well. It is characterised by a localised disease histologically more aggressive and some with specific molecular features. However, paediatric follicular lymphoma shows a much more indolent course and should be managed with local therapy only.

WHAT ARE THE TREATMENT OPTIONS?

The treatment should take place only in centres used to treat patients with lymphoma and offering an adequate multidisciplinary approach. You are also encouraged to ask about any clinical trials* for your current situation.



Treatment of follicular lymphoma is tailored to each individual based on the stage and patient characteristics, including age and other diseases that the patient may have such as diabetes, coronary heart disease or chronic obstructive pulmonary disease. Although this usually occurs in the management of solid tumours, surgery does not play a major role in the treatment of follicular lymphoma since the nature of the lymphatic system lymphoma is not often confined to only one area of the body.

Treatment may control or cure the lymphoma. It can also improve your quality of life by controlling symptoms of the disease. The goal of follicular lymphoma treatment is to apply one or more of these strategies, including killing the lymphoma cells as quickly as possible, stopping the growth of new lymphoma cells, treating side effects caused by lymphoma such as pain, fevers, chills and night sweats, and/or maintaining a sense of control over your treatment choices and life.

In general, several approaches are considered when treatment decisions are made for the management of follicular lymphoma. These include watchful waiting, radiotherapy*, chemotherapy* and targeted therapy* with monoclonal antibody*. Except for watchful waiting, these therapies may, and typically are, used in combination with each other.

Watchful waiting is a term used for a strategy featuring close monitoring of each patient's condition without giving any treatment until symptoms appear or change. This approach is meaningful in low tumour burden follicular lymphoma since spontaneous partial regression have been observed in some individuals. Moreover, evidence suggests that normal T cells* are capable of controlling the lymphoma in some individuals. Some patients may be watched closely for over 10 years before treatment is needed. During watchful waiting, patients are still being "treated" to track their situation in spite of no drugs or radiotherapy being used.



External radiotherapy is a cancer treatment that uses high-energy x-rays* or other types of radiation to kill cancer cells and keep them from growing. External radiotherapy uses a machine that focuses the radiation from outside the body and targets it towards the cancer.

Chemotherapy is anticancer treatment that uses drugs to stop the growth of cancer cells either by killing the cells or by stopping them from dividing. When chemotherapy is taken by mouth or injected into a vein, the drugs enter the bloodstream and can reach cancer cells throughout the body (systemic chemotherapy). Rarely when follicular lymphoma has spread to the brain, chemotherapy can be administered into the cerebrospinal fluid* to kill lymphoma cells in the brain or spinal cord. The way chemotherapy is given depends on the stage of the disease. Combination chemotherapy



provides treatment using two or more anticancer drugs. Steroid drugs may be added to kill the lymphoma cells as well.

Immunotherapy is a type of treatment that either boosts the patient's own immune system, or uses man-made drugs called **monoclonal antibodies*** that attack a specific target on the surface of lymphocytes (cells in which lymphoma starts). The monoclonal antibody rituximab* is a drug used to treat follicular lymphoma and administered by infusion into veins.

Radioimmunotherapy refers to a type of treatment where a radioactive substance is attached to the monoclonal antibody*. When the monoclonal antibody* is delivered to the cells' targets, the radioactive source acts on the lymphoma cells and potentially some nearby cells. This treatment is known as yttrium 90-ibritumomab tiuxetan*.

Bone marrow transplantation either with patients' own bone marrow cells or a donor's may be a part of lymphoma treatment. Before performing the bone marrow transplantation, the radiation and chemotherapy are applied with the aim to reduce the cells in bone marrow affected by the disease.

The treatment mainly depends on the stage of the disease. For more advanced stages (stage III and IV), the goal of the treatment involves two major strategies. Firstly, induce a regression of the tumour (induction phase). Secondly, consolidate or maintain this regression (consolidation/maintenance phase). Treatment details are presented below stage by stage.

Treatment plan for stage I-II follicular lymphoma

Stage I means that one lymph node group or lymphatic organ is affected.*

Stage II means that either two or more lymph node groups on the same side of the diaphragm are affected, or one or more lymph node groups together with a lymphatic* organ close to the lymph nodes involved on the same side of the diaphragm* are affected.*

In the small proportion of patients with limited non-bulky stage I-II disease, the administration of radiotherapy targeting the site of the involved lymph nodes has curative potential.

In selected cases, watchful waiting may be discussed to avoid the side effects of radiation and it could be of the same efficacy as active treatment.

The presence of bulky, large tumour, or with two or more sites involved and other risks help doctors to identify patients who could benefit from treatment with chemotherapy* and monoclonal antibody* rituximab*. In this case the role of radiotherapy may be considered after this initial treatment if the sites of involved lymph nodes are located in a way that radiotherapy can be given without major side effects.

Treatment plan for Stage III-IV

Stage III means that the lymphoma is in lymph nodes on both sides of the diaphragm. It may have also spread into a nearby organ.

Stage IV means that the lymphoma is in the bone marrow, or distant organs.

In up to 10-20% of lymphoma cases, the disease could disappear or regress without any treatment. Early initiation of therapy in asymptomatic patients did not show any improvement of survival in different studies. Therefore in that case, watchful waiting is recommended. Treatment should only be utilized due to symptoms, including B-symptoms (fever for an unknown reason, drenching night sweats and undesired or unintentional weight loss), impairment in blood cells formation, bulky disease, compression of important organs, abnormal presence of fluid in abdominal cavity (ascites), or in the space between the lungs and thoracic* wall (pleural effusion) and rapid progression of the disease. The treatment strategies are explained later in the section on induction and consolidation/maintenance treatment.

The induction treatment is the first step to start reducing the number of cancer cells. From there, a consolidation phase further reduces the number of cancer cells and increases the probability of the lymphoma not coming back. This is followed by a maintenance phase with goals to maintain the remission and prevent a relapse.

Complete remission is achieved when the tumours disappear completely and no further signs of disease exist. Partial remission comes from a shrinkage of the tumours with some remaining. This is shown through a physical examination or by imaging, as well as disease symptoms that might persist.

Induction treatment

In the majority of patients with advanced stage III and IV disease, chemotherapy does not result in a definite cure. But, remissions usually last for years and the average survival is longer than 20 years.

Combination of monoclonal antibody* rituximab* and chemotherapy* such as CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) or bendamustine* are recommended for disease remission and long-term maintenance of achieved response. When a physical examination or new biopsy indicates results to suspect that the disease turned into an aggressive course, a regimen such as CHOP is preferred. Studies also showed when monoclonal antibody* rituximab* is added to chemotherapy, improvements occur with tumour shrinkage, keeping the disease stable and prolonging patients' lives in general.

The chemotherapy regimen CVP (cyclophosphamide*, vincristine* and prednisone*) in combination with rituximab* may be given in case of contraindications for chemotherapy drug doxorubicin*.

Full courses of fludarabine* and cyclophosphamide* or fludarabine* and mitoxantrone* are not recommended due to higher haematological toxicities*.

In symptomatic patients with low volume tumour mass, and in case of slow disease progression, therapy with rituximab* alone may be considered.

In low-risk elderly patients, and elderly patients with contraindications for more intensive combination of chemotherapy* and rituximab*, the treatment with rituximab* plus chlorambucil*, rituximab* alone or radioimmunotherapy* are alternatives.

There are specific recommendations for monitoring and treatment of patients with hepatitis B virus infection. Often, blood tests will be taken to monitor activity of hepatitis B virus, as well as antiviral* medications recommended.

Consolidation/maintenance treatment

After induction treatment achieves complete or partial remission, rituximab* as maintenance therapy is administered in a single application every two months for up to two years. This strategy delays the progression of the disease.

Radioimmunotherapy* as consolidation delays progression of the disease only after chemotherapy, but the benefit seems inferior in comparison to rituximab* maintenance for 2 years.

Stem cell transplant using a patient's own stem cells may delay disease progression only if chemotherapy was administered before. However, such an approach is not recommended for patients that respond to first-line therapy. The benefit from a stem cell transplant would be limited after rituximab*.

Relapsed disease

Relapse is the reappearance of the disease. A repeated biopsy is strongly recommended to know if the lymphoma that relapsed turned into an aggressive form.

The treatment given when the disease relapsed is called salvage treatment and selection depends on effectiveness from the previous treatments administered. In early relapse (< 12-24 months disease-free) the disease might be resistant to the drugs used previously. As a result, a regimen of different drugs to overcome resistance is preferred. An example comes from bendamustine* after CHOP and vice versa. Rituximab* could be used again for the patient if previously it achieved a disease-free period of more than 6-12 months.

Radioimmunotherapy* (radioactive substance combined/attached to a monoclonal antibody*) represents an effective approach, especially in patients over 65 years of age with other diseases present. In those cases, they are not suitable for chemotherapy and therefore need other types of treatment such as radioimmunotherapy.

Rituximab* maintenance for up to 2 years as a single treatment every 3 months can be administered in patients who received it as a part of induction and did not receive it in the first-line treatment.

In young patients, high-dose chemotherapy with a stem cell transplantation using the patient's own stem cells could be considered. Research indicates that treatment combination for young cancer patients delays the progression of the disease and prolongs survival. However it is not always required now. Instead, rituximab is widely used for patients, especially in patients experiencing late relapses.

Evaluation of response to treatment

In all cases, scans should be performed halfway through treatment and after completion of the treatment. If insufficient or no response is detected, early treatment for relapsed disease should be considered.

PET*/CT scan to evaluate response to treatment continues to be under investigation, although it has shown some benefit as a predictor of the disease course outcome. However, further studies are needed.

A laboratory test to see if any cancer cells remain in the body (known as minimal residual disease analysis) after completion of treatment is known to be highly predictive. But, the test should not guide the treatment outside of clinical trials.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF THE TREATMENT?

Watchful waiting

This strategy becomes stressful for patients as they have to wait until the disease has turned aggressive to get active treatment. However, watchful waiting is valid considering the good prognosis of this disease compared to other malignances. You must discuss any concerns about this situation with your doctor.

Radiotherapy

Most people will have a few side effects, but often they are 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 some of these side effects. There have been important improvements in application of radiotherapy.

As a result, severe side effects are now very rare. Most of the side effects of radiotherapy disappear gradually once the course of treatment is over. But for some people, side effects may continue for a few weeks.

During radiotherapy, side effects may occur in organs that are directly targeted, but also in healthy tissues or organs close to the region that needs to be irradiated and cannot be protected from the X-rays. Side effects may be increased when radiotherapy* is administered with chemotherapy*. The symptoms and signs of the side effects vary according to the part of the body irradiated. For example, if neck irradiation occurs, then salivary glands may be affected. Also, dysfunction reflected in dry mouth might be persistent. Yet in most cases any side effects are transient. **Strategies to prevent and relieve post-radiation reactions must be provided by the radiation oncologist or the nurse.**

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 when small blood vessels are damaged. Radiotherapy itself can sometimes cause cancer and a small number of people will develop a second cancer due to the treatment. However, the chance of a second cancer developing is overall rare and the risks of getting radiotherapy are minimal compared to the benefits.

Immunotherapy

Monoclonal antibody/Rituximab

Although rituximab* is expected to affect only cancer cells, some side effects can occur and they should be reported to your doctor immediately. Although sometimes the side effects seem severe, generally approved drugs' benefits outweigh potential risks.

Rituximab may cause severe infusion-related side effects particularly during the first infusion or within 24 hours after the infusion. Later side effects are also possible. Your healthcare team will inform you about these possibilities.

Infusion-related side effects

- Allergic reactions with flu-like symptoms, breathing problems like shortness of breath, difficulty breathing, or wheezing, fever, body aches, redness and bumps on the skin, itching, swelling of lips, tongue, throat and face, low blood pressure, and/or chest pain.

In case of infusion-related side effects, the infusion should be discontinued and reinitiated when all symptoms have stopped. Your doctor should give you some medications before the infusion to decrease the chance of a severe infusion reaction.

Later side effects

- Heart problems.
- Feeling sick.
- Low red blood cell counts leading to anaemia*.
- Low white blood cell counts that could lead to infections.
- Low platelet counts impairing coagulation.

If you have had hepatitis B infection or carry hepatitis B virus, receiving rituximab* could cause the infection to become active again. Hepatitis B reactivation may cause serious liver problems. During the active phase of hepatitis B infection, you should not receive rituximab*. Please remember to tell your healthcare team before starting therapy that you have had hepatitis B.

Rituximab* may also cause tumour lysis syndrome* caused by a fast breakdown of cancerous cells, and characterised by kidney failure and abnormal heart rhythm. But this only occurs under certain circumstances depending on the size of the tumour.

Treatment with rituximab* may lower the ability of your immune system to fight infections.

In very rare cases, rituximab* may cause a serious brain virus infection. If you feel, or if anyone close to you notices confusion or problems thinking, loss of balance, changes in how you walk or talk, weakness on one side of your body, blurred vision or loss of vision, report it to your doctor immediately.

Radiolabelled monoclonal antibodies (Radioimmunotherapy)

All side effects described for rituximab are potential side effects of radioimmunotherapy as well. However, the most common side effects of yttrium 90-ibritumomab tiuxetan* are a low platelet count, bleeding, anaemia and low number of white blood cells.

Chemotherapy

Side effects of chemotherapy are very frequent. They will depend on the drug(s) administered, the doses and other individual factors.

Combinations of different drugs can lead to more side effects than taking a single drug. The nature, frequency and severity of the side effects vary for any chemotherapy drug combination used.

Effective supportive therapies for some of these side effects exist and treatments are possible.

Listed below are side effects known to occur with one or several of the chemotherapy drugs currently used for follicular lymphoma.

The most frequent side effects are:

- Decreased blood cell counts that may lead to anaemia, bleeding and bruising, and infections.
- Lack of energy.
- Fever, chills, body aches, and flu symptoms.
- Sores in mouth and throat.
- Feeling sick, vomiting and diarrhoea.
- Some of the chemotherapy drugs used can cause urination problems with little or no urine elimination and painful urination. The urine can also change colour and depends on the drug. Anthracyclines* (doxorubicin) could turn urine's color into reddish-orange. However, it is not harmful and disappears after one day or two.
- In women menstrual periods may also be affected. They may completely cease during and/or after the treatment, or you may miss some periods (for example, in case of chemotherapy drugs doxorubicin*, cyclophosphamide*, and mitoxantrone*) or bleeding may increase (for example, in case of mitoxantrone*). In men there is a risk of infertility as well. Your doctor will discuss with you about all the options to preserve fertility and offer available support before your treatment.

Other side effects that may occur frequently are:

- Numbness or tingling feeling around your mouth.
- Yellowing of the skin and the white part of your eyeballs (for example, in case of side effects from chemotherapy drugs that are metabolised through the liver, or liver damage induced by hepatitis B infection).
- Temporary or complete hair loss and/or thinning of the hair.
- Skin changes or reactions.
- Memory deficiencies and difficulties in concentrating.

Occasional side effects:

- Bone pain, constipation (in case of vincristine). Constipation may also appear as a result of some drugs given to prevent nausea and vomiting.
- Doxorubicin* can cause damage to heart muscles. Therefore, the assessment of heart function is important before its administration.
- Rarely, doxorubicin* can cause leukaemia or secondary cancers later on.



In general, all side effects should be reported to your physician as soon as they appear.

WHAT HAPPENS AFTER THE TREATMENT?

It is not unusual to continue to experience some treatment-related symptoms once the treatment is over.

- It is not rare that anxiety, sleep problems or depression take place during the post-treatment phase. Patients dealing with those symptoms need support and even from psychological professionals.
- Memory deficiencies with difficulty in concentrating are not uncommon chemotherapy side effects and generally reversible within a few months.



Follow-up with doctors

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

- detect a possible relapse as soon as possible
- evaluate adverse effects of the treatment and treat them
- provide psychological support and information to enhance returning to normal life

Under general consensus follow-up visits with the doctor should include:

- History-taking, monitoring of symptoms and physical examination every three months for two years, every four to six months for additional three years and subsequently once a year. Your doctor will be vigilant to the possibility that lymphoma may come back, or the disease considered under control then transformed into more an aggressive course, or that a new cancer or leukaemia may appear.
- Blood count and other routine blood analyses every six months for two years and then only if suspicious symptoms appear.
- Evaluation of thyroid function at one, two and five years if the patient received irradiation to the neck.
- Radiological* and ultrasound studies* every six months for two years and annually thereafter. However, CT scans are not mandatory outside clinical trials.
- Minimal residual disease analysis may also be performed within clinical trials.

Return to normal life

Returning to life after cancer offers good perspectives. Yet it can be challenging to live with the potential idea that the disease can come back. From what is known today, no specific ways to reduce the risk of recurrence after completion of the treatment can be recommended. As a consequence of the disease itself and treatment, depending upon the individual, returning to normal life may not be easy for some people. Questions related to body-image, sexuality, fatigue, work, emotions or lifestyle may be a concern. Discussing these questions with relatives, friends, other patients or the healthcare team may be helpful. Support from patient organisations providing advice on treatment effect management, as well as psycho-oncologist services, telephone conversations and email exchanges are available in many countries.

What if the lymphoma comes back?

If the lymphoma returns, it is called a relapse and the treatment depends on the age of the patient, prior treatment, and the possibility of a bone marrow transplant.

A new biopsy is strongly recommended to determine whether the relapsed lymphoma became aggressive. The treatment given after relapse called salvage treatment depends on how effective the treatments previously administered were. Different combinations of chemotherapy and rituximab can be given. For further details, please explore various sections in this guide about treatment.

In elderly patients not suitable for these regimens, radioimmunotherapy* is an option. In case of relapse in selected younger patients with a high-risk profile, potentially curative stem cell transplantation from a donor may be considered.

DEFINITIONS OF DIFFICULT WORDS

Abdomen

Part of the body between the thorax and pelvis. The muscles corresponding to this area enclose a cavity containing the stomach, intestines, liver, spleen, and pancreas. It is also known as belly.

Anaemia

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

Anthracyclines

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

Antiviral

Agent that kills a virus or that suppresses its ability to replicate.

Artery/Arteries

A blood vessel that carries blood from the heart to tissues and organs in the body.

Ascites

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

Bendamustine

The active ingredient in a drug that is used to treat chronic lymphocytic leukaemia (CLL), to treat slow-growing B-cell non-Hodgkin lymphoma (NHL) that has gotten worse within 6 months of treatment with other anticancer drugs, and is being studied in the treatment of other types of cancer. Bendamustine may damage the DNA in cancer cells and cause them to die. It is a type of alkylating agent and a type of antimetabolite.

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.

Cerebrospinal fluid

The fluid that surrounds and bathes the spinal cord and brain. Its main function is to protect the brain and the spinal cord.

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.

Chlorambucil

A drug used to treat several types of leukaemias and lymphomas. Chlorambucil blocks cell growth by damaging the cell's DNA and may kill cancer cells. It is a type of alkylating agent.

Clinical trial

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

Computed tomography CT

A form of radiography in which body organs are scanned with X-rays and the results 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.

Diaphragm

The thin muscle below the lungs and heart that separates the chest from the abdomen *.

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.

Extralymphatic

It refers to any organ or structure outside of the lymph nodes and lymphatic system.

Fludarabine

The active ingredient in a drug used to treat B-cell chronic lymphocytic leukaemia (CLL) that has not responded to treatment with other anticancer drugs or that has gotten worse. Fludarabine blocks cells from making DNA and may kill cancer cells. It is a type of purine antagonist and a type of ribonucleotide reductase inhibitor.

Haemoglobin

The substance inside red blood cells* that binds to oxygen in the lungs and carries it to the tissues.

Hematological toxicities

The extent to which something is poisonous or harmful to blood cells with, i.e. red blood cells, white blood cells and platelets.

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 tumour tissue.

Imaging studies/Imaging test/Imaging procedure

A type of test that makes detailed pictures of areas inside the body. Imaging tests use different forms of energy such as X-rays (high-energy radiation), ultrasound (high-energy sound waves), radio waves, and radioactive substances. They may be used to help diagnose disease, plan treatment, or find out how well the treatment is working. Examples of imaging tests are computed tomography (CT), ultrasonography, magnetic resonance imaging (MRI), and nuclear medicine tests. Also called imaging procedure.

Lactate deshydrogenase (LDH)

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

Lymphocyte

A type of white blood cell that is essential in the immune system. The three major types of lymphocyte are T cells, B cells and natural killer (NK) cells specific roles in the immune system.

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.

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.

Minimal residual disease analysis

Laboratory test to detect small numbers of cancerous cells that remain in the patient's body during or after treatment when other indicators show remission in patients (no signs or symptoms of disease).

Mitoxantrone

A drug used to treat advanced prostate cancer that does not respond to hormones, adult acute non-lymphocytic leukaemia, and advanced or multiple sclerosis. It is also being studied in the treatment of other cancers. It belongs to the family of drugs called antitumour antibiotics.

Monoclonal antibody

Monoclonal antibodies are antibodies exactly the same since they are produced by clones of the same parent cell.

Nitrates

Nitrates are naturally present in soil, water, and food. They are compounds containing nitrogen that can exist in the atmosphere or as a dissolved gas in water and which can have harmful effects on humans and animals. Once taken into the body, nitrates are converted into nitrites.

Nitrites

Nitrites are manufactured mainly for use as a food preservative. Both nitrates and nitrites are used extensively to enhance the colour and extend the shelf life of processed meats.

Non-Hodgkin Lymphoma (NHL)

Any of a large group of cancers of lymphocytes (white blood cells). Non-Hodgkin lymphomas can occur at any age and often marked by lymph nodes larger than normal, fever, and weight loss. There are many different types of non-Hodgkin lymphoma. These types can be divided into aggressive (fast-growing) and indolent (slow-growing) types formed from either B-cells or T-cells. B-cell non-Hodgkin lymphomas include Burkitt lymphoma, chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL), diffuse large B-cell lymphoma, follicular lymphoma, immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma, and mantle cell lymphoma. T-cell non-Hodgkin lymphomas include mycosis fungoides, anaplastic large cell lymphoma, and precursor T-lymphoblastic lymphoma. Lymphomas that occur after a bone marrow or stem cell transplantation are usually B-cell non-Hodgkin lymphomas. Prognosis and treatment depend on the stage and type of disease.

Polyunsaturated fatty acid

A fatty acid is a major component of fats used by the body for energy and tissue development. They are also known as “good” fatty acids as opposed to saturated fatty acids.

Positron emission tomography/PET

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

Prednisone

A drug that lessens inflammation and suppresses immune responses. It is used with other drugs to treat leukaemia and lymphoma and other types of cancer. Prednisone is also used to treat many conditions, including arthritis, certain skin diseases, allergies, low levels of some adrenal hormones, loss of appetite and anaemia. It is a therapeutic glucocorticoid.

Radioimmunotherapy

A type of radiation therapy in which a radioactive substance is linked to a monoclonal antibody and injected into the body. The monoclonal antibody can bind to substances in the body, including cancer cells. The radioactive substance gives off radiation, which may help kill cancer cells. Radioimmunotherapy is being used to treat some types of cancer such as lymphoma.

Radiological

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

The use of high-energy radiation from X-rays, gamma rays, neutrons, protons, and other sources to kill cancer cells and shrink tumours. Radiation may come from a machine outside the body (external-beam radiation therapy), or it may come from radioactive material placed in the body near cancer cells (internal radiation therapy). Systemic radiotherapy uses a radioactive substance, such as a radiolabeled monoclonal antibody, that travels in the blood to tissues throughout the body. Also called irradiation and radiation therapy.

Rituximab

A drug used to treat certain types of B-cell non-Hodgkin lymphoma. It is also used with other drugs to treat chronic lymphocytic leukaemia and rheumatoid arthritis. It is being studied in the treatment of other types of cancer and other conditions. Rituximab binds to a protein called CD20, which is found on B-cells, and may kill cancer cells. It is a type of monoclonal antibody.

Targeted therapy

A type of treatment that uses drugs or other substances, such as monoclonal antibodies, to identify and attack specific cancer cells. Targeted therapy may have fewer side effects than other types of cancer treatments.

T cell

A type of white blood cells (lymphocytes) that can determine whether something belongs to the body or not. They kill infected cells. They play an important role in the immune system.

Thoracic

Having to do with the chest.

Tumour lysis syndrome

A condition that can occur after treatment of a fast-growing cancer, especially certain leukaemias and lymphomas (cancers of the blood). As tumour cells die, they break apart and release their contents into the blood. This causes a change in certain chemicals in the blood, which may cause damage to organs, including the kidneys, heart, and liver.

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.

Vincristine

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

X-rays

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.

Yttrium 90-ibritumomab tiuxetan

A drug used with the drug rituximab to treat certain types of B-cell non-Hodgkin lymphoma. It is also being studied in the treatment of other types of B-cell tumours. Yttrium Y 90 ibritumomab tiuxetan contains a monoclonal antibody that binds to a protein called CD20, which is found on B cells. It also contains a radioactive substance called yttrium Y 90, which may help kill cancer cells. Yttrium Y 90 ibritumomab tiuxetan is a type of radioimmunoconjugate.

The ESMO / Anticancer Fund Guides for Patients are designed to assist patients, their relatives and caregivers to understand the nature of different types of cancer and evaluate the best available treatment choices. The medical information described in the Guides for Patients is based on the ESMO Clinical Practice Guidelines, which are designed to guide medical oncologists in the diagnosis, follow-up and treatment in different cancer types.

These guides are produced by the Anticancer Fund in close collaboration with the ESMO Guidelines Working Group and the ESMO Cancer Patient Working Group.

For more information please visit www.esmo.org and www.anticancerfund.org

