Understanding Lymphoma and Chronic Lymphocytic Leukemia (CLL)

Follicular Lymphoma

Lymphoma Research Foundation

Follicular lymphoma (FL) is the most common *indolent* (slow-growing) form of B-cell non-Hodgkin Lymphoma (NHL), accounting for 1 out of 5 lymphomas in the US.

Common symptoms of FL include:

- Enlargement of the lymph nodes (bean-shaped structures that help the body fight infection, Figure 1) in the neck, underarms, abdomen, or groin.
- Fatigue (extreme tiredness).

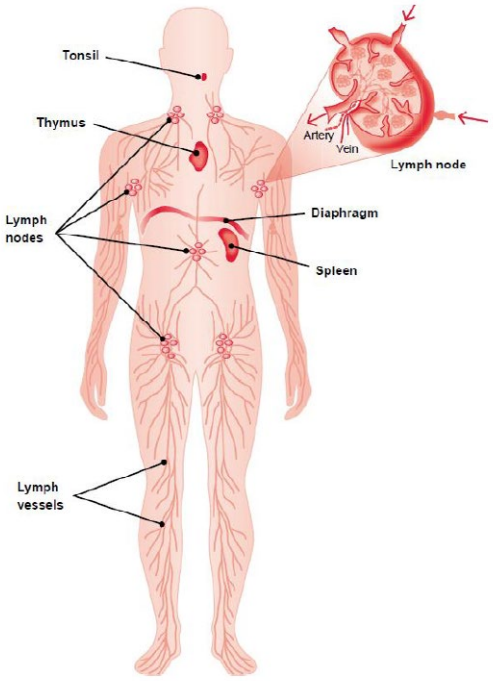

Figure 1: The lymphatic system (tissues and organs that produce, store, and carry white blood cells) and lymph nodes.

Diagnosis and Staging

Typically, patients with FL have no obvious symptoms of the disease at diagnosis. Patients often only have an enlarged lymph node examined by their doctor or found by chance on an imaging scan. Most patients with FL are aged 55 years or older when they are diagnosed.

To make a definite diagnosis of FL, doctors need to collect a sample of the affected lymph node. This procedure is called a *biopsy*. The biopsy is typically studied by a *pathologist* (doctor who specializes in the diagnosis of diseases by studying the cells from a patient's body fluids and tissue samples) and preferably a *hematopathologist* (pathologist who has undergone additional training in the diagnosis of blood cancers, including lymphoma) who is experienced in diagnosing lymphoma. Determining the grade (level of large lymphocytes present in the affected lymph nodes) and if and how far the lymphoma has spread (staging) is important to define the best treatment for each patient.

FL is graded as 1 or 2 (low grade), and 3A or 3B (high grade) depending on the number of abnormal lymphocytes found on the lymph node tissue examined under the microscope. Grades 1 to 3A FL are treated similarly. Grade 3B FL is usually fast-growing and looks like a high-grade diffuse large B-cell lymphoma (DLBCL), so it is treated the same way as DLBCL. In some patients (about 2-3% per year), FL may *transform* (when a slow-growing lymphoma becomes fast-growing) into a more aggressive type of lymphoma, most commonly DLBCL. This transformed lymphoma usually requires more intensive types of treatment. This change is characterized by an increase in the number of DLBCL cancer cells in the affected lymph node, which changes the follicular appearance of the cancer. For more information on transformed lymphomas, view the *Transformed Lymphomas* fact sheet on the Lymphoma Research Foundation's website (visit lymphoma.org/publications).

For staging, the results of the different tests (such as biopsies and scans) are used to determine the severity of the disease and the appropriate treatment. The Lugano staging system is used for FL and is depicted in Figure 1 below. This system categorizes FL from Stage I (limited disease) to IV (advanced disease), based on whether the disease is restricted to a single group of lymph nodes, has spread to other lymph nodes, or has reached the bone marrow (the spongy tissue inside the bones) and/or other organs (like the liver or lungs). Because FL is an indolent disease and might not cause any symptoms initially, it is often advanced (stage III or IV) when it is diagnosed. For more information on diagnosis and disease staging, please view the *Understanding Lymphoma and CLL Guide* on the Foundation's website (visit lymphoma.org/publications).

To predict the *prognosis* (how well the patient will do) of a patient with FL, physicians commonly use a score called the Follicular Lymphoma International Prognostic Index (FLIPI). The FLIPI score determines the risk level of each patient and predicts the chance of survival based on factors such as age and number of lymph nodes affected. Keep in mind that no two patients are alike and that statistics can only predict how a large group of patients will do (not what will happen to an individual patient). The doctor most familiar with the patient's situation is in the best position to interpret these statistics, understand how well they apply, and respond to any questions you might have.

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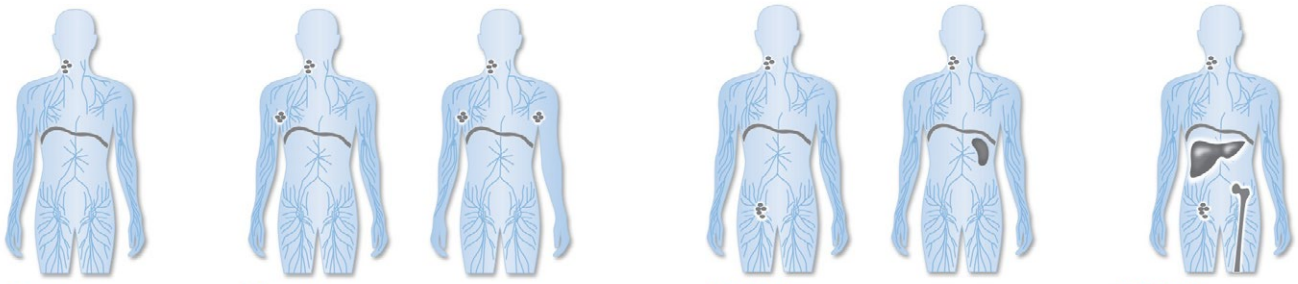
Figure 2: Staging of NHL according to the Lugano system. NHL, non-Hodgkin lymphoma.



Stage I
Involvement of a single lymph node or group of adjacent nodes

Stage II
Involvement of two or more groups of lymph nodes on the same side of the *diaphragm* (muscle that separates the chest from the abdomen)

Stage III
- Involvement of lymph nodes on both sides of the diaphragm, or
- Involvement of lymph nodes above the diaphragm plus spleen involvement

Stage IV
Widespread disease in lymph nodes, bone marrow, and organ involvement, such as liver or lungs

Treatment Options

If patients show no or very few symptoms, physicians may recommend to not treat the disease right away. This approach is referred to as active surveillance (also known as "watchful waiting" or "observation"). Patients managed with active surveillance have survival outcomes similar to those treated early. In this case, patients' overall health and disease are monitored through regular physical exams (to check for any swollen lymph nodes) or periodic imaging tests (like computed tomography [CT] scans). If patients begin to have symptoms or signs of disease progression, treatment is initiated. There are various therapeutic options for FL based on how severe the symptoms are and how fast the cancer is growing. The treatments for FL include:

- *Radiation therapy* (uses high-energy radiation to kill cancer cells). Radiation alone can provide long-lasting *remission* (disappearance of signs and symptoms) in some patients with early-stage disease.
- *Chemoimmunotherapy* (a combination of chemotherapy with *monoclonal antibodies* [proteins made in the laboratory that bind to cancer cells and help the body fight cancer]). Commonly used monoclonal antibodies are obinutuzumab (Gazyva), rituximab (Rituxan), and rituximab hyaluronidase human (Rituxan Hycela), a rituximab product that is administered under the skin.

Common chemoimmunotherapy regimens used to treat FL include:

- Bendamustine (Treanda) and obinutuzumab (Gazyva).
- R-Bendamustine (rituximab [Rituxan] and bendamustine).
- R-CHOP (rituximab, cyclophosphamide, doxorubicin/hydroxydaunorubicin, vincristine [Oncovin], and prednisone).
- R-CVP (rituximab, cyclophosphamide, vincristine, and prednisone).
- R-Lenalidomide (rituximab and lenalidomide [Revlimid]), often referred to as R² (R-squared).

Patients seeking information about monoclonal antibodies should view the *Immunotherapy and Other Targeted Therapies* fact sheet on the Foundation's website (lymphoma.org/publications).

Some monoclonal antibodies such as obinutuzumab (Gazyva) or rituximab (Rituxan), can also be used as maintenance therapy to prolong remission in patients with no signs of lymphoma after initial treatment. Patients seeking information about maintenance therapy should view the *Understanding Lymphoma and Maintenance Therapy* fact sheet on the Foundation's website (lymphoma.org/publications).

After treatment, many patients can go into durable remission (disappearance of signs of cancer for a long period) that lasts for years; however, FL should be considered a chronic or lifelong condition. In some cases, the disease can relapse (return after treatment) or become refractory (no longer responds to treatment). For more information on relapsed and refractory FL, view the Follicular Lymphoma Relapsed/Refractory fact sheet on the Foundation's website (visit lymphoma.org/publications).

For patients with relapsed or refractory FL, the same treatments listed above may be used, depending on the number and type of past treatments, duration of previous remission, age, health status, and patient preference. Below are other common treatment types for relapsed or refractory FL:

- Targeted therapies (drugs that target specific molecules that cancer cells use to survive and spread) include inhibitors of proteins involved in cell signaling and growth like kinases and other proteins like the EZH2 inhibitor tazemetostat (Tazverik).
- Immunotherapies (drugs that help the body's immune system fight cancer):
  - Bispecific antibodies are antibodies that recognize two different antigens, which can be on the same cell (a cancer cell) or two different cells (a cancer cell and a healthy immune cell). Bispecific antibodies used to treat lymphoma are called T-cell engagers and work by linking cancer cells to healthy immune cells such as mosunetuzumab (Lunsumio) and epcoritamab (Epkinly)
  - Immunomodulatory agents are drugs that work on the immune system directly by regulating (activating or slowing down) the activity of specific proteins like lenalidomide (Revlimid).
- Chimeric antigen receptor (CAR) T-cell therapies (a special type of immunotherapy that uses the patient's immune cells to fight cancer) like axicabtagene ciloleucel (Yescarta).
- Stem cell transplantation (the patient is treated with high-dose chemotherapy or radiation to remove their blood-forming cells or stem cells, and then receives healthy stem cells to restore the immune system and the bone marrow's ability to make new blood cells). For some patients with multiple relapsed FL, high-dose chemotherapy followed by stem cell transplantation may be an option.

Patients seeking more information about stem cell transplantation and/or CAR T-cell therapy should view the *Understanding Cellular Therapy* guide on the Foundation's website (lymphoma.org/publications).

Treatments Under Investigation

Many treatments (also referred to as investigational drugs) are currently being tested in clinical trials in patients who are previously untreated or newly diagnosed with FL. Results from these clinical trials may improve or change the current standard of care (the proper treatment that is widely used by healthcare professionals and accepted by medical experts). Table 1 (below) lists some of these investigational drugs that can be accessed through a clinical trial.

It is important to remember that scientific research is always evolving. Treatment options may change as new treatments are discovered and current treatments are improved. Therefore, it is important that patients check with their physician or with the Foundation for any treatment updates that may have recently appeared. It is also very important that patients consult with a specialist to clear up any questions.

Table 1: Selected Agents Under Investigation for Follicular Lymphoma

Agent (drug)	Class (type of treatment)
Atezolizumab (Tecentriq)	Immunotherapy; immune checkpoint inhibitor, anti-PD-L1
Zanubrutinib (Brukinsa)	Targeted therapy, BTK inhibitor
Golcadomide (CC 99282)	Immunomodulatory therapy; Cereblon E3 ligase modulator
Mosunetuzumab (Lunsumio)	Bispecific antibody; anti-CD20
Venetoclax (Venclexta)	Targeted therapy; BCL-2 inhibitor
Odronextamab (REGN1979)	Bispecific antibody; anti-CD20
Toripalimab	Immunotherapy, immune checkpoint inhibitor; anti-PD-1

BCL-2, B-cell lymphoma 2; BTK, Bruton's tyrosine kinase; CD20, cluster of differentiate 20; PD-1, programmed cell death protein 1; PI3K, phosphoinositide 3-kinase.

Clinical Trials

Clinical trials are crucial in identifying effective drugs and the best treatment doses for patients with lymphoma. Patients interested in participating in a clinical trial should view the *Understanding Clinical Trials* fact sheet on the Foundation's website (visit **lymphoma.org/publications**), and the *Clinical Trials Search Request Form* at lymphoma.org, or talk to their physician, or contact the Foundation's Helpline for an individualized clinical trial search by calling **(800) 500-9976** or emailing **helpline@lymphoma.org**.

Follow-up

Since FL is generally characterized by multiple disease relapses after responses to a variety of treatments, patients should have regular visits with their physician. During these visits, medical tests (such as blood tests, computed tomography [CT] scans, positron emission tomography [PET] scans, and biopsies of suspicious masses or the bone marrow) may be required to evaluate the need for additional treatment. Some treatments can cause side effects that are long-term (occur during treatment and continue for months or years) or late side effects (appear only months, years or decades after treatment has ended). These side effects can vary depending on the following factors:

- Duration of treatment (how long was the treatment given).
- Frequency of treatment (how often was the treatment administered).
- Type of treatment given.
- Age and gender of the patient.
- Patient overall health at the time of treatment.

A physician will check for these side effects during follow-up care. Visits may become less frequent the longer the patient stays in remission.

Patients and their care partners are encouraged to keep copies of all medical records. These include test results as well as information on the types, amounts, and duration of all treatments received. Medical records are important for keeping track of any side effects resulting from treatment or potential disease recurrence. The Foundation's award-winning Focus On Lymphoma mobile app (**lymphoma.org/mobileapp**) and Lymphoma Care Plan (**lymphoma.org/publications**) can help patients manage this documentation.

Lymphoma Care Plan

Keeping your information in one location can help you feel more organized and in control. This also makes it easier to find information pertaining to your care and saves valuable time. The Foundation's Lymphoma Care Plan document organizes information on your health care team, treatment regimen, and follow-up care. You can also keep track of health screenings and any symptoms you experience to discuss with your health care provider during future appointments. The Lymphoma Care Plan document can be accessed by visiting **lymphoma.org/publications**.

Patient Education Programs

The Foundation also offers a variety of educational activities, including live meetings and webinars for individuals looking to learn directly from lymphoma experts. These programs provide the lymphoma community with important information about the diagnosis and treatment of lymphoma, as well as information about clinical trials, research advances and how to manage/cope with the disease. These programs are designed to meet the needs of a lymphoma patient from the point of diagnosis through long-term survivorship. To view our schedule of upcoming programs, please visit **lymphoma.org/programs**.

Helpline

The Foundation's Helpline staff are available to answer your general questions about lymphoma and treatment information, as well as provide individual support and referrals to you and your loved ones. Callers may request the services of a language interpreter. The Foundation also offers a one-to-one peer support program called the Lymphoma Support Network and clinical trials information through our Clinical Trials Information Service. For more information about any of these resources, visit our website at **lymphoma.org**, or contact the Helpline at **(800) 500-9976** or **helpline@lymphoma.org**.

Para información en Español, por favor visite **lymphoma.org/es**. (For Information in Spanish please visit **lymphoma.org/es**).

Focus on Lymphoma Mobile App

Focus on Lymphoma is the first app to provide patients and their care partners with tailored content based on lymphoma subtype, and actionable tools to better manage diagnosis and treatment. Comprehensive lymphoma management, conveniently in one secure and easy-to-navigate app, no matter where you are on the care continuum. Get the right information, first, with resources from the entire Lymphoma Research Foundation content library, use unique tracking and reminder tools, and connect with a community of specialists and patients. To learn more about this resource, visit our website at **lymphoma.org/mobileapp**, or contact the Foundation's Helpline at **(800) 500-9976** or **helpline@lymphoma.org**.

Lymphoma Research Foundation

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