Patient education: Chronic lymphocytic leukemia (CLL) in adults (Beyond the Basics)

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CHRONIC LYMPHOCYTIC LEUKEMIA OVERVIEW — Chronic lymphocytic leukemia (also called CLL) is a chronic (long-term, slowly developing) leukemia. Leukemia is a type of cancer that affects the blood and bone marrow. Bone marrow is the spongy, red tissue that fills the large bones. All of the blood cells (red cells, white cells, platelets) are derived from stem cells in the bone marrow. CLL is one of a group of diseases that affects a type of white blood cell called a lymphocyte. Normal lymphocytes, but not CLL cells, help the body fight infection.

CLL and small lymphocytic lymphoma are variants of the same disease. If you have been diagnosed with small lymphocytic lymphoma, abbreviated as SLL, the information in this article applies to you, too.

In CLL, high numbers of abnormal lymphocytes are found in the blood, lymph nodes, spleen, and bone marrow. In SLL, these same cells are commonly found in the lymph nodes. The abnormal cells cannot fight infection as normal lymphocytes do, but instead collect in lymph nodes and other areas, such as the liver and spleen. The accumulation of ineffective lymphocytes can interfere with the production of other blood cells, such as red cells and platelets, and the immune system.

Unlike some other types of leukemia, CLL usually progresses slowly. In many cases, it causes the person few, if any, problems in its early stages. Some people can live with CLL for decades. Some people, however, live for a shorter period. Many times, it is diagnosed incidentally, by blood tests that are performed during a routine physical exam. In other cases, symptoms cause the person to seek medical care.

Careful analysis of the person's blood and physical condition help to determine the stage of the disease – a crucial first step in deciding on the proper course of treatment. Unlike people with many other types of cancer, some people with CLL do not benefit from early, aggressive treatment, but instead do better with careful long-term monitoring of the disease.

More detailed information about CLL, written for healthcare providers, is available by subscription. (See 'Professional level information' below.)

STAGING OF CHRONIC LYMPHOCYTIC LEUKEMIA — The progression of CLL may vary considerably from one person to another. Some people become sick within a short time of diagnosis; others live comfortably for

years without problems. Determining which people are most likely to get sick, and therefore most likely to benefit from treatment, is an important task. (See "Staging and prognosis of chronic lymphocytic leukemia".)

Two systems for staging CLL are now in use. Both systems are based upon results of the physical examination and a full blood count.

The Rai system — The Rai system is based on an analysis of how the body is affected by the abnormal lymphocytes [1]. There are five stages. The higher numbers indicate a more advanced stage of disease:

- Stage 0 – Increased numbers of abnormal lymphocytes are found in the blood or bone marrow; lymph nodes/organs are not swollen; and production of red cells and platelets is not significantly affected.
- Stage I – Increased abnormal lymphocytes and enlarged lymph nodes.
- Stage II – Increased abnormal lymphocytes with enlarged liver or spleen, with or without enlarged lymph nodes.
- Stage III – Increased abnormal lymphocytes with anemia (low red blood cell count), with or without an enlarged spleen, liver, or lymph nodes.
- Stage IV – Increased abnormal lymphocytes with a low platelet count, with or without anemia, enlarged liver, spleen, or lymph nodes.

The Binet system — This system considers the five possible sites where lymphocytes can collect (lymph nodes in the neck, armpit, and groin, and lymphocyte-containing channels in the spleen and liver) (figure 1), and also whether anemia or low platelet counts are present [2]. There are three stages:

- Stage A: Fewer than three involved sites; red cells and platelets are not significantly affected
- Stage B: Three or more involved sites; red cells and platelets are not significantly affected
- Stage C: Presence of anemia and/or low platelet counts regardless of the number of involved sites

What the CLL stages mean — Staging CLL helps determine how likely it is that you will develop serious problems related to your illness. Also, staging is one of the critical parameters to determine if treatment is needed (as discussed below). People at Rai stage 0 are considered to be at low risk, those at stages I or II are at intermediate risk, and those at stage III or IV are at high risk. Similarly, people characterized according to the Binet system have progressively increasing risk, with stage A as the lowest and stage C as the highest risk group.

When is treatment needed? — As noted above, treatment is not always required for CLL. Some studies have shown that people without symptoms of CLL (also called "smoldering" disease) are no more likely to die than a person of the same sex around the same age who does not have CLL. (See 'Management of asymptomatic, early stage chronic lymphocytic leukemia' below.)

However, there are certain groups of people in whom treatment is generally indicated. This includes people with:

- Symptoms of anemia and/or low platelets (Rai stages III or IV, or Binet stage C)
- Disease-related symptoms such as weakness, night sweats, weight loss, painful lymph node swelling, or fever
- Autoimmune hemolytic anemia and/or low platelets (when the immune system destroys red blood cells or platelets) that does not respond to treatment with glucocorticoids, such as prednisone

- Progressive disease, as demonstrated by rapidly increasing white cells in the blood, and/or rapidly enlarging lymph nodes, spleen, or liver
- Repeated infections

MANAGEMENT OF ASYMPTOMATIC, EARLY STAGE CHRONIC LYMPHOCYTIC LEUKEMIA — Although people who do not have symptoms of CLL are not usually treated for their disease, they should be monitored regularly with blood tests and a physical examination. This is usually performed every three months for at least the first year after diagnosis. Depending upon the results of these tests, it may be possible to estimate how aggressive your disease will be in the future.

TREATMENT OF ADVANCED OR SYMPTOMATIC CHRONIC LYMPHOCYTIC LEUKEMIA

Treatment options — People with advanced or symptomatic CLL are generally treated first with chemotherapy plus immunotherapy, sometimes called chemoimmunotherapy. Newly developed drugs for treating CLL ("novel agents") are usually reserved for people with relapsed disease, but should be used as initial therapy for people with certain types of CLL (particularly those with specific characteristics found on genetic testing, called deletion 17p and/or mutation of TP53) and are a preferred treatment option for older adults and patients with limitations in their daily activities.

- Chemotherapy refers to the use of medicines to stop or slow the growth and longevity of cancer cells. Chemotherapy targets growing cells, interfering with their ability to divide or multiply. Because most of an adult's normal cells are not actively growing, they are not as affected by chemotherapy as the cancer cells. However, the cells in the bone marrow (where the blood cells are produced), the hair follicles, and the lining of the gastrointestinal (GI) tract are all growing; the side effects of chemotherapy drugs (such as hair loss or nausea) are related to effects on these and other normal tissues.
- Immunotherapy, as referred to here, uses antibodies that target a specific group of cells (usually cancer cells). Rituximab, obinutuzumab, and ofatumumab are antibodies that target the type of lymphocytes (B lymphocytes) from which CLL is derived. As such, they also destroy CLL cells and are available for the treatment of CLL.
- Novel oral agents, as referred to here, include small molecules designed to target signalling pathways that are abnormally expressed in the cancer cells. Ibrutinib, idelalisib, and venetoclax are novel agents available for the treatment of CLL.

A chemotherapy drug or combination of drugs is referred to as a regimen. Regimens used for the treatment of CLL may include a single drug taken by mouth on a daily basis, while other regimens use multiple drugs given intravenously in treatment cycles.

A cycle of therapy refers to the time it takes to give the drugs and the time required for the body to recover. For example, a typical chemotherapy regimen is at least a one-hour intravenous (IV) infusion of two or more different chemotherapy medications given once every three to four weeks. This three- or four-week period is one cycle of therapy. If this regimen were repeated for a total of three or four cycles, it would take up to four months to complete.

People with advanced or symptomatic CLL are usually treated with a regimen that contains one or more of these agents:

Chemotherapy

- **Fludarabine** — Fludarabine (brand name: Fludara) is a chemotherapy drug that, when used in combination regimens, can often induce partial or complete remission of CLL. The most common side effects are low

blood counts and fever. Older people seem to be at higher risk of serious side effects from this medicine, including an increased risk of severe infections. Decreased kidney function may limit its use. (See 'Infection' below.)

- **Cyclophosphamide** — Cyclophosphamide (brand name: Cytoxan) is a chemotherapy drug that may be used in combination with other drugs in people with CLL. It can be given by mouth or through an IV line. Side effects include low blood counts, nausea and vomiting, hair loss, and irritation of the bladder.

- **Bendamustine** — Bendamustine (brand name: Treanda) is a chemotherapy drug that may be given in combination with immunotherapy (eg, rituximab, ofatumumab) as an initial treatment of advanced or symptomatic CLL, as well as in previously treated people. Side effects include low blood counts, nausea and vomiting, and allergic reactions.

- **Chlorambucil** — Chlorambucil (brand name: Leukeran) may be given in combination with one of the following antibodies: rituximab, obinutuzumab, or ofatumumab as the initial treatment of CLL. The most common side effects are low blood counts.

Immunotherapy — Rituximab, obinutuzumab, and ofatumumab are all monoclonal antibodies, which means that they are purified proteins that target specific groups of cells, in this case cancer cells. They treat CLL cells by attacking specific substances (antigens) on the surface of the leukemic cells. These drugs destroy the type of lymphocytes (B lymphocytes) from which CLL is derived. This type of treatment has advantages over other cancer treatments, such as chemotherapy, which targets all rapidly growing cells in the body (not just the cancer cells).

- **Rituximab** — Rituximab (brand name: Rituxan) was the first monoclonal antibody used for the treatment of CLL. Rituximab targets CD20, a marker found on the surface of B lymphocytes (including CLL cells). The incorporation of rituximab into the initial treatment regimens has improved survival in younger adults with CLL.

- **Obinutuzumab** — Obinutuzumab (brand name: Gazyva) is a monoclonal antibody that targets B lymphocytes. People treated with obinutuzumab plus chlorambucil are more likely to respond to therapy and have longer responses than those treated with chlorambucil alone. In addition, initial studies suggest that obinutuzumab helps these people live longer.

- **Ofatumumab** — Ofatumumab (brand name: Arzerra) is a monoclonal antibody that targets B lymphocytes. People treated with ofatumumab plus chlorambucil are more likely to respond to therapy and have longer responses than those treated with chlorambucil alone. Ofatumumab may also be given in combination with bendamustine.

Novel oral agents — Novel oral agents, as discussed here, include small molecules designed to target signaling pathways that are abnormally expressed in the cancer cells. In clinical trials, ibrutinib and idelalisib were effective in the majority of patients with relapsed or refractory CLL, with dramatic responses even in people who have already tried multiple other therapies.

Ibrutinib — Ibrutinib (brand name: Imbruvica) is a drug that can be given by mouth for people with relapsed CLL. It should also be used for the initial treatment of people with certain types of CLL (those with deletion 17p and/or mutation of TP53 on genetic testing). It is a preferred initial treatment option for older adults and those with limitations in their daily activities. Ibrutinib may be associated with an increased risk of bleeding, and should be used with caution in people taking anti-clotting medicines such as warfarin (sample brand name: Coumadin).

Idelalisib — Idelalisib (brand name: Zydelig) is a drug that can be given in combination with rituximab for people with relapsed CLL. It may also be used for the treatment of people with certain types of CLL (those with deletion 17p and/or mutation of TP53 on genetic testing). As a word of caution, there is a risk of infection and a minority of people develop severe diarrhea after several months on idelalisib. Because of this, it's important to tell your doctor if you develop significant diarrhea while taking this drug.

Venetoclax — Venetoclax (brand name: Venclexta) is a drug that can be given by mouth for patients with certain types of relapsed CLL (those with deletion 17p on genetic testing). This drug is very potent and requires a slow increase in dose and close monitoring for complications when it is started. Common side effects include diarrhea, nausea, and fatigue.

Choice of regimen — There is no single "best" standard treatment regimen for symptomatic CLL. Experts use different treatment approaches based on individual patient (eg, age, coexisting illnesses) and disease (eg, 17p deletion, TP53 mutation) characteristics. Because uncertainty exists regarding the optimal treatment, and further progress is needed, all people with CLL are advised to enroll in a clinical trial, if possible. (See 'Clinical trials' below.)

The combination of fludarabine and rituximab, commonly with cyclophosphamide, is often used as a first-line treatment of young patients without limitations in their daily activities with advanced or symptomatic CLL [3]. Overall survival rates appear to be the same with these two regimens, but response rates are higher with the combination of fludarabine, cyclophosphamide, and rituximab (FCR) while toxicity (side effects) is lower with fludarabine and rituximab (FR). Complete remission rates of approximately 47 and 70 percent are seen in people treated with FR or FCR, respectively [4]. Complete remission means that, for at least two months after treatment ends, the person has no signs or symptoms of their disease. Fludarabine-based regimens are not well tolerated by older people with CLL.

Ibrutinib may be preferred for older adults with symptomatic CLL. There is no strict age cutoff used to define older adult in this setting, and an assessment of physiologic age (ie, how well your body is functioning) is often more important than chronologic age. The combination of chlorambucil plus immunotherapy (obinutuzumab or ofatumumab) is an alternative for older adults who are not good candidates for ibrutinib.

The combination of bendamustine plus rituximab or ofatumumab has efficacy and side effects in between those of combinations that use fludarabine and those that use chlorambucil. Bendamustine plus rituximab or ofatumumab may be preferred for younger people who have poor kidney function or other health problems. It may also be preferred among older (eg, >65 years of age) people without relevant coexisting other disease.

People with markers of difficult-to-treat CLL (those with deletion 17p or TP53 mutation on genetic testing) require particular attention and should always primarily be considered for novel treatment options in clinical trials or the use of newer drugs such as ibrutinib (brand name: Imbruvica) as initial therapy and venetoclax or idelalisib at the time of relapse. The approach might include stem cell (bone marrow) transplant after initial response.

The choice between treatment regimens is an individual decision made by balancing patient and disease characteristics and drug side effects. Your doctor can help you figure out the best approach for you.

Duration of treatment — Treatment with FCR or FR is usually given every day for either three or five days, on a 28-day cycle. Typically, six cycles of this treatment are given. Treatment may be stopped sooner, however, if symptoms do not improve or intolerable side effects develop. More than six cycles is not clearly more effective.

TREATMENT OF RELAPSED OR REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA — Most people with CLL respond to initial treatment, but then develop relapsed disease at some point after treatment ends. A small number of people do not respond to chemotherapy at all; this is called refractory disease.

General approach — If relapse is long after treatment ends, it is often possible to successfully use the same chemotherapy regimen again or use another chemotherapy treatment. (See 'Treatment options' above.)

If a person's disease is refractory or relapses sooner than six months after treatment ends, the options for treatment are limited. Depending upon your individual situation, you can discuss the following options with your doctor:

- Participation in a clinical trial – new drugs are in development for people with CLL that target cellular processes that have not been targeted before (see 'Clinical trials' below)
- Treatment with one of the novel agents (ibrutinib, idelalisib, venetoclax) (see 'Novel oral agents' above)
- Stem cell transplantation (also called bone marrow transplantation or hematopoietic stem cell transplantation)
- Treatment to reduce CLL-related symptoms and complications

Removal of the spleen — A number of people with CLL will develop a very enlarged spleen. This often responds to treatment with chemotherapy or radiation, so removal of the spleen is rarely done. However, it may provide longer lasting benefits, including increases in red blood cell and platelet counts in some people [5].

Stem cell transplantation — Stem cell transplantation (also called bone marrow transplantation or hematopoietic cell transplantation) is being more seriously considered as a therapy for high-risk CLL (eg, refractory to therapy or with 17p deletion and/or TP53 mutation), especially for people under age 65. If stem cell transplantation is performed, it is usually done after treatment with chemotherapy. Giving chemotherapy often induces a complete or partial remission. (See "Hematopoietic cell transplantation in chronic lymphocytic leukemia".)

Stem cell transplantation is a treatment in which the person is given chemotherapy or radiation as "conditioning." This kills cancer cells but also destroys normal cells developing in the bone marrow. After the treatment, the person needs to have a healthy supply of very young blood cells, called stem cells, reintroduced or transplanted. The transplanted cells then re-establish the blood cell production process in the bone marrow. (See "Patient education: Hematopoietic cell transplantation (bone marrow transplantation) (Beyond the Basics)".)

The type of stem cell transplant used for people with CLL is called an allogeneic transplant. In allogeneic transplant, the person is given stem cells from a donor, ideally a brother or sister with a similar genetic make-up. If the person doesn't have a "matched" sibling, an unrelated person with a partially matched genetic makeup may be used.

Today, most CLL transplants are done as a reduced intensity transplant (called a "mini"-transplant or non-myeloablative transplant) from a relative or a matched unrelated donor, and may achieve long-term control of their CLL. Studies using non-myeloablative allogeneic transplants have shown significant promise, even in people with relatively high-risk or refractory disease [6].

TREATMENT OF CHRONIC LYMPHOCYTIC LEUKEMIA COMPLICATIONS — The major complications of CLL are caused by the low blood counts and immune system problems that either arise from the disease itself or the treatment.

Infection — Infection is one of the most serious risks of treatment of CLL, accounting for approximately 50 percent of deaths. Although less common, serious infections can also occur in people who have not yet received any treatment for their underlying leukemia. The most common infections affect the upper respiratory tract (sinuses, bronchi). Smokers are especially vulnerable, so if you smoke, you should quit as soon as possible. (See "Patient education: Quitting smoking (Beyond the Basics)".)

All people with CLL should make sure their vaccinations are up-to-date and receive yearly influenza vaccines and pneumococcal vaccination every five years. But they should in general **not** get live vaccines such as the shingles vaccine (herpes zoster vaccine), in particular when on treatment, and it should be discussed with the clinician. Household contacts of people with CLL should also receive annual influenza vaccination.

People with respiratory tract infections sometimes need antibiotic therapy. Infection is often related to low levels of infection-fighting proteins called immunoglobulins. For this reason, people who have repeated infections may be treated with intravenous immune globulin (also called IVIG or IGIV) to increase their immunoglobulin levels and decrease the chance of infection. Such infusions are usually recommended only for people with repeated infections and low serum gamma globulins. Infusions of IVIG can decrease the incidence of minor infections, but may not decrease the incidence of serious infections.

People treated with certain chemotherapy agents can develop low white blood cell counts, which increases the risk of infections. In some cases, medications that promote the growth of new blood cells may be given to boost the white cell count and decrease the infection risk. Those receiving certain drugs may need to take preventive antibiotics and may need to have special testing to monitor for infections.

Anemia — Anemia, or low red blood cell counts, is common in CLL. Red blood cells are needed to carry oxygen to all the cells in the body. People with anemia may experience fatigue, weakness, and chest pain. Treatment options include blood transfusion and use of a medicine called erythropoietin, which can boost the red cell count in people with certain types of anemia. Other forms of anemia may be treated with glucocorticoids (also called steroids).

Low platelet counts — Platelets are important components of the blood's clotting mechanism. Without adequate numbers of platelets, internal and external bleeding can occur. People with CLL and low platelet counts may see their counts improve with treatment of the CLL. In some cases, platelet transfusions are needed. Removal of the spleen or use of steroids or other treatments that suppress the immune response (as part of the treatment for CLL) usually improves the platelet counts.

Psychological aspects — People with CLL are forced to live with the uncertainties associated with a chronic illness. It can be puzzling and frightening to hear that you have leukemia and that no treatment is recommended. You and your healthcare providers must speak frequently and honestly to deal with any fears and clarify any misunderstandings about this sometimes confusing disease. Some people and families benefit from psychological counseling to help them cope with the strong emotions that can accompany this diagnosis.

CLINICAL TRIALS — Many patients with leukemia will be asked about enrolling in a clinical (research) trial. A clinical trial is a carefully controlled way to study the effectiveness of new treatments or new combinations of known therapies. Ask your doctor for more information, or read about clinical trials at:

- www.cancer.gov/clinicaltrials/
- http://clinicaltrials.gov/

Videos addressing common questions about clinical trials are available from the American Society of Clinical Oncology (http://www.cancer.net/pre-act).

WHERE TO GET MORE INFORMATION — Your healthcare provider is the best source of information for questions and concerns related to your medical problem.

This article will be updated as needed on our web site (www.uptodate.com/patients). Related topics for patients, as well as selected articles written for healthcare professionals, are also available. Some of the most relevant are listed below.

Patient level information — UpToDate offers two types of patient education materials.

The Basics — The Basics patient education pieces answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials.

Patient education: Leukemia in adults (The Basics)
Patient education: Chronic lymphocytic leukemia (CLL) (The Basics)
Patient education: Neutropenia and fever in people being treated for cancer (The Basics)

Beyond the Basics — Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are best for patients who want in-depth information and are comfortable with some medical jargon.

Patient education: Hematopoietic cell transplantation (bone marrow transplantation) (Beyond the Basics)

Professional level information — Professional level articles are designed to keep doctors and other health professionals up-to-date on the latest medical findings. These articles are thorough, long, and complex, and they contain multiple references to the research on which they are based. Professional level articles are best for people who are comfortable with a lot of medical terminology and who want to read the same materials their doctors are reading.

Classification of the hematopoietic neoplasms
Clinical manifestations, pathologic features, and diagnosis of small lymphocytic lymphoma
Evaluating response to treatment of chronic lymphocytic leukemia
Hematopoietic cell transplantation in chronic lymphocytic leukemia
Overview of the treatment of chronic lymphocytic leukemia
Risk of infections in patients with chronic lymphocytic leukemia
Prevention of infections in patients with chronic lymphocytic leukemia
Overview of the complications of chronic lymphocytic leukemia
Clinical presentation, pathologic features, diagnosis, and differential diagnosis of chronic lymphocytic leukemia
Pathophysiology and genetic features of chronic lymphocytic leukemia
Staging and prognosis of chronic lymphocytic leukemia
Treatment of relapsed or refractory chronic lymphocytic leukemia

The following organizations also provide reliable health information.

- National Library of Medicine

  (www.nlm.nih.gov/medlineplus/healthtopics.html)

- National Cancer Institute

  (www.cancer.gov/cancertopics/pdq/treatment/CLL/patient/)

- American Cancer Society

  (http://www.cancer.org)

- The Leukemia & Lymphoma Society

  (www.lls.org)

- The Lymphoma Research Foundation

(www.lymphoma.org)

- National Marrow Donor Program

  (www.marrow.org)

- The American Society of Hematology

  (www.hematology.org)

- The American Society of Clinical Oncology

  (www.cancer.net/cll)

- The Alliance for Clinical Trials in Oncology

  (www.allianceforclinicaltrialsinoncology.org)

- Deutsche CLL Studengruppe

  (http://www.dcllsg.de/)

[1-9]

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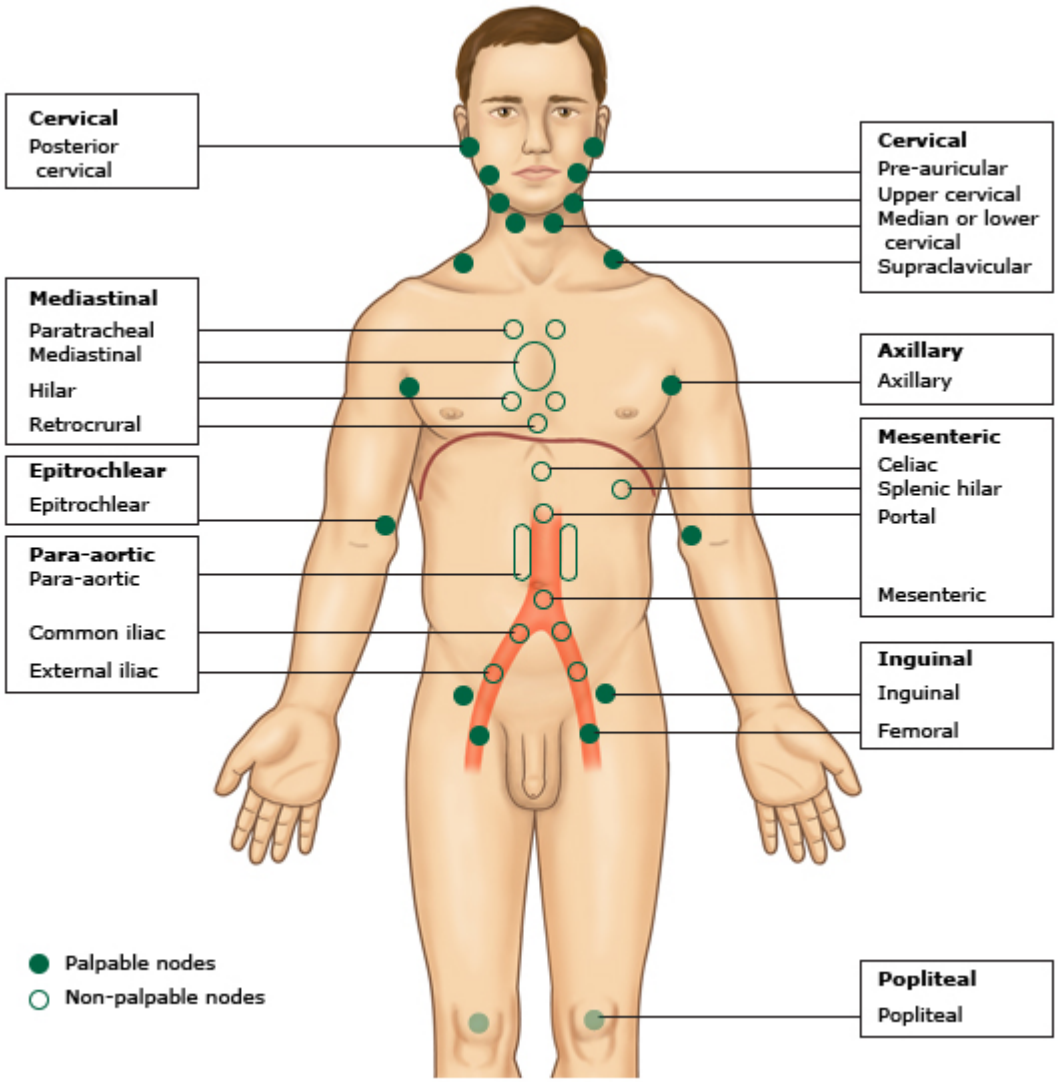
GRAPHICS

Lymph node groups



This figure shows the lymph node groups and sub-areas. Note that popliteal nodes are palpable behind the knee.

Modified with permission from: Celigny, P, Roy, P, Colombat, P, et al. Follicular lymphoma international prognostic index. Blood 2004; 104:1258. Copyright © 2004. American Society of Hematology.

Graphic 64350 Version 3.0