All About Adult Hodgkin Lymphoma

What are lymph nodes?

Lymph nodes are small, bean-sized glands that exist throughout the body and make up part of the lymphatic fluid circulation system. Lymphatic fluid is a clear fluid that leaks out of blood vessels, and in order for the body to keep the blood volume constant, lymphatic fluid is collected and returned to the blood via the lymphatic circulation. Lymph nodes are connected to each other by small lymph vessels that transfer the lymphatic fluid.

Before returning the lymphatic fluid to the blood, lymph nodes clean the fluid, looking for possible infection-causing germs (bacteria, viruses, etc.). Most people can remember having swollen "glands" under their neck when they had an infection. Those "glands" were swollen lymph nodes that were reacting to the infection. In most cancers, this network of lymph nodes is one of the first areas to which cancer can spread. However, in Hodgkin lymphoma the cancer arises from the lymph nodes themselves.

Clusters of lymph nodes exist in particular parts of the body, like the neck, the underarm, and the groin. There are also specific organs in the body that are considered part of the lymphatic system, like the spleen and the tonsils. Small amounts of lymph tissue can also be found in almost every other organ in the body. While there are certain areas in the body where lymph nodes are routinely found, the specific arrangement and number of these lymph nodes is different from person to person.

What is Hodgkin Lymphoma?

Hodgkin lymphoma is a cancer of lymph nodes and lymphatic tissues. It is named after the pathologist who originally described the disease in 1832, Dr. Thomas Hodgkin. Hodgkin lymphoma is a fairly uncommon cancer, with about 8,260 cases diagnosed in 2017 in the United States. Hodgkin lymphoma occurs slightly more commonly in men and much more frequently in Caucasians and Hispanic men. Hodgkin lymphoma most commonly affects people ages 15 to 40 (especially those in their 20s) and those over the age of 55. (Pediatric Hodgkin lymphoma is discussed separately).

There are other types of lymphomas besides Hodgkin lymphoma, known as non-Hodgkin lymphomas. Although non-Hodgkin lymphomas are also a cancer of the lymph nodes, they behave differently and are treated differently. Hodgkin lymphoma occurs when infection-fighting cells in the lymph nodes begin to grow out of control and compress nearby tissues or spread throughout the body via the lymphatic circulation. Hodgkin lymphoma is distinguished from the other types of lymphomas by the way it looks under a microscope and by the way it grows and spreads.

There are two main types of Hodgkin lymphoma: classical Hodgkin lymphoma and nodular lymphocyte-predominant Hodgkin disease. There are four subtypes of the classical type:

- Nodular sclerosing (70%)
- Mixed cellularity (20-25%)
- Lymphocyte-depleted (5%)
- Lymphocyte-rich (<1%)

Overall, classical Hodgkin lymphoma accounts for about 95% of all cases, while nodular lymphocyte-predominant (NLP) Hodgkin lymphoma is quite rare. The type of Hodgkin lymphoma a person has is determined by a pathologist, who examines a portion of tissue of the involved node(s). Pathologists look for a particular abnormal cell known as a Reed-Sternberg cell (also known as an "owl's eye" cell) in order to diagnose classic Hodgkin lymphoma, or a "popcorn" cell to diagnose NLP Hodgkin lymphoma. The distinction between classical Hodgkin and NLP is important because they are treated differently.
What causes Hodgkin Lymphoma and am I at risk?

No one knows what causes Hodgkin lymphoma. Several factors have been identified to be associated with Hodgkin lymphoma. It is important to note that these factors may increase the risk of developing Hodgkin lymphoma, but that the majority of people with these conditions still do not develop Hodgkin lymphoma.

- Epstein-Barr Virus: Infection with the Epstein-Barr virus may play a role in the development of certain types of Hodgkin lymphoma. Epstein-Barr virus also causes mononucleosis, also known as "mono" or "kissing disease."
- Family History: It appears that the relatives of people who develop Hodgkin lymphoma at very young age may be at increased risk of developing Hodgkin lymphoma.
- HIV Infection: People with depressed immune function, such as patients with HIV/AIDS or those taking medications that suppress the immune system (eg. people with organ transplants or autoimmune diseases), appear to be at increased risk for developing Hodgkin lymphoma. It has been recognized that Hodgkin lymphoma in HIV-infected patients is generally more aggressive and advanced than in non-HIV-infected patients.

How can I prevent Hodgkin lymphoma?

Because no one knows exactly what causes Hodgkin lymphoma, there are no specific steps you can take to prevent it.

What screening tests are used for Hodgkin lymphoma?

Hodgkin lymphoma is rare enough that it is not screened for in the general population with any specific blood tests or radiology studies. The best way to detect Hodgkin lymphoma early is to see your healthcare provider regularly for a thorough physical examination. Often, the patient is the first to notice a lump, and if this happens, you should see your healthcare provider for examination and further evaluation.

What are the signs of Hodgkin lymphoma?

The early stages of Hodgkin lymphoma often do not cause any symptoms. As the tumor grows in size it can produce a variety of symptoms. The most common lymph node site affected by Hodgkin lymphoma is in the neck, and neck swelling is what often brings people to the healthcare provider. However, Hodgkin lymphoma can also cause swelling of the lymph nodes in the underarm, upper chest, abdomen, or groin. These swellings are often not painful but can feel rubbery. Hodgkin lymphoma can also cause fevers, drenching night sweats, fatigue, weight loss, and even generalized itching.

If the Hodgkin lymphoma is affecting the lymph nodes in the chest, which are not typically seen or felt, the swelling can cause symptoms such as cough, shortness of breath, or chest pain. A chest x-ray can often detect these swollen nodes in the chest. Interestingly, some people with Hodgkin lymphoma will note pain in the lymph nodes after minimal alcohol consumption.

Many of these symptoms are non-specific, and could represent a variety of different conditions; however, your healthcare provider needs to see you if you have any of these problems.

How is Hodgkin lymphoma diagnosed?

When a patient presents with symptoms suggestive of Hodgkin lymphoma, their healthcare provider will perform a thorough history and physical examination. If there is a node that is enlarged, it will likely be surgically removed in what is called an excisional biopsy. Either part of or the entire node is removed so that a doctor, called a pathologist, can look at it under a microscope. A biopsy specimen is required to make the diagnosis of Hodgkin lymphoma. It is important that the provider use an excisional biopsy—the alternative is a core-needle biopsy, where a small needle is inserted into the swollen lymph node and a sample of the lymph node is taken. However, core-needle biopsies may not provide enough tissue to make a diagnosis.

Once the diagnosis is made, a healthcare provider will order a number of tests to get a sense of the extent and severity of the disease. A few different blood tests will probably be ordered, including blood counts, liver function tests, kidney function tests, erythrocyte sedimentation rate (ESR, a marker of inflammation), and a pregnancy test in women of childbearing age.

The physician will also plan for you to get a PET-CT scan to see the extent of the disease. A PET-CT scan combines a CT scan
of the body (a 3D x-ray) with PET. The CT portion helps your provider define the location of lymph nodes that are affected by cancer. The PET scan is a special type of scan where a sugar solution is injected through an IV. Tissues that are very active (like cancer cells) use the sugar for energy. These areas "light up" when they are scanned. The PET scan is important for two reasons: 1) It helps confirm where lymphoma is located in the body; and 2) It gives your provider the "before-treatment" picture. PET scan is used after treatment to determine if the cancer has been killed and it is important to be able to compare the "after-treatment" PET with a "before-treatment" PET.

You may have a bone marrow aspiration and biopsy done to determine if the disease is in your bone marrow. You may have a number of other tests depending upon the symptoms you are having. These tests include an echocardiogram to check your heart function, pulmonary function tests to check the function of your lungs, X-rays, CT scans, and MRIs. Your provider will determine which of these tests are necessary.

**How is Hodgkin lymphoma staged?**

After your full work-up is complete your care team will stage your cancer. Staging is important because it classifies your cancer by how much disease you have and if/where it has spread. Staging helps guide your treatment plan. The staging system for Hodgkin lymphoma is known as the Cotswold system. It has four different stages:

- **Stage I:** Also known as early stage. A single lymph node region is involved.
- **Stage II:** Also known as locally advanced disease. Two or more lymph node regions involved on the same side of the diaphragm (the muscle that controls breathing and that separates the chest from the abdomen) or one lymph node region plus a nearby area or organ. If the disease involves a nearby area or organ it is classified as "E" disease or "extension".
- **Stage III:** Also known as advanced disease. Lymph nodes above and below the diaphragm are involved, or one node area and one organ on the opposite side of the diaphragm. Disease involving one node area and one organ on the opposite side of the diaphragm is "E" disease
- **Stage IV:** Also known as widespread disease. The lymphoma has spread outside the lymph nodes and spleen and into one or more other areas of the body including the bone, bone marrow, skin and organs.

Early stage Hodgkin lymphoma (Stage I-II) is divided further into two groups, "favorable" and "unfavorable", to help predict which patients may benefit from more aggressive treatment. The criteria for unfavorable disease are as follows:

- Bulky disease (tumor >10 cm in size)
- Extension outside of lymph nodes ("extranodal" disease)
- Involvement of three or more lymph node areas, or ESR > 50 mm. The erythrocyte sedimentation rate (ESR) is a laboratory test that measures the rate at which red blood cells sediment in a period of one hour.

Your cancer staging may include the letters "E", "S", "B", "A" or "X". Explanations are as follows:

- **E:** The letter "E" represents that there is extension of the disease affecting an organ outside of the lymph system.
- **S:** The letter "S" represents that the disease involves the spleen.
- **B:** The letter "B" is used when a patient has presented with "B" symptoms related to the disease including: loss of more than 10% of body weight over the past 6 months, fever of 100.4 F or higher or night sweats.
- **A:** The letter "A" is used if the patient has had no "B" symptoms.
- **X:** The letter "X" represents bulky disease. Bulky disease is disease that describes tumors in the chest that are at least one third as wide as the chest.

Some other terms used when describing Hodgkin lymphoma are resistant or progressive disease. These terms are used when treatment does not make the disease go away or the disease gets worse. Recurrent or relapsed disease is the term used when the disease went away with treatment, but has returned in either the same place or in another part of the body.

**How is Hodgkin lymphoma treated?**

The treatment plan chosen is dependent upon the stage of the disease and the patient's current health status. The treatment plan should be developed by a provider who specializes in the treatment of lymphomas. The type and duration of treatment
depends on the stage of Hodgkin lymphoma, whether it is favorable or unfavorable, and if it is NLP Hodgkin.

The two standards of treatment for Hodgkin lymphoma are chemotherapy and radiation. Hodgkin lymphoma can also be treated with multimodal therapy (combination of therapies), which includes chemotherapy, radiation and stem cell transplant. Other therapies may include targeted therapy or clinical trials.

Chemotherapy
Chemotherapy is the use of medications that treat cancer. Chemotherapy is known as a "systemic" treatment, which means that it goes throughout the entire body. These medications may be given through a vein (IV, intravenously) or by mouth, as pills. Chemotherapy is frequently used to treat Hodgkin lymphoma, and combinations of different chemotherapy medications are typically used to kill the tumor cells. Some chemotherapy regimens may be given prior to treatment with radiation. The most common chemotherapy regimens used are called ABVD, BEACOPP, and Stanford Five (V).

- **ABVD:** adriamycin, bleomycin, vinblastine, and dacarbazine.
- **BEACOPP:** bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone.
- **Stanford V:** doxorubicin, vinblastine, mechlorethamine, vincristine, bleomycin, etoposide, and prednisone.

You may receive one of these regimens or a combination of other medications. It is not always clear that one chemotherapy regimen is better than the others, and thus, the regimen selected may vary between providers. Your provider can explain why they recommend one particular regimen over another.

The most common targeted therapy used in the treatment of Hodgkin lymphoma, especially in the treatment of NDL, is rituximab (Rituxan®). Rituximab can be given by itself or in combination with chemotherapy and/or radiation. Brentuximab vedotin is often used for patients whose disease has returned after other treatment regimens. Other targeted therapies used in the treatment of relapsed or refractory Hodgkin lymphoma include everolimus, nivolumab and pembrolizumab.

Because of potential risk to fertility associated with chemotherapy medications used to treat Hodgkin lymphoma, discuss fertility preservation options with your healthcare provider before starting treatment.

Radiation Therapy
Radiation therapy uses high-energy rays (similar to x-rays), delivered from an external source, to kill cancer cells. Unlike chemotherapy, which goes everywhere in the body, radiation therapy is a local treatment. It is targeted only to small areas. There are two main types of radiation used to treat Hodgkin lymphoma: photon (traditional radiation) and proton therapy. Proton therapy is only available at certain centers. You should discuss with your provider which type of radiation therapy is right for you.

Radiation therapy has evolved in the last few decades, as concern has grown over the long-term affects of having radiation that involves important organs, like the heart and lungs. For this reason, when possible, radiation is avoided. In patients who need radiation, there is considerable effort to make sure the surrounding healthy tissues receive the least amount of radiation exposure as possible. Advanced radiation techniques and methods, such as IMRT (can link), respiratory gating, breath holding and advanced simulation techniques (4D imaging), allow for highly conforming doses. This means the radiation beams are shaped tightly around the tumor and spare surrounding tissue as much as possible. In addition, the area treated has evolved over time. Many radiation oncologists now choose to treat just the lymph nodes that were involved and the surrounding areas where tumor had spread (called involved site radiation therapy, ISRT). This has largely replaced treating an entire field surrounding the involved lymph nodes (involved field radiation therapy). In the past, even larger fields were treated, including large areas of healthy tissue (called extended field radiation therapy). As you can see, the field of radiation has evolved as it has learned the dangers of exposing healthy tissue to radiation.

Radiation therapy typically requires patients to come to a radiation therapy treatment center 5 days a week, for several weeks. The radiation team will take scans and measurements to determine the number of doses needed and exactly where the radiation beams should be aimed. The treatment takes just a few minutes, and it is painless. You shouldn't feel anything, though you may see some lights on the machines and hear them as they move around. Most radiation providers see patients weekly while they are receiving treatment to monitor for side effects and answer questions.
Stem Cell Transplant

Sometimes patients receive chemotherapy and/or radiation therapy, but the Hodgkin lymphoma is still present (also known as refractory Hodgkin lymphoma). When this happens, the provider may recommend stem cell transplantation (SCT). Stem cells are precursor cells that can develop into other cells of the body when placed in the right environment. In the case of SCT, the stem cells used are pre-destined to become blood cells (white and red blood cells or platelets).

Stem cell transplant is used along with high doses of chemotherapy. The high doses of chemotherapy are so intense that they wipe out a person’s bone marrow. Without bone marrow, a person can’t make the components of blood and the immune system that are necessary to survive. In order to replace the patient’s bone marrow, stem cells are given. In the case of an autologous stem cell transplant, a patient’s own stem cells are harvested before the high dose chemotherapy is given, stored, and then finally returned to the patient after the chemotherapy is done. Another option is an allogeneic stem cell transplant, where the stem cells are taken from a donor whose cells “match” those of the recipient. These cells are used in the same way, given to the patient after high dose chemotherapy. In both cases, bone marrow cells can re-grow from the stem cells. This enables a patient to tolerate the high doses of chemotherapy that work against Hodgkin lymphoma but have the unwanted side effect of wiping out healthy bone marrow.

Stem cell transplantation can sometimes cure patients when other treatment strategies have failed. However, stem cell transplantation is a complex and intense treatment, so it is typically reserved for patients who aren’t cured with the initial treatment regimens of chemotherapy and/or radiation therapy.

Clinical Trials

Clinical trials are extremely important in furthering our knowledge of this disease. It is through clinical trials that we know what we do today, and many exciting new therapies are currently being tested. Talk to your healthcare provider about participating in clinical trials in your area. You can also explore currently open clinical trials using the OncoLink Clinical Trials Matching Service.

Follow-up Care and Survivorship

Once you have been treated for Hodgkin lymphoma, you will be followed closely by your care team. For the first two years after treatment, it is recommended you have a physical exam and complete blood counts every 3-6 months. After the first two years, you should see your care provider every 6-12 months until you are three years post treatment, and annually thereafter. It is recommended you receive a CT scan of the chest, abdomen and pelvis at 6, 12 and 24 months after completion of therapy. Survivors should also receive annual flu vaccines. If you received radiation to the spleen or had your spleen removed, you should receive pneumococcal, meningococcal, and H-flu revaccination 5-7 years after your have completed treatment.

Patients who are cured of their Hodgkin lymphoma can expect to live many decades after their treatment. However, this means that some late effects of treatments can be seen. These include:

- **Secondary cancers**: Other cancers, including lung and breast cancer, non-Hodgkin lymphoma and leukemia can occur, even many years after treatment for Hodgkin lymphoma, depending on the type of treatment received and the location where radiation therapy may have been targeted. Your treatment team will discuss cancer screening plans with you after you have completed treatment.
- **Cardiovascular disease**: Patients who have received radiation to the mediastinum (chest) and certain kinds of chemotherapy may be at a higher risk for developing heart disease, sometime 5 to 10 years after completion of treatment. Your team should monitor your blood pressure at all follow up appointments. Your care team may also recommend a stress test or echocardiogram every 10 years after the completion of treatment.
- **Hypothyroidism**: Decreased thyroid function (hypothyroidism) has been reported in 50% of Hodgkin lymphoma survivors who also received radiation to their neck or chest. Your thyroid should be examined as part of your regular exams and thyroid function tests should be performed every year after treatment.

Fear of recurrence, the financial impact of cancer treatment, employment issues, and coping strategies are common emotional and practical issues experienced by Hodgkin lymphoma survivors. Your healthcare team can identify resources for support and
management of these challenges faced during and after cancer.

Cancer survivorship is a relatively new focus of oncology care. With some 15 million cancer survivors in the US alone, there is a need to help patients transition from active treatment to survivorship. What happens next, how do you get back to normal, what should you know and do to live healthy going forward? A survivorship care plan can be a first step in educating yourself about navigating life after cancer and helping you communicate knowledgeably with your healthcare providers. Create a survivorship care plan today on OncoLink.

Resources for More Information

Leukemia and Lymphoma Society

Provides disease information and support resources. www.lls.org

Lymphoma Research Foundation

Offers education and patient services, information on research, co-pay assistance and stories of hope. www.lymphoma.org

American Society of Hematology

The official website of providers who treat blood disorders including Hodgkin lymphoma. www.hematology.org/Patients/Cancers/Lymphoma.aspx

LymphomaInfo.net

Aims to bring people together around lymphoma-related issues by providing concise, up-to-date information and a meeting place for lymphoma patients and those who care about them. www.lymphomainfo.net

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