Purpose

The goal of this course is to help health care professionals learn about the different types of lymphomas.

Objectives

1. Identify the incidence and etiology of Hodgkin’s and Non-Hodgkin’s lymphoma
2. State signs and symptoms of both types
3. Identify risk factors for each type of lymphoma
4. State how the diagnosis is made
5. Explain the staging system commonly used
6. Identify common treatments for both types of lymphomas

Lymphoma

Lymphomas are a heterogeneous group of neoplasm's arising in the reticuloendothelial and lymphatic systems. The major types are Hodgkin’s disease and non-Hodgkin’s lymphoma. An uncommon type is mycosis fungoides.

Hodgkin’s disease is a localized or disseminated malignant proliferation of tumor cells arising from the lymphoreticular system, primarily involving lymph node tissue and the bone marrow.

In the USA, 6,000-7,000 new cases are diagnosed annually. The male:female ratio is 1.4:1. Hodgkin’s disease is rare before age 10 and has a bimodal age distribution that peaks at ages 15-34 and after age 60. The cause is unknown, but patients with Hodgkin’s disease appear to have a genetic susceptibility and environmental associations. Diagnosis depends on identification of Reed-Sternberg cells (large binucleated cells) in lymph nodes or other sites.

### Histopathologic Subtypes of Hodgkin’s Disease

<table>
<thead>
<tr>
<th>Type</th>
<th>Appearance</th>
<th>Incidence</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocyte-predominant</td>
<td>Few Reed-Sternberg cells and many lymphocytes</td>
<td>3%</td>
<td>Relatively slow or indolent</td>
</tr>
<tr>
<td>Nodular sclerosis</td>
<td>Dense fibrous tissue surrounds nodules of Hodgkin’s tissue</td>
<td>67%</td>
<td>Intermediate or moderately progressive; relatively slow or indolent (occasionally)</td>
</tr>
<tr>
<td>Mixed cellularity</td>
<td>A moderate number of Reed-Sternberg cells with a mixed background infiltrate</td>
<td>25%</td>
<td>Intermediate or moderately progressive; aggressive</td>
</tr>
</tbody>
</table>
Non-Hodgkin’s lymphomas (NHL) are malignant monoclonal proliferation of lymphoid cells in sites of the immune system, including lymph nodes, bone marrow, spleen, liver, and GI tract. NHL occurs more often than Hodgkin’s disease. In the USA, about 50,000 new cases are diagnosed annually in all age groups, the incidence increasing with age. Its cause is unknown, although, as with the leukemias, substantial experimental evidence suggests a viral cause for some lymphomas.

**Working Formulation for NHL**

- Low-grade lymphomas (38%): diffuse, small lymphocytic; follicular, small cleaved cell; follicular mixed, small and large cell.
- Intermediate-grade lymphomas (40%): follicular large cell; diffuse, small cleaved cell; diffuse mixed, small and large cell; diffuse large cell.
- High-grade lymphomas (20%): Immunoblastic lymphoma; lymphoblastic lymphoma; small noncleaved cell lymphoma (Burkitt’s and non-Burkitt’s type).
- Miscellaneous lymphomas (2%): composite lymphomas, mycosis fungoides, true histiocytic, other, and unclassifiable types.

A new pathologic classification, the REAL (Revised European-American Lymphoma) Classification, has recently been introduced and is gradually being adopted. This classification is valuable for identifying entities not recognized in the Working Formulation. (1)

**Learning About Lymphoma**

Our bodies are made up of millions of cells that work together to support thousands of structural and biological functions. As these cells age and wear out, they are replaced by just enough healthy new cells to keep the body in good repair. Cell reproduction is controlled by genes, which are present in all cells and are the basic building blocks of heredity. From the time we are born, we are constantly under attack by a wide variety of germs, pollutants, and toxins that attempt to destroy or take over control of our body. The threat comes not only from these outside invaders, but also from within. When cells divide, errors can sometimes occur in the genes. These errors, also called mutations, result in an abnormal cell that does not work properly. Cancer occurs when an abnormal cell grows in an uncontrollable fashion that cannot be contained by the body’s natural defenses. These abnormal cells can multiply and eventually form a mass called a tumor.

Despite continuous attacks from outside and inside the body, most people remain reasonably healthy for most of their lives. When we do get sick, it is usually temporary, and we are able to heal ourselves in a relatively short time. Our ability to survive exposure to external invaders and internal mutations depends largely on the immune system. Lymphoma is a disease that starts in and affects the immune system. It is important to know how the healthy immune system functions when we try to understand lymphoma and its treatment. The immune system is a collection of cells, structures, and organs that exist to identify, contain, and destroy foreign invaders (such as bacteria or viruses) or abnormal cells before or after they harm the body. The immune system can be thought of as a small army that is always “on guard” to protect the body. Invading organisms and abnormal or cancerous cells are generally identified by the immune system through proteins known as antigens that are located on the surface of all cells, whether they are normal or malignant. Special receptors located on the immune cells lock on to these antigens. Just as a lock will only close with the right key, an antigen will only lock with a specific cell from the immune system. When an antigen and an immune cell lock together, the
immune response begins, and the body acts to destroy, remove, or wall off the foreign invaders or abnormal cells.

The lymphatic system is part of the body’s defense system. It protects the body from disease and infection and is one of the most important parts of the immune system. The lymphatic system is made up of a series of thin tubes called lymph vessels that branch into all parts of the body. Lymph vessels carry lymph, a watery fluid that contains white blood cells called lymphocytes. Within the vast network of vessels are groups of small, bean-shaped organs called lymph nodes. Thousands of nodes are found in almost all places in the body, including the elbows, groin, neck, and under the arms. Lymph flows through lymph nodes and specialized lymph tissues such as the spleen, tonsils, bone marrow, and thymus gland.

**Treating Hodgkin’s Disease**

More than 80% of all patients with Hodgkin’s disease can be cured. The plan of treatment depends on many factors, including the extent of the disease and various prognostic factors. Most people who are treated for Hodgkin’s disease will receive radiation, chemotherapy, or a combination of the two. Bone marrow or stem cell transplantation may also be used under special circumstances.

Some patients also may have the option of participating in clinical trials (research studies) to evaluate promising new ways to treat Hodgkin’s disease. Clinical trials are very important because they are designed to improve the way disease is treated now and in the future. Because most patients are cured of this disease, major research efforts are underway to investigate methods of minimizing the short- and long-term toxicities of treatments. For example, radiation therapy has traditionally been the standard initial therapy for treating limited or local Hodgkin’s disease. Because radiation may be associated with serious long-term toxicities, clinicians are not investigating the effectiveness of using chemotherapy to avoid the use of radiation. (2)

**Non-Hodgkin Lymphoma**

In the U.S., about 54,370 people (28,850 men and 25,520 women) are expected to be diagnosed with non-Hodgkin lymphoma in 2004. These statistics include both adults and children. It is the fifth most common cancer in this country, not counting non-melanoma skin cancers. A person’s risk of developing non-Hodgkin lymphoma during their lifetime is about 1 in 50.

Since the early 1970’s, incidence rates for non-Hodgkin lymphoma have nearly doubled. The increase is not completely understood, although many people believe that is was partly due to human immunodeficiency virus (HIV) infections. A small part of the increase was due to better methods of diagnosis. However, since the end of the 1990’s, the overall incidence rates have remained steady.

Although some types of non-Hodgkin’s lymphoma are among the most common childhood cancers, over 95% of cases occur in adults. The average age at diagnosis is in the 60s. The risk of developing non-Hodgkin lymphoma increases throughout life, and the elderly have the highest risk. The increasing average age of the American population is expected to contribute to the increase in non-Hodgkin lymphoma cases during the coming years. The type of non-Hodgkin lymphoma seen in children is often very different from that seen in adults.

Non-Hodgkin lymphoma is more common in men than in women. African Americans and Asian Americans are less likely than whites to develop non-Hodgkin lymphoma.
The American Cancer Society estimates that approximately 19,410 people in the US (10,390 men and 9,020 women) will die of non-Hodgkin lymphoma in 2004. A person’s risk of dying of NHL during their lifetime is about 1 in 100. Overall survival statistics for NHL are not very helpful because survival depends on the type of lymphoma. Nevertheless, the 5-year relative survival for all people with lymphoma is 55%. The 5-year survival rate refers to the percentage of patients who live at least 5 years after their cancer is diagnosed. Although many of these patients live much longer than 5 years after diagnosis, 5-year rates are used to produce a standard way of discussing prognosis. Of course, 5-year survival rates are based on patients diagnosed and initially treated more than 5 years ago. Recent improvements in treatment often result in a more favorable outlook for recently diagnosed patients. Five-year relative survival rates only count people who die of the cancer. People who die of other causes are not counted.

**Risk Factors of NHL**

The causes of NHL remain unknown, but immune system impairment and exposure to environmental carcinogens, pesticides, herbicides, viruses, and bacteria may play a role. There may be a higher risk for getting NHL in individuals:

- Exposed to chemicals such as pesticides, fertilizers, or solvents;
- Infected with the Epstein-Barr virus;
- Infected with human T-lymphotropic virus type 1;
- With a family history of NHL (though no hereditary pattern has been well established);
- Affected with HIV;
- Who received an organ transplant. (3)

**Signs and Symptoms**

**Common Symptoms**

- Chills
- Painless swelling of lymph nodes
- Fever
- Night Sweats
- Unexplained weight loss
- Lack of energy
- Itching

A symptom is anything out of the ordinary that could be caused by a disease. Symptoms are not specific to lymphomas and are, in fact, similar to those of many other illnesses. People often first go to the doctor because they think they have a cold, the flu, or some other respiratory infection that does not go away.

The most common presentation of lymphoma is usually a painless swelling of lymph nodes that often occurs in the neck or under the arms. Some people may also experience swelling of lymph nodes in other parts of the body. For example, enlarged lymph nodes in the groin can cause a swelling in the legs or ankles, while enlarged lymph nodes in the abdomen can cause abdominal discomfort or a feeling of bloating. Less commonly, patients with lymphoma may present without swollen lymph nodes. Other patient complaints that may indicate the presence of lymphoma can include fever, unexplained weight loss, sweating (often at night), chills, a lack of energy, or itching. There is usually no pain involved, especially when the lymphoma is in the early stage of development. Most people who have these non-specific complaints will not have lymphoma. However, it is important that persistent symptoms be seen by a doctor to make sure that lymphoma is not present. (4)
Treatment

The NHL can be divided into two prognostic groups: the indolent lymphomas and the aggressive lymphomas. Indolent NHL types have a relatively good prognosis, with median survival as long as 10 years, but they usually are not curable in advanced clinical stages. Early-stage (I and II) indolent NHL can be effectively treated with radiation therapy alone. Most of the indolent types are nodular (or follicular) in morphology. The aggressive type of NHL has a shorter natural history, but a significant number of these patients can be cured with intensive combination chemotherapy regimens. In general, with modern treatment of patients with NHL, overall survival at 5 years is approximately 50% - 60%. 30% - 60% of patients with aggressive NHL can be cured. The vast majority of relapses occur in the first two years after therapy. The risk of late relapse is higher in patients with a divergent histology of both indolent and aggressive disease.

While indolent NHL is responsive to radiation therapy and chemotherapy, a continuous rate of relapse is usually seen in advanced stages. However, patients can often be retreated with considerable success as long as the disease histology remains low grade. Patients who present with or convert to aggressive forms of NHL may have sustained complete remissions with combination chemotherapy regimens or aggressive consolidation with marrow or stem cell support.

Radiation techniques differ somewhat from those used in the treatment of Hodgkin’s lymphoma. The dose of radiation therapy usually varies from 2,500 cGy to 5,000 cGy and is dependent on factors that include the histologic type of lymphoma, the patient's stage and overall condition, the goal of treatment (curative or palliative), the proximity of sensitive surrounding organs, and whether the patient is being treated with radiation therapy alone or in combination with chemotherapy. Given the patterns of disease presentations and relapse, treatment may need to include unusual sites such as Waldeyer’s ring, epitrochlear, or mesenteric nodes. However, the associated morbidity of the treatment must be considered carefully. The majority of patients who receive radiation are usually treated on only one side of the diaphragm. Localized presentations of extranodal NHL may be treated with involved-field techniques with significant (>50%) success.

In asymptomatic patients with indolent forms of advanced NHL, treatment may be deferred until the patient becomes symptomatic as the disease progresses. When treatment is deferred, the clinical course of patients with indolent NHL varies; frequent and careful observation is required so that effective treatment can be initiated when the clinical course of the disease accelerates. Some patients have a prolonged indolent course, but others have disease that rapidly evolves into more aggressive types of NHL that require immediate treatment. Aggressive lymphomas are increasingly seen in HIV-positive patients; treatment of these patients requires special consideration. (5)

Various Treatment Options

Biological therapy (including immunotherapy) is a treatment that uses forms of the body's own disease-fighting capabilities to treat cancer or to lessen the side effects caused by cancer treatments. These therapies can boost, direct, or restore the natural defenses against disease. Examples of biologic therapies include monoclonal antibodies, radioimmunotherapies, interferons, vaccines, antisense therapies, anti-angiogenesis therapies, and gene therapy.

Monoclonal antibodies, (MAbs) are similar to a guided missile that homes in on a target. When an invader such as a virus, bacteria, or foreign cell enters the body, the immune system produces many different protein molecules (called polyclonal antibodies) which attack multiple unique sites (called antigens) on each foreign invader. It is useful to think of the antigen as a
beacon that attracts antibodies and immune cells (such as lymphocytes). Plasma cells, the most mature B-cells in the body, are white blood cells that specialize in making antibodies. Each plasma cell is responsible for one antibody – otherwise known as a monoclonal antibody. Each monoclonal antibody acts against a particular antigen. Using new technologies, scientists can now produce large amounts of antibody directed to a single target (or antigen) on the cell’s surface. This antibody can often destroy the targeted cell. A number of strategies involving the use of MAbs to treat cancer are being studied, including: (a) MAbs that react with specific types of cancer cells, thereby enhancing a patient’s immune response to cancer, (b) MAbs that are combined with other anticancer drugs, toxins, or radioisotopes, allowing the delivery of these drugs directly to the tumor and bypassing toxicity to most normal cells, and (c) MAbs that are used to help destroy cancer cells before a patient undergoes an autologous transplant.

Scientists are working to develop other monoclonal antibodies that will target the antigens found on cancer cells. One promising treatment method is to attach a radioactive molecule to a MAb to deliver radiation therapy directly to a tumor. It is thought that cancer cells are attacked both by the immune system response caused by the MAb and by allowing a greater concentration of radiation to the tumor.

Interferon alfa is a protein produced naturally in the body that helps fight cancer cells. Interferon has also been produced artificially as a medication. Interferon alfa probably kills tumor cells directly and may also signal normal immune system cells to kill tumor cells. Some studies have shown that giving interferon alfa with chemotherapy may improve outcomes in selected patients with low-grade NHL. Some oncologists also recommend administration of interferon as maintenance therapy to patients who are in remission after treatment with chemotherapy. Most studies to date show some improvement in the length of remission, but little improvement in survival. The most common side effects (toxicities) of interferon therapy are flu-like symptoms, including fever, weakness, or tiredness, and muscle and joint aches. Injecting interferon shortly before bed, drinking a lot of non-alcoholic and non-caffeinated fluids to stay well hydrated, and (if your doctor recommends) taking nonprescription pain relievers such as acetaminophen or ibuprofen, usually reduces the impact of these flu-like symptoms. Interferons can cause depression, which is sometimes severe. You should therefore let your physician know if you become depressed while taking an interferon. Uncommon side effects include a diminished appetite or aversion to food (anorexia) or a decrease in thyroid function.

Vaccines are not yet available as standard treatments, but various vaccines are being evaluated in clinical trials. Lymphoma vaccines enhance the patient’s own natural defenses to fight the disease. These vaccines are custom-made, using a sample of the tumor that is obtained from each patient’s lymph nodes. Preliminary studies show that there may be an anti-tumor effect in patients who are vaccinated, particularly in those who have minimal disease or are in a remission.

Antisense drugs are in various stages of research. Antisense drugs are being developed to stop the production of proteins at the genetic level, which are in some cases cancer-specific so that cancer cells cannot survive. Antisense drugs can be designed that are very specific for a particular cancer. These drugs may also have less toxicity than traditional medications because they spare most healthy cells.

Anti-angiogenesis and gene therapies are two other biologic treatments that are currently being investigated. The development of new blood vessels is called angiogenesis. Many cancers are able to stimulate angiogenesis, causing new blood vessels to form that help the tumor grow and spread. Anti-angiogenesis medications stop the development of new blood vessels and destroy the network of abnormal blood vessels that provide tumors with blood. It is thought that by preventing the development of blood vessels, anti-angiogenesis therapies may be able to limit the growth of some cancers. Scientists are also investigating the use of gene therapies. In some instances, cancer arises when abnormal cells develop that cannot be recognized or
controlled by the body’s immune system. Scientists may be able to design gene therapies that will change the genetic structure of the tumor cells so that the body’s natural immune system can recognize theses cells as foreign invaders. Other types of gene therapy may make tumor cells more susceptible to the effects of chemotherapy drugs, while still others make normal cells less susceptible to this effect. (6)

**Fatigue**

Fatigue is the most common symptom experienced by cancer patients. There are many factors, both physical and emotional, which can cause fatigue. These include lymphoma treatments, medications, pain, nutritional deficits, anxiety and depression. In addition, lymphoma and its treatments can cause anemia, a decrease in red blood cells.

**Symptoms of Fatigue**

- Extreme weariness, lack of energy
- Leg pain, difficulty climbing stairs or walking short distances
- Shortness of breath
- Difficulty performing simple tasks, such as cooking, cleaning, making a bed or taking a shower
- Difficulty concentrating or making decisions (5)

**Hair Dye May Raise Risk of NHL**

On January 28, 2004, after years of conflicting studies showing risks and no risks from hair dye for Non-Hodgkin’s Lymphoma, a study published in the January 15 issue of the American Journal of Epidemiology by researchers at Yale University said women who dyed their hair starting before 1980 were one-third more likely to develop Non-Hodgkin’s lymphoma, or NHL, and those who used the darkest dyes for more than 25 years were twice as likely to develop cancer. (7)

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**References**

1. Monoclonal antibodies (MAbs) are similar to a guided missile that homes in on a target.  
   - True  - False

2. The most common side effects of interferon therapy are flu-like symptoms.  
   - True  - False

3. Antisense drugs can be designed that are very specific for a particular cancer.  
   - True  - False

4. Vaccines are now available for lymphoma.  
   - True  - False

5. Fatigue is the most common symptom experienced by cancer patients.  
   - True  - False

6. The patients with Hodgkin's disease do not appear to have a genetic susceptibility nor environmental association.  
   - True  - False

7. In the USA, about 75,000 new cases of NHL are diagnosed annually in all age groups.  
   - True  - False

8. The incidence of NHL increases with age.  
   - True  - False

9. Substantial experimental evidence does not suggest a viral cause for lymphomas.  
   - True  - False

10. A new pathologic classification, the REAL, is gradually being adopted.  
    - True  - False

11. Women who dyed their hair starting before 1980 were 1/3 more likely to develop NHL.  
    - True  - False

12. Women who used the darkest hair dyes for more than 25 years were twice as likely to develop cancer.  
    - True  - False

13. The cause of lymphoma is unknown.  
    - True  - False

    - True  - False

15. The cause of lymphoma is unknown.  
    - True  - False
16. Antisense drugs have more toxicity than traditional medications.
   ○ True   ○ False

17. Interferon alfa is a protein produced in the body of rats that helps fight cancer cells.
   ○ True   ○ False

18. In the USA, 6,000-7,000 new cases of Hodgkins Lymphoma are diagnosed annually.
   ○ True   ○ False

19. Common side effects of interferon alfa include diminished appetite or aversion to food.
   ○ True   ○ False

20. The major types of lymphomas are Hodgkin's and Non-Hodgkin's lymphoma.
   ○ True   ○ False