Non-Hodgkin Lymphoma
– Richard Orlowski, MD

The American Cancer Society (ACS) estimates that 69,740 Americans will be diagnosed with non-Hodgkin lymphoma (NHL) in 2013. Excluding non-melanoma skin cancers, it is the sixth most common cancer in this country. It is more common in men than women. In 2012, 33 people were diagnosed or treated at Catawba Valley Medical Center (CVMC) for NHL. The ACS also estimates that 19,020 Americans will die of this cancer in 2013.

From years 2008 to 2012, CVMC diagnosed and/or treated 171 patients with NHL as seen in graph below.

Ages of those diagnosed from 2008-2012 are comprised of the following with an average age of 67:

<table>
<thead>
<tr>
<th>Age at Diagnosis (in years)</th>
<th>Count (N)</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 29</td>
<td>3</td>
<td>1.75%</td>
</tr>
<tr>
<td>30 - 39</td>
<td>5</td>
<td>2.92%</td>
</tr>
<tr>
<td>40 - 49</td>
<td>19</td>
<td>11.11%</td>
</tr>
<tr>
<td>50 - 59</td>
<td>18</td>
<td>10.53%</td>
</tr>
<tr>
<td>60 - 69</td>
<td>42</td>
<td>24.56%</td>
</tr>
<tr>
<td>70 - 79</td>
<td>40</td>
<td>23.39%</td>
</tr>
<tr>
<td>80 - 89</td>
<td>38</td>
<td>22.22%</td>
</tr>
<tr>
<td>90+</td>
<td>6</td>
<td>3.51%</td>
</tr>
<tr>
<td>Total</td>
<td>171</td>
<td>100.00%</td>
</tr>
</tbody>
</table>

Range: 13 to 96
Mean: 67
Lymphomas are comprised of a diverse group of neoplasms that arise from uncontrolled proliferation of the cellular components of the lymphoreticular system. The two main types of lymphomas are Hodgkin lymphomas and non-Hodgkin lymphomas. Non-Hodgkin lymphomas differ from Hodgkin lymphomas both microscopically and in the manner that they present. Non-Hodgkin lymphomas can develop from either B lymphocytes (B-cell lymphomas) or T lymphocytes (T-cell lymphomas). B-cell lymphomas account for 85% of all non-Hodgkin lymphomas. Further classification of NHL can be quite confusing even for health professionals because there are many types of NHL and several types of classification systems.

The histologies of the 171 seen at CVMC from 2008-2012 are comprised of the following:

### Histology /Behavior for Non-Hodgkin Lymphoma CVMC 2008-2012

<table>
<thead>
<tr>
<th>Histology/Behavior</th>
<th>Count (N)</th>
<th>Percent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(95913) Lymphoma, malignant, non-Hodgkin, NOS</td>
<td>14</td>
<td>8.19%</td>
</tr>
<tr>
<td>(95963) Composite Hodgkin and non-Hodgkin lymphoma</td>
<td>1</td>
<td>0.58%</td>
</tr>
<tr>
<td>(95973) Primary cutaneous follicle centre lymphoma</td>
<td>1</td>
<td>0.58%</td>
</tr>
<tr>
<td>(96703) Lymphoma, malig, small B lymphocytic, NOS</td>
<td>4</td>
<td>2.34%</td>
</tr>
<tr>
<td>(96713) Lymphoma, malignant, lymphoplasmacytic</td>
<td>1</td>
<td>0.58%</td>
</tr>
<tr>
<td>(96733) Lymphoma, mantle cell</td>
<td>4</td>
<td>2.34%</td>
</tr>
<tr>
<td>(96803) Lymphoma, malig, large B-cell, diffuse, NOS</td>
<td>58</td>
<td>33.92%</td>
</tr>
<tr>
<td>(96873) Burkitt lymphoma, NOS</td>
<td>1</td>
<td>0.58%</td>
</tr>
<tr>
<td>(96903) Lymphoma, follicular, NOS</td>
<td>12</td>
<td>7.02%</td>
</tr>
<tr>
<td>(96913) Lymphoma, follicular, grade 2</td>
<td>12</td>
<td>7.02%</td>
</tr>
<tr>
<td>(96953) Lymphoma, follicular, grade 1</td>
<td>7</td>
<td>4.09%</td>
</tr>
<tr>
<td>(96983) Lymphoma, follicular, grade 3</td>
<td>9</td>
<td>5.26%</td>
</tr>
<tr>
<td>(96993) Lymphoma, marginal zone B-cell, NOS</td>
<td>12</td>
<td>7.02%</td>
</tr>
<tr>
<td>(97003) Mycosis fungoides</td>
<td>4</td>
<td>2.34%</td>
</tr>
<tr>
<td>(97023) Lymphoma, mature T-cell, NOS</td>
<td>4</td>
<td>2.34%</td>
</tr>
<tr>
<td>(97053) Lymphoma, angioimmunoblastic T-cell</td>
<td>1</td>
<td>0.58%</td>
</tr>
<tr>
<td>(97093) Lymphoma, cutaneous T-cell, NOS</td>
<td>1</td>
<td>0.58%</td>
</tr>
<tr>
<td>(97143) Lymphoma, anaplastic Ig cell, T cell &amp; Null cell type</td>
<td>2</td>
<td>1.17%</td>
</tr>
<tr>
<td>(97183) Primary cutaneous CD30+ T-cell lymphoproliferative disorder</td>
<td>1</td>
<td>0.58%</td>
</tr>
<tr>
<td>(97293) Lymphoma, precursor T-cell lymphoblastic</td>
<td>1</td>
<td>0.58%</td>
</tr>
<tr>
<td>(98233) B-cell CLL/small lymphocytic lymphoma</td>
<td>21</td>
<td>12.28%</td>
</tr>
<tr>
<td>Total</td>
<td>171</td>
<td>100.00%</td>
</tr>
</tbody>
</table>
The most frequent histologies are:

![Most Frequent Histologies of NonHodgkin Lymphoma 2008-2012 at CVMC](image)

The most current staging system for NHL is the Ann Arbor system, which has been adopted by the American Joint Committee on Cancer. It is also the one used by Catawba Valley Medical Center. Although it has Stages I-IV like the TNM systems used for solid tumors, the Ann Arbor system is different in several aspects. Lymphomas that affect an organ outside the lymph system (an extranodal organ) have E added to their stage (for example, stage IIE), while those affecting the spleen have an S added. Below is a simplified version of the staging system, courtesy of the American Cancer Society.

**Stage I**
Either of the following means the disease is stage I:
- The lymphoma is in only 1 lymph node area or lymphoid organ such as the thymus (I).
- The cancer is found only in 1 area of a single organ outside of the lymph system (IE).

**Stage II**
Either of the following means the disease is stage II:
- The lymphoma is in 2 or more groups of lymph nodes on the same side of (above or below) the diaphragm (the thin band of muscle that separates the chest and abdomen). For example, this might include nodes in the underarm and neck area but not the combination of underarm and groin nodes (II).
- The lymphoma extends from a single group of lymph node(s) into a nearby organ (IIE). It may also affect other groups of lymph nodes on the same side of the diaphragm.
**Stage III**
Either of the following means the disease is stage III:
- The lymphoma is found in lymph node areas on both sides of (above and below) the diaphragm.
- The cancer may also have spread into an area or organ next to the lymph nodes (IIIE), into the spleen (IIIS), or both (IIISE).

**Stage IV**
Either of the following means the disease is stage IV:
- The lymphoma has spread outside the lymph system into an organ that is not right next to an involved node.
- The lymphoma has spread to the bone marrow, liver, brain or spinal cord, or the pleura (thin lining of the lungs).

For further information regarding classification and staging of non-Hodgkin lymphomas, see the American Joint Committee on Cancer Staging Manual, Seventh Edition. These manuals can be located in Cancer Registry, Medical Oncology and Radiation Oncology at CVMC. NHL is also classified by grade as either low-grade (indolent), intermediate-grade or high grade.

Stage distribution for NHL seen at CVMC from 2008-2012:

![Distribution by AJCC Stage Non-Hodgkin Lymphoma 2008-2012](image)

Most people who develop non-Hodgkin lymphoma have no preventable risk factors and for these people there is no way to prevent the disease. The most avoidable cause is immune deficiency related to human immunodeficiency virus (HIV). Immune deficiency related to organ transplantation or genetic congenital conditions also increase the risk of developing NHL. Other risk factors include:
- Age – most occur in people 60 and older
- African-American or Asian-American ethnicities
- Exposure to radiation, such as survivors of atomic bombs and nuclear reactor accidents
- Chemicals, such as benzene and certain herbicides and insecticides
- Autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus
• Certain chemotherapy drugs, particularly alkylating agents
• Radiation therapy
• Certain infections, such as Epstein-Barr virus, human T-cell leukemia/lymphoma virus, human herpes virus 8, chlamyphila psittaci, Campylobacter jujuni (MALT lymphoma), hepatitis C virus, and Helicobacter pyloria bacteria (for gastric lymphomas)

Currently, there are no specific tests for early detection of non-Hodgkin lymphoma. According to ACS, the best way to find this cancer early is prompt attention to the signs and symptoms of this disease. Some NHL patients may present with easily seen or palpated lymph nodes. Although NHL may present as a local disease, the majority are widespread at the time of diagnosis. Although symptoms will vary with the disease location, the most common signs and symptoms are:

• Unexplained fever
• Night sweats
• Constant fatigue
• Anemia
• Unexplained weight loss
• Itchy skin
• Reddened patches on the skin
• Swelling in the abdomen
• Early satiety

B symptoms is a term used for the symptoms of lymphoma that are may be either fast growing or widespread or both. B symptoms include:

• Unexplained weight loss
• Fever
• Drenching night sweats

Biopsy is the only way to diagnose non-Hodgkin lymphoma. Biopsies may be obtained by fine needle aspiration, excision of the entire lymph node, partial incision of a large tumor, bone marrow aspiration or lumbar puncture. Other diagnostic tests used to either diagnose or stage NHL are:

• Immunohistochemistry
• Flow cytometry
• Cytogenetics
• Molecular genetic studies
• Chest x-ray
• Ultrasound
• Computed tomography (CT)
• Magnetic resonance imaging (MRI)
• Positron emission tomography (PET)
• Gallium scan
• Bone scan

Treatment for non-Hodgkin lymphoma will depend on type, grade and stage of the disease, as well as, individual variables. Surgery is seldom used to treat non-Hodgkin lymphoma. It is more commonly used to obtain the tissue sample for a biopsy or to insert permanent central venous catheters to be used for treatment. Most frequently used treatments are chemotherapy, immunotherapy, and
radiation therapy.

The most common chemotherapy regimen for CVMC patients is CHOP. CHOP stands for cyclophosphamide, doxorubicin (which has a chemical name beginning with H), vincristine (Oncovin) and prednisone. Other chemotherapy regimens may be used for certain types of lymphomas or if patients are not able to tolerate CHOP. Other commonly used chemotherapy drugs for NHL are:

- Bendamustine (Treanda®)
- Bleomycin
- Carboplatin
- Chlorambucil
- Cladribine (2-CdA, Leustatin®)
- Cisplatin
- Cytarabine (ara-C)
- Doxorubicin (Adriamycin®)
- Etoposide (VP-16)
- Fludarabine (Fludara®)
- Gemcitabine (Gemzar®)
- Ifosfamide (Ifex®)
- Methotrexate
- Mitoxantrone
- Oxaliplatin
- Pentostatin (Nipent®)
- Pralatrexate (Folotyn®)
- Vincristine (Oncovin®)

Rituximab (Rituxan), an immunotherapy drug, is often given with CHOP for patients whose lymphoma is CD20 positive. While chemotherapy targets all fast growing cells (including cancer cells); Rituxan is a monoclonal antibody that targets just a certain protein receptor (CD20) on B (white blood) cells. Many B cell lymphomas over express or have an abundance of these receptors. Unfortunately, normal B cells also have these receptors. Zevalin (ibritumomab) is a targeted therapy for follicular B-cell non-Hodgkin lymphoma in patients with relapsed or refractory disease. They combine antineoplastic monoclonal antibodies with radioactive isotopes. Other immunological drugs used for NHL are:

- Obinutuzumab (Gazyva™)
- Ofatumumab (Arzerra®)

Radiation therapy may be used for patients with Stage I or II, especially if they have an indolent tumor. It may be useful in reducing tumor burden and relieving symptoms, such as pain or dyspnea. Radiation therapy may also be used prior to stem cell transplant to help irradiate cancer cells.

Stem cell transplants may be used to treat lymphoma patients who are in remission or who have a relapse during or after treatment. Although only a small percentage of patients with lymphoma are treated with this therapy now, this number is growing.

Over the past forty years, lymphomas have been one of the fastest growing cancer categories in the United States. On the positive side, the survival rate has been steadily increasing since the early 1990s due to improved cancer treatments. According to the ACS, the overall 5-year relative survival rate for
people with NHL is 69%, and the 10-year relative survival rate is 58%. With additional research, the survival rate will continue to rise. NHL survival rates for those seen at CVMC between 2008-2012: