Cancer Association of South Africa (CANSA)

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Fact Sheet
On
Non-Hodgkin's Lymphoma

Introduction

Lymphoma is a type of cancer involving cells of the immune system, called lymphocytes. Just as cancer represents many different diseases, lymphoma represents many different cancers of lymphocytes -- about 35 different subtypes. Lymphoma is a group of cancers that affect the cells that play a role in the immune system and primarily represents cells involved in the lymphatic system of the body.

[Picture Credit: Lymphatic System]

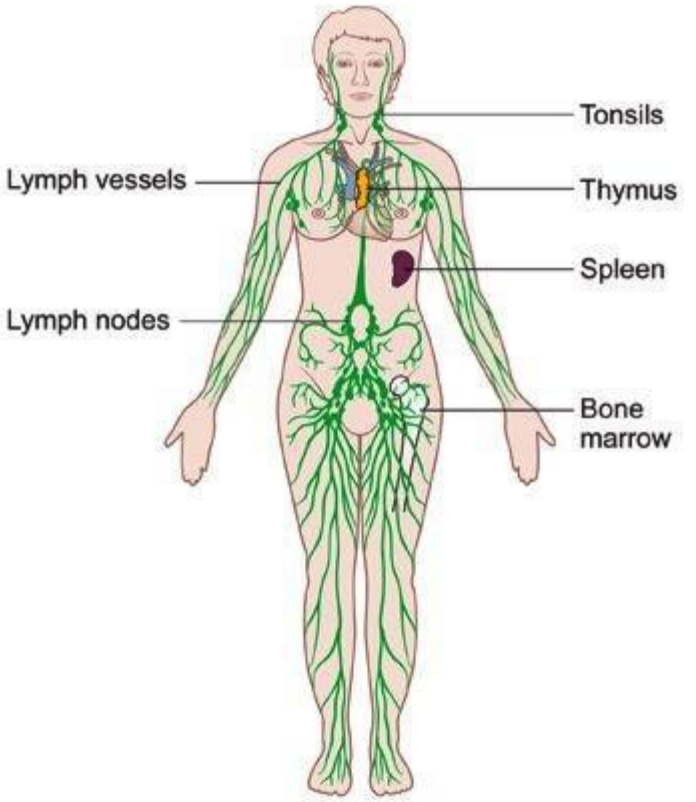

Diagram of the lymphatic system
Copyright © CancerHelp UK

The Lymphatic System

The lymphatic system is an extensive drainage network that helps keep bodily fluid levels in balance and defends the body against infections. It is made up of a network of lymphatic vessels that carry lymph - a clear, watery fluid that contains protein molecules, salts, glucose, urea, and other substances - throughout the body.

Types of Lymphoma

Lymphomas fall into one of two major categories:

- Hodgkin's lymphoma (HL, previously called Hodgkin's disease)
- Non-Hodgkin's Lymphoma (NHL, all other lymphomas)

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These two types occur in the same places, may be associated with the same symptoms, and often have similar appearance on physical examination. However, they are readily distinguishable via microscopic examination.

Many of the NHL subtypes look similar, but they are functionally quite different and respond to different therapies with different probabilities of cure. HL subtypes are microscopically distinct, and typing is based upon the microscopic differences as well as extent of disease.

Non-Hodgkin's Lymphoma

Non-Hodgkin's lymphoma is cancer of the lymphoid tissue, which includes the lymph nodes, spleen, and other organs of the immune system.

There are many different types of non-Hodgkin lymphoma (NHL), so classifying it can be quite confusing (even for doctors). Several different systems have been used, but the most recent system is the World Health Organization (WHO) classification. The WHO system groups lymphomas based on:

- The type of lymphocyte the lymphoma starts in
- How the lymphoma looks under a microscope
- The chromosome features of the lymphoma cells
- The presence of certain proteins on the surface of the cancer cells

Causes, Incidence, and Risk Factors for Non-Hodgkin's Lymphoma

White blood cells called lymphocytes are found in lymph tissues. They help prevent infections. Most Non-Hodgkin's Lymphomas (NHL) start in a type of white blood cells called B lymphocytes, or B cells.

Some of the Known Risk Factors for Non-Hodgkin's Lymphoma include:

- Age - Non-Hodgkin's lymphoma can develop in people of all ages, including children, it is most common in adults. The most common types of NHL usually appear in people in their 60s and 70s.
- Sex - In general, NHL is more common in men than in women.
- Race - Overall, the risk for NHL is slightly higher in Caucasians than in African-Americans and Asian Americans.
- Family History - People who have close family relatives who have developed NHL may be at increased risk for this cancer. However, no definitive hereditary or genetic link has been established.
- Infections - Viral or bacterial infections may play a role in some lymphomas. These include:

    - Epstein-Barr virus (EBV), the cause of mononucleosis, is highly associated with Burkitt's lymphoma and NHLs associated with immunodeficiency diseases. It is also a risk factor for Hodgkin's disease.
    - The human immodeficiency virus (HIV), which causes AIDS, increases the risk for Burkitt lymphoma and diffuse large B-cell lymphoma
    - The hepatitis C virus (HCV) may increase the risk for certain types of lymphomas.
    - The *Helicobacter pylori* bacterium, which causes stomach ulcers, is associated with increased risk for mucosa-associated lymphoid tissue lymphomas (MALT). (The use of antibiotics to get

rid of the bacteria may cause remission in some patients who have an early stage form of lymphoma in an early stage.)

- Immune System Deficiency Disorders - Patients with diseases or conditions that affect the immune system may be at higher risk for lymphomas:
    - HIV-positive patients and those with full-blown AIDS are at higher risk for NHL, and the disease is more likely to be widespread in these patients than in those without the immune disease. Most AIDS-related NHLs are high-grade lymphomas.
    - People who have organ transplants are at higher risk for NHL, probably due to multiple factors, including the drugs used to suppress the immune system and the transplanted organ itself.
    - Patients who have had high-dose chemotherapy with stem-cell transplantation are at higher risk.

- Other immunodeficiency syndromes that put people at risk for NHL include Chediak-Higashi syndrome, ataxia-telangiectasia, B-cell lymphoproliferative syndrome, Bruton agammaglobulinemia, common variable immunodeficiency, and Wiskott-Aldrich syndrome.
- Autoimmune Disorders - Patients with a history of autoimmune diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus, Hashimoto's thyroiditis, Crohn's disease, and Sjogren syndrome, are at an increased risk for certain NHLs, such as marginal zone lymphomas.
- Chemical Exposure - Overexposure to a number of industrial and agricultural chemicals (such as pesticides, herbicides, and petrochemicals) has been frequently linked to an increased risk for lymphomas. The data, however, are not consistent.
- Lifestyle Factors - Lifestyle does not seem to be a major risk factor for NHL. Some studies have suggested that obesity may increase risk, but this association is not definite. Other studies have investigated the role of diet. Although some research has indicated an increased risk for diets high in consumption of red meat and lower risk for diets high in vegetables, for the most part a strong association remains speculative. There is no evidence that smoking increases the risk for NHL itself, although it has been linked with high-grade and follicular NHLs in people with lymphoma.

Armitage, J.O., Gascoyne, R.D., Lunning, M.A. & Cavalli, F. 2017. Non-Hodgkin lymphoma. *Lancet*. 2017 Jul 15;390(10091):298-310. doi: 10.1016/S0140-6736(16)32407-2. Epub 2017 Jan 31.
"Lymphomas can affect any organ in the body, present with a wide range of symptoms, and be seen by primary care physicians and physicians from most specialties. They are traditionally divided into Hodgkin's lymphoma (which accounts for about 10% of all lymphomas) and non-Hodgkin lymphoma. Non-Hodgkin lymphoma represents a wide spectrum of illnesses that vary from the most indolent to the most aggressive malignancies. They arise from lymphocytes that are at various stages of development, and the characteristics of the specific lymphoma subtype reflect those of the cell from which they originated."

Incidence of Non-Hodgkin's Lymphoma in South Africa

According to the outdated National Cancer Registry (2014), known for under reporting, the following number of Non-Hodgkin's Lymphoma cases were histologically diagnosed in South Africa during 2014:

Group - Males 2014	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	932	1:221	2,53%
Asian males	36	1:182	3,84%
Black males	533	1:331	4,81%
Coloured males	89	1:189	2,11%
White males	274	1:113	1,33%

Group - Females 2014	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	870	1:296	2,30%
Asian females	39	1:206	3,28%
Black females	492	1:448	3,06%
Coloured females	91	1:205	2,22%
White females	249	1:156	1,52%

The frequency of histologically diagnosed cases of Non-Hodgkin's Lymphoma in South Africa for 2014 was as follows (National Cancer Registry, 2014):

Group - Males 2014	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	42	53	161	219	180	143	82	33
Asian males	2	4	3	5	5	10	5	1
Black males	31	36	128	149	98	43	15	5
Coloured males	4	3	8	20	22	16	10	4
White males	5	10	18	40	48	74	51	22

Group - Females 2014	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All females	22	59	168	179	115	139	104	58
Asian females	0	1	3	10	8	12	1	2
Black females	14	50	140	133	58	37	21	7
Coloured females	6	2	12	7	10	24	19	9
White females	1	4	13	22	38	63	61	39

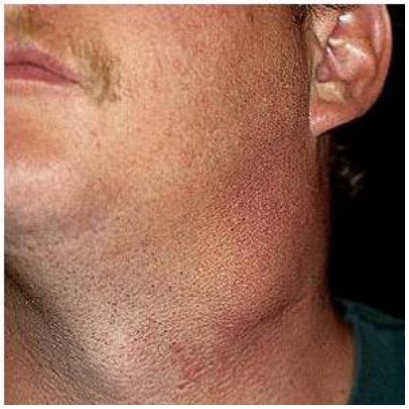
N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females', however, always reflect the correct totals.

According to **Bruni, *et al.*,** (2019), the burden of non-Hodgkin's Lymphoma for South Africa for 2018 is estimated as (based on Globocan estimates):

- Annual number of non-Hodgkin's Lymphoma cases 3 709
- Annual number of non-Hodgkin's Lymphoma deaths 1 767

Symptoms of Non-Hodgkin's Lymphoma

Symptoms depend on what area of the body is affected by the cancer and how fast the cancer is growing. Symptoms may include:



[Picture Credit: Non-Hodgkin's Lymphoma]

- Night sweats (soaking the bedsheets and pyjamas even though the room temperature is not too hot)
- Fever and chills that come and go
- Itching
- Swollen lymph nodes in the neck, underarms, groin, or other areas
- Weight loss
- Coughing or shortness of breath may occur if the cancer affects the thymus gland or lymph nodes in the chest, which may put pressure on the windpipe (trachea) or other airways.
- Some patients may have abdominal pain or swelling, which may lead to a loss of appetite, constipation, nausea, and vomiting.
- If the cancer affects cells in the brain, the person may have a headache, concentration problems, personality changes, or seizures.

Signs and Tests for Non-Hodgkin's Lymphoma

The doctor will perform a physical exam and check body areas with lymph nodes to feel if they are swollen.

The disease may be diagnosed after:

- Biopsy of suspected tissue, usually a lymph node biopsy
- Bone marrow biopsy

Other tests that may be done include:

- Blood test to check protein levels, liver function, kidney function, and uric acid level
- Complete blood count (CBC)
- CT scans of the chest, abdomen and pelvis
- Gallium scan
- PET (positron emission tomography) scan

Diagnosis of non_Hodgkin's Lymphoma

Melani, C., Wilson, W.H. & Roschewski, M. 2019

"ctDNA provides an important new strategy that will aid in the treatment of non-Hodgkin's lymphoma. Immunoglobulin sequencing provides a tumor specific marker for disease activity with a sensitivity equivalent to one tumor cell per 10-6. Furthermore, it can provide an estimate of tumor bulk and tumor response dynamics during treatment. Interim monitoring can identify patients at high risk of treatment failure and surveillance monitoring can identify patients months before radiographic disease progression. Tumor specific mutations can also be detected in ctDNA and may

reflect an averaging of mutations present within multiple tumor masses. Such analysis may aid in the molecular characterization of tumors and selection of targeted treatments for precision medicine."

Treatment of Non-Hodgkin's Lymphoma
Treatment depends on:

- The type of lymphoma
- The stage of the cancer when you are first diagnosed
- Your age and overall health
- Symptoms, including weight loss, fever, and night sweats

Common treatments may include:

- Radiation therapy may be used for disease that is confined to one body area.
- Chemotherapy is the main type of treatment. Most often, multiple different drugs are used in combination together.
- Another drug, called rituximab (Rituxan), is often used to treat B-cell non-Hodgkin's lymphoma.
- Radioimmunotherapy may be used in some cases. This involves linking a radioactive substance to an antibody that targets the cancerous cells and injecting the substance into the body.
- People with lymphoma that returns after treatment or does not respond to treatment may receive high-dose chemotherapy followed by a bone marrow transplant (using stem cells from the patient).

Additional treatments depend on other symptoms. They may include:

- Transfusion of blood products, such as platelets or red blood cells
- Antibiotics to fight infection, especially if a fever occurs

Chu, Y., Gardenswartz, A., Termuhlen, A.M. & Cairo, M.S. 2019.
"Patients with relapsed, refractory or advanced stage B non-Hodgkin lymphoma (NHL) continue to have a dismal prognosis. We review summarises current and novel cellular and immunotherapy for these high-risk populations, including haematopoietic stem cell transplant, bispecific antibodies, viral-derived cytotoxic T cells, chimeric antigen receptor (CAR) T cells, and natural killer (NK) cell therapy."

Hüttmann, A., Rekowski, J., Müller, S.P., Hertenstein, B., Franzius, C., Mesters, R., Weckesser, M., Kroschinsky, F., Kotzerke, J., Ganser, A., Bengel, F.M., La Rosée, P., Freesmeyer, M., Höffkes, H.G., Hertel, A., Behringer, D., Prange-Krex, G., Griesshammer, M., Holzinger, J., Wilop, S., Krohn, T., Raghavachar, A., Maschmeyer, G., Brink, I., Schroers, R., Gaska, T., Bernhard, H., Giagounidis, A., Schütte, J., Dienst, A., Hautzel, H., Naumann, R., Klein, A., Hahn, D., Pöpperl, G., Grube, M., Marienhagen, J., Schwarzer, A., Kurch, L., Höhler, T., Steiniger, H., Nückel, H., Südhoff, T., Römer, W., Brinkmann, M., Ose, C., Alashkar, F., Schmitz, C., Dürig, J., Hoelzer, D., Jöckel, K.H., Klapper, W. & Dührsen, U. 2019.
"Standard first-line treatment of aggressive B cell lymphoma comprises six or eight cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) plus eight doses of rituximab

(R). Whether adding two doses of rituximab to six cycles of R-CHOP is of therapeutic benefit has not been systematically investigated. The Positron Emission Tomography-Guided Therapy of Aggressive Non-Hodgkin Lymphomas (PETAL) trial investigated the ability of [^{18}F]-fluorodesoxyglucose PET scanning to guide treatment in aggressive non-Hodgkin lymphomas. Patients with B cell lymphomas and a negative interim scan received six cycles of R-CHOP with or without two extra doses of rituximab. For reasons related to trial design, only about a third underwent randomization between the two options. Combining randomized and non-randomized patients enabled subgroup analyses for diffuse large B cell lymphoma (DLBCL; n = 544), primary mediastinal B cell lymphoma (PMBCL; n = 37), and follicular lymphoma (FL) grade 3 (n = 35). With a median follow-up of 52 months, increasing the number of rituximab administrations failed to improve outcome. A non-significant trend for improved event-free survival was seen in DLBCL high-risk patients, as defined by the International Prognostic Index, while inferior survival was observed in female patients below the age of 60 years. Long-term outcome in PMBCL was excellent. Differences between FL grade 3a and FL grade 3b were not apparent. The results were confirmed in a Cox proportional hazard regression model and a propensity score matching analysis. In conclusion, adding two doses of rituximab to six cycles of R-CHOP did not improve outcome in patients with aggressive B cell lymphomas and a fast metabolic treatment response."

Kanate, A., Kumar, A., Dreger, P., Drevling, M. Le Gouill, S., Corradini, P., BAredeson, C., Fenske, T.S., Smith, S.M., Sureda, A., Moskowitz, A., Friedberg, J.W., Inwards, D.J.,Herrera, A.F., Kharfan-Dbaja, A.K., Reddy, N., Montoto, S., Robinson, S.P., Abutalib, S.A., Gisselbrecht, C., Vose, J., Gopal, A., Shadman, M., Perales, M-A., Carpenter, P., Savani, N. & Hamadani, M. 2019.

Importance: Maintenance therapies are often considered as a therapeutic strategy in patients with lymphoma following autologous hematopoietic cell transplantation (auto-HCT) to mitigate the risk of disease relapse. With an evolving therapeutic landscape, where novel drugs are moving earlier in therapy lines, evidence relevant to contemporary practice is increasingly limited. The American Society for Blood and Marrow Transplantation (ASBMT), Center for International Blood and Marrow Transplant Research (CIBMTR), and European Society for Blood and Marrow Transplantation (EBMT) jointly convened an expert panel with diverse expertise and geographical representation to formulate consensus recommendations regarding the use of maintenance and/or consolidation therapies after auto-HCT in patients with lymphoma.

Observations: The RAND-modified Delphi method was used to generate consensus statements where at least 75% vote in favor of a recommendation was considered as consensus. The process included 3 online surveys moderated by an independent methodological expert to ensure anonymity and an in-person meeting. The panel recommended restricting the histologic categories covered in this project to Hodgkin lymphoma (HL), mantle cell lymphoma (MCL), diffuse large B-cell lymphoma (DLBCL), and follicular lymphoma. On completion of the voting process, the panel generated 22 consensus statements regarding post auto-HCT maintenance and/or consolidation therapies. The grade A recommendations included endorsement of: (1) brentuximab vedotin (BV) maintenance and/or consolidation in BV-naïve high-risk HL, (2) rituximab maintenance in MCL undergoing auto-HCT after first-line therapy, (3) rituximab maintenance in rituximab-naïve FL, and (4) No post auto-HCT maintenance was recommended in DLBCL. The panel also developed consensus statements for important real-world clinical scenarios, where randomized data are lacking to guide clinical practice.

Conclusions and relevance: In the absence of contemporary evidence-based data, the panel found RAND-modified Delphi methodology effective in providing a rigorous framework for developing consensus recommendations for post auto-HCT maintenance and/or consolidation therapies in lymphoma.

Munshi, P.M. & Ujjani, C. 2019.
"Recent advances in diffuse large B-cell lymphomas have included both identification of high-risk subtypes characterized by multiply relapsed and/or refractory disease as well as novel treatment in the form of cellular therapy. Chimeric antigen receptor (CAR)-T cell therapy is a recently developed approach to address the poor outcomes in this patient population. The CAR-T cell construct has evolved although several iterations as it transitioned from the lab to the clinic. Three major studies have evaluated the efficacy of CD19-directed CAR-T cell therapy in aggressive B-cell non-Hodgkin lymphoma; each demonstrating durable complete remissions in heavily pretreated patients. The cost of this remarkable therapy, however, includes cytokine release syndrome and neurotoxicity shortly after administration as well as delayed infectious complications due to B-cell aplasia. Future investigations are focused on the optimizing both safety and efficacy of CAR-T cell therapy."

Expectations (Prognosis) of Non-Hodgkin's Lymphoma
Low-grade non-Hodgkin's lymphoma usually cannot be cured by chemotherapy alone. However, the low-grade form of this cancer progresses slowly, and it may take many years before the disease gets worse or even requires any treatment. Chemotherapy can often cure many types of high-grade lymphoma. However, if the cancer does not respond to chemotherapy drugs, the disease can cause rapid death.

Complications of Non-Hodgkin's Lymphoma
Complications may include:

- Autoimmune haemolytic anaemia
- Infection
- Side effects of chemotherapy drugs

Relationship of Staging Systems – Hodgkin Lymphoma and Non-Hodgkin Lymphomas

Description of Extent (Based on Ann Arbor Staging Systems)	Summary Stage	Ann Arbor Staging*	AJCC Staging Stage**
Involvement of a single lymph node region	Localised	I	I
A single extralymphatic organ or site	Localised	Ie	Ie
Involvement of more than one lymphatic region on only one side of the diaphragm	Regional NOS	II	II
Localised involvement of one extralymphatic organ or site and its regional lymph nodes with or without other nodes on the same side of the diaphragm	Regional NOS	IIe	IIe
Involvement of more than one lymphatic region on only one side of the diaphragm plus involvement of the spleen	Distant	IIs	IIs
Involvement of lymph node regions on both sides of the diaphragm	Distant	III	III
Involvement of lymph node regions on both sides of the diaphragm plus localised involvement of an extralymphatic organ or site	Distant	IIIe	IIIe
Involvement of lymph node regions on both sides of the diaphragm plus involvement of the spleen	Distant	IIIs	IIIs

Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node enlarge3ment. Organs considered distant include liver, bone, bone marrow, lung and/or pleura and kidney	Distant	IV	IV
Isolated extralymphatic organ involvement with distant (non-regional) nodal involvement	Distant	IV	IV

About Clinical Trials

Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

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Lymphatic System
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Lymph Node
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