Cancer Association of South Africa (CANSA)

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Fact Sheet
On
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.

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.

The spleen, which is located in the upper left part of the abdomen under the ribcage, works as part of the lymphatic system to protect the body, clearing worn out red blood cells and other foreign bodies from the bloodstream to help fight off infection.

[Picture Credit: Lymphatic System]

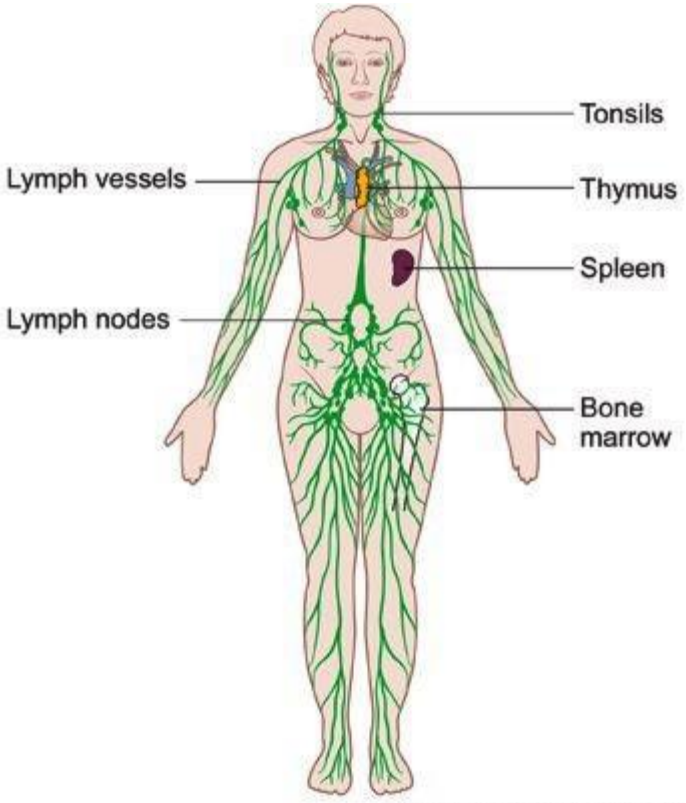


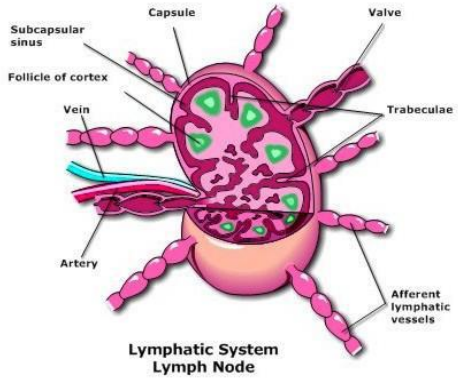
Diagram of the lymphatic system
Copyright © CancerHelp UK

One of the lymphatic system's major jobs is to collect extra lymph fluid from body tissues and return it to the blood. This process is crucial because water, proteins, and other substances are continuously leaking out of tiny blood capillaries into the surrounding body tissues. If the lymphatic system did not drain the excess

Researched and Authored by Prof Michael C Herbst
[D Litt et Phil (Health Studies); D N Ed; M Art et Scien; B A Cur; Dip Occupational Health; Dip Genetic Counselling; Diagnostic Radiographer; Dip Audiometry and Noise Measurement; Medical Ethicist]
Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]

fluid from the tissues, the lymph fluid would build up in the body's tissues, and the tissue would swell.

The lymphatic system also helps defend the body against germs like viruses, bacteria, and fungi that can cause illnesses. Those germs are filtered out in the lymph nodes, small masses of tissue located along the network of lymph vessels. The nodes house lymphocytes, a type of white blood cell. Some of those lymphocytes make antibodies, special proteins that fight off germs and stop infections from spreading by trapping disease-causing germs and destroying them.



[Picture Credit – Lymph Node]

The spleen also helps the body fight infection. The spleen contains lymphocytes and another kind of white blood cell called macrophages, which engulf and destroy bacteria, dead tissue, and foreign matter and remove them from the blood passing through the spleen.

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)

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.

Hodgkin's lymphoma develops from a specific abnormal B lymphocyte lineage. NHL may derive from either abnormal B or T cells and are distinguished by unique genetic markers. There are five subtypes of Hodgkin's lymphoma and about 30 subtypes of non-Hodgkin's lymphoma.

Hodgkin's Lymphoma

Hodgkin's lymphoma is a cancer of lymph tissue found in the lymph nodes, spleen, liver, bone marrow, and other sites.

Connors, J.M., Cozen, W., Steidl, C., Carbone, A., Hoppe, R.T., Flechtner, H.H. & Bartlett, N.L. 2020. "Hodgkin lymphoma (HL) is a B cell lymphoma characterized by few malignant cells and numerous immune effector cells in the tumour microenvironment. The incidence of HL is highest in adolescents and young adults, although HL can affect elderly individuals. Diagnosis is based on histological and immunohistochemical analyses of tissue from a lymph node biopsy; the tissue morphology and antigen expression profile enable classification into one of the four types of classic HL (nodular sclerosis, mixed cellularity, lymphocyte-depleted or lymphocyte-rich HL), which account for the

majority of cases, or nodular lymphocyte-predominant HL. Although uncommon, HL remains a crucial test case for progress in cancer treatment. HL was among the first systemic neoplasms shown to be curable with radiation therapy and multiagent chemotherapy. The goal of multimodality therapy is to minimize lifelong residual treatment-associated toxicity while maintaining high levels of effectiveness. Recurrent or refractory disease can be effectively treated or cured with high-dose chemotherapy followed by autologous haematopoietic stem cell transplantation, and prospective trials have demonstrated the potency of immunotherapeutic approaches with antibody-drug conjugates and immune checkpoint inhibitors. This Primer explores the wealth of information that has been assembled to understand HL; these updated observations verify that HL investigation and treatment remain at the leading edge of oncological research."

Kaseb, H. & Babiker, H.M. 2020.
"Hodgkin lymphoma (HL), formerly called Hodgkin's disease, is a rare monoclonal lymphoid neoplasm with high cure rates. Biological and clinical studies have divided this disease entity into two distinct categories: classical Hodgkin lymphoma and nodular lymphocyte-predominant Hodgkin lymphoma (NLP-HL). These two disease entities show differences in the clinical picture and pathology. Classical Hodgkin lymphoma accounts for approximately 95% of all HL, and it is further subdivided into four subgroups: nodular sclerosis (NSHL), lymphocyte-rich (LRHL), mixed cellularity (MCHL), and lymphocyte-depleted (LDHL). Four features characterize Hodgkin lymphomas. They commonly arise in the cervical lymph nodes; the disease is more common in young adults; there are scattered large mononuclear Hodgkin and multinucleated cells (Reed-Sternberg) intermixed in a background of a mixture of non-neoplastic inflammatory cells; finally, T lymphocytes are often observed surrounding the characteristic neoplastic cells. Hodgkin lymphoma has an excellent overall prognosis with approximately an 80% cure rate."

Incidence Hodgkin's Lymphoma in South Africa
According to the National Cancer Registry (2017) the following number of Hodgkin's Lymphoma cases was histologically diagnosed in South Africa during 2017. Histologically diagnosed means that a tissue sample (biopsy) was forwarded to an approved laboratory where a specially trained pathologist confirmed the cancer diagnosis:

Group - Males 2017	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	356	1:831	0,89%
Asian males	15	1:638	1,54%
Black males	235	1:1 004	1,78%
Coloured males	36	1:833	0,77%
White males	70	1:405	0,34%

Group - Females 2017	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	293	1:1 208	0,70%
Asian females	12	1:830	0,93%
Black females	198	1:1 385	1,04%
Coloured females	29	1:1 227	0,59%
White females	54	1:612	0,32%

The frequency of histologically diagnosed cases of Hodgkin's Lymphoma in South Africa for 2017 was as follows (National Cancer Registry, 2017):

Group - Males 2017	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	57	52	76	84	54	21	9	3
Asian males	0	2	2	4	6	1	0	0
Black males	39	35	59	61	35	10	2	2
Coloured males	7	5	12	7	3	1	1	0
White males	11	10	11	12	10	9	6	1

Group - Females 2017	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	32	68	85	54	34	20	13	1
Asian females	4	1	3	4	0	0	0	0
Black females	20	49	67	21	18	6	1	0
Coloured females	2	5	10	5	2	3	2	0
White females	6	11	5	6	10	7	8	1

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.

Causes and Risk Factors of Hodgkin's Lymphoma

The cause of Hodgkin's Lymphoma is not known. Hodgkin's lymphoma is most common among individuals aged 15 - 35 and 50 - 70. Past infection with the Epstein-Barr virus (EBV) is thought to contribute to some cases. Patients with HIV infection are also said to be more at risk than the general population.

Risk Factors

Factors that may increase the risk of Hodgkin's lymphoma include:

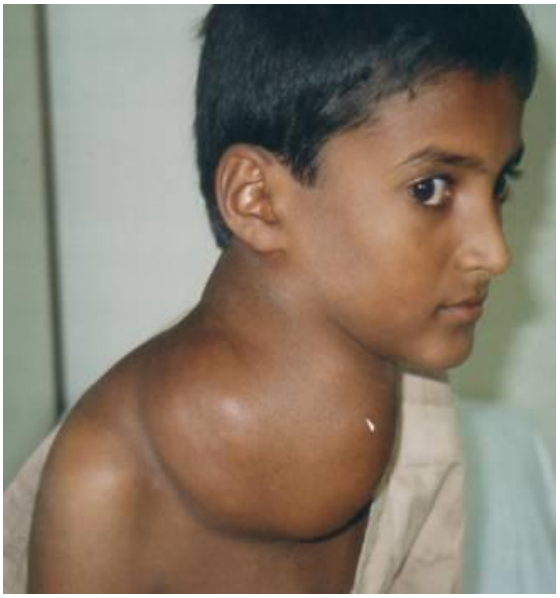
- Age - Hodgkin's lymphoma is most often diagnosed in people between the ages of 15 and 35, as well as those older than 55
- A family history of lymphoma - anyone with a brother or a sister who has Hodgkin's lymphoma has an increased risk of developing Hodgkin's lymphoma. Studies also show up to a seven-fold increased risk in people with a parent or sibling diagnosed with Hodgkin's lymphoma or with any blood or lymphatic cancer
- Sex - males are slightly more likely to develop Hodgkin's lymphoma
- Past Epstein-Barr infection - individuals who have had illnesses caused by the Epstein-Barr virus, such as infectious mononucleosis, are more likely to develop Hodgkin's lymphoma
- A weakened immune system - having a compromised immune system, such as from HIV/AIDS or from having an organ transplant requiring medications to suppress the immune response, increases the risk of Hodgkin's lymphoma.

Symptoms of Hodgkin's Lymphoma

The following symptoms may present:

- Fatigue
- Fever and chills that come and go
- Itching all over the body that cannot be explained

- Loss of appetite
- Soaking night sweats
- Painless swelling of the lymph nodes in the neck, armpits, or groin (swollen glands)
- Weight loss that cannot be explained



[Picture Credit: Hodgkin's Lymphoma]

Other symptoms that may occur:

- Coughing, chest pains, or breathing problems if there are swollen lymph nodes in the chest
- Excessive sweating
- Pain or feeling of fullness below the ribs due to swollen spleen or liver
- Pain in lymph nodes after drinking alcohol
- Skin blushing or flushing

Note: Symptoms caused by Hodgkin's lymphoma may also occur with other conditions. One should consult a doctor about the meaning of specific symptoms.

Signs and Tests

The first sign of Hodgkin's lymphoma is often a swollen lymph node, which appears without a known cause. The disease can spread to nearby lymph nodes. Later it may spread to the spleen, liver, bone marrow, or other organs.

Piris, M.A., Medeiros, L.J. & Chang, K-C. 2020.

"Hodgkin lymphoma (HL) is composed of two distinct pathological entities, nodular lymphocyte predominant HL and classic HL, the latter with four subtypes. In contrast with most other human lymphomas, in which the neoplastic cells are a major population of the tumour constituents, the neoplastic 'Hodgkin (H) and Reed-Sternberg (RS)' cells usually account for less than 10% of tumour bulk against an inflammatory background. The neoplastic cells of HL are of B-cell lineage (PAX5+) in virtually all cases. HL usually affects young patients with a localised nodal disease and its clinical behaviour is typically indolent. Patients respond well to chemotherapy with cure rates of 80-90% and the recent finding of PD-L1 expression, an immune checkpoint, warrants the use of immunotherapy for some patients with recurrent and/or refractory HL. The enigmatic RS cells of HL are unique in their abundant cytoplasm and characteristic bilobed nuclei with eosinophilic prominent nucleoli, imparting an 'owl-eye' appearance. H cells are mononuclear variants. The viral inclusion-like morphology was a clue on the way to discovering an association between classic HL and Epstein-Barr virus (EBV). However, this association is variable in different geographic regions and in pathological subtypes, and correlates with older age (>60 years) and socioeconomic status, indicating that environmental factors are likely involved in HL pathogenesis. Virus-associated endoplasmic reticulum (ER) stress also may contribute to mechanisms underlying the characteristic morphological features of HRS cells. ER stress has been found to induce aberrant, cytoplasmic cyclin A expression, leading to nuclear hyperdiploidy. Aberrant expression of cyclin A is commonly associated with HRS cell morphology in HL, probably through EBV-latent membrane protein-1

(LMP1) signalling. Shelterin also may play a role in the morphogenesis of multinucleated RS cells. In addition, EBV-positive and -negative HL cases express survival, but not death signals of ER stress at similar levels and EBV-LMP1 transfection increases expression of survival signals in HL cell lines. These data suggest that surviving ER stress may be involved in HL pathogenesis."

The disease may be diagnosed after:

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

Spina, V. & Rossi, D. 2019.
"In the era of personalised medicine, genetic information is critical to directing therapeutic options, aiding risk stratification and disease monitoring of lymphomas. Liquid biopsy is a novel noninvasive, real-time and tumour-specific technique, reliably reflecting the comprehensive tumour genetic profile, and thus holds great promise for the genetic assessment, response monitoring and relapse detection of lymphomas. Standard methods for disease response assessment in patients with lymphoma, including positron emission tomography, are imperfect. In other haematological malignancies, particularly leukaemias, the ability to detect minimal residual disease (MRD) is increasingly influencing treatment paradigms. However, in some subtypes of lymphoma, such as diffuse large B-cell lymphoma and classic Hodgkin’s lymphoma, the application of MRD assessment techniques such as flow cytometry or polymerase chain reaction-based methods has been challenged by the absence of circulating disease. The review summarises the applications of liquid biopsy in the assessment of tumour burden and response to therapy, noninvasive genomic profiling, and monitoring of clonal dynamics in patients with diffuse large B-cell lymphoma and classic Hodgkin’s lymphoma."

The following procedures may also be done:

- Blood chemistry tests including protein levels, liver function tests, kidney function tests, and uric acid level
- Bone marrow biopsy
- CT scans of the chest, abdomen, and pelvis
- Complete blood count (CBC) to check for anaemia and white blood count
- PET scan

Ansell, S.M. 2015.
"Hodgkin lymphoma is a rare B-cell malignant neoplasm affecting approximately 9000 new patients annually. This diseaserepresents approximately 11% of all lymphomas seen in the United States and comprises 2 discrete disease entities--classical Hodgkin lymphoma and nodular lymphocyte-predominant Hodgkin lymphoma. Within the subcategorization of classical Hodgkin lymphoma are defined subgroups: nodular sclerosis, mixed cellularity, lymphocyte depletion, and lymphocyte-rich Hodgkin lymphoma. Staging of this disease is essential for the choice of optimal therapy. Prognostic models to identify patients at high or low risk for recurrence have been developed, and these models, along with positron emission tomography, are used to provide optimal therapy. The initial treatment for patients with Hodgkin lymphoma is based on the histologic characteristics of the disease, the stage at presentation, and the presence or absence of prognostic factors associated with poor outcome. Patients with early-stage Hodgkin lymphoma commonly receive combined-modality therapies that include abbreviated courses of chemotherapy followed by involved-field

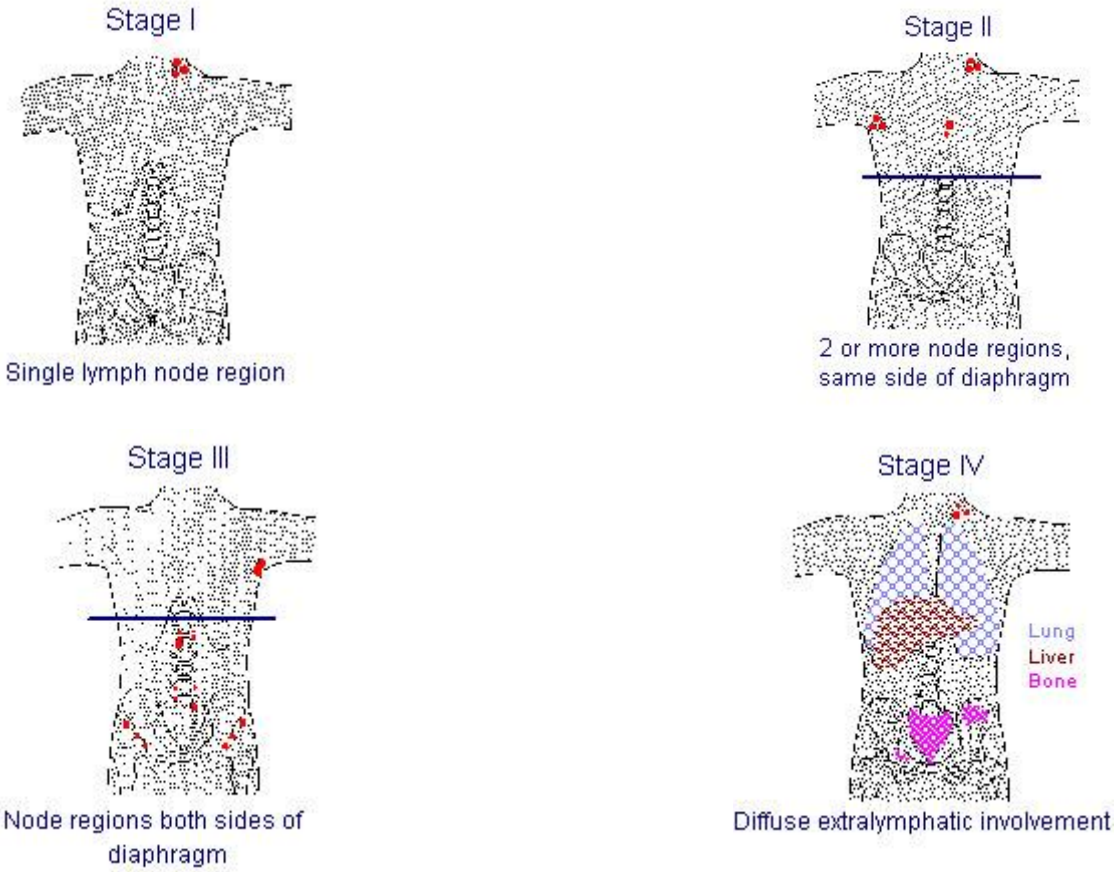
radiation treatment. In contrast, patients with advanced-stage Hodgkin lymphomacommonly receive a more prolonged course of combination chemotherapy, with radiation therapy used only in selected cases. For patients with relapse or refractory disease, salvage chemotherapy followed by high-dose treatment and an autologous stem cell transplant is the standard of care. For patients who are ineligible for this therapy or those in whom high-dose therapy and autologous stem cell transplant have failed, treatment with brentuximab vedotin is a standard approach. Additional options include palliative chemotherapy, immune checkpoint inhibitors, nonmyeloablative allogeneic stem cell transplant, or participation in a clinical trial testing novel agents."

Staging of Hodgkin's Lymphoma

The doctor considers the following to determine the stage of Hodgkin's lymphoma:

- The number of lymph nodes that have Hodgkin lymphoma cells
- Whether these lymph nodes are on one or both sides of the diaphragm (see picture)
- Whether the disease has spread to the bone marrow, spleen, liver, or lung.

Staging is important as it assists the doctor to determine treatment.



Treatment of Hodgkin's Lymphoma
Treatment of Hodgkin's Lymphoma may include:

Targeted Therapy - newer drugs that work differently from standard chemo drugs are currently being studied.

Monoclonal antibodies - antibodies are proteins normally made by the immune system to help fight infections. Each antibody attacks only a specific target (usually a protein on the surface of an unwanted cell).

Immunotherapy - also called biologic therapy, is designed to boost the body's natural defenses to fight the cancer.

Gene profiling - some researchers are looking at the specific genes and proteins that are found in Hodgkin's lymphoma. These genes and proteins provide more information about the behaviour of Hodgkin's lymphoma, which may help better target the lymphoma with chemotherapy or immunotherapy.

Other treatments that may be considered - stem cell transplantation is being studied in combination with chemotherapy and immunotherapy regimens for new or recurrent Hodgkin's lymphoma. Mini-allogeneic, also called non-myeloablative or reduced intensity transplant, and allogeneic transplantation are being tested in combination with chemotherapy and immunotherapy for new or recurrent Hodgkin lymphoma.

Palliative care - clinical trials are underway to find better ways of reducing symptoms and side effects of current Hodgkin's lymphoma treatments in order to improve patients' comfort and quality of life.

Chemotherapy - Cancer therapy selection, dosing, administration, and the management of related adverse events can be a complex process that should be handled by an experienced healthcare team.

Ansell, S.M. 2020.
Disease overview: Hodgkin lymphoma (HL) is an uncommon B-cell lymphoid malignancy affecting 8480 new patients annually and representing approximately 10% of all lymphomas in the United States.
Diagnosis: Hodgkin lymphoma is composed of two distinct disease entities: classical HL and nodular lymphocyte predominant HL. Nodular sclerosis, mixed cellularity, lymphocyte depletion, and lymphocyte-rich HL are subgroups of classical HL.
Risk stratification: An accurate assessment of the stage of disease in patients with HL is critical for the selection of the appropriate therapy. Prognostic models that identify patients at low or high risk for recurrence, as well as the response to therapy as determined by positron emission tomography (PET) scan, are used to optimize therapy.
Risk-adapted therapy: Initial therapy for HL patients is based on the histology of the disease, the anatomical stage and the presence of poor prognostic features. Patients with early stage disease are typically treated with combined modality strategies utilizing abbreviated courses of combination chemotherapy, followed by involved-field radiation therapy. Patients with advanced stage disease receive a longer course of chemotherapy, often without radiation therapy. However, newer agents

including brentuximab vedotin and anti-PD-1 antibodies are now being incorporated into frontline therapy.

Management of relapsed/refractory disease: High-dose chemotherapy (HDCT) followed by an autologous stem cell transplant (ASCT) is the standard of care for most patients who relapse following initial therapy. For patients who fail HDCT with ASCT, brentuximab vedotin, PD-1 blockade, non-myeloablative allogeneic transplant or participation in a clinical trial should be considered.

Treatment of Older Patients

Evens, A.M., Carter, J., Loh, K.P. & David, K.A. 2019.

"Hodgkin lymphoma (HL) in older patients, commonly defined as ≥60 years of age, is a disease for which survival rates have historically been significantly lower compared with younger patients. Older HL patients appear to have different disease biology compared with younger patients, including increased incidence of mixed cellularity histology, Epstein-Barr virus-related, and advanced-stage disease. For prognostication, several studies have documented the significance of comorbidities and functional status in older HL patients, as well as the importance of achieving initial complete remission. Collectively, selection of therapy for older HL patients should be based in part on functional status, including pretreatment assessment of activities of daily living (ADL), comorbidities, and other geriatric measures (eg, cognition, social support). Treatment of fit older HL patients should be given with curative intent, regardless of disease stage. However, attention should be paid to serious treatment-related toxicities, including risk of treatment-related mortality. Although inclusion of anthracycline therapy is important, bleomycin-containing regimens (eg, doxorubicin, bleomycin, vinblastine, dacarbazine) may lead to prohibitive pulmonary toxicity, and intensive therapies (eg, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) are too toxic. Brentuximab vedotin given sequentially before and after doxorubicin, vinblastine, and dacarbazine to fit, untreated advanced-stage older HL patients was recently shown to be tolerable and highly effective. Therapy for patients who are unfit or frail because of comorbidities and/or ADL loss is less clear and should be individualized with consideration of lower-intensity therapy, such as brentuximab vedotin with or without dacarbazine. Altogether, therapy for older HL patients should be tailored based upon a geriatric assessment, and novel targeted agents should continue to be integrated into treatment paradigms."

Complications of Hodgkin's Lymphoma

Treatments for Hodgkin's lymphoma may have complications. Long-term complications of chemotherapy or radiation therapy may include:

- Bone marrow diseases (such as leukaemia)
- Heart disease
- Inability to have children (infertility)
- Lung problems
- Other cancers
- Thyroid problems

Frick, M.A., Vachani, C.C., Hampshite, M.K., Bach, C., Arnold-Korzeniowski, K., Metz, J.M. & Hill-Kayzer, C.E. 2018.

PURPOSE: Multimodal treatment of Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) yields excellent outcomes; however, survivors are at risk of developing myriad late and long-term effects.

METHODS: From a convenience sample of 964 survivors of HL (37%) and NHL (63%) using a publicly available Internet-based survivorship care plan (SCP) tool between 2011 and 2016, we examined patient-reported cancer care, toxicities, and survivorship care data.

RESULTS: Of all survivors, 67% were female and 84% were white and 88% were free of cancer. Median age of diagnosis was 28 years for survivors of HL and 49 years for NHL. Many survivors reported treatment with chemotherapy (92%), surgery (52%), and/or radiation (41%), with most radiation delivered to chest/mantle fields (81%). Survivors reported a diversity of radiation- and chemotherapy-related sequelae, including thyroid dysfunction, speaking and/or swallowing changes, pulmonary fibrosis/pneumonitis, heart disease, chronic fatigue, neurocognitive decline, neuropathy, sexual changes, and secondary breast cancers. Few reported receipt of previous survivorship information. Most reported management/comanagement by an oncology specialist after active treatment; however, a shift to management by primary care provider alone was observed as a trend over time in follow-up. Sixty-six percent of users who responded to a follow-up survey reported that they intend to share the SCP with their health care team.

CONCLUSION: Survivors of lymphoma, many of whom are free of disease, report a substantial burden of late and long-term adverse effects, suboptimal delivery of survivorship information, and transitions of care in follow-up in which fragmented systems and/or poor communication may contribute to unmet survivor needs. Multiple opportunities thus exist for which SCPs may be used to improve awareness regarding survivorship and associated adverse effects in addition to communicating follow-up care plans between survivors and treatment teams.

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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Lymph Node
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