# Chapter 1

# Introduction

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## Introduction

Lymphomas are a heterogeneous group of malignancies of the lymphoid system. Lymphomas are some of the most diverse and most curable human malignancies. They are defined as a group of tumors that develop from lymphocytes and can be thought of as 'solid tumors' of the immune system. These cancers come from the cells of the immune system at different stages of development, which causes a diverse range of morphologic and clinical findings.

There are three types of lymphocytes, which include natural killer (NK) cells, which function in cell-mediated, cytotoxic innate immunity, T cells for cell-mediated cytotoxic adaptive immunity, and B cells, for humoral antibody-driven adaptive immunity. Other parts of the lymphatic system include the tonsils, thymus, and spleen, and lymphatic tissue is also found in the stomach, skin, and small intestine. Because lymphatic tissue is in many parts of the body, lymphoma can develop anywhere.

There are two large subdivisions of lymphoma: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). In 2014 approximately 80,000 new cases of lymphoma were diagnosed in the US (9000 cases of HL and 71,000 cases of NHL) and 20,000 patients are expected to die from lymphoma per year [1]. NHL is the seventh most common cancer in the US with the age-adjusted incidence rising by 89.5% from 1975 to 2010 [1]. Worldwide NHL is the eighth most common cancer in men and 11th in



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women, accounting for 5.1% of all cancers and 2.7% of all cancer deaths [2]. The highest incidence of NHL occurs in North America, Europe, Australia and several African countries [1]. It is most frequently diagnosed in older people, with an average age of 65–74 years [1]. However, specific, less common subtypes such as HL and Burkitt lymphoma are more frequently diagnosed in younger patients. NHL is broadly classified into B-cell lymphoma, T-cell lymphoma, and NK-cell lymphoma (Figure 1.1).

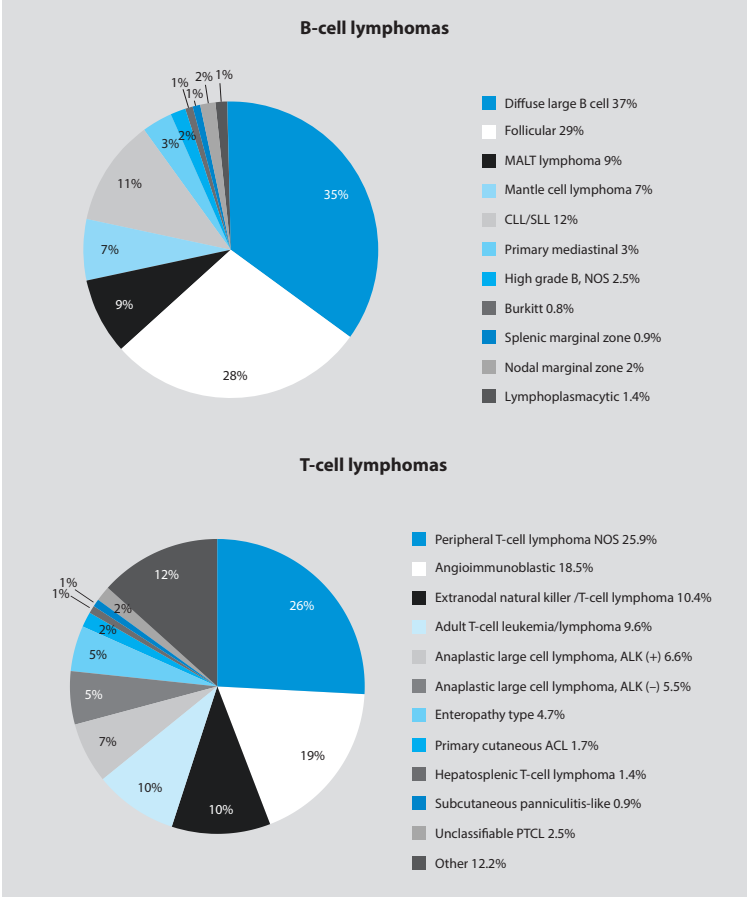


**Figure 1.1 Frequencies of B-cell and T-cell lymphomas by subtype.** (A) B-cell lymphoma subtype frequencies across eight countries representative of geographic regions from January 1, 1988 and December 31, 1990. Data from [3]. (B) T-cell lymphoma subtype frequencies by consensus diagnosis of International Peripheral T-Cell and Natural Killer/T-Cell Lymphoma Study. Data from [4].

About 90% of people will have a B-cell lymphoma and 10% will have a T-cell lymphoma (though this number is higher in Asia). Less than 1% of people will have a NK-cell lymphoma [1]. However, there is a large variation in the geographical distribution of subtypes, with higher proportions of follicular and diffuse large B-cell lymphoma in North America and Europe, and T-cell lymphomas in Asia [2].

The incidence of HL is lower than that of NHL. HL is an uncommon disorder with an annual incidence of 2–3 per 10,0000 in Europe and the US. It has a bimodal age distribution in early adulthood (20–30 years of age) and late adulthood (over 55 years of age). The nodular sclerosis subtype is more common in younger people, while mixed cellularity subtype is more common in older people. The 1-year relative survival rate of patients with HL is 92% [1]. The 5-year and 10-year relative survival rates are 85% and 80%, respectively [1].

Different lymphomas arise from cells of the immune system at different stages of differentiation. NHLs were separated from HLs in the early 20th century due to the recognition of Reed-Sternberg cells. The World Health Organization (WHO) classified lymphomas based on morphologic, clinical, immunologic, and genetic information, and attempted to divide NHLs and other lymphoid malignancies into entities with clinical and therapeutic relevance (for more detailed information see Chapter 3).

## Risk factors

The risk of NHL increases with age and most commonly occurs in people in their 60s and 70s, and typically more often in men than women. HL has a bimodal age distribution and typically has a male predominance as well. The cause of lymphomas is not clearly understood, but there have been some associations with the development of lymphoma. Both bacterial and viral infections have been associated with lymphoma (reviewed in Chapter 2). For example, mucosa-associated lymphoma tissue (MALT) of the stomach is frequently associated with Helicobacter pylori infection, and antibiotic therapy can lead to lymphoma regression. Hepatitis C infection has also been associated with an increased risk of marginal zone lymphomas. Epstein-Barr virus (EBV) is associated with Burkitt lymphoma, high-grade B-cell lymphoma, primary effusion lymphoma, NHL

in older people (60–90 years of age), and lymphoproliferative disorders post organ transplant. Patients with a history of EBV-related infectious mononucleosis are at a two- to three-fold higher risk for development of HL [5]. Human immune deficiency virus (HIV) infection is associated with several types of aggressive B-cell lymphoma. Another human herpes virus, HHV8, is also associated with the development of primary effusion lymphoma that tends to affect HIV-positive patients. Adult T-cell leukemia/lymphoma (ATLL) is associated with human T-cell lymphotropic virus (HTLV-1), which is a human retrovirus. ATLL is endemic in parts of Japan, the Caribbean, South America, and Central and West Africa, which parallels the highest incidences of HTLV-1.

Patients with autoimmune disorders also appear to have an increased risk of lymphoma, including rheumatoid arthritis, celiac disease, systemic lupus erythematosus, and Sjogren's syndrome. Some of the medications that treat these disorders may increase this risk as well, such as the tumor necrosis factor (TNF) inhibitors. There may also be a further risk for patients taking immunosuppressant medications that are used after organ transplantation.

## Diagnosis

The standard for diagnosis of lymphoma is a biopsy. Typically, an excisional biopsy with an intact lymph node is preferred and can be examined under the microscope by a pathologist. However, core needle biopsies may be helpful in situations where an excisional biopsy is unable to be performed. In addition to routine histology and immune phenotyping by immunohistochemistry, flow cytometry, polymerase chain reaction (PCR) for B- and T-cell clonality and T-cell receptors, cytogenetics for specific translocations and clonality, and fluorescence in situ hybridization (FISH) for specific translocations are performed on the tissue and have now become an essential part of lymphoma diagnosis, classification and prognostication.

90% of lymphomas are of B-cell origin and they express HLADR, CD10, CD19, CD20, CD21, CD22, CD5, CD38, and Tdt. They also express immunoglobulin heavy and light chain gene rearrangements, which distinguish B cells and lymphomas [6]. CD1, CD2, CD3, CD4, CD5, CD6, CD7,

CD8, CD38, CD71, and T-cell receptor gene rearrangements distinguish T cells [6]. Cytogenetic analysis is now a routine part of the diagnosis and management of a significant number of lymphoid malignancies. Many recurring cytogenetic abnormalities have been identified, and significant correlations with these abnormalities, morphology, immunophenotyping, and clinical outcomes have been recognized. Unfortunately, not all lymphoma subtypes have specific cytogenetic patterns and those that do, do not always express these patterns

Once there is a diagnosis of lymphoma further staging is done to assess the extent of disease. This typically includes imaging with computed tomography (CT) scans of the chest, abdomen and pelvis, or positron emission tomography (PET)/CT scan, and this may or may not include a bone marrow biopsy. The Ann Arbor Staging Classification (Table 1.1) is used to classify the extent of disease, and the International Prognostic Index has been used to prognosticate groups of patients with NHLs. The International Prognostic Score (IPS) is used to risk stratify advanced HL.

## Clinical presentation

HL typically presents with painless lymphadenopathy with or without splenomegaly, fevers, night sweats, weight loss, and pruritis. Pain in a lymph node can be associated with alcohol consumption. It can also be associated with HIV and EBV infections. There are two major subdivisions within HL: classical HL (95%) and lymphocyte predominant HL (5%).

| Grade | Description |
|---|---|
| I | Involvement of a single lymph node or a group of nodes in the same region. Single extranodal lesion without nodal involvement |
| II | Involvement of two or more lymph node regions on the same side of the diaphragm. Stage I or II by nodal extent with limited contiguous extranodal involvement |
| III | Involvement of lymph node regions or lymphoid structures on both sides of the diaphragm. Nodes above the diaphragm with spleen involvement. |
| IV | Involvement of more than one extranodal site at any location. |
| A | No symptoms |
| B | B symptoms: weight loss >10% body weight during prior 6 months, recurrent fevers >38°C during prior month, recurrent drenching night sweats in prior month |

**Table 1.1 The Ann Arbour lymphoma staging system.** Adapted from © American Society of Clinical Oncology, 2014. All rights reserved. Cheson et al [7].

Within classical HL there are four subtypes: nodular sclerosis (60%), mixed cellularity (20%), lymphocyte-rich (15%), and lymphocyte-depleted (5%) [6,8]. Classical HL has the classic Reed-Sternberg cells ('owl eyes') that express CD15 and CD30, but typically no B-cell markers. Lymphocyte-predominant HL typically has 'popcorn' or lymphocytic and histiocytic cells that express typical B-cell proteins such as CD20, CD79a, CD45, but do not express CD15 or CD30. This is typically a slow progressive disease associated with prolonged survival.

HL at any stage is curable in the majority of patients. The standard treatment for classical HL is a combination of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) and the number of cycles varies with stage. Involved field radiation is also used in early stage classical HL, typically following short-course chemotherapy. In the relapsed/refractory setting, a complete or partial response is not achieved in 10–20% of people and 10–30% of people relapse after an initial complete response [6]. Different combinations of chemotherapies may treat relapses successfully, but high-dose therapy with an autologous stem cell transplantation is the standard of care for relapsed chemosensitive disease. More recently, brentuximab vedotin, an anti-CD30 monoclonal antibody conjugated to a mitotic spindle inhibitor has been approved for relapsed/refractory disease.

NHL subtypes are divided into indolent (low grade-slow growing), aggressive (intermediate grade – fast growing), and highly aggressive types (high grade – very rapidly growing). Indolent lymphomas include: follicular (grade 1, 2, and 3a), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), marginal zone, and lymphoplasmacytic (Waldenströms) lymphoma. These lymphomas grow slowly and are not considered curable, but typically respond well to treatment and can go into remission and people live for several years. Many times, people can be asymptomatic and can defer treatment and be monitored expectantly. Indications for treatment include The Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria, which include B symptoms, cytopenias, large mass >7 cm, multiple lymph nodes >3cm in size, splenomegaly, or end organ damage. However, because indolent lymphomas cannot be cured they are characterized by treatment, remission, and then relapse. Mantle cell lymphoma is more of an intermediate lymphoma than can behave

like an indolent lymphoma, but more often behaves more aggressively and is not curable. Aggressive lymphomas include: diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma, lymphoblastic, and double hit large cell lymphomas and B-cell lymphoma unclassifiable with features intermediate between DLBCL and Burkitt/Gray zone. These lymphomas grow rapidly and require treatment. They differ in that they are curable with treatment. Most relapses occur within the first 2 years, but relapsed/refractory disease is more difficult to treat and cure.

## Prognostic factors

### Diffuse large B-cell lymphoma

The International Prognostic Index (IPI) is based upon a multivariate analysis of survival of 2031 patients with aggressive NHLs. Several histological subtypes were included, and patients were treated with various doxorubicin-containing chemotherapy combinations [9]. In addition to Ann Arbor stage, the characteristics that were found to be significant were age, elevated serum lactate dehydrogenase (LDH), performance status, and the number of extranodal sites of disease [9]. One point is assigned for each of these risk factors:

- age >60 years;
- stage III or IV disease;
- elevated serum LDH;
- Eastern Cooperative Oncology Group (ECOG) performance status of >1; and
- extranodal site >1.

The sum of the points correlates with the following risk groups:

- low risk (0–1 points): 5-year survival of 73%;
- low–intermediate risk (2 points): 5-year survival of 51%;
- high–intermediate risk (3 points): 5-year survival of 43%; and
- high risk (4–5 points): 5-year survival of 26%.

There have been additional IPI risk scores and adaptations. A simplified risk score is the age-adapted IPI that only includes three factors and is used for groups older or younger than 60 [9]:

- stage;
- LDH;

- performance status;
- low risk (0 points): 5-year survival of 83%;
- low–intermediate risk (1 point): 5-year survival of 69%;
- high–intermediate risk (2 points): 5-year survival of 46%; and
- high risk (3 points): 5-year survival of 32%.

## Follicular lymphoma and mantle cell lymphoma

There are also FLIPI and MIPI scores for follicular and mantle cell lymphoma respectively. The prognostic factors that were significant in follicular lymphoma were age, stage, number of lymph node areas involved, serum hemoglobin level, and serum LDH; for mantle cell lymphoma they were age, performance status, LDH, and white blood cell count. Although, oncologists continue to use the IPI scoring system for risk stratification, it should be noted that these risk models were developed prior to the advent of rituximab, which has significantly improved outcomes for patients with lymphoma. However, the addition of rituximab improves survival across risk groups and the IPI remains a valid tool.

## Hodgkin Lymphoma

The IPS score gives 1 point for each of the following factors [10]:

- albumin <4g/dL;
- hemoglobin <10.5 g/dL;
- male;
- age ≥45;
- stage IV disease;
- leukocytosis (white blood cell count at least 15,000 $mm^3$); and
- lymphocytopenia (lymphocyte count less than 8% of white blood cell count, and/or lymphocyte count less than 600$mm^3$).

Freedom from progression (FFP) at 5 years is directly related to the number of factors present in a patient. The 5-year FFP for patients with zero factors is 84%. Each additional factor lowers the 5-year FFP rate by 7%, such that the 5-year FFP for a patient with 5 or more factors is 42% [10]. Other reported unfavorable risk factors include: mixed-cellularity or lymphocyte-depleted type, male sex, large number of involved nodal sites, age over 40 years, the presence of B symptoms, advanced stage,

high erythrocyte sedimentation rate (ESR), bulky disease (widening of the mediastinum by more than one third, or the presence of a nodal mass measuring more than 10 cm in any dimension) [10].

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