# Lymphoma
## the good, the bad and the ugly

**There are more than 20 related but discrete syndromes covered by the term 'lymphoma', and they each have their own unique requirements for optimal clinical management.**

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Lymphoma is an increasing health problem in Australia. Its overall incidence, unlike those of most other malignancies, has risen progressively over the last few decades, for unknown reasons, and it now represents the sixth most common cancer in men and fifth most common in women in this country. Almost 4000 new cases of all types of lymphoma are diagnosed in Australia each year, predominantly in people over 50 years of age. Apart from lymphoma associated with HIV infection and other immunodeficiencies, the causes of this cancer are largely unknown. There are no screening tests for early diagnosis, and the large number of discrete biological subtypes complicates research into the pathogenesis.

Clinicians involved in the management of lymphoma face several challenges, including the complexity of pathological classification and subsequent therapeutic choices. Unlike most other cancers, the treatment of most lymphomas is based more on the precise pathological subtype than on the clinical and radiological stage (or extent) of the disease at the time of diagnosis. The pathological subtype of a lymphoma predicts strongly for both biological behaviour and treatment response. Accurate histological diagnosis is thus of paramount importance, and a close working relationship between the clinician and the pathologist is the key to excellence in management of the lymphomas.

## Classification

Clinical classification of lymphomas is broadly into Hodgkin's lymphoma and non-Hodgkin's

**IN SUMMARY**

- **Lymphomas can be broadly classified into Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL).**
- **NHL is almost 10 times more common than HL in Australia, and its incidence is increasing.**
- **NHL consists of about 20 different syndromes on biological, pathological and clinical criteria.**
- **Most NHL cases are derived from malignant transformation of B-lymphocytes in lymph nodes. Follicular and diffuse large cell lymphomas are the most frequent forms, each comprising around 30% of total cases of NHL.**
- **Treatment for NHL is largely dictated by histology and anticipated clinical course rather than disease stage, with predominantly palliative intent for indolent NHL and curative intent for aggressive disease.**
- **Management of lymphomas should ideally be carried out by a multidisciplinary team of experienced diagnostic and clinical experts.**

## Table 1. Classifications of lymphomas

### Based on presenting features

Indolent lymphomas
Aggressive lymphomas
Highly aggressive lymphomas

### Based on the WHO Lymphoma Classification*[1,2]

**Non-Hodgkin's lymphoma:**
**B-cell lymphomas**
Small lymphocytic
Lymphoplasmacytic
Splenic marginal zone
Nodal marginal zone
Extranodal marginal zone, of mucosa-associated lymphoid tissue (MALT lymphoma)
Follicular†
Mantle cell
Diffuse large cell†
Mediastinal large cell
Intravascular large cell
Primary effusion
Burkitt's
Post-transplant lymphoproliferative

**Non-Hodgkin's lymphoma:**
**T-cell lymphomas**
T-lymphoblastic
Extranodal NK/T lymphoma, nasal
Enteropathy-type T-cell
Subcutaneous panniculitis-like T-cell
Mycosis fungoides
Sézary syndrome
Primary cutaneous anaplastic large cell
Angioimmunoblastic
Peripheral T-cell

**Hodgkin's lymphoma**
Classical Hodgkin's lymphoma
Nodular lymphocyte predominant Hodgkin's lymphoma

* The 2001 WHO Lymphoma Classification is based on the 1994 Revised European–American Lymphoma (REAL) classification.[1,2]
† Follicular and diffuse large cell lymphomas are the most frequent forms of B-cell lymphoma, each comprising around 30% of total cases of non-Hodgkin's lymphoma.

lymphoma, and within the latter category there are more than 20 different types of tumours arising from B- and T-lymphocytes (Table 1).[1,2] In Australia, non-Hodgkin's lymphoma is almost 10 times more common than Hodgkin's lymphoma.

The clinical behaviour of non-Hodgkin's lymphoma is diverse, ranging from highly malignant and rapidly growing tumours in people of all ages to relatively benign and even nonprogressive lymph node enlargement in elderly people.

## Lymph node biopsy

Lymphomas usually arise in lymph nodes, but not all lymphadenopathy is due to lymphoma. Careful clinical assessment is required to establish the likely need for performing a biopsy on an enlarged lymph node, bearing in mind that in general practice only a small minority of enlarged nodes are due to malignancy. Factors predicting for malignancy are:[3]

- patient age over 40 years
- involvement of supraclavicular lymph nodes
- affected lymph node:
  - diameter over 2.5 cm
  - firm to hard texture
  - lack of tenderness.

Patients with enlarged lymph nodes but aged less than 40 years and without any of the above lymph node features and no specific symptoms or signs are very unlikely to have a sinister cause of lymph node enlargement, and can be safely observed. In any event, before proceeding to a biopsy, a careful history and physical examination, particularly for symptoms and signs suggestive of recent viral infection, is essential. A full blood count is mandatory, and viral serology may be indicated, particularly in younger patients.

### Biopsy technique

The two techniques available for biopsy of enlarged lymph nodes, fine needle aspiration and excision biopsy, both have roles to play in the management of lymphoma. Fine needle aspiration has a place in the early diagnostic process for some patients, in establishing a likely diagnosis of lymphoma as opposed to some other form of cancer or a nonmalignant cause. However, diagnosis using this technique is often inadequate to distinguish between lymphoma subtypes.

The overwhelming consensus of opinion now is that excision biopsy is the gold standard for making a precise diagnosis of lymphoma, and should be carried out in all newly diagnosed patients unless there are extenuating circumstances.

## Clinical features of lymphomas

The spectrum of presentation of lymphoma is diverse. Lymphomas have been reported to arise from virtually every site in the body, including the central nervous system, gonads, skin, breast and bone. Primary intravascular and effusion lymphomas have also been described.

Nevertheless, most lymphomas arise within lymphatic glands, and lymphadenopathy is the most common presentation. The lymphadenopathy may be slow and insidious in onset and occur in an otherwise asymptomatic person or, conversely, may develop rapidly and be associated with local or constitutional symptoms, such as fevers, sweats, weight loss or pruritus. Compression of vital internal structures (for example, ureters, trachea or major blood vessels) may occur with rapidly progressive lymphomas, occasionally resulting in acute medical emergencies.

### The good, the bad and the ugly

The clinical separation of lymphomas into two main types on the basis of presenting features – indolent (the good) versus aggressive (the bad) behaviour – is useful, and often predictive of histological type. A small minority of cases show highly aggressive behaviour (the ugly), more like that which is seen with acute leukaemia. However, pathological

diagnosis based on tissue biopsy is required for all patients suspected of having lymphoma.

## Pathological subtypes

The histological features of lymphomas tend to relate to their presenting clinical features. Patients with indolent lymphomas predominantly have follicular histology (Figure 1), although a few will have a histological pattern of diffuse replacement by small mature lymphocytes. In contrast, patients with aggressive lymphomas usually have diffuse large cell lymphoma, with diffuse replacement of lymph nodes by large lymphoma cells (Figure 2). In both follicular and diffuse large cell lymphomas, the abnormal cells are usually B-cell in origin. As these subtypes each comprise around 30% of the total cases of non-Hodgkin's lymphoma, most lymphomas are due to malignant transformation of B-cells in lymphoid tissues.

Hodgkin's lymphoma is a biologically and histologically distinct disease. Unlike the non-Hodgkin's lymphomas, the tumour cells in Hodgkin's lymphoma (which are known as Reed– Sternberg cells) are present in the abnormal lymph nodes in only small numbers, against a background of reactive cells.

### Indolent lymphomas

Indolent lymphomas are mainly seen in men over the age of 50 years, with the usual presenting feature being lymphadenopathy, most commonly in the neck. Most patients are otherwise asymptomatic, but a few report 'B' symptoms (that is, weight loss, sweats and fevers) and other generalised symptoms. The enlarged lymph nodes are usually firm, mobile and not tender, and may fluctuate in size; spontaneous regression has been well documented. Rapid growth of nodes is unusual. Staging x-rays and CT scans often show more extensive disease than is clinically apparent, with involvement of intra-abdominal lymph nodes (mesenteric and para-aortic) commonly seen. Bone marrow biopsies often show evidence of lymphoma.

Follicular lymphoma, the most common of the indolent lymphomas, is always derived from malignantly transformed B-lymphocytes in the germinal centres of lymph nodes. Chromosomal and molecular studies have demonstrated that there is a translocation involving the immunoglobulin heavy chain gene on chromosome 14 and the *bcl-2* oncogene on chromosome 18. The resulting abnormal fusion gene, through overexpression of the bcl-2 pro-survival protein, markedly enhances the survival of the malignant B-lymphocytes, effectively preventing apoptosis and allowing growth of the tumour.[4]

### Aggressive lymphomas

Aggressive lymphomas, as the term suggests, grow more rapidly than indolent lymphomas, and patients more frequently present with local or constitutional symptoms. These lymphomas may present at any age, but occur more frequently in the elderly. Staging investigations show that only a small minority of cases are truly localised, with spread of disease to adjacent or distant sites being evident in 90% of cases.

Chromosomal and molecular studies have shown a much more complex pattern of pathogenesis than in the follicular lymphomas. However, more than half of cases of diffuse large cell lymphoma, like follicular lymphoma, overexpress the *bcl-2* pro-survival protein, although not as a result of the 14;18 chromosome translocation.

### Hodgkin's lymphoma

The mode of presentation of Hodgkin's lymphoma is variable. Patients are generally younger than those with non-Hodgkin's lymphoma but the disease

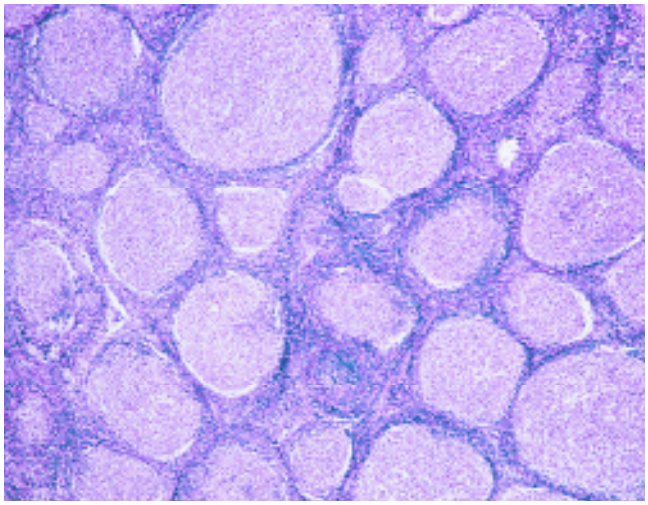

Figure 1. Follicular lymphoma.

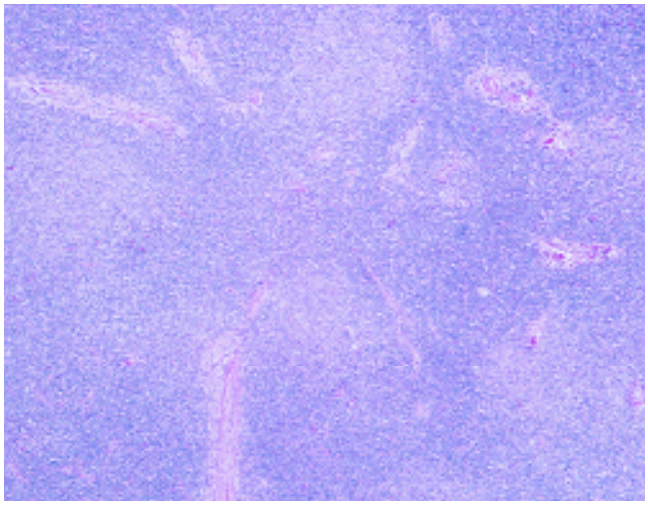

Figure 2. Diffuse pattern lymphoma.

**Table 2. Non-Hodgkin's lymphomas: CVP and CHOP chemotherapy protocols**

| Protocol acronym | Drugs used | Route | Days |
|---|---|---|---|
| CVP | • Cyclophosphamide (Cycloblastin; Endoxan) | Intravenous | 1 |
| | • Vincristine (Vincristine Sulfate Injection) | Intravenous | 1 |
| | • Prednisone or predsolone (Panafcort, Panafcortelone; Predsone, Predsolone; Sone; Solone) | Oral | 1 to 5 |
| CHOP | • Cyclophosphamide | Intravenous | 1 |
| | • Doxorubicin (Adriamycin; Doxorubicin Hydrochloride Injection; Doxorubicin Ebewe) – H from alternative name, hydroxydaunorubicin | Intravenous | 1 |
| | • Vincristine – O from Oncovin (no longer available) | Intravenous | 1 |
| | • Prednisone or prednisolone | Oral | 1 to 5 |

can occur at any age. Some patients present with clinically localised lymphadenopathy, most often in the neck or mediastinum, without other symptoms, while others have more extensive disease that is often associated with systemic symptoms such as weight loss, sweats and fever.

### Rare lymphomas

A small minority, around 5%, of non-Hodgkin's lymphomas have highly malignant clinical features, with very rapid growth and dissemination. Acute medical presentations, with sudden development of large blood vessel or airway obstruction, pleural or pericardial effusions, or acute renal failure due to ureteric obstruction or urate nephropathy, are often seen. Rapid leukaemic spread and involvement of the central nervous system are also common features.

One of these highly aggressive lymphomas, the T-lymphoblastic type, arises from the thymus gland in the anterior mediastinum, usually in adolescent males. Another, Burkitt lymphoma, is a tumour of B-lymphocyte precursors resulting from chromosome translocations (*c-myc* oncogene on chromosome 8 and immunoglobulin genes on other chromosomes) that lead to rapid and unregulated tumour growth.

## Treatment

Some lymphomas need no treatment, and patients with these may have extended periods of nonprogressive disease. Others require treatment, and will respond, at least initially, to a variety of chemotherapeutic drugs as well as to radiation therapy. The major difficulty in the treatment of lymphoma is deciding the most appropriate management plan for each patient, given the wide spectrum of clinical behaviour, the curability of some lymphomas with optimal treatment and the range of treatments now available.

Current practice is to plan the management of each case of lymphoma within a multidisciplinary team comprised of pathologists, radiologists, radiation therapists, physicians trained in medical oncology or clinical haematology, and palliative care physicians. A comprehensive management plan, including access to clinical trials, can be formulated and implemented by this approach, enabling optimal treatment and co-ordinated care for each patient.

### Follicular lymphoma

The treatment of follicular lymphoma has never been standardised, and is subject to individual physician preference and, more importantly, the individual

**Table 3. Hodgkin's lymphoma: ABVD chemotherapy protocol**

| Protocol acronym | Drugs used | Route | Days |
|---|---|---|---|
| ABVD | • Doxorubicin – A from Adriamycin | Intravenous | 1, 15 |
| | • Bleomycin (Blenamax; Blenoxane; Bleomycin Sulfate for Injection) | Intravenous | 1, 15 |
| | • Vinblastine (Velbe; Vinblastine Injection) | Intravenous | 1, 15 |
| | • Dacarbazine (Dacarbazine for Injection; D.T.I.C.) | Intravenous | 1, 15 |

characteristics of each patient and his or her disease. The choice of initial treatment is influenced by the age and general health of the patient, disease 'bulk' (large tumour masses or small lymph nodes) and extent (localised or widespread), the speed of disease progression and the presence of symptoms due to lymphoma. For example, elderly asymptomatic patients with slowly progressive localised non-bulky disease may need no treatment initially and may be managed by observation alone, while progressive localised disease may be treated with local radiotherapy alone, and younger patients with progressive symptomatic disease will require chemotherapy.[5,6]

First line chemotherapy is usually either an oral alkylating agent such as chlorambucil (Leukeran) or combination chemotherapy such as CVP or CHOP (Table 2). In recent years, the treatment of follicular lymphoma has been revolutionised by the availability of rituximab (Mabthera), a chimeric monoclonal antibody against the CD20 protein expressed on human B-cells, including follicular lymphoma. When rituximab is given as a weekly intravenous infusion for four weeks to follicular lymphoma patients who have progressed after prior chemotherapy, more than half show regression of their disease.[7]

## Aggressive lymphomas

Virtually all patients with aggressive lymphomas have progressive and disseminated disease, and require combination chemotherapy. The 'gold standard' is CHOP (Table 2) given in courses every 14 to 21 days for a total of six to eight courses.[8] Recent data from randomised clinical trials support the addition of rituximab to CHOP, with improved response rates without additional toxicity.[9]

## Highly aggressive lymphomas

Lymphoblastic and Burkitt's lymphomas require very prompt and highly specialised care, using protocols based on those developed for the treatment of childhood acute lymphoblastic leukaemia, including prophylactic treatment to the central nervous system.

## Hodgkin's lymphoma

The management of Hodgkin's lymphoma is dictated by accurate staging of the disease. Truly localised disease can be cured by radiation therapy, but modern thinking has moved to using combined modality treatment, with radiation therapy given in reduced doses and more limited fields, and abbreviated courses of combination chemotherapy with the ABVD protocol (Table 3).[10]

More extensive disease requires more intensive chemotherapy. The role of using

eight cycles of chemotherapy with ABVD is well established in this setting, but more recent trials using more complex and toxic protocols suggest improved results with increased treatment intensity.[11,12]

### Treatment of relapsed disease

#### Relapsed follicular lymphoma

Relapse is inevitable in follicular lymphoma, even when intensive combination chemotherapy is used for initial treatment. However, responses to subsequent therapy, including the same modality used previously, are usually seen, and multiple re-treatments are often possible. Several agents have value in the treatment of relapsed follicular lymphoma, including rituximab and the purine analogue fludarabine (Fludara), and these seem most useful in combination with other chemotherapy agents.

In younger patients, high dose chemotherapy with haemopoietic stem cell rescue using the patient's stored cells (autologous stem cell transplantation) produces prolonged complete responses in more than half of cases after first relapse. Transplantation of stem cells from a matched family donor, after reduced intensity conditioning treatment, also has a high response rate in younger patients with relapsed disease, but remains an experimental procedure in specialised transplant centres.

#### Relapsed aggressive lymphomas and Hodgkin's lymphoma

The treatment of relapsed aggressive lymphomas and Hodgkin's lymphoma is a greater therapeutic challenge. Without transplantation, the outlook is usually grim, with less than 10% of patients surviving in the long term.

Re-treatment with intensive salvage protocols is required to obtain a second response prior to stem cell transplantation, and patients whose lymphoma is refractory to chemotherapy are usually considered ineligible for transplantation. Patients who show a response to salvage treatment are usually offered autologous stem cell transplantation, a procedure feasible up to the age of 70 years. There is a high response rate to this procedure, with approximately 40% of patients with relapsed chemotherapy-sensitive aggressive lymphoma remaining free of lymphoma after an autograft.[13]

## Prognosis

The overall prognosis in lymphoma depends mainly on the type of disease and the response to initial treatment.

### Follicular lymphoma

In follicular lymphoma, the average

survival from diagnosis is seven years, and this has neither changed over the past two decades nor been altered by the different forms of treatment. Interestingly, however, around 20% of patients survive more than 10 years even without therapy, emphasising the highly heterogeneous behaviour of the disease.

### Aggressive lymphomas

Prognosis in aggressive lymphomas is heavily influenced by factors relating to both the patient (age and general health) and the disease (tumour stage and bulk), but the most important determinant is response to chemotherapy. About 60% of cases of diffuse large cell lymphoma have a complete response to CHOP. Those failing have a very poor outlook. About one-third of complete responders relapse, often within 12 months of treatment; some of these may be rescued by stem cell transplants.

### Hodgkin's lymphoma

The prognosis in Hodgkin's lymphoma is dependent on disease stage. Patients with localised disease have an excellent outcome, with more than 90% having prolonged disease-free survival. The outlook for patients with more advanced disease treated with chemotherapy is predictably worse, but more than half have prolonged complete responses.

## Conclusions

Management of the lymphomas presents an increasing challenge to the medical profession. The incidence of these diseases continues to rise, with no satisfactory explanations for the causes. The generic term 'lymphoma' disguises a situation where in reality there are more than 20 related but biologically discrete diseases, each with its own separate molecular pathogenetic features, differing response to treatment and, therefore, unique requirements for optimal clinical management. The most likely way to avoid confusion and to offer the best treatment for each lymphoma patient is through specialisation and teamwork, using the combined expertise of diagnostic and clinical experts in multidisciplinary teams. Access to clinical trials, a critical issue in such a rapidly evolving area of medicine, is also enhanced by this approach. MT

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**DECLARATION OF INTEREST: Professor Bradstock is a member of the international and national Advisory Boards of Hoffman-La Roche.**