INTRODUCTION
The Clinical practice guidelines for the diagnosis and management of lymphoma (www.cancer.org.au/clinical_guidelines) was produced under the auspices of the Australian Cancer Network by specialist working parties managing malignant lymphoma in Australia and was approved by the National Health and Medical Research Council. Lymphoma is a heterogeneous disease comprising a diverse range of subtypes and anatomical sites. This guide provides a summary of the main recommendations from the clinical practice guidelines relating to the identification, classification and management of this complex group of diseases. The guide is intended to:

- update general practitioners on the diagnosis and management of lymphoma and
- assist them guide patients with lymphoma through the evolving and complex forms of investigation and treatment they may have with their specialist team.

LYMPHOMA IN AUSTRALIA
Lymphomas encompass a group of lymphoproliferative malignant diseases that originate from T and B cells in the lymphatic system. Approximately 70-80% of lymphomas arise from the lymph nodes; the remainder are extranodal.

There are two main classifications of lymphoma, Hodgkin lymphoma (HL) and Non-Hodgkin lymphoma (NHL: B-cell, T-cell and NK-cell neoplasms).

HL is distinguished by the histopathological presence of Hodgkin or Reed Sternberg cells and is comprised of four subtypes: nodular sclerosis, lymphocyte predominance, mixed cellularity, and lymphocyte depletion. HL is uncommon. HL accounts for approximately 10% of all lymphomas.

While over 30 specific subtypes of NHL exist, B-cell lymphomas represent greater than 85% of all NHL. T-cell lymphomas account for less than 15% of all NHL.

In 2001, NHL was the sixth most common cancer in men, the fifth most common cancer in women, and the third most common cancer in children under 14 years of age. NHL is the sixth most common cause of cancer death. Incidence and mortality rates increase with age, peaking in the seventh decade, and the lifetime risk of NHL is 1 in 64 for men and 1 in 88 for women. Over the last several decades the incidence of NHL has been increasing in Australia in both men and women, however, the reasons for this increase are unknown.

The incidence of HL peaks between the ages of 15 and 34 years and again after the seventh decade of life. The lifetime risk of HL is 1 in 559 for men and 1 in 766 for women and the incidence has remained stable over time.

RISK FACTORS
In most cases the causes of lymphoma are unknown. Epstein Barr virus (EBV) infection in conjunction with immune deficiency is associated with an increased risk of lymphoma. Infectious mononucleosis is a moderate risk factor for HL increasing risk by two to three fold. Other infectious organisms, occupation exposure, medical procedures and medical history, and lifestyle factors only represent moderate or weak risk factors in the development of lymphoma.

In families with a history of lymphoma, HL or leukaemia among first-degree relatives there is an increased risk of lymphoma (relative risk 3-4).

PREVENTION
There is little practical role for preventive measures in the prevention of lymphoma. However, either limiting exposure to, or avoiding risk factors may lessen the risk of lymphoma, though the degree of risk reduction is yet to be quantified.

SCREENING
There are no specific screening tests for lymphoma. However, surveillance is recommended for individuals at risk of immunodeficiency-associated lymphoma.

<table>
<thead>
<tr>
<th>Incidence*</th>
<th>Mortality*</th>
<th>5-year relative survival (%)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHL</td>
<td>3499</td>
<td>1502</td>
</tr>
<tr>
<td>HL</td>
<td>401</td>
<td>48</td>
</tr>
</tbody>
</table>

COMMON PRESENTATIONS
Patients may present with a range of clinical features. The accurate workup of patients with lymphoma requires integrating a series of various investigations and the approach will vary depending on the presentation.

PERIPHERAL LYMPHADENOPATHY
(<1% of these patients will have malignant disease)
• > 50 years of age the chance of malignant disease as a cause of lymphadenopathy increases
• Nodes > 2cm in diameter serves as a discriminate predicting malignant or granulomatous disease.
• Tender lymph nodes are usually benign

Investigations
• Full medical history it would be useful to ask some key questions e.g. history of EBV etc
• Physical examination, especially lymph nodes and spleen)
• FBE and Chest X-Ray (where appropriate)
• Indications for lymph node biopsy are:
  □ Age >40 years
  □ Supraclavicular location
  □ Node diameter >2.25cm
  □ Firm hard texture
  □ Lack of tenderness
  □ Present more than a few weeks

Refer to specialist for
• FNA for triage with cytology and flow cytometry
Subsequent excisional biopsy essential for primary diagnosis, with prior FBE and chest x-ray.

INTRACAVITY (CHEST OR ABDOMINAL)
PRESENTATION – SPECIFIC ORGAN INVOLVEMENT EG MEDIATINAL ENLARGEMENT ON CXR, PROTACTED COUGH
Differential diagnosis may include metastatic carcinoma, sarcoidosis, thymoma, infection e.g. tuberculosis.

Refer to specialist for
• Mediastinal mass
• Mediastinoscopy, thoroscopy, laparoscopy or laparotomy for biopsy
  Abdominal and retroperitoneal
• CT or US guided core biopsy

CONSTITUTIONAL ILLNESS – WEIGHT LOSS AND FEVER
Investigations
• Full medical history - specific key questions should include, fever, night sweats, objective confirmation of weight loss
• Physical examination
• FBE
• Serum LDH
• ESR
• Chest x-ray

Refer to specialist for
• CT examination of the abdomen and bone marrow biopsy – where appropriate

PET scans in specialist centres are becoming increasingly used in staging and evaluation of response to disease.

REFERRAL
Refer all patients with suspected Lymphoma to a Clinical Haematologist or Medical Oncologist, working in association with a multidisciplinary team, with appropriate expertise in the management of lymphoma. In rural areas, refer as appropriate to a general physician or surgeon.

DIAGNOSIS OF LYMPHOMA
An adequate pathologic diagnosis of lymphoma requires careful assessment of nodal architecture in addition to assessment of cytologic abnormality. As an accurate diagnosis is vital of management decisions, biopsy is the most important step in diagnosis. After pathological diagnosis of lymphoma the patient requires staging, prognostic assessment, and a treatment plan developed in conjunction with the patient, with the aim of treatment defined in terms of potentially curative treatment or a palliative management plan.

STAGING
The Ann Arbor staging system is used to characterise disease in patients with HL but is also applied to other lymphomas.

| Stage I | Involvement of a single lymph node region (I) or involvement of a single extralymphatic organ or site (IE) |
| Stage II | Involvement of two or more lymph node regions on the same side of diaphragm alone (II) or with involvement of contiguous extralymphatic organ or tissue (IIE) |
| Stage III | Involvement of lymph node regions on both sides of the diaphragm (III), which may include the spleen (IIIS) and/or limited contiguous extralymphatic organ or site (IIIE, IIIES) |
| Stage IV | Multiple or disseminated foci of involvement of one or more extralymphatic organs or tissues with or without lymphatic involvement |
PROGNOSIS
Prognosis and treatment are determined by:
- Pathologic sub-classification
- Stage and disease bulk
- Age
- Patient performance status (see below)
- Molecular and biological markers

Prognosis with reference to 5- and 10-year survival is presented below for the most common forms of lymphoma.

PERFORMANCE STATUS

<table>
<thead>
<tr>
<th>Grade</th>
<th>ECOG performance status</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physical strenuous activity but ambulatory and able to carry out work of a light or sedentary nature</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all selfcare but unable to carry out any work activities</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited selfcare, confined to bed or chair more that 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Can not carry on any self care. Totally confined to bed or chair</td>
</tr>
</tbody>
</table>

MULTIDISCIPLINARY CARE
Patients should be managed in a multidisciplinary team involving the haemat-oncologist, radiotherapist, surgeons and other members of the medical team as required. Multidisciplinary teams need to be familiar with management protocols and guidelines, they must be equipped to manage complications of both the disease and its treatments, and provide long-term follow-up as well as supportive and psychosocial care.

HODGKIN LYMPHOMA

Treatment

<table>
<thead>
<tr>
<th>Stage</th>
<th>Optimal Rx</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td>3-6 cycles combination chemotherapy (+haemopoietic growth factors if indicated) Involved field radiotherapy should be delivered to all sites that were involved by HL at diagnosis</td>
<td>80% 10-year overall survival 84% 10-year relapse-free rate</td>
</tr>
<tr>
<td>Advanced</td>
<td>6-8 cycles combination chemotherapy Radiotherapy for bulky or non-responding sites</td>
<td>&gt;50% long term survival</td>
</tr>
</tbody>
</table>

FOLLOW-UP
Follow-up of patients treated for HL should be indefinite.
- Year 1–2, 3 monthly
- Year 3, 4 monthly
- Year 4–5, 6 monthly
- Annually thereafter

The type of imaging investigations and frequency may depend on the site of original disease.

Patients should be informed of the increased risk of secondary malignancies (e.g. leukaemia, myelodysplastic syndrome, lung cancer, breast cancer, thyroid cancer) and encouraged to seek early medical attention.

Late effects of treatment can include:
- malignancies
- cardiac disease
- endocrine dysfunction eg hypothyroidism and sterility
- psychological trauma eg cancer survivor, anxiety, depression, reduced quality of life
- lung damage secondary to irradiation
- dental caries
- hyposplenism

SPECIFIC INVESTIGATIONS AND CLINICAL ASSESSMENTS INCLUDE:

**Thyroid function test**
Hypothyroidism can occur 1-20 years post-treatment
- Performed yearly for patients having radiotherapy to the neck

**Clinical examination of the thyroid**
Excess risk of thyroid cancer
- Annual exam is advised
- Any abnormality should be fully investigated

**Full blood count**
Risk of leukaemia and myelodysplastic syndrome is maximal between 3–12 years post-treatment
- Performed yearly

**Mammography**
Increased risk of breast cancer after radiotherapy is apparent 10 years post-treatment and risk persists >25 years after diagnosis
- Yearly mammographic screening in conjunction with breast self exam should commence 10 years following treatment. MRI will become available in this group of patients*
- The use of mammography in women <30 years is controversial
- Any breast mass should be investigated, this may include ultrasound and biopsy

Smoking significantly increases risk of lung cancer in patients treated previously with chemotherapy and radiotherapy.
All patients should be encouraged to stop smoking.
The role of routine chest X-ray is unclear.

*New information
**RELAPSED HODGKIN LYMPHOMA**

The rate of relapse after primary treatment is related to:
- initial management strategy,
- original extent of disease and
- the influence of other prognostic factors.

The choice of salvage therapy is dependent upon the initial treatment strategy, extent of relapsed disease and time that has elapsed from completion of primary treatment. Salvage therapies may include chemotherapy and radiotherapy and in some cases bone marrow transplant with high dose chemotherapy.

**NON-HODGKIN LYMPHOMA**

**Clinical groupings**

Lymphomas fall into three clinical groupings

- Low grade
- Aggressive (intermediate) grade
- High grade

Follicular lymphoma (FL) (low grade) and diffuse large B cell lymphoma (DLBCL) (aggressive) account for more than 50% of all non-Hodgkin lymphoma.

**FOLLICULAR LYMPHOMA (LOW GRADE)**

Follicular lymphomas account for about 20% of all non-Hodgkin lymphomas. Prognostic factors which constitute the Follicular Lymphoma International Prognostic Index (FLIPI) and are independently associated with long-term outcome of patients with follicular lymphoma are:

- Age ≥60 years
- Haemoglobin ≤12g/dl
- Ann Arbor stage III or IV disease
- ≥5 lymph nodes or other sites of disease involvement

Using these four factors the estimated survival rates for follicular lymphoma are:

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>5-year survival</th>
<th>10-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1 risk factors (36% of patients)</td>
<td>91%</td>
<td>71%</td>
</tr>
<tr>
<td>2 risk factors (37% of patients)</td>
<td>78%</td>
<td>51%</td>
</tr>
<tr>
<td>≥3 risk factors (27% of patients)</td>
<td>53%</td>
<td>27%</td>
</tr>
</tbody>
</table>

**DIFFUSE LARGE B CELL LYMPHOMA (AGGRESSIVE)**

Aggressive lymphomas account for about 50% of all lymphomas. The most common type of aggressive lymphoma is the diffuse large B cell lymphoma, comprising 30-40% of all adult lymphomas, and approximately 35% of all non-Hodgkin lymphomas. Pre-treatment prognostic factors are critical in determining treatment and predicting outcome. The International Prognostic Index (IPI) is based on five pre-treatment characteristics, which have been found to be independent predictors of survival outcomes in patients with aggressive lymphomas. These are:

- Age (≤60 versus >60 years)
- Stage I or II versus III or IV
- Number of extranodal sites involved (≤1 versus >1)
- Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 versus ≥2)
- Serum LDH (normal versus greater than normal)

The cure rate and 5-year survival rate are provided in the IPI below.

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Cure rate</th>
<th>5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1 risk factors (35% of patients)</td>
<td>87%</td>
<td>73%</td>
</tr>
<tr>
<td>2 risk factors (27% of patients)</td>
<td>66%</td>
<td>51%</td>
</tr>
<tr>
<td>3 risk factors (22% of patients)</td>
<td>53%</td>
<td>27%</td>
</tr>
<tr>
<td>4–5 risk factors (16% of patients)</td>
<td>34%</td>
<td>26%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage</th>
<th>Optimal Rx</th>
<th>Outcome 10-year overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I or II</td>
<td>Involved field radiotherapy + combination chemotherapy + monoclonal antibody therapy (Rituximab)</td>
<td>50-80%</td>
</tr>
<tr>
<td>III</td>
<td>Wide field radiotherapy or manage as for stage IV</td>
<td>50%</td>
</tr>
<tr>
<td>IV</td>
<td>Watch and wait -monitor for progression Combination chemotherapy Monoclonal antibody therapy (Rituximab)</td>
<td>27-71%</td>
</tr>
</tbody>
</table>

Relapsed disease

Re-biopsy of dominant or clinically suspicious disease site Rx with antimetabolites

In patients with relapsed follicular lymphoma, the addition of rituximab to fludarabine-based combination chemotherapy is associated with improved outcomes, including better overall survival.
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Optimal Rx</th>
<th>Outcome 5-year overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Non-bulky I &amp; II Normal LDH ECOG 0 or 1</td>
<td>3 cycles combination chemotherapy + monoclonal antibody therapy (Rituximab) + involved field radiotherapy</td>
<td>&gt;80%</td>
</tr>
<tr>
<td>Late Bulky I or II High LDH ECOG ≥2 And/or ≥3 disease sites</td>
<td>6-8 cycles combination chemotherapy + monoclonal antibody therapy (Rituximab) + involved field radiotherapy</td>
<td>75-80%</td>
</tr>
<tr>
<td>Advanced III or IV</td>
<td>6-8 cycles combination chemotherapy + monoclonal antibody therapy (Rituximab)</td>
<td>45%</td>
</tr>
</tbody>
</table>

**OTHER LYMPHOMAS**

The other less common forms of lymphoma include: mantle cell lymphoma, Burkitt lymphoma, gastric lymphoma, primary cutaneous lymphoma and primary cerebral lymphoma. These lymphomas all require treatment in specialist centres.

**NON-HODGKIN LYMPHOMA FOLLOW-UP**

Patients should be informed about the risks of secondary malignancy at the time of treatment as well as at completion of therapy.

Lifelong surveillance of secondary cancers is appropriate.

A management plan should be organised for surveillance relevant to each individual patient, with the patient, their family, the GP, and the specialist.

**Follow-up should encompass appropriate detection of:**

- Current or relapsed disease
- Long term side effects of therapy

**Specific investigations and clinical assessments include appropriate screening for:**

- Breast and bowel cancer
- Diabetes

**RELAPSED LYMPHOMA**

For patients with relapsed or progressive disease that is not responding to appropriate anti-lymphoma therapy which may have included bone marrow transplantation, symptom control and palliative care measures would be appropriate (see below).

**MANAGEMENT AND SIDE EFFECTS**

The use of radiotherapy and chemotherapy can result in a wide range of acute and chronic side effects.

**Acute side effects include:**

- Nausea and vomiting, malaise
- Febrile neutropenia
- Alopecia

**Chronic side effects may include:**

- sterility and in rare instances there may be cardiac damage due to doxorubicin.

**When managing patients with lymphoma it is important to:**

- Address any psychosocial issues
- Ensure patient’s questions are answered e.g. treatment, prognosis
- Discuss long-term side effects including risks of secondary malignancy
- Discuss implications of chemotherapy on fertility – arrange referral to a fertility specialist or fertility protection (e.g. sperm and ovarian tissue banking) in younger patients

**IMMUNODEFICIENCY ASSOCIATED LYMPHOMA**

The World Health Organisation (WHO) classifies immunodeficiency associated lymphomas into four major groups:

- Lymphoproliferative diseases associated with primary immune disorders
- Human immunodeficiency virus (HIV) -related lymphomas
- Post-transplant lymphoproliferative disorders
- Methotrexate-associated lymphoproliferative disorders

Surveillance is recommended for individuals at risk of immunodeficiency-associated lymphoma.

Immunodeficiency associated lymphomas are mainly aggressive B-cell, CNS and Hodgkin Lymphomas. Patients should be treated in a specialist centre as optimal treatment will vary with the type of lymphoma.

**CHILDHOOD LYMPHOMA**

Lymphomas comprised 7-8% of all childhood cancers. About 40-50 new cases are diagnosed in Australia each year. The majority of children (75%) with lymphoma present with advanced disease and childhood lymphoma is usually extranodal at presentation. The tumours are rapidly growing and there is frequent visceral spread and involvement of bone marrow and central nervous system.

All patients should be treated at a paediatric oncology centre and entered into a clinical trial where possible.
PALLIATIVE CARE
Palliation is appropriate whenever a decision is made, based upon the patient’s best wishes and the clinical evidence, that further intensive or curative treatment is not indicated.

In terminally ill patient with lymphoma consideration should be given to active treatments such as:

- Single-agent chemotherapy
- Corticosteroids
- Monoclonal antibodies
- Radiotherapy

Recruitment into clinical trials is recommended.

NUTRITION, EXERCISE AND LIFESTYLE
Patients should be informed about the effects of smoking, diet, sun exposure and lifestyle habits that may increase their risk of developing secondary malignancy at specific sites.

Adults should be advised to:

- Maintain a health weight range—restrict fat intake <25% of total energy intake
- Eat ≥5 serves of fruit and vegetables
- Consume a minimum of 30g of fibre daily
- Undertake regular aerobic and resistance exercise
- Quit smoking

ALTERNATIVE AND COMPLEMENTARY THERAPIES
There is no evidence that complementary and alternative therapy practices can cure lymphoma.

Alternative medicine should be questioned when suspected drug reactions occur and included in notification reports.

The use of acupuncture to treat nausea and vomiting has been demonstrated.

Some forms of relaxation therapy have been shown to reduce stress and pain and improve quality of life.

The Clinical Practice Guidelines for the Diagnosis and Management of Lymphoma (www.cancer.org.au/clinical_guidelines) provides reviews of evidence of other complementary and alternative therapies.

COMMUNICATION WITH THE PATIENT
Communication with patients includes the ability to converse and provide best evidence-based and culturally appropriate information on issues that are important to their well-being.

Patient information
Information for patients with lymphoma should be provided in collaboration with the GP, multidisciplinary team, nurse coordinator, and psychosocial health professional.

Information should include:

- meaning of lymphoma, suspected risk factors and the extent of disease
- proposed approach to investigation and treatment, including information on expected benefits, the process involved, common side effects, whether the intervention is standard or experimental and who will undertake the intervention
- the likely consequence of choosing a particular treatment, or no treatment
- the time involved
- the costs involved
- the effect of cancer and its therapy on interpersonal, physical and sexual relationships
- typical emotional reactions
- entitlements to benefits and services, such as subsidies for travel or prostheses
- access to cancer information services

Counselling and support
Support needs for individuals with lymphoma and their families may include:

- counselling
- exploring feelings with a member of the treatment team
- access to a cancer support service and/or support group education
- assistance with practical needs (e.g. child-minding, transport)

The Cancer Council Helpline (13 11 20) can provide access to support services and consumer information on Hodgkin Lymphoma and Non-Hodgkin Lymphoma.