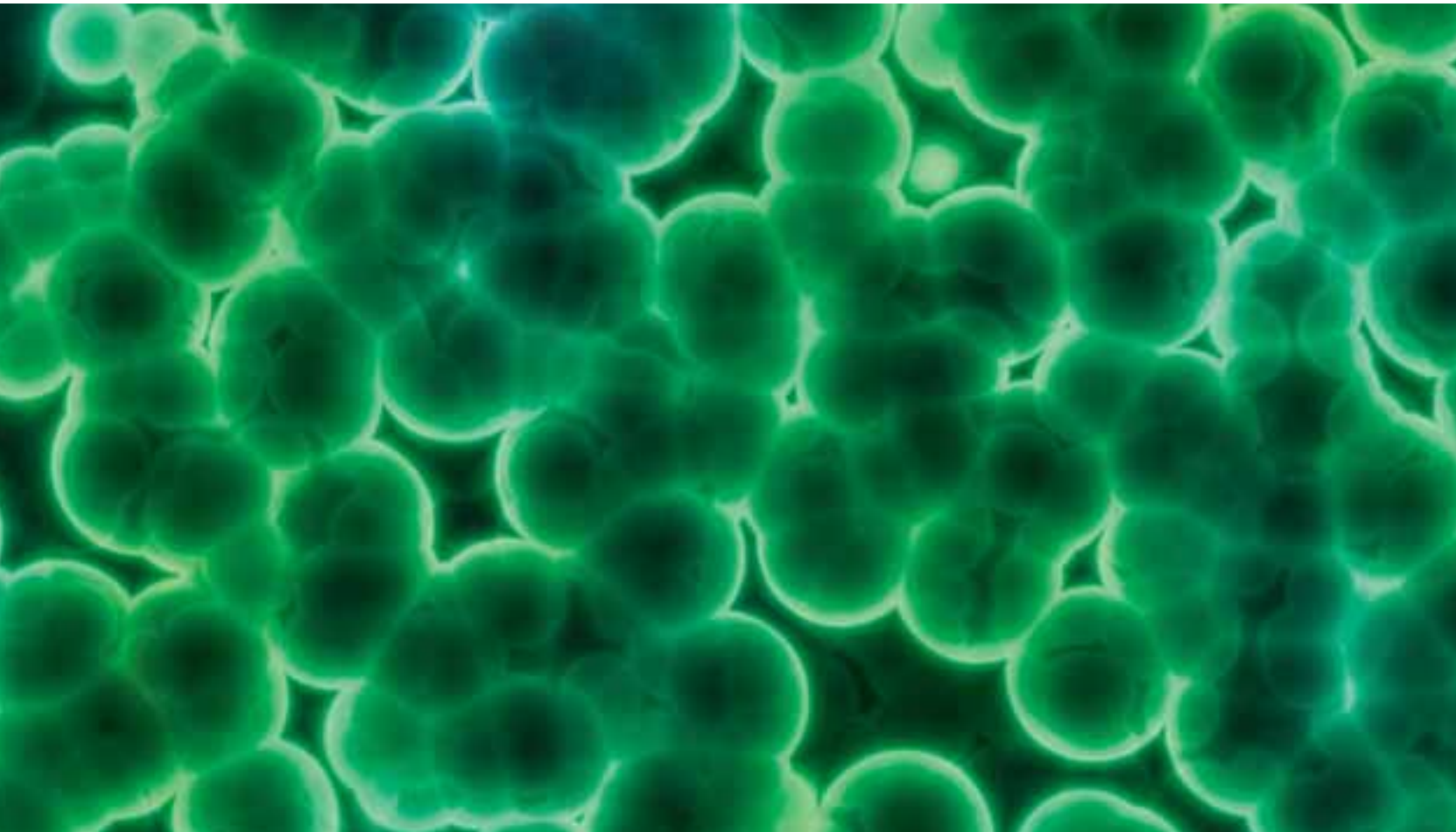
# LYMPHOMA Forum of Ireland

## Guidelines on Diagnosis and Treatment of Malignant Lymphomas



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# Guidelines on Diagnosis and Treatment of Malignant Lymphomas

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# Introduction

In Ireland and Northern Ireland approximately 800 new cases of malignant lymphoma, Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL), are registered each year. In line with the rest of the western world, the incidence of NHLs appears to be increasing, probably by 3-5% per year and, being largely a disease of the elderly, these tumours represent an increasing cause of cancer-related death. The reasons for increasing incidence are multiple, ranging from the increasing elderly population, greater accuracy of diagnosis and unknown environmental factors. The increase has not been noted in HL and in all subtypes of NHL and cannot solely be explained on the basis of the HIV epidemic.

NHLs are a heterogeneous group of diseases which are mainly linked by their origin within the lymphoid system and its different cellular components. Over 60% of NHLs are accounted for by two diseases, diffuse large B-cell lymphoma (DLBCL) which is an aggressive disease and follicular lymphoma (FL) which is an indolent or non-aggressive entity. Many other less- common and often rare sub-types of NHL exist. All display distinct natural histories and require complex diagnostic approaches and management.

Over the last forty years there have been numerous efforts to classify lymphoid malignancies culminating in the WHO classification introduced after much international effort in 2001. It is clear that malignant lymphomas require a sophisticated diagnostic approach based on clinical features, morphology, immunophenotyping and genetic analysis. It is essential that such an approach underpins the clinical management of these diseases, many of which are amenable to cure. Clinical care should be delivered by those with expertise and experience in the area, within a multidisciplinary setting.

The Lymphoma Forum of Ireland (LFI) first met in October 2002 and outlined its aims as: the promotion of a high standard of care and the development of all aspects of lymphoma diagnosis and treatment in Ireland and Northern Ireland, development and fostering of research initiatives relating to malignant lymphomas and interaction with other relevant bodies towards achieving these aims. Members of the LFI include medical oncologists, haematologists, pathologists and radiation oncologists involved in the diagnosis and management of malignant lymphomas. After a number of exploratory meetings, it was agreed that the initial step required was the development of management guidelines for these diseases in line with the WHO classification and best international treatment practices. As an initial effort, guidelines for the diagnosis and management of 22 diseases have been developed as well as guidelines for the management of some generic issues. This is the first update of the guidelines issued in parallel with the updated WHO guidelines published in 2008 and these will be made available on the Haematology Association of Ireland website.



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# Standards In Diagnosis of Lymphoma

## Tissue collection

### Investigations prior to biopsy

A full blood count (FBC) and film (with flow cytometry if appropriate), should be carried out before a node biopsy to avoid biopsying patients with CLL or acute leukaemia.

Monospot: in patients < 30 years with lymphadenopathy.

Epithelial carcinoma should be considered in patients >40 with head and neck adenopathy, who should have an ENT examination and FNA.

### Designated surgeons should perform all lymph node biopsies in lymphoma diagnosis

A designated surgeon ensures appropriate and uniform specimen collection and prompt referral of patients to the lymphoma service. The preliminary biopsy report should be available to the multidisciplinary team (MDT) within 2 weeks of the patient's hospital referral.

### An excision lymph node biopsy is preferable for diagnosis

An excision biopsy allows detailed assessment of architecture, which is a key feature in lymphoma diagnosis. Needle biopsies are more prone to artefact and may be inadequate for all the diagnostic investigations. A lymph node biopsy is preferable to a biopsy of an extra-nodal site.

### Approach to diagnosis of a patient with lymphadenopathy

- FBC with film (and cell marker studies where appropriate)
- Monospot in patients < 30 years
- Consider ENT examination and FNA to exclude epithelial malignancy of the head and neck in patients >40
- Designated surgeon(s)
- Excision biopsy preferred method; trucut biopsy if node not accessible
- Node biopsy – send unfixed to laboratory

### Lymph node biopsies should be sent fresh to the laboratory

This requires local arrangements for the prompt and safe transport of the specimen. Fresh material is essential for good quality histology and facilitates the use of new diagnostic techniques. See Royal College of Pathologists minimum dataset for lymphoma reports.

## Laboratory diagnosis

### Sample handling

In the laboratory, the lymph node should be sliced and imprint preparations made. Thin slices should be placed in formalin for 24 hours before processing as paraffin blocks. This is essential for high-quality morphology and reproducible results with marker studies performed on paraffin sections. The remaining tissue may be snap frozen and disaggregated into a single-cell suspension.



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### Classification system

The World Health Organization (WHO) classification of neoplastic diseasesTumours of the haematopoietic and lymphoid tissues, 4th edition 2008 should be used.

### Diagnostic requirements for haematopathology diagnosis

The diagnosis of lymphoma should be made, or reviewed, in a laboratory with the necessary specialist expertise and facilities.

A pathology laboratory diagnosing lymphoma requires access to the following resources:

a. ***Morphological expertise:*** *Pathologists/haematologists involved in lymphoma diagnosis should have the necessary training to undertake this work.*

b. ***Immunophenotyping:*** *All marker studies should be carried out using panels designed to test the validity of the morphological diagnosis and to demonstrate key prognostic variables. Marker studies should be carried out using flow cytometry and immunohistochemistry. An appropriate panel for the lymphoma sub-types is included in the lymphoma-specific sections in this document.*

c. ***Molecular techniques:*** *The two main techniques are polymerase chain reaction (PCR) to detect monoclonality and some translocations, and fluorescence in situ hybridisation (FISH) techniques for translocations. These techniques should be used to confirm a provisional diagnosis and identify prognostic factors. Formal links with a molecular/cytogenetics service are required.*

d. ***Integrated reporting:*** *Most patients with lymphoproliferative disorders have different specimens taken during their clinical course. Departments should have a mechanism for correlating results from lymph node biopsies, bone marrow aspirates and biopsies as well as different analyses of a single sample.*

### Reporting

A preliminary report should be available 5 working days after the specimen is received. This interim report should state specific outstanding investigations and be followed by a definitive report.

### Quality assurance and audit

The main component of quality assurance is access to a robust and timely diagnostic process. An audit system designed to test the quality of the service should be in place. Laboratories should be able to provide users of the laboratory with details of their diagnostic criteria and technical methods.

Laboratories should participate in the relevant quality assurance schemes for immunocytochemistry, flow cytometry and other diagnostic methods. Individual histopathologists should have access to a lymphoma review panel.

**Diagnosis – laboratory procedures and standards**

- Unfixed node biopsy imprint preparation – formalin preparation of material, snap freezing and disaggregation into single-cell suspension
- WHO classification
- Access to immunophenotyping, molecular techniques and molecular genetic techniques
- Preliminary report within 5 working days
- Systems of quality assurance in place: Standard Operating Procedures (SOPs); Lab Accreditation; National Quality Assurance Scheme
- Access to review panel

### Multidisciplinary team (MDT) working

MDT meetings are a desirable part of the diagnosis and management of lymphoma. The arrangements will vary with local circumstances but it is essential that diagnostic pathology and staging radiology be reviewed in both new and relapsed patients before making a management plan. This plan should be clearly documented in patients' notes.



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# Standards in Staging of Lymphoma

## Ann Arbor staging classification for NHL

| Stage | Area of involvement |
|---|---|
| **I** | One lymph node region |
| **IE** | One extralymphatic (E) organ or site |
| **II** | Two or more lymph node regions on the same side of the diaphragm |
| **IIE** | One extralymphatic organ or site (localised) in addition to criteria for stage II |
| **III** | Lymph node regions on both sides of the diaphragm |
| **IIIE** | One extralymphatic organ or site (localised) in addition to criteria for stage III |
| **IIIS** | Spleen (S) in addition to criteria for stage III |
| **IIISE** | Spleen and one extralymphatic organ or site (localised) in addition to criteria for stage III |
| **IV** | One or more extralymphatic organs with or without associated lymph node involvement (diffuse or disseminated); involved organs should be designated by subscript letters (P, lung; H, liver; M, bone marrow) |

*A = asymptomatic;*
*B = symptomatic; unexplained fever of ≥ 38ºC; unexplained drenching night sweats; or loss of > 10% body weight within the previous 6 months).*

## The International Prognostic Index (IPI)

**The IPI is a prognostic model based on 5 parameters**

- Age (< 60 vs > 60 years)
- Ann Arbor stage (I/II vs III/IV)
- Serum LDH (normal vs elevated)
- Extra-nodal involvement (≤ 1 site vs ≥ 1 site)
- Performance status (0,1 vs 2–4)

Based on these factors, patients with DLBCL can be divided into 4 prognostic categories as summarised below:

| | Number of risk factors |
|---|---|
| **IPI risk group** | **All patients** |
| Low-risk | 0,1 |
| Low/intermediate-risk | 2 |
| High/intermediate-risk | 3 |
| High risk | 4, 5 |

The IPI describes a predictive model for patients with DLBCL at presentation. It has been adjusted for use in FL (FLIPI) and is less useful in ALCL, mediastinal B cell lymphoma and T-NHL. It should not used in Burkitt lymphoma or lymphoblastic lymphoma.



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## ECOG performance status

| Grade | ECOG |
|---|---|
| 0 | Fully active, able to carry on all pre-disease performance without restriction |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work |
| 2 | Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours |
| 3 | Capable of only limited self care, confined to bed or chair more than 50% of waking hours |
| 4 | Completely disabled. Cannot carry out any self care. Totally confined to bed or chair |
| 5 | Dead |

## Staging procedures-all patients

### Clinical

- Clinical history with reference to B symptoms and family history
- Physical examination with particular attention to node-bearing areas, Waldeyer's ring, and size of liver and spleen
- Performance status (ECOG) including co-morbidity

### Radiology

- CXR
- Chest and abdominopelvic computed tomography (CT)

### Haematology

- FBC, differential and film
- Bone marrow aspirate and trephine
- Immunophenotyping of marrow +/- blood in low grade lymphomas and any other lymphomas with morphological evidence of marrow/blood involvement

### Biochemistry

- LDH, urea and electrolyte, creatinine, albumin, aspartate transaminase (AST), bilirubin, alkaline phosphatase, serum calcium, uric acid
- Pregnancy test in females of child-bearing age

### Serology

- Hepatitis B and C
- HIV status

## Staging procedures (sometimes indicated)

### Radiology

- Plain bone X-ray and bone scintigraphy
- Neck CT
- Head CT or magnetic resonance imaging (MRI)
- PET scan

### Haematology

- Coagulation screen
- ESR
- DCT

### Biochemistry

- Serum immunoglobulins/electrophoresis
- Beta 2 microglobulin
- CRP
- Tissue transglutaminase test (tTG) to exclude coeliac disease

### Serology

- EBV, HTLV serology

### Molecular genetics

- FISH or PCR on involved marrow/blood for specific lymphoma-associated translocations
- IgH and TCR rearrangements on marrow/blood if molecular staging clinically indicated

### Others

- ECHO and PFTs
- Lumbar puncture if lymphomatous meningitis is suspected or if indications for prophylactic treatment are present. CNS prophylaxis is currently used in patients with Burkitt Lymphoma, lymphoblastic lymphoma, HIV-related lymphoma, HTLV-1 related lymphoma and post-transplant lymphoproliferative disease. About 5% of patients with DLBCL develop CNS disease but there is no consensus about which patients need to have a diagnostic lp.



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# Pathologic Diagnosis of Lymphoma

## General comments

**1. Primary diagnosis**

***a.*** Complete lymph node excision in the presence of nodal disease is the optimum diagnostic material and should be utilised wherever possible. *

***b.*** The complete lymph node excision should be transported immediately in a fresh state to the laboratory.

***c.*** The fresh lymph node should be handled as per algorithm on page 15.

***d.*** *Where full lymph node excision is not possible e.g. inaccessible mass or extranodal disease, core biopsy is the next best option for accurate primary diagnosis unless a resection has been or will be undertaken. Multiple large cores should ideally be submitted fresh to the laboratory on saline soaked gauze otherwise they should be submitted in 10% buffered formalin.

***e.*** All cases must be received with relevant clinical information.

**2. The role of Flow Cytometry (FCM)**

***a.*** FCM is useful for accurate diagnosis in all small cell / follicular pattern lesions.

***b.*** FCM on aspirated material may provide a reasonable alternative to biopsy in recurrent disease where tissue is not easily obtainable e.g. elderly/frail patient, inaccessible site. Such FNA samples require co-ordination with the laboratory as special fixation (RPMI) and immediate processing is required

**3. Optimum handling of fresh lymph node excision**

***a.*** Ensure immediate transfer from the theatre to laboratory.

***b.*** Bisect node and perform touch preparations.

- ***i.*** Air dried x 2 – Giemsa stain
- ***ii.*** Air dried X6-8 FISH studies if required
- ***iii.*** Fixed x 2 – H & E stain

***c.*** Sample portion of tissue for:

- ***i.*** Freezing – 1 portion in "RNA later", 1 portion fresh frozen (this will preserve material for molecular study should this be required).
- ***ii.*** RPMI for FCM (this will preserve the cells and allow transport to nearest centre offering FCM and/or Cytogenetics service).
- ***iii.*** Formalin for routine fixation and processing.

**4. Classification and grading**

***a.*** Use WHO classification 4th edition 2008

***b.*** Where applicable use WHO grading e.g. Follicular Lymphoma (see page 29)

**5. The role of FCM/Cytogenetics/ Gene expression profiling**

Material should be preserved in RPMI and frozen for availability for cytogenetic analysis and other relevant evaluation



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## Immunohistochemistry (IHC)

### Hodgkin Lymphoma (HL)

**BASIC IHC PANEL ON FFPET (Formalin fixed, paraffin-embedded tissue)**

- CD45
- CD3
- CD20
- CD15
- CD30
- EMA (EMA should be negative in classic HL; positive in NLPHL)

**IF H&E MORPHOLOGY IS TYPICAL**

CD45, CD3, CD20, CD15, CD30 ..... NEGATIVE / POSITIVE ..... HL

CD3, CD20 ..... NEGATIVE
CD15 ..... NEGATIVE
CD30 ..... POSITIVE
..... Consider ALCL, Perform ALK1

If ALK 1 NEG ..... HL
If ALK 1 POS ..... ALCL

**IF H&E MORPHOLOGY IS ATYPICAL ADD THE FOLLOWING TO THE INITIAL BASIC IHC PANEL**

CD79A

CD5

CD10

ALK 1

Myeloperoxidase – to exclude myeloid origin.

MCT – to exclude mast cell origin.

Non-lymphoid markers as appropriate e.g. to exclude – Germ Cell tumours

Malignant melanoma

Poorly differentiated carcinoma



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## Hodgkin lymphoma and its differential diagnosis

| | CD20 | CD79a | T-Cell antigen | CD4 CD8 | CD30 | CD15 | EMA |
|---|---|---|---|---|---|---|---|
| **Nodular lymphocyte predominant HL** | + | + | - | - | -/+ | - | + |
| **Classical HL** | -/+ | -/+ | - | - | + | + | -/+ |
| **T-cell rich large B-cell lymphoma** | + | + | - | - | - | - | - |
| **Anaplastic large cell lymphoma** | - | - | +/- | CD8>CD4> CD4&8-ve | + | - | + |

***KEY*** *+/- The lymphoma cells are commonly but not always positive*
*-/+ The lymphoma cells are usually but not always negative*

## Potential diagnostic pitfalls in Hodgkin lymphoma

**With "Typical" H&E Morphology**

- ALCL
- T cell rich B cell lymphoma
- Diffuse large B cell lymphoma

**With "Atypical" H&E Morphology**

- ALCL
- T cell rich B cell lymphoma
- Diffuse large B cell lymphoma
- Intermediate CHL/DLBCL (Grey zone lymphoma)
- Myeloid origin
- Mast cell origin
- Non-lymphoid neoplasms



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## Large/Intermediate Cell Morphology on H&E

**BASIC IHC PANEL ON FFPET**

**CLA**
**CD20**
**CD3**
**CD5 + Cyclin D1** (To exclude Blastic Mantle Cell Lymphoma)
**CD30**
**Ki67**

**BCL2**
**BCL6**
**CD10**
**IRF4/MUM1**

**To provide additional prognostic/ therapeutic information to clinician**

| | |
|---|---|
| **CLA** | **+** |
| **CD20** | **+** |
| **CD79a** | **.....Profile of Diffuse large B Cell lymphoma** |
| **CD3** | **-** |
| **CD30** | **-** |
| **CD5** | **-** |

**IF CD20+ /CD79a + but proliferative index (Ki67) is high (>90%)**

- Consider BURKITT (look for "starry sky" morphology; BCL2 NEG) or Intermediate BL/DLBCL Confirm with Molecular testing for MYC , BCL2, BCL6
- Consider Lymphoblastic – Do TdT

**IF CD20 - Do CD79A and CD138**

**IF CD79a +**

- Consider MYELOMA (CD138 +)
- Consider Myeloid neoplasms (MPO, CAE)

**IF CLA –**

- Consider ALCL (CD30+, ALK +) or Non Lymphoid Malignancy

**T CELL**

- IF CD20- / CD79A-/CD3+
- T-Cell Lymphoma
- Do CD30, ALK-1
- CD56, CD4, CD8



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## Potential diagnostic pitfalls for large/intermediate cell morphology

**Non-lymphoid malignancy**

- Germ Cell tumour
- Carcinoma
- Melanoma
- Sarcoma

**Burkitt lymphoma is missed** – (If proliferative index (Ki67) is high and BCL2 is negative – think Burkitt)

Confirm with Molecular genetic studies for MYC and BCL2 translocations

**B Cell Lymphoblastic lesions** - (include TdT in panel)

**Myeloid lesions** If CD20 is negative but CD79A positive

**Plasma Cell lesions** consider these

**"Blastic" Mantle Cell lymphoma** – include CD5 in initial panel. Confirm with Cyclin D1 or molecular genetic studies for BCL1 translocation.



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## Nodular/Follicular pattern

***a.*** **Nodular/follicular pattern with small cell morphology**

Follicular Lymphoma
Mantle Cell Lymphoma
Marginal Zone Lymphoma
SLL/CLL

**BASIC IHC PANEL ON FFPET**

**CD20**

**CD3**
**CD5**

**CD10**
**CD23**
**Cyclin D1**
**BCL 2**
**Ki67**

**FCM**
**Cytogenetics**

***b.*** **Nodular/follicular pattern with larger cells or "atypical" morphology consider –**

NLPHL
Lymphocyte Rich HL
NSHL
And handle as per HL

***c.*** **Non-nodular small cell morphology**

Investigate as per basic IHC panel
Consider Lymphoplasmacytic lymphoma

## Potential diagnostic pitfalls for small cell morphology

- Lymphoplasmacytic lesions



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## Summary of the usual Immunostaining Pattern of B-cell Neoplasms

| | CD20 | CD79 | CD5 | CD23 | CD10 | CD30 | CD15 | CyclinD1 |
|---|---|---|---|---|---|---|---|---|
| **Precursor B-cell neoplasms** | | | | | | | | |
| Precursor B-lymphoblastic leukaemia/lymphoma | - | +/- | - | - | + | - | - | - |
| **Mature B-cell neoplasms** | | | | | | | | |
| B-cell chronic lymphocytic leukaemia/lymphoma | + | + | + | + | - | - | - | - |
| B-cell prolymphocytic leukaemia | + | + | - | +/- | - | - | - | -/+ |
| Lymphoplasmacytic lymphoma | + | + | - | -/+ | - | - | - | - |
| Mantle Cell lymphoma | + | + | + | - | - | - | - | + |
| Follicular lymphoma | + | + | - | -/+ | + | - | - | - |
| Marginal zone B-cell lymphoma of mucosa associated lymphoid tissue type | + | + | - | - | - | - | - | - |
| Nodal marginal zone lymphoma +/- (monocytoid B-cells) | + | + | - | - | - | - | - | - |
| Splenic marginal zone lymphoma | + | + | - | - | - | - | - | - |
| Hairy cell leukaemia | + | + | - | - | - | - | - | - |
| Plasmacytoma | - | + | - | - | - | -/+ | - | - |
| Plasma cell myeloma | - | +/- | - | - | - | -/+ | - | - |
| Diffuse large B-cell lymphoma | + | + | -/+ | -/+ | -/+ | -/+ | - | - |
| Mediastinal (thymic) | + | + | - | +/- | -/+ | -/+ | -/+ | - |
| Intravascular | + | + | -/+ | - | -/+ | -/+ | - | - |
| Primary effusion lymphoma | - | + | - | - | - | + | - | - |
| Burkitt lymphoma | + | + | - | - | + | - | - | |

***KEY*** *+/- The lymphoma cells are commonly but not always positive*
*-/+ The lymphoma cells are usually but not always negative*

***Note that for T-cell and putative NK-cell neoplasms, immunostaining is complex and variable.***



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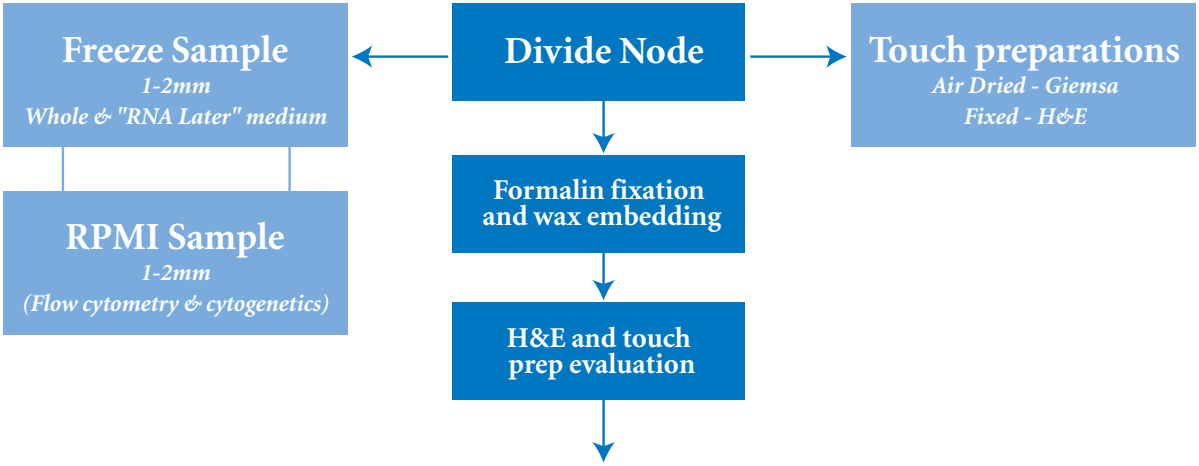
# Pathological diagnosis of suspected lymphoid disease

***Receive whole Lymph Node FRESH****




| ? Reactive | Lymphoma | | | ? Other Malignancy |
|---|---|---|---|---|
| | Large Cell | Small Cell | Hodgkin-like | |
| **Basic IHC**<br>CD3, CD20<br>Ki 67<br>Kappa/Lambda<br>Bcl-2 | **Basic IHC**<br>CLA, CD3,<br>CD5, CD20,<br>CD30, CD79a,<br>ALK-1, Ki 67 | **Basic IHC**<br>CD3, CD5,<br>CD10, CD19<br>CD20, CD23<br>CD79a, Bcl-2<br>Ki 67, CyclinD1<br>Kappa/Lambda | **Basic IHC**<br>CD3, CD15<br>CD20, CD30<br>EMA | **Basic IHC**<br>Cytokeratin<br>S100<br>Vimentin |
| | **Further IHC**<br>TdT, MPO | **Further IHC**<br>CD15, CD30 | **Further IHC**<br>CD5, CD10, CD57<br>CD79a, ALK-1<br>MPO, MCT | |

** For extranodal disease receive resection or core biopsy fresh*
*Issue Report using WHO Classification*



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# Mature B-Cell Neoplasms

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# Mature B-Cell Neoplasms

## Chronic Lymphocytic Leukaemia/ Small Lymphocytic Lymphoma Definition and Incidence:

Chronic lymphocytic leukaemia / small lymphocytic lymphoma (CLL/SLL) is a neoplasm of monomorphic small, round B- lymphocytes in the peripheral blood, bone marrow and lymph nodes admixed with prolymphocytes and para-immunoblasts expressing CD5 and CD23. The term SLL is restricted to cases with the tissue morphology and immunophenotype of CLL but without a leukaemic component. CLL comprises 90% of chronic leukaemias in the USA and Europe and 7% of NHLs present as CLL/SLL. The majority of patients are >50 years old (median age 65) and the M: F ratio is 2:1. The incidence is 0.72cases /100,000 per year.

**ICD – O Codes:** **CLL 9823/3**
**B-SLL 9670/3**

## Clinical presentation

Most patients with CLL are asymptomatic and the disease is diagnosed incidentally on routine full blood count. Presenting features can include lymphadenopathy, fatigue, auto-immune haemolytic anaemia, infection, or evidence of bone marrow failure.

## Pathology

The lymphoid infiltrate effaces normal lymphoid architecture with a pseudo-follicular pattern of regularly distributed pale areas containing larger cells in a dark background of small cells The cells are slightly larger than normal lymphocytes, have a high nuclear-cytoplasmic ratio, round nucleus and occasional small nucleolus. The pseudofollicles contain a continuum of small, medium and large cells i.e. lymphocytes, prolymphocytes and para-immunoblasts. The size of the pseudofollicles and the number of para-immunoblasts vary but there is no well-documented correlation between histological findings and clinical outcome.

Cell morphology can vary and may be confused with mantle cell lymphoma (MCL). Plamacytoid differentiation may also be present.

In the blood and bone marrow similar small lymphocytes are found and smudge, smear or basket cells are typically seen on blood films. Prolymphocytes, which are larger cells with a prominent nucleolus, usually account for <25% of the lymphoid population and an increasing number is associated with a worse prognosis. Bone marrow involvement can be nodular, interstitial or diffuse, with a diffuse pattern associated with a worse prognosis and marrow failure.

Transformation to DCLBL (Richter's syndrome) is characterised by confluent sheets of large cells, with a centroblast or immunoblast-like appearance.



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## Immunophenotype

The tumour cells express pan B markers CD19 and 20 (weak), surface IgM and IgD (weak) and CD5 and CD23. The lymphocytes do not express CD10, cyclin D1, FMC7 and CD79b.

## Staging

There are two clinical staging systems for CLL, the Rai (0-IV) and Binet (A-C) classifications.

## Recommended investigations

**Clinical:** History and examination with reference to any family history

**Diagnostic Imaging:** CXR, CT thorax abdomen and pelvis. Abdominal Ultrasound is acceptable for patients being treated with low intensity treatment or on a watch and wait policy

**Blood tests:**

**Haematology:**
Full blood count, differential white cell count,
Immunophenotyping
Direct Coomb's test
Reticulocyte count

**Biochemistry:**
Renal, liver and bone profiles
Lactate dehydrogenase (LDH)
Beta-2 microglobulin

**Other:**
Immunoglobulins and electrophoresis
BM aspirate and biopsy
FISH analysis of blood

## Prognostic factors and Genetics

Conventional bad prognostic indicators are; male gender, lymphocyte doubling time of <6 months, high serum beta-2 microglobulin, atypical morphology, increasing prolymphocyte count and diffuse marrow infiltration. Cytogenetic abnormalities detected by FISH analysis include trisomy 12, 11q and 17p deletion which are associated with a poor prognosis, with 13q14 deletion conferring a better prognosis as a sole abnormality. The presence or absence of immunoglobulin gene somatic hypermutations (SHM) is prognostically significant; an unmutated Ig gene is associated with progressive disease, require treatment and have a shorter survival than those with mutations. Expression of CD38 and ZAP-70 protein are independent negative prognostic markers in CLL.

## Potential pitfalls

*a.* Surgical excision of a lymph node without prior review of peripheral blood thereby missing a diagnosis of CLL

*b.* Confusion with Mantle Cell Lymphoma (also CD5+ve)

*c.* Failure to recognise that a case of DLBCL represents Richter syndrome

## Treatment

Approximately 25% of patients with CLL (ie stable CLL , Binet stage A) do not require treatment and are managed with a watch and wait policy. Indications for treatment are progressive stage A disease or stage B or C CLL.

### Monotherapy in CLL

Traditionally CLL was treated with Chlorambucil with symptomatic intent to control progressive disease or B symptoms. Fludarabine monotherapy results in an increased complete remission rate and longer treatment free intervals. Bendamustine has been recently licensed for the treatment of CLL resulting in response rates of 59% and a median progression free survival (PFS) of 18 months.

### Combination treatments

Combined Fludarabine and Cyclophosphamide (FC) increases oS at 5 years from 44% for Chlorambucil and 48% for Fludarabine to 57% for combined FC.

Combining FC with Rituximab (FCR) achieves a complete remission rate of 70-80% and treatment free interval at 4 years was 69% This benefit is less pronounced in the over 70 age group and most significant in the under 60's.

### MRD Negative CLL

Combination chemo-immunotherapy or single agent Campath, can result in MRD negative complete remission; which is associated with prolonged survival.

### Refractory/ poor risk CLL

Patients who are refractory to Fludarabine, have p53 dysfunction or deletion of 17p have a median survival of <2 years. These patients may respond to high dose methylprednisolone, Campath IH, or lenalidomide but long term survival remains poor.

### Allogeneic SCT in CLL

Non-myeloablative allogeneic stem cell transplants can sure patients with high risk CLL achieving long term cure rates of up to 50-60%.

### Richter Syndrome

Patients with Richter syndrome are conventionally treated with R-CHOP, however long term survivals are rare.



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# Lymphoplasmacytic Lymphoma

## Definition and Incidence

Lymphoplasmacytic lymphoma (LPL) is composed of an admixture of small B lymphocytes, lymphoplasmacytoid cells and plasma cells involving the bone marrow, lymph nodes and spleen and usually associated with a serum paraprotein of IgM subtype.

LPL is rare and comprises <5% of reported lymphomas with a median age of onset of 63 years.

**ICD-O Code** **9671/3**

## Clinical Presentation

Most patients present as a consequence of the IgM paraprotein, which causes hyperviscosity in 30% at presentation. Hyperviscosity causes non–specifc symptoms especially in elderly patients including confusion, memory loss, headaches and decreased visual acuity and predisposes the patient to stroke. The paraprotein may act as an auto-antibody causing coagulopathies (antibody directed against clotting factors), neuropathies and haemolysis. Patients may present with symptoms relating to a cryoglobulin, especially common in hepatitis C infected patients. Patients may also present with pancytopaenia secondary to marrow involvement, splenomegaly or lymphadenopathy.

## Pathology

The growth pattern in lymph nodes varies from retention to almost complete destruction of normal architecture with dilated sinuses. Marrow involvement may be nodular or diffuse. The cells are composed of an admixture of small B lymphocytes, lymphoplasmacytoid cells and plasma cells. Progression to an immunoblastic lymphoma rarely occurs

## Immunophenotype

Strong cytoplasmic and surface Ig expression is usual (usually IgM). Pan-B markers are positive including CD19, CD20, CD22 and CD79a. CD5, CD10 and CD23 are usually not expressed.

## Investigations

| | |
|---|---|
| **Generic** | See page 2 |
| | Abdominal US and CXR may be adequate for staging purposes |
| **Specific** | Bone marrow aspirate for morphology and immunophenotype |
| | Serum protein electropheresis |
| | Plasma viscosity |
| | Coagulation screen |
| | Hepatitis C and cryoglobulin analysis (if indicated) |

## Potential Pitfalls

- Failure to recognise hyperviscosity syndrome in an elderly patient who presents with non –specific symptoms
- Failure to initiate plasma exchange for symptomatic hyperviscosity
- Transfusion of red cells to patients with anaemia and hyperviscosity
- Failure to recognize another specific lymphoma subtype with plasmacytic morphology e.g MZL



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## Treatment

This is an indolent lymphoma, which is incurable with conventional treatment. Patients with a hyperviscosity syndrome should be treated as an emergency with plasma exchange until plasma viscosity has normalised. Plasma exchange should be continued regularly until IgM production has been controlled sufficiently to prevent further episodes of hyperviscosity.

Oral Chlorambucil and Fludarabine are the most commonly used agents in LPL, usually for 6 months.

Combination immunochemotherapy can be used as first line therapy in young patients or as second line therapy. Combinations include Rituximab with Fludarabine, or Cycophosphamide. Bortezomib is active in LPL and combining it with Dexamethasone and Fudarabine results in an ORR of 96% and CR in over 20% of patients. Vincristine and possibly anthracyclines may not be active in LPL. Rituximab is active in LPL but should only be used when the paraprotein is low (eg after plasma exchange) because of the risk of aggravating hyperviscosity and a high incidence of severe infusional reactions.

## Response Evaluation

Normalisation of blood count, total, reduction of igM with plateau levels of the protein and a normal viscosity. The viscosity should be checked weekly until normalisation and then monthly while on treatment

## Follow Up

Two monthly for 1 year, 3 monthly for the second year, followed by long term follow up between 6 – 12 monthly with FBC, biochemistry profile, paraprotein level and viscosity.



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# Splenic Marginal Zone Lymphoma

## Definition and Incidence

SMZL is an indolent B-cell lymphoma usually involving spleen, bone marrow and blood. Patients usually present with splenomegaly and/or anaemia. Splenic hilar lymph nodes may be involved, although other lymphadenopathy is rare. Bone marrow and peripheral blood involvement is common. The disease is rare, comprising <1% of lymphoid neoplasms, and occurs equally in males and females.

**ICD-O Code** **9689/3**

## Clinical Presentation

Patients present with splenomegaly, sometimes with anaemia, thrombocytopenia or leukopenia. The bone marrow and peripheral blood are usually involved, but peripheral lymphadenopathy is rare. A monoclonal gammopathy is present in 30% of patients.

## Pathology and Genetics

Diagnosis is based on a combination of splenic or marrow morphology, lymphocyte morphology and immunophenotype. In the splenic white pulp a central zone of small round lymphocytes surrounds or replaces reactive germinal centres with effacement of the normal follicle mantle. This zone merges with a peripheral zone of small- to medium-sized cells with more dispersed chromatin and abundant pale cytoplasm which resemble marginal zone cells and are interspersed with transformed blasts. The red pulp is always infiltrated with both small nodules of the larger cells and sheets of small lymphocytes, which often invade sinuses. Epithelioid histiocytes and cells with plasmacytic differentiation may be identified.

In splenic hilar lymph nodes the sinuses are dilated and lymphoma surrounds and replaces germinal centres. In the bone marrow, a nodular interstitial infiltrate similar to that in lymph nodes is present. Intrasinusoidal lymphoma cells are characteristic. When lymphoma cells are present in the peripheral blood, they usually display short polar villi and may appear plasmacytoid.

### Immunophenotype

Tumour cells have surface IgM and IgD, and are CD20+, CD79a+, CD5-, CD10-, CD23 -, CD45-.

### Genetics

Immunoglobulin heavy chain and light chain genes are rearranged in most cases, and somatic mutations are often present. A t(14,18) with BCL2 rearrangement is not found,. BCL1 rearrangement has been described, but t(11,14) and cyclin D1 expression are suggestive of a mantle cell lymphoma.

## Staging

As for other indolent lymphomas.

## Recommended Investigations

As for other indolent lymphomas.

Hepatitis C virus serology.



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## Potential Pitfalls

- Failure to establish a diagnosis in the patient presenting with isolated, unexplained splenomegaly – the decision to proceed with diagnostic splenectomy may be difficult, especially in elderly patients.
- Failure to distinguish from other CD5-negative indolent B cell lymphomas.
- Failure to distinguish from nodal marginal zone lymphoma.

## Treatment

Most behave in an indolent fashion, and patients should be treated as for low-grade/follicular lymphoma. Median survival is 10-13 years. Splenectomy may be followed by haematological responses and prolonged survival, and is the treatment of choice for fit patients. Other treatment options include splenic irradiation, alkylating agents, purine analogues or anti-CD20 antibody. Transformation to large cell lymphoma may occur.

## Response Evaluation and Follow Up

As for other indolent lymphomas.



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# Extra-nodal Marginal Zone B-Cell Lymphoma (Malt-Lymphoma)

## Definition and Incidence

Extranodal Marginal Zone B-cell Lymphoma of Mucosa Associated Lymphoid Tissue (MALT Lymphoma) is an extranodal lymphoma consisting of heterogeneous small B-cells. The gastrointestinal tract is the commonest site of development of MALT lymphoma, and the stomach is the most common location (85%). Gastric MALT lymphoma is considered to be derived from MALT acquired as a result of Helicobacter pylori infection. The incidence is 0.6 new cases / 100,000 population per year, median age 60 years and sex ratio shows a slight female excess.

**ICD-O Code** **9699/3**

## Clinical Presentation

Most patients have a history of chronic inflammation, secondary to autoimmune disorders or low grade infections which result in accumulation of extranodal lymphoid tissue. Examples include Helicobacter pylori associated chronic gastritis, Sjogren's Syndrome or Hashimoto's thyroiditis. Helicobacter pylori is detectable in most cases of gastric MALT lymphoma. Patients with Sjogren's syndrome and lymphoepithelioid sialadenitis have a 40-fold increased risk of developing lymphoma, and most of these are MALT lymphomas. Patients with Hashimoto's thyroiditis have a 3-fold increased risk of lymphoma development. Most patients present with Stage I or II disease, but 20% of patients have bone marrow involvement. Multiple extranodal sites are present in 10% of patients at presentation, with 30% becoming disseminated over time, and some transforming to DLBCL.
The 5-years overall survival is >80%.

## Pathology and Genetics

The lymphoma cells infiltrate around reactive B-cell follicles, external to a preserved follicle mantle, in a marginal zone distribution, and spread out to form larger confluent areas which eventually overrun some or most of the follicles. The characteristic marginal zone B cells have small to medium sized, slightly irregular nuclei with moderately dispersed chromatin and inconspicuous nuclei, resembling those of centrocytes with relatively abundant, pale cytoplasm. Plasmacytic differentiation is present in approximately one-third of gastric MALT-type lymphomas. Lymphoepithelioid lesions are usually present.

**Phenotype:**

CD19+ CD20+ CD22+ CD79a+ Slg+ Cd11c± CD43± CD5- CD10- CD23-. The tumour cells typically express IgM, and less often IgA or IgG, and show light chain restriction.

**Genetics:**

Trisomy 3 is found in 60% of cases, and the t(11,18)(q21;q21) in 25-50% and is not found in other lymphomas.

## Staging

As for other indolent lymphomas



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## Recommended Investigations

As for other indolent B-cell lymphomas. Additional investigations recommended for patients with Gastric MALT lymphomas are:

- Biopsy with H pylori stain and culture
  (H pylori serology may be useful if infection is not confirmed histologically)
- Urea breath test

Endoscopic Ultrasound may be useful but is not universally available. The t(11;18) status should be established.

## Prognostic Factors / Index

The clinical course is typically indolent, and these lymphomas are slow to disseminate. Involvement of multiple extranodal sites and bone marrow involvement do not appear to confer a worse prognosis.

Adverse prognostic factors identified for Gastric MALT lymphomas include:

- H.pylori negative
- Tumour invasion beyond the submucosa
- t(1;14)(p22;q21)
- t(11;18)(q21;q21) - this translocation does not respond to H pylori eradication
- Bcl-10 nuclear expression

## Potential Pitfalls

- Failure to properly identify diffuse large B cell lymphoma in the presence of an accompanying MALT lymphoma or to distinguish from de novo gastric diffuse large B Cell lymphoma.
- Failure to distinguish from other conditions. The differential diagnosis includes reactive processes (Helicobacter pylori gastritis, lymphoepithelial sialadenitis, Hashimoto's thyroiditis), and other small B-cell lymphomas (follicular lymphoma, mantle-cell lymphoma, small lymphocytic lymphoma).
- Ann Arbour staging is misleading – for example, involvement of multiple extranodal sites, especially within the same organ (e.g., salivary gland, skin, GI tract) does not indicate disseminated disease.

## Treatment

**Gastric MALT Lymphoma:**

**Limited disease:**

For disease confined to the mucosa or submucosa, H. Pylori eradication produces complete remission rates of approximately 70%. There is no clinical trial evidence to support the use of consolidation Chlorambucil therapy for patients with successful H.pylori eradication

Various effective regimens for H Pylori Eradication are available. One is:

- Omeprazole 20mg po bid x 1 week
- Amoxycillin 1g po bid x 7 days
- Clarithromycin 500mg po bid x 7 days
- Metronidazole 400 mg po bid x 7 days



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## Persistent / progressive disease or disease requiring specific anti-lymphoma treatment at diagnosis:

Additional treatment is needed for persistant or progressive disease, infiltration of the muscularis mucosa, nodal involvement or presence of t(11;18).

Management includes chemotherapy +/- Rituximab, with Chlorambucil being the commonest therapy used in gastric MALT lymphomas at a dose of 6mg/m2/day for 14 days q 28 days for 6-12 cycles (2 cycles beyond CR). Rituximab therapy is active in this lymphoma, though there is no consensus about when it should be used. Loco-regioal RT of 30Gy (20 fractions) RT to stomach and adjacent lymph nodes has been advocated as second line therapy.

## Response Evaluation and Follow Up

Follow-up is essential following HP eradication in early stage disease. Serial endoscopy with biopsy is recommended to ensure eradication of HP and disappearance of lymphoma for:

- 2-3 months after antibiotic therapy
- Twice annually for 2 years at least
- Annually thereafter

If H.pylori has not been eradicated by 2 months, alternative second line antibiotic therapy should be given. If there is tumour progression at any stage, chemotherapy +/-radiotherapy should be given.

Patients who are well and showing stable disease or partial responses should not be deemed 'failures' until 1 year after treatment as responses can be slow, unless the patient has poor prognostic features (tumour invasion beyond the submucosa, H. pylori negative patients, t(1;14)(p22;q21), t(11;18)(q21;q21), Bcl-10 nuclear expression). These patients should be deemed 'failures' to H.pylori eradication if there is no PR at 2 months or CR at 6 months.

**Non-gastric MALT lymphomas** behave in an indolent fashion and should be treated in the same way as Gastric MALT Lymphomas but without H. pylori eradication. Stage I and II disease may be treated with observation post surgical resection, chemotherapy or locoregional radiotherapy. Stage III and IV disease (uncommon) should be treated as for other indolent lymphomas, unless transformation to high-grade histology is demonstrated.



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# Nodal Marginal Zone B-Cell Lymphoma

## Definition and Incidence

Nodal Marginal Zone Lymphoma is a primary nodal B-cell neoplasm that morphologically resembles lymph nodes involved by marginal zone lymphoma of extranodal or splenic types, but without evidence of extranodal or splenic disease. Monocytoid B-cells may be prominent. The disease is rare, comprising <2% of lymphoid neoplasms.

**ICD-O Code** **9699/3**

## Clinical Presentation

Patients present with localised (rare) or generalised lymph node involvement. Blood involvement is rare.

## Pathology and Genetics

The marginal zone and interfollicular areas of the lymph node are infiltrated by marginal zone (centrocyte-like) B cells, monocytoid B-cells, or small B-lymphocytes, with scattered centroblast and immunoblast-like cells present. Two types have been described, one that resembles nodal involvement by MALT lymphoma, and the other that resembles splenic marginal zone lymphoma. Transformation to large cell lymphoma may occur.

## Immunophenotype

Most cases are similar to extranodal marginal zone (MALT) lymphoma. Some are reported to be IgD+, CD43-, similar to splenic marginal zone lymphoma.

## Staging

As for other indolent lymphomas.

## Recommended Investigations

As for other indolent lymphomas.

## Prognostic Factors / Index

The clinical course of this disease has not been well studied. Median survival is consistent with that seen in indolent lymphomas.

## Potential Pitfalls

- In patients with extranodal (MALT) lymphoma, Hashimoto's thyroiditis or Sjogren's Syndrome, nodal involvement by marginal zone lymphoma should be considered secondary to the MALT lymphoma.

## Treatment

Median survival is 5 years. No prospective study has identified the most appropriate treatment. Early progression is common in younger patients. Consider chlorambucil in older patients and CVP or fludarabine in younger patients. Rituximab may also have a role. Most patients respond to chemotherapy, but early relapse is common.

## Response Evaluation and Follow Up

As for other indolent lymphomas.



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# Follicular Lymphoma

## Definition and incidence

Follicular Lymphoma (FL) is a neoplasm of follicle centre B cells (centrocytes/ cleaved follicle centre cells (FCC) and centroblasts/ non cleaved FCC).

Worldwide FL is the second most frequent subtype of nodal lymphoid malignancies. The incidence of this disease has been increasing steadily during recent decades rising from 5-6 cases/ 100,000/ year in the 1950s to about 15/ 100,000/ year according to recent US figures. It accounts for about a third of cases of adults with NHL in the USA and 22% worldwide. The incidence of FL is lower in Asia and in underdeveloped countries. FL accounts for 70% of cases of indolent lymphomas enrolled in clinical trials in the USA. The median age of diagnosis is 59 years with a male: female ratio 1:1.7. It rarely affects people under the age of 20.

### ICD-O Codes

| | |
|---|---|
| **Follicular Lymphoma** | **9690/3** |
| **Grade 1** | **9691/3** |
| **Grade 2** | **9695/3** |
| **Grade 3** | **9698/3** |

## Clinical Presentation

FL predominantly involves lymph nodes but also involves spleen, bone marrow, peripheral blood and Waldeyer's ring. Involvement of non- haematopoietic extra-nodal sites such as skin, gastrointestinal tract, and soft tissues is usually in the context of widespread nodal disease. Primary follicular lymphoma of the skin (cutaneous follicular lymphoma) is rare but is one of the commonest cutaneous B- cell lymphomas.

Most patients have widespread disease at diagnosis with peripheral and central (abdominal and thoracic) nodal enlargement as well as splenomegaly. Bone marrow involvement is found in 40% of patients at diagnosis and only 30% will have stage I/II disease. Most patients are asymptomatic apart from lymph node swelling, despite widespread disease. The disease is characterised by a recurring and remitting course (usually in response to treatment) over several years with increasing resistance to chemotherapy and radiation over time. Death usually occurs due to bulky, resistant disease or high grade transformation to diffuse large B-cell lymphoma (DLBCL)

## Pathology and Genetics

Four growth patterns can be found in FL (1) follicular (>75% follicular), follicular and diffuse (25-75% follicular) and minimally follicular (< 25% follicular) and diffuse (0% follicular). FL is composed of two cell types normally found in the germinal centre; centrocytes or cleaved follicle centre cells and the larger transformed centroblasts.



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FL is graded on the proportion of centroblasts present and the WHO classification describes three grades based on counting the absolute number of centroblasts present per 40 x high-power microscopic field/hpf. It is recognised that distinction between grades 1 and 2 is not clinically useful and the use of a Grade 1-2 (low grade) category is encouraged.

- Grade 1-2 (low grade) 0-15 centroblasts/hpf
- Grade 1 cases have 0-5 centroblasts/hpf
- Grade 2 cases have 6-15 centroblasts/hpf
- Grade 3 cases have >15 centroblasts/hpf
- Grade 3A centrocytes still present
- Grade 3B solid sheets of centroblasts

In bone marrow, FL characteristically localises to the paratrabecular region but can involve the interstitial areas.

Rare FLs have a completely diffuse growth pattern, but must have either a typical FL immunophenotype or a t(14;18) before this diagnosis can be made. The cells must resemble centrocytes with only a minor component of centroblasts. If there are >15 centroblasts/hpf in a diffuse area, then this should be diagnosed as diffuse large B cell lymphoma.

'In situ' FL is another rare variant in which there is colonization of lymphoid follicles with bcl2-overexpressing FL cells. Its' clinical significance is unclear but it may represent a precursor lesion to true FL.

## Immunophenotype

Immunophenotype: FL cells express the B-cell antigens CD 19, CD 20, CD 22 and CD 79a and are usually Slg +, BCL 2+, CD10+, CD5-. The nuclear protein BCL6 is usually expressed. Cutaneous FL is typically BCL 2-ve.

## Genetics

FL is characterised by the t(14;18)(q32;q21) which involves juxtaposition of the BCL 2 gene and the immunoglobulin heavy-chain locus and is present in 70- 95% of cases leading to up-regulation of the anti-apoptotic BCL-2 gene. The translocation can be detected by PCR technology in 85% of cases.

## Staging

Staging of disease is reported according to the Ann Arbor staging classification. Nodal areas are defined as follows:

| | |
|---|---|
| **Cervical:** | pre-auricular, cervical, supraclavicular. |
| **Mediastinal:** | paratracheal, mediastinal, hilar, retrocrural. |
| **Axillary** | |
| **Para-aortic:** | Para-aortic, common iliac, external iliac |
| **Mesenteric:** | Coeliac, splenic, portal, mesenteric |
| **Inguinal:** | Inguinal , femoral |
| **Other:** | eg trochlear |

## Recommended investigations

| | |
|---|---|
| **Generic** | See page 2 |
| **Specific:** | Immunoglobulins and electrophoresis |

## Prognostic factors/ FLIPI index

**Prognostic factors:** Age > 60 vs <60

Ann Arbor III /IV vs I/II

Hb <12 vs >12

Nodal areas > 4 vs< 4 (see staging)

LDH, high vs normal

| Risk Group: | Adverse Factors | % patients | 10yr OS |
|---|---|---|---|
| Low Risk | 0-1 | 36% | 70% |
| Intermediate Risk | 2 | 37% | 50% |
| High Risk | ≥3 | 27% | 35% |



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## Potential Pitfalls

*a.* Failure to differentiate from reactive disease

*b.* Failure to differentiate from mantle cell lymphoma

*c.* Failure to grade and especially to distinguish grade 3b

*d.* Failure to recognise as a component of DLBCL (diffuse large B-cell lymphoma) when FL has undergone high- grade transformation

## Treatment

### Stage I /II

Radiation therapy with curative intent is the treatment of choice. Involved field radiotherapy using doses of 24-40Gy with potential dose adaption according to disease response should be used.

### Stage III/IV

Conventional treatment is not curative and there is no evidence that early treatment of asymptomatic patients improves overall survival. Treatment should be delayed until disease becomes symptomatic, leads to critical organ impairment or undergoes high- grade transformation. Spontaneous regression may occur in 10- 20% of patients being observed.

The least toxic, effective treatment should be used to avoid long term effects in patients who may have a prolonged survival. Patients should be treated to a stable or asymptomatic disease status and then observed until disease progression. At this stage re-evaluation is undertaken (tissue sampling and re-staging) and further treatment planned. Disease which has not progressed for >2 years may be managed without escalated therapy. This approach results in a median survival of 8-13 years with patients receiving an average of 3 courses of treatment. Younger patients with good performance status at first or second progression should be considered for potentially “curative approaches” using stem-cell transplantation.

### Single agent chemotherapy

Chlorambucil: can be used as pulse therapy (10mg/m2) for 5 days every 28 days or continuous low dose therapy, usually for 6 months resulting in an ORR of about 80%. Chlorambucil is stem cell toxic and should be avoided if a stem cell harvest is being considered.

Fludarabine: Results in an ORR rate of 30-60% in relapsed disease and should be avoided if a stem cell harvest is being envisaged

Rituximab: Active in >80% as a single agent in de novo patients and 65% of previously treated/refractory patients. No data supports its use as a first line single agent, but it may be useful in patients with compromised marrow or poor performance status.

### Combination chemotherapy

R-CVP has an ORR of 81% and EFS of 32 months after 8 cycles. R-CVP is not stem cell toxic and is useful first line therapy in patients <65 where stem cell harvesting may be contemplated.

Rituximab combinations with a purine analogue such as the FCR combination has an ORR rate of 92% however the associated immunosuppression is a significant consideration in treating patients >65 years.

R-combination (anthracycline-containing): R-CHOP is indicated for rapid disease control, in disease refractory to non-anthracycline containing therapy, in patients with grade 3 disease or as second line therapy. The use of RCHOP as primary chemotherapy is associated with a lower rate of high grade transformation.

Rituximab maintenance (RM) can be given in various schedules of which the commonest is Rituximab 375mg/m2 every 3 months for 2 years. A meta-analysis confirms the survival advantage of RM as part of the primary therapy and at relapse.

The radioimmunisotope Zevalin is licensed for FL which has relapsed after Rituximab based treatment resulting in response rates of up to 78%. Zevalin has also been used as consolidation after first line treatment and prolongs PFS by a median of 2 years.

**Stem cell transplantation**

High dose therapy (HDT) with autologous blood stem cell support (PBSCT) can be considered for patients <65 years at first or second disease progression following treatment. This approach results in a disease free survival of 31%-47% at 5-10 years with different groups emphasisng the impotance of varying prognostic factors such as molecularly detectable disease in the marrow, FLIPI index and histological grade. Selected patients will benefit from allogeneic transplantation, with a DFS of up to 85% at 8 years reported using the Mc Kinnon non-myeloablative regimen.

## Response Evaluation

Clinical response should be monitored every 2 cycles of treatment with an interim scan after 4 cycles and at the end of treatment. Patients with an inadequate response should receive escalated therapy.

## Follow up

**Clinical:**

History and physical examination every 3 months for 2 years, every 6 months for a further 3 years and then yearly to exclude disease progression and the development of secondary malignancies.
The role of follow-up scanning is unclear but is useful in patients with bulky, intra-abdominal disease.

**Laboratory:**

FBC and biochemical profile including LDH at 3, 6, 12 and 24 months.



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# Mantle Cell Lymphoma

## Definition and incidence

Mantle cell lymphoma (MCL) is a B-cell neoplasm composed of monomorphic small to medium sized lymphoid cells with irregular nuclei which most closely resemble centrocytes/ follicle centre cells but with less-irregular nuclei. MCL accounts for 3-10% of non-Hodgkin lymphomas, occurring predominantly in middle-aged or older individuals (median age 63) with an incidence of 0.72 cases/100,000/year and a male: female ratio of 5:1.

**ICD – O Code** **9673/3**

## Clinical Presentation

Patients usually present with enlarged lymph nodes at multiple sites and frequently a massively enlarged spleen. Bone marrow involvement with occasional leukaemic spill is present in 80% of patients. Waldeyer's Ring and the gastrointestinal tract are frequent extra-nodal sites of involvement. Lymphomatous polyposis of the gastrointestinal tract is a form of mantle cell lymphoma and can occur as variably-sized polyps in any part of the gastrointestinal tract.

## Pathology and Genetics

MCL shows architectural destruction by a monomorphic lymphoid proliferation with a vaguely nodular or mantle zone growth pattern. Many cases have scattered single epithelioid histiocytes which can produce a 'starry sky' appearance. Hyalinized small blood vessels are commonly seen. Disease progression or relapse is characterised by an increase in nuclear size, pleomorphism, nuclear chromatin dispersal and an increase in mitotic activity. Blastoid variants with cells resembling lymphoblasts and a high mitotic index are associated with a worse prognosis.

## Immunophenotype

The neoplastic cells are monoclonal B-cells with intense surface IgM+/- IgD. They are CD19+ve, CD20+ve, CD5+ve, FMC7+ve and CD10-ve and express Cyclin D1. Cases with gastrointestinal involvement express the alpha4B7 homing receptor.

## Genetics

MCL is defined by the presence of the t(11;14)(q13;q32) resulting in juxtaposition of CyclinD1 and the IgH gene which leads to upregulation of CyclinD1. The translocation can be detected reliably by FISH and in about 40% of cases by PCR.

## Staging

Staging of disease, if nodal, can be reported using the Ann Arbor classification, but is clearly not appropriate for extranodal presentation such as multiple lymphomatous polyposis.

## Recommended Investigations

**Generic:** see page 2

**Specific** Gastrointestinal endoscopy (if appropriate)

BMA and trephine, with immunophenotyping and FISH / PCR if marrow involved.



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## Prognostic factors/ index

The IPI is generally used, however this has been modified for advanced MCL to the MIPI, which has not gained widespread popularity because of the complex statistics needed to score patients based on age, ECOG score, LDH and leucocyte count (Blood 2008,111:558-565)

| IPI Score | OS at 5 years |
|---|---|
| 0 | 23% |
| 1 | 45% |
| 2 | 54% |
| 3 | 25% |
| 4 | 23% |
| 5 | 0% |

## Potential pitfalls

***a.*** Confusion with other lymphomas notably FL and CLL/SLL

***b.*** Blastic MCL may be mis-diagnosed

***c.*** Failure to recognise multiple lymphomatous polyposis

## Treatment

There are no randomised controlled trials defining optimal first line treatment. The best published outcome is with R-HCVAD which gave a CR rate of 90% and a progression-free survival (PFS) of 75% at 5 years. This should be considered for younger patients and possibly all patients with a good performance status. Regimens containing anthracyclines in historical series offered no advantage over those without an anthracycline. The Nordic group has obtained equivalent outcomes using intensified CHOP with additional cytosine arabinoside followed by a first remission autograft.

Rituximab with fludarabine, cyclophosphamide and mitoxantrone (FCMR or FCM) may be effective for those unable to tolerate R-HCVAD. Proteasome inhibitors are a biologically logical treatment and in Phase II studies show encouraging results.

MCL is considered incurable with conventional-dose chemotherapy. It is appropriate therefore to consider allogeneic transplant for those who achieve a CR or good PR, are fit and have an HLA compatible sibling donor. If a sibling donor is not available then high-dose chemotherapy with autologous stem cell support should be considered in first complete remission. Results for those given autologous transplantation in partial remission or in complete remission at a later stage in their disease are poor (OS< 20% at 5 years).

## Response Evaluation and Follow up

There are no agreed recommendations for the evaluation and follow-up of patients with MCL, but the recommendations for FL can be applied. Approaches may need to be revised as treatments and treatment outcomes improve.

# Diffuse Large B-Cell Lymphoma

## Definition and Incidence

Diffuse large B-cell lymphoma (DLBCL) is composed of B lymphoid cells with nuclear size equal to or exceeding macrophage nuclei or more than twice the size of a normal lymphocyte. DLBCL accounts for about 30% of cases of non-Hodgkin Lymphoma with an incidence of 4 cases/ 100,000/ year. The incidence increases with age from 0.3 at 35-39 years to 26.6 at 80-84 years. The median age of diagnosis is 64 years with an equal sex ratio. In recent decades the incidence has been increasing independent of HIV infection as a risk factor.

**ICD – O Code:** **9680/3**

## Clinical Presentation

DLBCL can present with nodal or extranodal disease, with up to 40% of cases presenting with extranodal disease. The most common extranodal site is the gastrointestinal tract (mainly stomach and ileocaecal region) but the disease can present at virtually any location including skin, central nervous system (CNS), bone, testis, soft tissue, salivary gland, female genital tract, lung, kidney, liver, Waldeyer's ring and spleen. Primary presentation with bone marrow or peripheral blood involvement is rare. Primary mediastinal large B-cell lymphoma differs in that the disease is limited to the mediastinum and is seen more frequently in women between 20-40 years. Patients typically present with a single, rapidly enlarging mass which on staging may be more disseminated. Transformed DLBCL following an indolent lymphoma such as chronic lymphocytic leukaemia/ small lymphoctic lymphoma (CLL/SLL), follicular lymphoma, marginal zone B-cell lymphoma or lymphocyte predominant Hodgkin lymphoma is well described. Underlying immunodeficiency and auto-immune diseases are significant risk factors and are frequently associated with Epstein-Barr virus (EBV) positivity.

DLBCL replaces the normal architecture of the lymph node or tissue of origin diffusely, though the infiltration can be partial, inter-follicular or rarely sinusoidal. The perinodal soft tissues are often infiltrated. DLBCLs are morphologically diverse including a number of specific subtypes and specific entities (see below) and a large number of cases which are grouped together as DLBCL not otherwise specified (NOS). DLBCL NOS includes the common morphologic variants centroblastic, immunoblastic and anaplastic in addition to rare morphologic variants. DLBCL NOS can also be divided into subgroups based on immunophenotype (CD5+, Germinal centre B cell-like (GCB), non-GCB) or based on gene expression profile (Germinal center B cell-like (GCB) and activated B cell-like (ABC)) although use of these subgroups to determine therapy is not currently recommended.

Specific subtypes of DLBCL include T cell/histiocyte rich DLBCL, Primary CNS DLBCL, Primary cutaneous DLBCL (leg type) and EBV positive DLBCL of the elderly.

Specific DLBCLs with characteristic clinicopathological features include Primary mediastinal large B cell lymphoma, Intravascular large B cell lymphoma, DLBCL associated with chronic inflammation, Lymphomatoid Granulomatosis, ALK-positive large B cell lymphoma, Plasmablastic lymphoma, Primary effusion lymphoma and Large B cell lymphoma arising in HHV-8 associated Castleman's disease.

## Immunophenotype

DLBCL express pan-B markers including CD19, CD20, CD22 and CD 79a. Surface and/or cytoplasmic immunoglobulin (IgM>IgG>IgA) can be demonstrated in 50-75%. CD30 is expressed in some with anaplastic morphology. Some cases of DLBCL (<10%) express CD5, most of which represent de novo DLBCL rather than transformation from CLL/SLL. CD5 +ve DLBCL is cyclin D1 –ve, allowing differentiation from blastoid mantle cell lymphoma. CD10 is expressed in 30-60% of cases, BCL6 in 60-90%, BCL2 in 30-50%, and IRF4/MUM1 in 35-65% of cases (IRF4/MUM1 and BCL6 co-expression may be present). Immunophenotypic subgrouping of DLBCL is based on expression of CD10/BCL6/IRF4/MUM1.

The proliferation fraction, measured by Ki-67 staining is usually high (>40%) and may be greater than 90% in some cases.

## Genetics

The t(14;18)(q32;q21) occurs in 20-30% of cases. Up to 30% show abnormalities of the 3q27 region involving BCL6. Microarray studies have shown two major molecular categories of DLBCL with germinal centre (GC) and activated B cell (ABC) patterns suggestive of malignant transformation at different stages of B-cell development. The immunophenotypic profile of GC DLBCL is CD10+ve, BCL6+ve and the ABC pattern is usually CD10-ve, BCL6-ve and BCL2+ve

## Staging

Staging of DLBCL is described according to the Ann Arbor staging classification with mention of bulky disease. The International Prognostic Index, IPI (see below) is clinically useful and should be included in the patient evaluation.

## Recommended Investigations

**Generic**: see page 2

**Specific:** LP and CSF examination if patients have the following risk factors: involvement of the spine, base of skull, testis or bone marrow or =>3 adverse prognostic factors on the IPI index. Intrathecal methotrexate or cytarabine should be given in association with any diagnostic tap.

| Prognostic Factor | |
|---|---|
| Age | > 60 |
| LDH | > normal |
| Performance Status | 2-4 |
| Extra-nodal Disease | > 1 |
| Stage | III or IV |

| IPI | No. of Risk Factors |
|---|---|
| Low Risk | 0, 1 |
| Low / Intermediate Risk | 2 |
| High / Intermediate Risk | 3 |
| High Risk | 4, 5 |

## Potential Pitfalls

*a.* Failure to differentiate histologically from carcinomas and sarcomas, especially at extranodal sites.

*b.* Failure to differentiate from mantle cell lymphoma or Burkitt Lymphoma variants.

*c.* Failure to recognise origin of DLBCL from pre-existing lymphoproliferative diseases.

*d.* Failure to recognise background immunodeficiency, notably HIV infection.

## Treatment

Multidisciplinary treatment planning is required.

**Stage I non-bulky disease**

- Nodal disease <10cm
- Treat with Rituximab – CHOP (R-CHOP) x 4 cycles. and involved field radiation (IFRT) using 40Gy or 6 cycles of R-CHOP



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**Stage 1 (bulky) and stages II – IV**

R-CHOP for 6-8 cycles. The decision in low or low-intermediate risk IPI patients is based on giving 2 cycles beyond achievement of complete response. Those with high-intermediate or high IPI scores should have maximum treatment. Accelerated R-CHOP at 14 day intervals with G-CSF for 6 cycles may be equally effective. Consolidation radiation to sites of bulky disease should be considered. The OS at 5 years of 65% remains sub-optimal and approaches such as the NCI-sponsored DA-R-EPOCH using infusional chemotherapy appears to result in a higher OS of 73% and PFS of 70% at 5 years. Prognostic factor adjusted chemotherapy in DLBCL has not yet been adopted in a uniform fashion, though it is clearly an area of critical importance.

## Response Evaluation

Response should be evaluated every two cycles of treatment, with radiological evaluation after 4 cycles and at the end of treatment. Infiltration of marrow or CSF at diagnosis, needs to be rechecked at the end of treatment. Patients who are not in PET negative CR at the end of treatment have primary refractory disease and should be considered for salvage therapy.

## Follow up

**Clinical:** History and physical examination every 3 months for 2 years, every 6 months for 3 years and then yearly with particular attention to second malignancies.

**Laboratory:** Blood counts and biochemistry including LDH at 3, 6, 12, and 24 months and then as needed. Thyroid function should be evaluated yearly following neck irradiation.

**Diagnostic Imaging:** Chest radiograph and CT evaluation if appropriate at 6, 12 and 24 months after completion of therapy and then as clinically indicated.

## Relapsed or Resistant DLBCL

Patients with primary refractory disease may not need to be re-biopsied before initiating salvage therapy, but all patients with relapsed disease should be re-biopsied. Assessment and staging is the same as in newly-diagnosed disease. The total anthracycline dose must be assessed if they are to be used in salvage therapy and a pre-treatment ECHO is advised.

**Treatment:** In patients <65 years without critical organ dysfunction, who received adequate first line therapy, salvage chemotherapy followed by high-dose treatment with blood stem cell support is recommended. There are many salvage regimens in use eg R-DHAP, R-ESHAP, R-IEV and R-ICE, with no randomised trial to show superiority of a particular regimen. Salvage treatment should be chosen based on local experience, transplant team preference and patient co-morbidity, with an aim to attain PET –ve CR prior to BEAM transplant. Involved field radiotherapy may be used at day 100 post-transplant in some patients. For those not suitable for high-dose treatment the same salvage regimens can be used but with low expectation of success. Allogeneic stem cell transplant may be indicated in a small group of patients with relapsed DLBCL.

## Response Evaluation and follow up

as described for patients in first complete remission.

# Mediastinal (Thymic) Large B-Cell Lymphoma

## Definition and incidence

Mediastinal (thymic) large B-cell lymphoma (med-DLBCL) is a subtype of DLBCL of putative thymic B-cell origin arising in the mediastinum which has distinctive clinical, immunophenotypic and genetic features. It primarily affects people in the third or fourth decades with a female:male ratio of 2-4:1 and has an incidence rate of .25/100,000/year.

**ICD – O Code** **9679/3**

## Clinical Presentation

Patients present with localized disease and signs and symptoms related to large anterior mediastinal masses, sometimes with superior vena cava obstruction, pleural and/or pericardial effusions. Disease at extranodal sites is frequently present at relapse involving the CNS, liver, adrenal glands, kidneys and gastrointestinal tract.

## Pathology and Genetics

There is marked diffuse lymphoid proliferation associated with variably dense compartmentalizing fibrosis. Immunohistochemical staining with cytokeratin markers may identify thymic remnants and resemble carcinoma. The neoplastic cells are medium to large sized cells, typically with abundant pale cytoplasm and oval nuclei. Some cases exhibit more pleomorphic nuclei.
An admixture of benign small lymphocytes and eosinophils may suggest Hodgkin Lymphoma and occasionally Med-DLCBCL and Nodular Sclerosis Hodgkin Lymphoma (NSHL) may co-exist as a composite lymphoma.

## Immunophenotype

Med-DLBCL expresses CD45 (CLA) and classical B-cell markers such as CD19 and CD20. CD30 is expressed in >80% of cases but is often weak and heterogenous. CD15 is usually negative, IRF4/MUM1 and CD23 are positive in >75% of cases. CD10 is rarely positive (<30%)

## Genetics

BCL2, BCL6 and MYC rearrangements are rare. Med-DLBCL has a unique transcriptional signature but shares some characteristics with classical Hodgkin lymphoma.

## Investigations and staging

As for DLBCL

## Prognostic Factors

Disease bulk and response to treatment are the major determinants of outcome. Spread to infra-diaphragmatic organs is associated with an unfavourable outcome. Histological variations are not of prognostic significance.

## Potential Pitfalls

***a.*** Failure to provide clinical information to the pathologist which suggests the diagnosis.

***b.*** Failure to differentiate from a carcinoma (thymic) or germ cell tumour.

***c.*** Confusion with Nodular Sclerosis Hodgkin Lymphoma, which may co-exist as a composite lymphoma.

***d.*** Basing a diagnosis on an inadequate tissue sample.



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## Treatment

Standard chemotherapy for DLBCL with 6-8 cycles of R-CHOP can be used but is traditionally followed by involved field radiation to the mediastinum. Recent experience with DA-R-EPOCH and no radiotherapy is associated with an OS of 78% and EFS of 67%, which may be preferably as it avoids the need to irradiate breast tissue in women and the myocardium in both sexes. If a sub-optimal response is obtained from chemotherapy, the decision to use radiotherapy versus peripheral blood stem cell transplantation must be made with care, as the mortality risk of transplant following radiotherapy is substantial.

## Response Evaluation and Follow up

As outlined for DLBCL. PET scanning is recommended at the end of treatment evaluation.



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# Organ-Specific Variants of Diffuse Large B-Cell Lymphoma

## Primary CNS Lymphoma

### Clinical

This may occur in HIV+ or HIV- patients. The prognosis is poor in patients treated with radiation therapy alone (<6 months in HIV+ patients and 1-2 years in immuno-competent patients), with significant treatment-related morbidity.

Current recommendations are for early chemotherapy with high dose methotrexate or high dose ara-C followed by whole brain radiation therapy, which may improve survival and be associated with a lower risk of leukoencephalopathy than radiation therapy alone. Current trials are evaluating the role of chemotherapy as a single modality. Patients should be treated in a centre where neurological, haematological/medical oncological and radiation oncological expertise are available on-site as careful multidisciplinary planning is essential.

### Other subsets outside the scope of these guidelines

- Primary cutaneous DLBCL, leg type
- EBV positive DLBCL
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- Intravascular large B cell lymphoma
- ALK positive large B cell lymphoma
- Plasmablastic lymphoma
- Primary effusion lymphoma
- Large B cell lymphoma arising in HHV8-associated multicentric Castleman disease



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# Burkitt Lymphoma/Leukaemia

## Definition and Incidence

Burkitt lymphoma (BL) is an aggressive lymphoma, which frequently presents at extranodal sites or as acute leukaemia. The lymphoid proliferation is composed of monomorphic, medium-sized B-cells with basophilic cytoplasm and numerous mitotic figures. Translocation involving MYC is a constant genetic feature and EBV is found in a variable proportion of cases. The disease is rare with an incidence rate of < 0.2 / 100,000 / year and sporadic BL accounts for 1-2% of lymphomas in Western Europe and the USA. BL accounts for 30-50% of all childhood lymphomas. The median adult age of onset is 30 years and the male:female ratio is 2-3:1. Endemic BL occurs in equatorial Africa and Papua New Guinea which corresponds to the distribution of malaria and has a peak incidence in childhood (4 - 7 years). Immunodeficiency associated BL is primarily associated with HIV infection and is often the AIDS – defining illness.

**ICD – O Code:** **9687/3 (lymphoma)**
**9826/3 (leukaemia)**

## Clinical Presentation

Patients with sporadic BL present with abdominal masses frequently of the ileo-caecal region, a nasopharyngeal mass or leukaemia. Other presentations include involvement of the ovaries, kidneys and breasts. Retroperitoneal disease may be associated with spinal epidural compression resulting in paraplegia. Bone marrow involvement in a primarily lymphomatous presentation is a poor prognostic feature and is found in patients with a high tumour burden. Such patients have a high LDH and uric acid levels and are at risk of the tumour lysis syndrome.

## Pathology

Classical BL is composed of medium sized cells, with round nuclei, clumped chromatin and numerous nucleoli. The cytoplasm is deeply basophilic and usually contains lipid vacuoles. There is a high proliferation rate with numerous mitotic figures and "starry sky" pattern due to the presence of numerous benign macrophages which have ingested apoptotic tumour cells.

## Immunophenotype

Tumour cells express membrane IgM with light chain restriction and B-cell associated antigens such as CD 19, 20 and 22. CD10 and BCL6 are also expressed. The cells are negative for CD5, CD23 and BCL2. A very high growth fraction is observed and nearly 100% of cells are positive for Ki 67. Infiltrating T-cells are rare.

The blast cells of BL presenting as leukaemia have a mature B-cell phenotype with surface Ig, light chain restriction and expression of CD10, CD19, CD20, CD22 and CD79a, but not TdT.

## Genetics

Burkitt lymphoma is defined by translocation of MYC at band q24 to chromosome 14 q32 (t(8;14)) or less commonly to light chain loci at 2q11 or 22q11 leading to MYC over–expression. In endemic cases the breakpoint on chromosome 14 involves the heavy chain joining region (early B-cell) whereas in sporadic cases the translocation involves the Ig switch region (later stage B-cell). EBV genomes can be demonstrated in most endemic cases, 20-40% of immunodeficiency BL and <30% of sporadic BL.



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## Staging

St Jude modification of Ann Arbor

| Stage | Definition |
|---|---|
| I | A single tumour (extranodal) or single anatomic area (nodal) with the exclusion of mediastinum or abdomen. |
| II | A single tumour (extranodal) with regional node involvement. Two or more nodal areas on the same side of the diaphragm. Two single (extranodal) tumours + regional node involvement on the same side of the diaphragm. Primary gastrointestinal tract tumour, usually in the ileocaecal area + involvement of associated mesenteric nodes only. |
| IIR | Completely resected abdominal disease. |
| III | Two single (extranodal) tumours on opposite sides of the diaphragm. Two or more nodal areas above and below the diaphragm. All primary intrathoracic tumours (mediastinal, pleural, thymic). All paraspinal or epidural tumours, regardless of other tumour sites. All extensive primary intra-abdominal disease. |
| IIIA | Localized but non-resectable abdominal disease. |
| IIIB | Widespread multiorgan abdominal disease. |
| IV | Any of the above with initial CNS and/or bone marrow involvement (<25%). |

Prognostic factors/index: A working modification of the St Jude's staging developed by Magrath is as follows:

**Low risk**

Stage I, II disease
ECOG 0-2
No tumour mass ≥10 cm
Normal LDH level

**High risk**

All other patients

## Recommended Investigations

**Generic** see page 2

**Specific** LP and CSF evaluation

Bone marrow aspirate and biopsy with immunophenotype and cytogenetics

EBV serology

## Potential Pitfalls

*a.* Failure to recognise the disease and institute therapy promptly.

*b.* Failure to recognise tumour lysis syndrome risk and to prepare for and treat appropriately.

*c.* Failure to use specific treatment regimens designed for BL.

## Treatment

Treatment for BL consists of intensive in-patient treatment delivered within a 4 month period and therefore differs from both conventional high grade lymphoma and lymphoblastic lymphoma treatment. The risk of tumour lysis syndrome is high with the first cycle of therapy and the treatment should only be delivered in a unit familiar with the monitoring and management of this complication.



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CODOX-M, (3 cycles) for low risk disease and CODOX-M/IVAC (2 cycles) for high risk disease is the current treatment of choice. Dose intensity is vital for optimal outcome and treatment should be given in full doses without delays. Cure rates with this approach are 90% for low risk disease and 60% for high risk disease. There is no randomised control trial evidence for the addition of Rituximab; however it is active in BL and its use is logical. Patients who relapse generally die and there is no proven indication for high-dose treatment strategies.

## Response Evaluation

The key factor is to deliver treatment with maintenance of dose intensity. The patient should be assessed with CT scan, BM aspirate and CSF after the first course of chemotherapy to ensure remission. At the end of treatment, tests which were abnormal at diagnosis such as CT scan, bone marrow or CSF examination should be repeated.

## Follow Up

Relapse is usually seen within one year and patients remaining free of disease at two years can be considered cured. Rare late “relapses” due to the evolution of a second BL clone have been described.

Monthly follow up for first 6 months, 2 monthly for 6 months, 4 monthly for a year and then annual follow up is recommended, with particular attention to late effects.

Female patients usually maintain fertility following CODOX-M/IVAC but the fertility outcome for post-pubertal males is unclear.



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# B Cell Lymphoma

## Definition and Incidence

Aggressive large cell B cell lymphomas with morphologic and genetic features of both DLBCL and Burkitt lymphoma but with atypical features which preclude classification with either of these entities. Some of these cases were previously classified as Burkitt-like lymphoma. Some cases have mixed morphology intermediate between DLBCL and BL, others have typical morphology of BL but atypical immunophenotype or genetic features.

This disease category is heterogenous, infrequently diagnosed, and is not a distinct entity but allows classification of cases which are impossible to classify as classical DLBCL or BL.

**ICD – O Code: 9680/3**

## Clinical Presentation

Many cases present with extra-nodal disease but there is no particular association with ileocaecal or jaw location. Bone marrow and peripheral blood may be involved.

## Pathology

There is a diffuse proliferation of medium to large sized lymphoid cells with frequent mitotic and apoptotic activity and many macrophages with a "starry sky" appearance.

Nuclear morphology is more variable than in classical BL including variation in nuclear size, nuclear irregularity and/or prominent nucleoli. In some cases morphology is typical of BL but immunophenotype and/or genetic features are not. Occasional cases have smaller nuclei resembling lymphoblasts.

**Cases of morphologically typical DLBCL with very high proliferation fraction should NOT be included.**

## Immunophenotype

B cell markers are positive, including CD20, CD19 and CD79a. Surface Ig is typically positive. Ki67 labelling index is usually very high. Many cases in this category demonstrate a typical immunophenotype for BL (CD10+, BCL6+, BCL2- IRF4/MUM1-) but atypical morphology. Cases with typical morphology of BL but atypical immunophenotype (BCL2+) are also included although such cases may also represent a "double-hit" phenomenon with both *BCL2* and *MYC* translocations.

## Genetics

Clonal Ig gene rearrangements are present. 35-50% of cases have 8q24/MYC translocation but unlike BL many of these are non IG-MYC translocations. BCL2 translocation is present in up to 15% of cases and may be associated with MYC ("double hit") and/or BLC6 translocations. A complex karyotype is frequent, unlike BL.

## Staging

As for Burkitt Lymphoma

## Recommended investigations

As for Burkitt Lymphoma



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## Potential pitfalls

Failure to differentiate from DLBCL

## Treatment

Standard DLBCL therapy is unlikely to be curative. Chemotherapy regimens used in Burkitt's lymphoma are active. Another approach is to use DA-R-EPOCH, which is more anthracycline intensive than classical Burkitt's regimens. Patients should receive CNS directed therapy. Patients with double hit lymphomas originating from a follicular lymphoma have a very poor prognosis.

## Response evaluation and Follow-up

Restage after first course of chemotherapy (Burkitt regimen) or second / fourth course with DA-R-EPOCH and then at the end of treatment. The risk of relapse remains high for up to 2 years following treatment compared to Burkitt's lymphoma

# Precursor T-Cell Neoplasms

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# Precursor T Cell Neoplasms

## PRECURSOR T LYMPHOBLASTIC LEUKAEMIA/LYMPHOBLASTIC LYMPHOMA

### Definition and Incidence

Precursor T lymphoblastic leukaemia (T-ALL)/lymphoblastic lymphoma (T-LBL) is a neoplasm of T-precursor lymphoblasts with an immature immunophenotype. Patients typically present with a mediastinal mass and frequent marrow involvement. The condition accounts for 15% of childhood and 25% of adult ALL. Adolescent males are the most commonly affected group.

**ICD-O Code** **Leukaemia: 9837/3**
**Lymphoma: 9729/3**

### Clinical Presentation

Patients usually present with short history of increasing dyspnoea secondary to a rapidly-evolving mediastinal mass associated with a high leukocyte count. Other sites involved include lymph nodes, liver, spleen, skin, Waldeyer's ring, and gonads.

### Pathology

The lymph node architecture is effaced by a monomorphic population of lymphoblasts. The lymphoblasts are medium sized with a high nuclear–cytoplasmic ratio, irregular nuclei, fine chromatin and inconspicuous nucleoli.

### Immunophenotype

T-ALL/T-LBL is always TdT positive. Pan T markers including CD3, 4, 5 ,7 and 8 are variably expressed with cytoplasmic CD3 and CD7 most commonly expressed. Co-expression of CD4 and CD8 may occur.

### Genetics

One third of T-ALL/T-LBL have translocations involving the T-Cell Receptor (TCR) loci at 14q11 (TCR alpha and delta), 7q35 (TCR beta) and 7p14 (TCR gamma). Translocation partner chromosomes include 8q24 (MYC), 1p32 (TAL1) and others. 25% of cases have TAL1 dysregulation either by translocation or microscopic deletion. More than 30% have del(9p) resulting in loss of the tumour suppressor gene CDKN2A, an inhibitor of the cyclin-dependent kinase CDK4.

### Investigations

**Generic** see page 2

**Specific** BMA to be assessed by morphology and immunophenotype. If the marrow is morphologically involved, cytogenetics are mandatory.

CSF analysis to exclude meningeal disease



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## Potential pitfalls

***a.*** Failure to investigate a mediastinal mass urgently, and failure to start treatment promptly.

***b.*** Failure to assess bone marrow with morphology, immunophenotyping and molecular analysis.

***c.*** Failure to recognise tumour lysis syndrome risk.

## Treatment

Patients are treated on ALL type regimens (eg UKALL XII) for induction and consolidation (usually 3-4 months of intensive treatment) with CNS directed prophylaxis followed by stem cell transplantation. Asparaginase may be particularly useful in treating patients with TLyL and it is advisable to use regimens which include this agent. There is no clear survival difference between autologous and allogeneic transplantation. The relapse rate is higher after autologous transplantation and therefore patients with high risk features (such as marrow involvement) and a matched sibling donor should be offered an allogeneic transplantation in first remission. Young adults (up to the age of 25) are increasingly being treated on paediatric-type protocols with intensified chemotherapy and no transplantation, however long follow up is not available for this treatment approach.

Patients who relapse with T-ALL and are transplanted in CR2 have a poor prognosis and so the initial management decision is crucial.

## Response Evaluation

CT scan of affected area after initial chemotherapy. Bone marrow and CSF evaluation (if involved at diagnosis) after initial chemotherapy. Complete restaging within 2 weeks of stem cell transplantation (SCT) and at 100 days post SCT.

## Follow Up

Two monthly follow up for 1 year, 3 monthly follow up for 1 year, 6 monthly for 1 year and then annual follow up. CXR, FBC and biochemical profile at each follow up visit up to 2 years and then as indicated.



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# Mature T-Cell and NK-Cell Neoplasms



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# Mature T Cell and NK Cell Neoplasms

## EXTRANODAL NK/T-CELL LYMPHOMA, NASAL TYPE

### Definition and Incidence

Extranodal NK/T cell lymphoma, nasal type is a predominantly extranodal lymphoma characterised by a broad morphologic spectrum. The lymphoma typically presents as a locally destructive proliferative lesion. The disease is most common in Asia, Mexico, Central and South America. Males predominate and the median age of presentation is 50 to 55 years. These lymphomas have also been described in patients immunosuppressed following organ transplantation.

**ICD-O Code** **9719/3**

### Clinical Presentation

The commonest site is the nasal cavity. Identical neoplasms may be seen in other extranodal sites, including the nasopharynx, palate, skin, soft tissue, gastrointestinal tract and testis. Patients typically present with facial swelling and or mid-line facial destruction and the disease has an aggressive course. It is localised (stage I and II) in 80% at presentation but may disseminate to the skin, gastrointestinal tract, orbit, CNS or testis.

### Pathology and Genetics

This lymphoma is described as an angiocentric and angiodestructive, proliferative lesion. Fibrinoid changes, coagulative necrosis and apoptotic bodies are common. There is a broad spectrum of tumour cell morphology. Cells may be small, medium, large or anaplastic. They may have irregular nuclei which may be elongated, and nucleoli are generally inconspicuous. Mitotic figures are easily found. There may be a prominent inflammatory infiltrate.

### Phenotype

The most common phenotype is CD2+, CD3-, CD56+, CD7-, Granzyme +. Other T and NK cell antigens are usually negative, including CD4, CD5, CD8, CD16 and CD57.

### Genetics

T-Cell receptor and immunoglobulin genes are in germline configuration in the majority of cases, although T-cell receptor gene rearrangement may be detected. EBV genome is detected in tumour tissue using in situ hybridization for EBV-encoded RNA.

### Staging

As for other high grade lymphomas.

### Recommended Investigations

As for other high grade lymphomas but should include in addition: a CT scan and MRI of nasal sinuses and brain. Lumbar puncture with cytology for malignant cells should also be performed.

### Prognostic Factors / Index

The prognosis is variable, with some patients achieving complete responses to treatment, and others dying of progressive, disseminated disease. Extranodal involvement in nasal disease or disease occurring outside the nasal cavity is very aggressive and associated with a short survival.

## Potential Pitfalls

Treatment planning must involve both a radiation oncologist and a medical oncologist/haematologist.

## Treatment

Localised disease is best treated with intensive radiation therapy which results in a complete remission in two-thirds of patients although local relapse occurs in 50% and 25% of patients and progress to disseminated disease. For late stage disease (stages III and IV) combined modality therapy with radiation and chemotherapy and CNS prophylaxis is recommended.

## Response Evaluation and Follow Up

As for other aggressive lymphomas.

# Enteropathy-Type T-Cell Lymphoma

## Definition and Incidence

Enteropathy associated T-Cell Lymphoma or enteropathy-type T-cell lymphoma (EATCL) is a tumour of intraepithelial T-lymphocytes showing varying degrees of transformation but usually presenting as a tumour composed of large lymphoid cells. This most commonly occurs in the setting of pre-existing or underlying (often undiagnosed) coeliac disease. These recommendations apply to EATCL but there is little evidence to suggest that non-EATCL should be treated differently. The median age of presentation is 50 years with a male predominance.

**ICD-O Code** **9717/3**

## Clinical Presentation

EATCL usually presents with abdominal pain, weight loss, diarrhoea and vomiting but may present acutely with small bowel obstruction and/or perforation. The tumour occurs most commonly in the jejenum or ileum with multiple ulcerating raised mucosal masses, one or more ulcers or a large exophytic mass.

## Pathology and Genetics

The tumour cells are relatively monomorphic, medium sized to large cells with round or angulated vesicular nuclei, prominent nucleoli and moderate to abundant pale-staining cytoplasm. Less commonly, the tumour exhibits pleomorphism with multinucleated cells resembling anaplastic large cell lymphoma. Most tumours show infiltration by inflammatory cells, including large numbers of histiocytes and eosinophils. The adjacent intestinal mucosa usually shows features of enteropathy.

## Immunophenotype

Tumour cells are CD3+, CD5-, CD7+, CD8+/-, CD4-, CD103+ and contain cytotoxic granule associated proteins. In most cases, a proportion of the tumour cells express CD30. The intraepithelial lymphocytes in the adjacent enteropathic mucosa may show an abnormal immunophenotype, usually CD3+, CD5-, CD8-, CD4-, identical to that of the lymphoma. Likewise the intraepithelial lymphocytes in refractory coeliac disease are usually CD8-.

## Genetics

The TCR genes are clonally rearranged. Similar clonal rearrangements may be found in the adjacent enteropathic mucosa, suggesting that immunophenotypically aberrant intraepithelial lymphocytes are part of the neoplastic population. In refractory coeliac disease, the intraepithelial lymphocytes also comprise a monoclonal population and share the same clonal TCR gene rearrangements as the subsequent T-cell lymphomas which develops.

## Staging

As for DLBCL.

## Recommended Investigations

**Evaluation of patients with refractory coeliac disease**

Most patients with EATCL have a prior history of coeliac disease or simultaneous diagnosis of underlying coeliac disease. There is currently no recommendation for routine surveillance of coeliac disease patients who have responded to a gluten free diet. Refractory coeliac disease and ulcerative jejunitis probably represent a pre-neoplastic condition with frequent evolution to clonal disease and associated phenotypic changes. For these reasons a high level of suspicion in patients with coeliac disease with persistent symptoms is necessary. Immunophenotyping of the intraepithelial lymphocytes in serial biopsies in these patients may be useful in detecting phenotypic change (evolution to CD3+, CD8-, CD4- phenotype).

**Patients with established diagnosis of lymphoma**

Investigations should be carried out as for other high grade lymphomas. In addition, a small bowel follow through should be performed, and nutritional status assessed. Clonal T-cell populations may be identified in the peripheral blood, but the clinical significance of this is unclear.

## Prognostic Factors / Index

EATCL has a poor prognosis with a median survival of approximately 8 months and one year failure free survival of less than 20%.

## Potential Pitfalls

Failure to recognise the development of EATCL in patients with refractory coeliac disease or ulcerative jejunitis. Frequent surveillance with endoscopic biopsy and immunophenotyping is recommended in patients with persistent or suspicious symptoms, and in those with refractory coeliac disease or with ulcerative jejunitis.

## Treatment

Standard treatment with anthracycline containing combination chemotherapy is usually used despite poor results. The Nottingham group have pioneered an approach using IEV chemotherapy (2 cycles) followed by 2 courses of Methotrexate 3gms/m2 for CNS prophylaxis followed by an autologous PBSCT with survival of 4 of 6 patients beyond 2 years. Gemctabine based therapy may be useful in aggressive T-NHLs such as EATCL. Perforation may occur during initial chemotherapy. Patients often require parenteral nutrition.

In patients with refractory coeliac disease or ulcerative jejunitis, consideration may be given to pre-emptive treatment with combination chemotherapy if phenotypic change in the intraepithelial lymphocytes or clonally rearranged T-cells are detected, but this remains an experimental approach..

## Response Evaluation and Follow Up

Re-evaluation at intervals should include endoscopic evaluation, small bowel follow through and small bowel biopsy.

# Hepatosplenic T-Cell Lymphoma

## Definition and Incidence

Hepatosplenic T-cell lymphoma is a rare extranodal neoplasm derived from cytotoxic T-cells usually of gamma-delta T-cell receptor type, with sinusoidal infiltration of the spleen, liver and bone marrow. Young men present typically with hepatosplenomegaly and marked B symptoms. The alpha-beta sub-type is extremely rare.

**ICD-O Code** **9716/3**

## Clinical Presentation

Splenomegaly occurs in 98%, hepatomegaly in 80%, anaemia and thrombocytopenia in 85% with bone marrow involvement in most patients. Lymph node involvement is rare. The disease behaves aggressively, with a median survival of less than 2 years. The alpha-beta variant has a similar prognosis and outcome.

## Pathology and Genetics

The tumour cells are monotonous, medium in size, with a rim of pale cytoplasm. The nuclear chromatin is loosely condensed with small inconspicuous nucleoli. The liver and spleen show marked sinusoidal infiltration with sparing of portal tracts and the white pulp.

### Immunophenotype and genetics

The neoplastic cells are CD3+ and usually TCR gamma-delta+, TCR alpha-beta-, CD56+/-, CD4-, CD8- and CD5-.
The cells have rearranged TCR gamma and delta.

## Staging

As for other aggressive lymphomas.

## Recommended investigations

As for other aggressive lymphomas.

## Potential pitfalls

Failure to recognise this rare disease in patients with splenomegaly and systemic symptoms.

## Treatment

Patients respond poorly to anthracycline-containing chemotherapy with a complete remission rate of less than 15% and short survival. Pentostatin appears to be effective in controlling disease. Long-term survival has been described following allogeneic stem cell transplantation.

## Response Evaluation and Follow Up

As for other aggressive lymphomas.



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# Mycosis Fungoides and Sézary Syndrome

## Definition and Incidence

Mycosis Fungoides is the commonest primary cutaneous lymphoma, accounting for almost 50% of all primary cutaneous lymphomas. Mycosis fungoides is a mature T-cell lymphoma presenting in skin with patches or plaques and showing epidermotropism by T lymphocytes.

Sézary syndrome (SS) is a related but generalised T-cell leukaemia presenting with erythroderma, generalized lymphadenopathy and circulating clonally related neoplastic cerebriform T-lymphocytes in the peripheral blood, and behaves more aggressively. In addition, one or more of the following criteria are required: an absolute Sézary cell count of at least 1000 cells per mm3, an expanded CD4 T-cell population resulting in a CD4/CD8 ratio of more than 10 and/or loss of one or more T-cell antigens. Sezary syndrome comprises less than 5% of primary cutaneous T cell lymphomas.

**ICD-O Code** **9700/3 (Mycosis fungoides)**
**9701/3 (Sézary syndrome)**

## Clinical Presentation

Mycosis Fungoides has a long natural history, and patients may have non-specific scaly lesions for years before diagnostic histology develops. Eventually, progression occurs to more generalised plaques and eventually to tumours in some patients. Some patients develop generalised erythroderma. Extra-cutaneous dissemination is a late event and occurs mostly in patients with extensive or advanced cutaneous disease with spread to lymph nodes, liver, spleen, lungs and blood. Bone marrow involvement is rare. Folliculotropic MF preferentially affects the head and neck and often presents with grouped follicular papules associated with alopecia. Sezary syndrome is a generalized disease with widespread visceral organs involvement but frequently a clear bone marrow.

## Pathology and Genetics

Biopsy of the skin lesions shows epidermal infiltration of small- to medium-sized cells and irregular cerebriform nuclei may not be seen in early lesions. Pautrier microabscesses (aggregates of cells with cerebriform nuclei, generally in nonspongiotic epidermis) are characteristic but not common in early lesions. Epidermal involvement with epidermotropism by single lymphocytes is more common and lining up of haloed lymphocytes along the dermo-epidermal junction can be seen. Dermal infiltrates may be patchy, band-like or diffuse, depending on disease stage. There is often an associated inflammatory infiltrate of small lymphocytes and eosinophils. With progression, epidermotropism can be lost. Histologic transformation is defined by the presence of >25% large lymphoid cells in the dermal infiltrate and is seen mainly in tumour stage disease. These cells may be CD30 positive or negative. Enlarged lymph nodes when present frequently show dermatopathic changes with paracortical expansion due to the presence of large numbers of Langerhans cells with abundant pale cytoplasm.

In Sezary Syndrome, T-cells with markedly convoluted (cerebriform) nuclei are present in the peripheral blood (Sezary cells).

### Phenotype

Most are CD2+, CD3+, CD4+, CD5+, Alpha-beta TCR+, and CD8-. Occasionally they may be CD8+ or gamma-delta TCR+. Some cases may express activation-associated antigens including HLADR, CD25, CD30, CD38 and proliferation associated antigens such as CD71 and Ki67, especially in advanced stages.



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Alternatively, there may be an aberrant T-cell phenotype with decreased or absent pan T Markers (CD2, CD3, or CD5), absent T subset antigen expression (CD4, CD8), co-expression of CD4+ and CD8+ or decreased or absent CD7. A CD8 + phenotype has been reported more commonly in paediatric MF. In Sezary Syndrome, tumour cells are CD2+, CD3+, TCR Beta+, CD5+ and CD7+/-. Most cases are CD4+ and expression of CD8 is rare. Demonstration of a clonal rearrangement of TCRs in peripheral blood T-cells may be diagnostically useful.

### Genetics

T cell receptor genes are clonally rearranged in most cases. Complex karyotypic changes are often present, especially in advanced stages.

## Staging

**Clinical Staging system for cutaneous T-cell lymphoma**

| **TNM classification** | |
|---|---|
| **T1:** | Patches or plaques <10% body surface area |
| **T2:** | Patches or plaques >10% body surface area |
| **T3:** | Tumours |
| **T4:** | Erythroderma |
| **N0:** | No palpable nodes |
| **N1:** | Palpable nodes without histological involvement (dermatopathic) |
| **N2:** | Non palpable nodes with histological involvement |
| **N3:** | Palpable nodes with histological involvement |
| **M0:** | No visceral disease |
| **M1:** | Visceral disease |
| **B0:** | No haematological involvement |
| **B1:** | Sézary cell count >5% of total peripheral blood lymphocytes. |

| **Bunn & Lambert system** | |
|---|---|
| **Stage IA:** | T1 N0 |
| **Stage IB:** | T2 N0 |
| **Stage IIA:** | T1/2 N1 |
| **Stage IIB:** | T3 N0/1 |
| **Stage III:** | T4 N0/1 |
| **Stage IVA:** | T-any N2/3 |
| **Stage IVB:** | T-any N-any M1 |

## Recommended Investigations

All patients except those with early stage mycosis fungoides (IA) should be reviewed by a multidisciplinary team including a dermatologist, haematologist or oncologist and dermatopathologist.

The following are recommended:

- Generic investigations.
- History and physical examination, including whole body mapping of skin lesions.
- Peripheral blood film and immunophenotyping to diagnose Sézary and exlude other T cell leukaemias
- Human T-cell lymphotropic virus (HTLV)-1 serology to exclude ATLL
- T-cell receptor (TCR) gene analysis of peripheral blood may be useful.
- Skin Biopsy: If MF is suspected multiple (2-3) skin biopsies from different lesions should be taken. Fungal infection should be excluded by a special stain (PAS). Repeated skin biopsies (ellipse in preference to punch) are often required to confirm a diagnosis of CTCL. Histology, immunophenotyping (CD3, CD4, CD8, CD30) and preferably TCR gene analysis should be performed on representative tissue samples



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- Lymph node biopsy if there is palpable adenopathy.
- CT scans of the chest, abdomen and pelvis are indicated in patients with non-mycosis fungoides CTCL variants, stage IIA/B/III/IV mycosis fungoides and Sezary syndrome. Scanning is not required in patients with stage IA/IB disease or lymphomatoid papulosis.

## Prognostic Factors / Index

Prognosis in mycosis fungoides is related to age at presentation (worse if >60 years), clinical stage and elevated LDH. Patients with limited stage disease may have a normal life expectancy, but those with advanced disease have a poor prognosis, especially if there is extra-cutaneous dissemination. Folliculotropic MF is less accessible to skin-targeted therapies because of deep dermal infiltration and disease-specific 5 year survival is approximately 70-80% which is worse than classical MF. The median survival in Sézary syndrome is 32 months from diagnosis with an overall survival of 10-20% at 5 years.

## Potential Pitfalls

***a.*** Diagnosis of cutaneous T cell lymphoma may be difficult and differential diagnosis includes a number of other entities including benign conditions such as small and large plaque parapsoriasis, eczematous disorders and erythroderma secondary to drug reactions, psoriasis or eczema .

***b.*** Traditional anti-lymphoma regimens of combination chemotherapy are not effective.

## Treatment

- Patients should be jointly managed by an oncologist/haematologist and a dermatologist.
- **Skin-directed therapy** (phototherapy, topical therapy or superficial radiotherapy) is appropriate for patients with early stage mycosis fungoides (stages IA-IIA) with the choice of therapy dependent on the extent of cutaneous disease and plaque thickness. Agents used include topical high-intensity steroids and bexarotene gel.

  Combined PUVA and α-interferon therapy can be effective for patients with resistant early-stage disease (stage IB-IIA).
- **Systemic therapy** is required for patients with **stage IIB or higher** mycosis fungoides with interferon or one of the newer agents described below.
- Bexarotene is an oral retinoid with an overall response rate of about 45% as monotherapy which is increased when combined with interferon and/or PUVA. Bexarotene causes central hypothyroidism and hypertryglyceridaemia which must be monitored and treated appropriately
- Gemcitabine monotherapy is also active in CTCL, using 1000 mg/m2 on day 1,8 +/-15 resulting in an ORR of 68% in heavily pre-treated patients.
- Campath IH given iv or sc three times a week for up to 12 weeks in patients with heavily pre-treated, advanced disease resulted in an ORR of 38%-55%, but associated with a high incidence of infections

- Denileukin diftitox is not available in Ireland because of specialised storage requirements, but is an iv preparation resulting in an ORR of 38%
- Extracorporeal photopheresis may be effective in patients with erythrodemic disease or Sezary syndrome..
- Total skin electron beam therapy may be effective for stage IB and stage III mycosis fungoides, but is toxic and only available in Belfast for Irish patients.
- Chemotherapy regimens in advanced stages of mycosis fungoides generally achieve short-lived complete responses of about 30%.
- Allogeneic non-myeloablative transplant is curative and a recent EBMT survey reported an DFS and OS of >50%

## Response Evaluation

The evaluation of response to therapy is primarily clinical. CT evaluation is appropriate in late stage disease with visceral involvement.

## Follow Up

Early stage disease patients should be reviewed with careful clinical examination at 6-monthly intervals.



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# Primary Cutaneous CD30-Positive T-Cell Lymphoproliferative Disorders

## Definition and Incidence

Primary cutaneous CD30+ T-cell lymphomas are the second most common group of cutaneous T cell lymphomas, accounting for 30% of cases. This group represents a spectrum of disease with overlapping histopathologic and phenotypic features including lymphomatoid papulosis, anaplastic large cell lymphoma and borderline cases. The clinical appearance and course are critical for definite diagnosis. Lymphomatoid papulosis (LyP) is an indolent form characterised by recurrent crops of self-healing papules and nodules, which may become necrotic and usually resolve to leave varioliform scars. From a clinical perspective LyP is not considered a malignancy, despite monoclonality in many cases. Primary cutaneous CD30+ anaplastic large cell lymphoma (ALCL) is a T-cell lymphoma presenting in the skin, and accounts for 25% of all cutaneous T-cell lymphomas. The disease occurs almost exclusively in adults and patients are mostly elderly. The male:female ratio is approximately 2:1.

**ICD-O Code** **9718/3**

## Clinical Presentation

In almost all instances the disease is confined to the skin at diagnosis, with solitary or (less commonly) multicentric lesions, which may be tumours, nodules or plaques. Extra-cutaneous dissemination, mostly to local lymph nodes, may occur in ALCL. LyP is characterized by the presence of papular, papulonecrotic and/or nodular skin lesions at different stages of development. Individual lesions disappear within 2-12 weeks. Oral mucosa can rarely be involved in LyP. Duration of LyP may vary from months to > 40 years. In up to 20% of patients LyP may be preceded by, associated with, or followed by another type of lymphomas, generally MF, cutaneous ALCL or Hodgkin lymphoma.

## Pathology and Genetics

Histologically, lymphomatoid papulosis shows a wedge-shaped polymorphic infiltrate consisting of atypical mononuclear cells with cerebriform, anaplastic (CD30+) and pleomorphic cytology in a background of smaller lymphocytes that may show epidermotropism. There may be a marked inflammatory background, If only sparse atypical lymphocytes are seen, it is termed LyP type A, if there are sheets of atypical cells it is termed LyP type C. In <10% of cases the pattern of cutaneous involvement can mimic MF (LyP type B). In contrast, larger tumours which do not resolve spontaneously and which histologically show a monomorphic infiltrate of large anaplastic CD30+ mononuclear cells (>80% of dermal infiltrate) represent primary cutaneous ALCL. Infiltrates are diffuse and usually involve both upper and deep dermis and subcutaneous tissue.

### Immunophenotype

The neoplastic cells express T-cell antigens, and are usually CD4+. Most (>70%) of the cells express CD30. In LyP type B, the lymphocytes are usually CD30 negative and CD3+, CD4+ CD8-. Rare cases of LyP and ALCL are CD8+. Cytotoxic granule-associated proteins (granzyme, perforin) are positive in 70%. Aberrant T-cell phenotypes with variable loss of CD2, CD5, or CD3 are common.



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Cutaneous ALCL (in contrast to systemic ALCL) express cutaneous lymphocyte antigen but not EMA, ALK and rarely CD15. CD56 expression is rare and has no prognostic significance.

**Genetics**

The T-cell receptor genes are clonally rearranged in most cases. Cutaneous ALCL does not have ALK associated translocations.

## Staging

Disease is usually confined to the skin at diagnosis. Patients with primary cutaneous ALCL should be staged as for DLBCL.

## Recommended Investigations

As for DLBCL.

## Potential Pitfall(s)

Failure to distinguish primary skin lymphoma from systemic Anaplastic Large Cell Lymphoma with cutaneous involvement and from secondary high grade lymphomas with CD30 expression.

## Response Evaluation and Follow Up

Clinical skin examination for skin disease,.

## Prognosis

Both conditions have an excellent prognosis with 100% and 96% 5-year survival for LyP and cutaneous ALCL. Patients with multifocal skin lesions and those with involvement of regional lymph nodes have a similar prognosis to patients with skin lesions only.

## Treatment

Patients with LyP may not require treatment. In patients with either LyP or primary cutaneous CD30+ ALCL requiring therapy, PUVA, local radiotherapy or low-dose oral methotrexate are effective at preventing recurrent lesions. Systemic chemotherapy is usually not effective..

# Angioimmunoblastic T-Cell Lymphoma

## Definition and Incidence

Angioimmunoblastic T-Cell Lymphoma, AILT (formerly AILD) is a peripheral T-cell lymphoma characterised by systemic symptoms, a polymorphous infiltrate involving lymph nodes, with a prominent proliferation of high endothelial venules and follicular dendritic cells. It occurs in the middle aged and elderly, with an equal incidence in males and females.

**ICD-O Code** **9705/3**

## Clinical Presentation

Patients usually present with B symptoms, generalised peripheral lymphadenopathy, hepatosplenomegaly, and frequent skin rash. The bone marrow is commonly involved. Para-neoplastic manifestations are common and include skin rashes, autoimmune haemolytic anaemia, hypergammaglobulinaemia, eosinophilia, vasculitis, and haemophagocytosis. The clinical course is aggressive, with a median survival of less than 3 years.

## Pathology and Genetics

The lymph node architecture is partially effaced, and regressed follicles are often present. The paracortex is diffusely infiltrated by a polymorphous population of medium-sized lymphocytes, usually with clear to pale cytoplasm and distinct cell membranes. The lymphocytes show minimal cytological atypia, and this form of lymphoma may be difficult to distinguish from atypical T-zone hyperplasia. The abnormal lymphoid cells are admixed with small, reactive lymphocytes, eosinophils, plasma cells and histiocytes. There is marked proliferation of high endothelial venules and follicular dendritic cell meshworks are often increased. Increased numbers of B immunoblasts are usually present in the paracortex.

### Immunophenotype

The infiltrates are composed of mature T-cells, usually with an admixture of CD4 and CD8 cells, with CD4 cells usually out-numbering CD8 cells. Follicular dendritic cells (CD21+) are prominent. The neoplastic T-cells may aberrantly express CD10.

### Genetics

T-cell receptor genes are rearranged in 75% of cases. Immunoglobulin gene rearrangement is present in 20-30%, correlating with clonally expanded EBV+ B cells. Gene expression studies confirm that the neoplastic cells are CD4+ TFH type.

## Staging

As for other aggressive lymphomas.

## Recommended Investigations

As for other aggressive lymphomas.

## Potential Pitfalls

Failure to diagnose lymphoma in the context of a clinical presentation characterised by a profound immune disturbance.

## Treatment

Treatment options include CHOP or CVP-like regimens, depending on patient age and co-morbidity. There is a high initial response rate with these approaches, but early relapse or progression is common and there are few long-term survivors. Long term disease control may be achieved with weekly methotrexate and prednisolone. High dose therapy and autologous SCT have been reported by the EBMT to results in a 5 year 60% disease free survival.

## Response Evaluation and Follow Up

As for other aggressive lymphomas.



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# Anaplastic Large Cell Lymphoma

## Definition and Incidence

ALCL-ALK+ve is a T cell lymphoma characterised by translocation involving the ALK gene, expression of the ALK protein and CD30. Primary systemic ALCL must be distinguished from Anaplastic large cell lymphoma (ALK negative), primary cutaneous ALCL and other T and B cell lymphomas with anaplastic morphology and/or expression of CD30.

ALCL-ALK-ve is a provisional entity defined as a CD30+ T cell neoplasm, morphologically indistinguishable from ALCL, ALK+, but lacking ALK protein expression.

ALCL accounts for about 3% of adult NHLs and 10-30% of childhood lymphomas. It has an incidence of 0.24 new cases/100,000 population/year. ALK+ve ALCL is most frequent in the first 3 decades of life and has a M:F ratio of 6:1. ALK –ve ALCL occurs in older patients with a slight female predominance.

**ICD-O code** **9714/3**

## Clinical Presentation

ALCL frequently involves both lymph nodes and extra-nodal sites including the skin (21%), bone (17%), soft tissue (17%), lung (11%) and liver (8%). Involvement of the CNS and gastrointestinal tract is rare. Marrow involvement occurs in 10% of cases but this increases to 30% if immunohistochemistry for CD30, EMA and ALK is used.

70% of patients present with stage III or IV disease and most have B symptoms, particularly high fevers.

## Pathology

Pathological appearance is variable. Lymph node/tissue architecture may be partly effaced and the disease typically grows within node sinuses. Morphology is variable, ranging from small cell neoplasms to cases with large anaplastic nuclei. All cases contain cells with eccentric reniform nuclei known as “hallmark cells” although the proportion of these cells present is variable. Morphologic variants include lympho-histiocytic, small cell, and Hodgkin-like patterns.

### Immunophenotype

Cells are CD30+ve with cell membrane and Golgi region pattern. Most cases are EMA positive. CD2, CD4, CD5 are positive in 70% of cases. Most cases express T cytotoxic associated antigens including TIA-1, perforin and granzyme B. CD3, CD8, CD15 are negative in most cases.

ALK protein is positive, most cases demonstrating both nuclear and cytoplasmic expression. Variant expression patterns, cytoplasmic, nuclear and membranous, exist.

### Genetics

90% of cases show clonal T cell receptor gene rearrangements. Various ALK translocations are described: the most common, accounting for >80% of cases, is the t(2;5)(p23;p35) translocation involving the ALK gene and the nucleophosmin gene on 5q25 resulting in nuclear and cytoplasmic ALK protein expression. Variant translocations involving ALK and partner genes on chromosomes 1,2,3,17,19,22,X occur and are associated with variable protein expression patterns.

## Staging

As for DLBCL.



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## Prognostic factors

The IPI is of limited value and survival is most significantly affected by ALK expression with a 5-year OS of 93% in ALK +ve cases vs 37% in ALK -ve cases.

## Potential Pitfalls

***a.*** Failure to differentiate ALCL from carcinomas or sarcomas.

***b.*** Failure to differentiate between primary cutaneous ALCL and primary systemc ALCL.

***c.*** Failure to stain for ALK protein.

## Management

ALK +ve ALCL should be treated with standard first-line anthracycline containing chemotherapy such as CHOP. Consideration should be given to treating patients <22 years of age on the UKCCSG protocol after discussion with paediatricians or haematologists familiar with this protocol. ALK-ve patients are treated with standard DLBCL treatment, however with an awareness of their poor prognosis and escalation to salvage treatment if necessary. Patients with relapsed ALCL should be salvaged with standard salvage treatment eg. ICE with CNS prophylaxix and consolidated with an allogeneic or autologous transplantation.

## Follow up

As for DLBCL.

# Hodgkin Lymphoma (HL)



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# Hodgkin Lymphoma (HL)

## Definition and Incidence

The crude incidence of Hodgkin lymphoma in the European Union is 2.2/100,000/year and mortality is 0.7/100,000/year. HLs account for approximately 15% of lymphomas and, in contrast to non-Hodgkin lymphomas, their absolute incidence has not increased in recent decades.

The goal of HL therapy is the "least complicated cure" with a personalised approach. The associated risks of treatment, including sterility and the risk of second malignancy, have influenced the current management of early stage non-bulky HL towards brief chemotherapy followed by involved field irradiation with more chemotherapy and less irradiation in those with higher-staged illness. ABVD remains the international standard cytotoxic chemotherapy. The role of BEACOPP in advanced disease is under investigation with a view to optimising frontline treatment to avoid the need for salvage therapy and transplant. $F^{18}DG$ PET/CT scan is a now well established in staging, response assessment and evaluation of residual masses.

### ICD – O Codes:

| | | |
|---|---|---|
| **Nodular lymphocyte predominant Hodgkin lymphoma** | NLPHL | 9659/3 |
| **Classical Hodgkin lymphoma** | CHL | 9650/3 |
| ■ Nodular sclerosis classical Hodgkin lymphoma | NSHL | 9663/3 |
| ■ Mixed cellularity classical Hodgkin lymphoma | MCHL | 9652/3 |
| ■ Lymphocyte-rich classical Hodgkin lymphoma | LRCHL | 9651/3 |
| ■ Lymphocyte-depleted classical Hodgkin lymphoma | LDHL | 9653/3 |

## Clinical Presentation:

Classical Hodgkin lymphoma (CHL) accounts for 95% of HL with a bimodal age curve showing a peak at 15-35 years and a second peak in later life. Patients with a history of infectious mononucleosis have a higher incidence of HL and both familial and geographic clustering has been described. Patients usually present with peripheral lymphadenopathy at one or two sites. Mediastinal involvement is most frequently seen with Nodular Sclerosis Hodgkin lymphoma (NSHL) while abdominal and splenic involvement is more common with Mixed Cellularity Hodgkin lymphoma (MCHL). About 40% will have systemic symptoms consisting of fever, drenching night sweats and significant weight loss.

Patients with Nodular Lymphocyte Predominant Hodgkin lymphoma (NLPHL) usually present with localized peripheral lymphadenopathy (stage I or II). Between 5% and 20% of patients present with advanced stage disease. NLPHL is an indolent disease and previous lymph node biopsies may have been interpreted as representing a reactive process. Relapses are frequent but the disease usually remains responsive to treatment and is thus rarely fatal. Transformation to diffuse large B-cell lymphoma (DLBCL) may rarely occur.

## Pathology and Genetics

Pathologic diagnosis should be made according to the WHO classification as described above.



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## Staging

A clinical staging classification is a guide towards treatment and determining prognosis. It is mandatory for comparing the outcome with treatment at different centres and in clinical trials. The Cotswold Revision of the Ann Arbor staging classification for HL serves to determine the extent of disease (staging), define the location of disease within the lymphoid system along with associated prognostic factors and establishes disease manifestations which can be re-evaluated during and after treatment to determine the effectiveness of therapy.

## Cotswold Revision of the Ann Arbor Staging Classification

| Stage | Definition |
|---|---|
| **I** | Involvement of a single lymph node region or lymphoid structure (eg, spleen, thymus, Waldeyer's ring) |
| **II** | Involvement of two or more lymph node regions on the same side of the diaphragm (the mediastinum is a single site: hilar lymph nodes are lateralized); the number of anatomic sites should be indicated by suffix (eg $II_3$) |
| **III** | Involvement of lymph node regions or structures on both sides of the diaphragm |
| **III1** | With or without splenic, hilar, coeliac or portal nodes |
| **III2** | With paraaortic, iliac or mesenteric nodes |
| **IV** | Involvement of extranodal site(s) beyond those designated E |

***Annotation:***

*A = No B symptoms*
*B = Fever, drenching sweats or weight loss*
*X = Bulky disease, >⅓ widening of mediastinum at T5-6 and/or ≥10 cm nodal mass*
*E = Involvement of a single extranodal site, contiguous or proximal to known nodal site*
*CS = Clinical stage*
*PS = Pathologic stage*

## Cheson criteria Radiological Definition of Treatment Outcome Related to Nodal Disease

Criteria used to assign CR, CR(u) and PR categories from post-treatment CT scans

| Anatomic Site | CR | CR(u) | PR[a] |
|---|---|---|---|
| Thorax (cm) | ≤ 1.0 | 1.1 - 2.0 | ≥ 2.1 |
| Retrocrural (cm) | ≤ 0.6 | 0.7 - 1.6 | ≥ 1.7 |
| Abdomen (cm) | ≤ 1.5 | 1.6 - 2.5 | ≥ 2.6 |

*[a] Less than 50% of original nodal mass*
*CR = complete remission*
*CR(u) = unconfirmed / uncertain complete remission*
*PR = partial remission*

## Recommended Investigations

**Clinical:**

Full history and examination.

**Diagnostic Imaging:**

- Chest radiograph.
- Computed tomography of neck, chest, abdomen and pelvis.
- $F^{18}DG$ PET/CT scan

**Blood Tests:**

**Haematology:**

- Full blood count and differential white cell count
- ESR
- Bone marrow aspirate and biopsy (Not required in Stage I or II A)

**Biochemistry:**

- Liver function profile
- Renal function profile

**Other:**

- Pulmonary Function Tests with DLCO
- ECHO



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## Prognostic Factors / Index:

***i.*** Early stage disease (I – IIA)

| | |
|---|---|
| Adverse factors: | Age > 50 years<br>ESR > 50 mm /hr or > 30 mm /hr with B symptoms<br>Four or more separate nodal sites involved<br>Mediastinial mass ratio > 1/3 |

***ii.*** Advanced stage disease (IIB – IV)

| | |
|---|---|
| Adverse factors: *(International Prognostic score)* | Age > 45 years<br>Male sex<br>Stage IV<br>Haemoglobin < 10.5 g/dl<br>Albumin < 40 g/l<br>Lymphocytes < 0.6 x $10^9$ /l or < 8%<br>White blood count > 15 x $10^9$ /l |

## Potential Pitfalls

***i.*** Failure to differentiate between NLPHL and CHL

***ii.*** Confusion with DLBCL and its variants

***iii.*** Incorrect stage

## Treatment of nodular lymphocyte predominant HL

The treatment of NLPHL is undergoing review. Where there is stage I disease and no B symptoms or adverse clinical risk factors, the patient may be treated with involved field radiation therapy (IFRT) 30Gy or may be observed following nodal excision in the absence of residual disease. Rituximab may be used as an alternative or in addition to radiotherapy. Patients with extensive or relapsed disease can be treated with Rituximab containing CHOP or ABVD.

## Treatment of classical HL

**Early stage disease**

Clinical stage IA or IIA

| | |
|---|---|
| Treatment: | ABVD x 4 cycles and involved field radiation therapy (IFRT) 20-30Gy<br>Or<br>ABVD x 6 cycles |

The use of radiotherapy in stage I and II disease is associated with a lower risk of relapse, and this has to be off set by concerns about long term morbidity following radiotherapy.

**Advanced Stage Disease**

Clinical stages IIB to IV

Standard treatment is with ABVD x6-8 cycles or escalated BEACOPP. A rational approach using the known prognostic value of PET scanning after 2 courses of ABVD may be to intensify treatment to escalated or dose-dense BEACOPP if the PET scan is deemed positive at this stage. This approach is currently being tested in the RATHL study sponsored by the British NCRN group.

Little consensus exists on the role of radiation in advanced stage disease. Ideally all patients should be reviewed in an MDT setting at the beginning and end of therapy to review the indication for radiotherapy

## Response Evaluation

Patients should have careful clinical evaluation with each cycle of chemotherapy and treatment delays should be avoided. ABVD can be safely administered on schedule in the presence of moderate neutropenia without GCSF support

Response evaluation with repeat radiology of abnormal sites at presentation is traditionally undertaken after four cycles of therapy, however if F18DG-PET/CT scanning is used this evaluation is most usefully carried out after two courses of chemotherapy



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Patients with primary refractory disease or partial response to therapy will need to have treatment intensified. Switching to BEACOPP-14 is recommended in patients with positive PET after 2 cycles of ABVD. If PET is negative after 4 cycles consolidate with 2 further cycles of BEACOPP-14. If PET remains positive salvage treatment followed by autologous stem cell transplantion should be considered.

## Follow-Up

**Clinical:**

History and physical examination every three months for one year, every six months for three years, then yearly.

**Laboratory:**

FBC and biochemistry along with clinical evaluations for up to two years. Thyroid function to be assessed at one year then yearly for life in patients who have had neck or mediastinal irradiation.

**Diagnostic imaging:**

Chest radiographs, along with clinical evaluations up to two years. Then as indicated. CT scan to define initial remission status and then, if necessary, to monitor residual abnormalities if chest radiograph does not suffice. PET scan is not needed at the end of treatment if interim scan is negative.

Mammography or other suitable screening should be offered in a structured fashion to young women given chest irradiation before age 25 years.

## Treatment at Relapse

Salvage chemotherapy (eg ICE) followed by autologous transplant should be considered standard therapy for all patients with an adequate performance status previously treated with chemotherapy including those with late relapse. Early referral to a centre with the capacity to deliver such therapy is mandatory. Patients should be scheduled for harvest after 2 cycles of salvage chemotherapy. A further course of salvage chemotherapy is then administered prior to high dose chemotherapy and autologous stem cell rescue.

Repeat CT scan post 2 cycles of salvage chemotherapy and PET scan after third and final cycle. CT scan after second cycle is to confirm responsive disease and PET scan after third cycle is to confirm CR. Patients who are PET positive at this stage should be considered for further salvage therapy with Gemcitabine based treatment or allogeneic transplantation.

In patients unfit for transplant palliative chemotherapy and radiotherapy can be administered as required. Rituximab may be a useful adjunct in CD20 positive cases.

***Selected References:***

*PET for response adapted in advanced Hodgkin's Lymphoma (RATHL) – NCRI*

*VEPEMB in elderly Hodgkin's lymphoma patients. Results from Intergruppo Italiano Linfomi (IIL) study. Levis,A et al. Annals of Oncology 15: 123-128, 2004.*

*G-CSF is not necessary to maintain over 99% dose-intensity with ABVD in treatment of Hodgkin Lymphoma: low toxicity and excellent outcome in a 10-year analysis. Evens AM et al. British Journal of Haematology 2007 137, 545-552.*

# Immunodeficiency Associated Lymphoproliferative Disorders



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# Immunodeficiency Associated Lymphoproliferative Disorders

## HUMAN IMMUNODEFICIENCY VIRUS-RELATED LYMPHOMAS

### Definition and Incidence

Lymphomas that develop in HIV-positive patients are predominantly aggressive B-cell lymphomas. In a proportion of cases they represent the AIDS-defining illness. These disorders are heterogeneous and include lymphomas commonly diagnosed in immunocompetent patients, as well as some seen more commonly in the setting of HIV infection. The most common HIV-associated lymphomas include: Burkitt lymphoma (BL), diffuse large B-cell lymphoma (DLBCL), often involving the central nervous system, primary effusion lymphoma (PEL) and plasmablastic lymphoma of the oral cavity and Hodgkin lymphoma.

The incidence of all subtypes of NHL is increased 60-200 fold in the HIV setting. Before the introduction of HAART, primary CNS lymphoma and BL had an incidence 1000 fold that of the general population. The incidence of HL is increased about eight fold. NHL used to be the AIDS-defining illness in 3-5% of patients, but this has increased since the introduction of HAART.

This heterogeneous group of diseases reflect several pathogenetic mechanisms of lymphoma development, notably: chronic antigen stimulation, cytokine dysregulation and viral carcinogenesis involving the herpes viruses, EBV and Kaposi Sarcoma Human Virus (KSHV / HHV8).

**ICD – O Codes:** **As for cases occurring in the immunocompetent patient.**

### Clinical Presentation

Clinical presentations are similar to those found in immunocompetent patients, but usually are more advanced with bulky disease reflected by a high LDH level. There is a significant relationship between the subtype of lymphoma and the HIV disease status. DLBCL usually occurs late in the course of AIDS with a prior history of opportunistic infection and low CD4 count usually $<100 \times 10^6$. In contrast BL occurs at an earlier stage in the AIDS illness with a mean CD4 count of $>200 \times 10^6$. Primary effusion lymphoma (PEL) and plasmablastic lymphoma of the oral cavity occur in HIV+ patients almost exclusively. PEL typically presents with a pleural or peritoneal effusion but can present as a solid tumour mass. Plasmablastic lymphoma of the oral cavity presents as a rapidly growing tumour of the jaw or oral cavity.

### Pathology and Genetics

Those diseases which also present in the immunocompetent patient such as DLBCL, BL and HL will have the usual features.

PEL is associated with both Kaposi sarcoma (KL) and multicentric Castleman's disease (MCD) in HIV-positive patients.

In PEL the diagnosis is based on cytology with pleomorphic cells varying from large immunoblastic or plasmablastic cells to those with an anaplastic appearance. The PEL immunophenotype is EMA+ve, CD30+ve, CD38+ve , CD71 +ve and may express CD3.

Plasmablastic lymphoma of the oral cavity has a diffuse pattern of growth with interspersed macrophages. The tumour cells are large, with eccentric nuclei and usually a central, prominent nucleolus. The cytoplasm is deeply basophilic with a perinuclear hof. Cyctoplasmic immunoglobin can be detected in about 20%



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of cases and EBV in about 50%, but no association with KSHV/HHV8 has been found. Markers of plasmacytic differentiation such as CD138 are positive.

## Staging

Staging of HIV-related lymphomas uses the classification used in other settings such as the Ann Arbor classification and that used for BL.

## Recommended Investigations:

**Generic:** see page 2

**Specific:** Full history and examination with particular reference to AIDS status and HAART therapy

CD4 count

## Potential Pitfalls

***a.*** Failure to recognise HIV-positive status

***b.*** Inappropriate nihilism in face of better treatment outcomes

***c.*** Failure to consider drug interactions in the context of HAART

***d.*** Failure to use appropriate prophylaxis against opportunistic infections

## Treatment

Patients need to be managed in a multidisciplinary setting with joint management by an infectious disease team and a team skilled in the management of lymphoma.

Comorbidities and the status of HIV will determine the intensity of treatment possible.

HL and BL are treated using standard therapy and continuing HAART. The outcome of patients with DLBCL treated with dose adjusted R-EPOCH appears particularly encouraging. Favourable prognostic factors include good performance status, low IPI, preserved CD4 count and no history of IV drug abuse. Patients with BL are usually treated with standard Burkitt regimens, though good results have also been obtained with DA-R-EPOCH and both DFS and OS at 5 years of about 50% can be achieved.

PEL and primary CNS lymphoma remain almost uniformly fatal with a median survival of 6 months.

## Relapse Evaluation and Follow Up

Response evaluation and follow up should be the same as for immune competent patients. Patients with HIV-related lymphomas will also be on lifetime follow up by the infectious disease service.



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# Post-Transplant Lymphoproliferative Disease

## Definition and Incidence

A spectrum of lymphoproliferative disease (PTLD) is described in transplant recipients, including post-transplant infectious mononucleosis, benign polyclonal polymorphic B-cell hyperplasia, and monoclonal polymorphic lymphoma. Most are EBV-related.

**ICD – 0 Code:** **9970 / 1 (Polymorphic PTLD)**

## Management

Patients with post-transplant infectious mononucleosis or benign polyclonal polymorphic B-cell hyperplasia may be treated with antiviral drugs such as acyclovir. Patients with overt lymphoma should be treated with withdrawal of immunosuppression to levels consistent with graft survival, and appropriate intensive Rituximab containing chemotherapy such as R-CHOP. Close attention is required for prevention and management of opportunistic infections in these high-risk patients. Patients should be managed in a centre where a multidisciplinary team with expertise in both NHL and management of transplant patients is available

# Common Issues in Lymphoma Management

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# Common Issues in Lymphoma Management

## CNS-DIRECTED THERAPY

**CNS-directed therapy is indicated for patients with:**

- Lymphoblastic Lymphoma
- Burkitt Lymphoma
- HIV-related lymphoma
- HTLV-I-related lymphoma
- Post-transplant lymphomproliferative disease
- High risk DLBCL as described below

DLBCL patients with high-risk IPI scores, para-nasal sinus or testicular involvement and marrow involvement are at higher risk of CNS disease, which is associated with poor survival. The overall risk based on high IPI (↑ LDH, marrow involvement) is around 5%. Where there is involvement of sinus or testis the risk of CNS disease is 20 – 50%.

There is no general agreement about a preferred CNS-directed therapy schedule. The following have been suggested:

- Intrathecal methotrexate (12.5mg) once per chemotherapy cycle for 4 – 6 doses.
- Cytarabine (50mg) can be substituted for methotrexate or the liposomal preparation of cytarabine can be considered.
- Regimens including intermediate or high-dose methotrexate, high-dose cytarabine and ifosfamide also provide effective CNS-directed therapy.



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# Tumour Lysis Syndrome

Tumour Lysis Syndrome (TLS) may occur in patients with lymphoma at institution of therapy. It is characterised by hyperphosphataemia, hyperkalaemia, hyperuricaemia, hypocalcaemia and acute oliguric renal failure. Patients at risk are those with pre-existing renal impairment, a high LDH, a high tumour burden and aggressive lymphomas such as Burkitt's lymphoma. It is important to note that in patients with aggressive lymphoma, TLS may occur in those treated solely with corticosteroids.

All patients with high grade disease or bulky low grade disease should be adequately hydrated and given allopurinol prior to starting treatment. Patients at high risk for TLS should be managed with intensive intravenous hydration to promote a brisk urine output, alkalinisation of urine, and rasburicase. Specific therapy for electrolyte imbalance and haemodialysis may be required. Serum calcium, phosphate, magnesium, potassium, creatinine and uric acid should be monitored every 2 – 6 hours for the first 24 hours and as indicated thereafter.



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# Irradiation Of Blood Products

Transfusion-associated graft-versus-host disease (GVHD) has been reported in lymphoma patients. To avoid this complication transfusion of irradiated blood components is recommended in the following situations:

- Patients with Hodgkin lymphoma. This is a life-long requirement even after successful treatment.
- All recipients of allogeneic haematological stem cell support from commencement of conditioning therapy. This is a life-long requirement.
- Patients during priming for stem cell harvesting.
- Patients treated with purine analogues (fludarabine, pentostatin, cladribine). This is a life-long requirement.



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# Haematopoietic Recombinant Growth Factor Support

## Erythropoietin

Erythropoietin may be used to reduce transfusion requirements in selected patients with lymphoma undergoing chemotherapy.

## Granulocyte colony stimulating factors

Haematopoietic growth factors currently in use include:

| | | | |
|---|---|---|---|
| **Filgrastim** | **-** | **r-met HuG – CSF** | **Neupogen** |
| **Lenograstim** | **-** | **r-HuG – CSF** | **Granocyte** |
| **Pegylated Filgrastim** | | | **Neulasta** |

## Indications

Haematopoietic growth factors may be indicated in the following circumstances and are particularly important for maintaining dose intenstity when chemotherapy is being given with curative intent:

1. Chemotherapy support
2. Peripheral blood stem cell harvest / progenitor cell mobilisation
3. Post peripheral blood stem cell infusion
4. Neutropenic sepsis
5. Invasive fungal infection

## Chemotherapy Support

**Primary prophylaxis**

May be used in 'at risk patients' or those who have had a previous episode of febrile neutropenia receiving curative chemotherapy, as recommended below.

**At risk patients**

- Patients receiving chemotherapy who are at 'high risk' (e.g. ≥ 40% likelihood) of developing febrile neutropenia or infection e.g.
- Pre-existing neutropenia due to disease
- Extensive prior chemotherapy
- Previous irradiation to the pelvis or other areas containing large amounts of bone marrow
- History of recurrent febrile neutropenia while receiving earlier chemotherapy of similar or lesser dose-intensity
- Conditions potentially enhancing the risk of serious infection e.g. poor performance status, decreased immune function, open wounds or already active tissue infection

**Secondary prophylaxis –**

**Previous episode of febrile neutropenia**

The use of GCSF should be considered in patients receiving curative chemotherapy who have had a previous episode of febrile neutropenia.

## Peripheral blood stem cell harvest

Both Filgrastim and Lenograstim may be used for priming (either alone or in combination with chemotherapy). The choice and dose used depends on the protocol for harvesting. Plerixifor with G-CSF may be used for patients who have failed to achieved successful mobilisation with conventional approaches.



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## Post autologous peripheral blood stem cell or marrow infusion

Patients should receive GCSF support according to protocol.

## Severe neutropenic sepsis

GSCF should not be routinely used for patients who are neutropenic or have uncomplicated fever. G-CSF may be considered for high-risk febrile neutropenic patients with prognostic factors predictive of poor clinical outcome: profound neutropenia (ANC $< 0.1 \times 10^9/1$), uncontrolled primary disease, pneumonia, hypotension, multi-organ dysfunction and invasive fungal infection.

## Exclusion criteria

Patients receiving palliative chemotherapy should not receive GCSF for chemotherapy support.

## Administration details

Start at least 24 hours after completion of chemotherapy and stop at least 24 hours before the next cycle. The optimal timing and duration of GCSF administration has not been defined.

## Duration of treatment

Post PBSCT or BMT or following an episode of neutropenic sepsis:

Stop the GCSF if a neutrophil count of $> 0.5 \times 10^9/1$ has been achieved for two consecutive days.



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# Follow-Up

## Follow-up for patients with HL and aggressive NHL

At completion of treatment and restaging evaluation, consider giving each patient an information sheet stressing the importance of new symptoms.

## Clinic Visits

See recommendations for individual diseases

### At each visit

- Ask about new symptoms
- Examine for lymphadenopathy, hepatomegaly, splenomegaly, abdominal masses
- Reinforce advice about smoking cessation and avoiding sunburn
- Encourage patients to make an earlier appointment

### Investigations

- Blood count and chemistry (to include LDH) at each visit
- Thyroid function tests annually from year 3 after previous radiotherapy to mediastinum/neck.
- Chest X-Ray at alternate visits in years 1 and 2, then annually to year 5 (if mediastinal, lung or pleural disease at presentation and complete remission at end of treatment)

All other investigations should be arranged in response to new symptoms / signs of disease, abnormal results from the above investigations or in the context of clinical trial protocols.

## Follow-up for patients with indolent NHL

### Clinic Visits

- 3-monthly in year 1
- 4-monthly in year 2
- 6-monthly in year 3
- annually thereafter

### At each visit

- Ask about new symptoms
- Examine for lymphadenopathy, hepatomegaly, splenomegaly, abdominal masses
- Reinforce advice about smoking cessation and avoiding sunburn
- Encourage patients to make an earlier appointment if new problems arise

### Investigations

- Blood count and chemistry (to include protein electrophoresis if a paraprotein was detected at presentation and LDH)
- Thyroid function tests annually after previous radiotherapy to mediastinum / neck

All other investigations should be arranged in response to new symptoms / signs of disease, abnormal results from the above investigations or in the context of clinical trial protocols.



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# Prevention and Management of Late Treatment Effects

## Hypothyroidism, Premature Menopause and Infertility

Hypothyroidism is commonly seen in patients following involved or extended field radiotherapy to the neck and mediastinium and total body irradiation. Annual thyroid function tests should be carried out on these patients.

Premature menopause is caused by radiotherapy and chemotherapy (particularly alkylating agents). Hormone replacement therapy should be considered for all patients <45 years after assessing breast cancer and other HRT associated risks. Patients should be made aware of the possible return of fertility months to years after apparent menopause and the increased risk of early menopause in all patients treated with cytotoxic therapy.

Patients unsuitable for HRT should be monitored every 2-5 years for osteoporosis by DEXA scanning. Calcium/Vitamin D treatment is appropriate for all patients with osteopenia and raloxifene or biphosphonate may be indicated in patients with osteoporosis.

The testosterone producing Leydig cells are rarely affected by therapy, however LH, FSH and testosterone levels should be checked if symptoms suggestive of hormone deficiency are present and a referral to endocrinology made, if appropriate.

## Protection of reproductive function

For men, semen cryopreservation has been available for some time. Stored semen can be used at a later date for either artificial insemination of a female partner or in vitro fertilisation with subsequent implantation of embryos. The development of advanced fertility treatment, in particular intracytoplasmic sperm injection (ICSI), means that semen containing extremely low numbers of spermatozoa (as sometimes seen in very ill patients with lymphoma) is now worth preserving. Obtaining semen is not an option for pre-pubertal boys and methods of preserving fertility in this group are still experimental.

The ovary is more resistant to the effects of treatment than the testes, older women (>30 years and particularly >35 years) are more likely to develop permanent amenorrhoea / infertility, and high-dose chemotherapy is likely to cause ovarian ablation at any age.

In vitro fertilisation of thawed, mature eggs harvested and cryopreserved before the start of chemotherapy has resulted in very few pregnancies worldwide. Cryopreservation of embryos is a technique that works well but is only possible for women with a partner. Harvesting mature eggs requires several weeks of hormone stimulation of the ovary, and delaying treatment may not be feasible in the majority.



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## Follow-up for patients with concerns about fertility / sex hormone status

### Men

- Semen analysis is the best way of assessing germinal epithelial function. Recovery of spermatogenesis may take some time and one negative result may not indicate permanent azoospermia.
- There is no need to measure the serum follicle-stimulation hormone (FSH), luteinizing hormone (LH), testosterone or sex hormone binding globulin (SHBG) on a routine basis. Patients with a depressed libido or fatigue should, be tested for subnormal levels of serum testosterone and referred to an endocrinologist. A more common finding is a raised FSH and a low normal level of testosterone. There is no evidence supporting the use of testosterone replacement in these circumstances.

### Women

- If menstruation is regular, sex hormone analysis is unnecessary. If menstruation is irregular or absent, the serum oestrogen, progesterone, FSH, LH and SHBG should be measured and the patient's management discussed with an endocrinologist.
- Even if normal menstruation resumes following treatment, a woman's reproductive lifespan is likely to have been curtailed, and pregnancy, if desired, should not be unduly delayed.
- If women have stored mature eggs, ovarian cortical tissue or embryos before the start of sterilising treatment, their use of these should be in close collaboration with the local fertility clinic.

## Second Malignancy

Chemotherapy for lymphoma is associated with an increased risk of myelodysplasia and acute myeloid leukaemia (AML) some 4-6 years later, often presenting with unexpected anaemia or pancytopenia. The incidence of second solid tumours is also increased by previous exposure to chemotherapy, but radiation treatment is thought to be the biggest risk factor. Other known risk factors for developing malignancy (particularly smoking and sunburn) have an additive effect, and patients should be advised to modify their lifestyle accordingly. They should also be encouraged to report new symptoms without delay to maximise early diagnosis of second tumours.

Young women (≤ 25 years old) whose breasts have been incidentally irradiated have an increased relative risk of developing breast cancer 10-15 years later. This experience is primarily in patients with HL receiving mantle field irradiation, but there may also be a risk associated with radiotherapy to the lower neck, supraclavicular fossae and axillae which results in scattered radiation to the breasts. The benefits of breast screening in this population are unproven but mammographic screening is recommended.

## Cardiopulmonary dysfunction

Cardiac function can be affected by anthracyclines which can cause cardiomyopathy and heart failure. Using a threshold total dose of less than 450mg/m2 of doxorubicin minimises this risk but it can occur at much lower doses. In patients >70 years of age or those of any age with symptoms or a history of cardiac disease, measurement of left ventricular function (by MUGA scan or echocardiography) is mandatory. Doxorubicin should be avoided with possible substitution of potentially less-cardiotoxic analogues (e.g. epirubicin or mitoxantrone) if there is evidence of impaired cardiac function. When the heart is included in a radiotherapy field there is an increased risk of coronary artery disease and its complications.

Some chemotherapy agents (bleomycin, busulfan, cyclophosphamide and BCNU) and radiotherapy can cause lung fibrosis. Cough, exertional dyspnoea and a restrictive pattern of lung function may develop. The effect of bleomycin is exacerbated by larger doses, advanced age, pre-existing lung disease, previous radiotherapy and smoking.

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# Vaccination Policy

Splenectomy may be carried out to de-bulk low grade lymphomas such as marginal zone lymphomas or to treat itp which is commoner in lymphoma patients. Functional hyposplenism may be present in patients with lymphoma e.g. enteropathy-type T-cell lymphoma associated with splenic atrophy and immunodeficiency of varying degrees will exist among this patient population. There fore patients with lymphomas benefit from a formal vaccination and prophylactic antibiotics strategy

**Pneumococcal and Haemophilus influenzae Type B vaccine:**

If splenectomy is required or if there is functional hyposplenism, vaccination should be given ideally > 72 hours before surgery but otherwise as soon as possible. All patients with HL and hyposplenic states should have these vaccinations. Pneumococcal vaccination should be repeated every 5 years.

**Meningococcal Type C vaccine:**

This vaccine should be given prior to splenectomy or in hyposplenic states.

**Influenza vaccination:**

Annual vaccination is advised.

**Prophylactic antibiotics:**

Post-splenectomy patients are at risk of fulminant pneumococcal sepsis and vaccination gives incomplete protection. They should take prophylactic antibiotics in the form of penicillin V 333mg BD or erythromycin 250mg BD if there is allergy to penicillin. Patients should have prompt access to broad-spectrum antibiotics at all times for use in the event of fever especially if they opt to avoid the use of prophylactic antibiotics.



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# Appendix

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## Appendix - Radiotherapy guidelines

Radiotherapy guidelines have been included in specific lymphoma sub-type chapters. It is advisable to ensure radiotherapy input when initial management plan is being instituted for a patient with lymphoma. The guidelines for delineating involved field irradiation are included in this appendix but individual planning remains necessary in all cases.

### Guidelines For Delineating Involved Field Irradiation in Lymphoma

Treat a region, not an individual lymph node. The main involved field regions are neck (unilateral), mediastinum,

(including hilar regions bilaterally) axilla (including the supraclavicular and infraclavicular lymph nodes), spleen, para-aortic lymph nodes and inguinal (including the femoral and iliac) lymph nodes.

Use the initially involved pre-chemotherapy sites and volume, with the exception of the transverse diameter of the mediastinum and para-aortic lymph nodes, where the reduced post-chemotherapy volume should be used.

**Supraclavicular**
The supraclavicular lymph nodes are considered part of the cervical region and if involved alone or with other cervical nodes, the whole neck is unilaterally treated. If the supraclavicular involvement is an extension of mediastinal disease and other neck areas are not involved (based on CT imaging with contrast or PET-CT scanning) the neck above the larynx is not treated to avoid salivary gland irradiation. Pre- and post-chemotherapy information regarding lymph-node localization and size is critical and should be available at the time of planning the field.

**I. Unilateral cervical/supraclavicular region**
Involvement at any cervical level with or without involvement of the supraclavicular (SCL) nodes.

Upper border: 1-2 cm above the lower tip of the mastoid process and midpoint through the chin.

Lower border: 2 cm below the bottom of the clavicle.

Lateral border: To include the medial 2/3 of the clavicle.

Medial border: If the supraclavicular nodes are not involved, place the border at the ipsilateral transverse processes, except when medial nodes close to the vertebral bodies are seen on the initial staging neck CT scan. For medial nodes include the entire vertebral body. When the supraclavicular nodes are involved, the border should be placed at the contralateral traverse processes.

For stage I patients, the larynx and vertebral bodies above the larynx can be blocked.

**II. Bilateral cervical/supraclavicular region**
Treat both cervical and supraclavicular regions as described above regardless of the extent of disease on each side.

**III. Mediastinum**
Involvement of the mediastinum and/or the hilar nodes. The field includes the medial SCL nodes even if not clinically involved.

Upper border is C5-C6 interspace: If supraclavicular nodes were also involved the upper border should be placed at the top of the larynx and the lateral border should be adjusted as described in the section on treating neck nodes.



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Lower border: The lower of (i) 5 cm below the carina or (ii) 2 cm below the pre-chemotherapy inferior border.

Lateral border: The post-chemotherapy volume with 1.5 cm margin.

Hilar area: To be included with 1 cm margin unless initially involved where as the margin should be 1.5 cm.

**IV. Mediastinum with involvement of the cervical nodes**

When both cervical regions are involved, the field is a mantle without the axilla using the guidelines described above. If only one cervical chain is involved the vertebral bodies, contra-lateral upper neck and larynx can be blocked as described previously. Because of the increased dose to the neck (the isocentre is in the upper mediastinum), the neck above the lower border of the larynx should be shielded at 30.6 Gy.

If paracardiac nodes are involved, the whole heart should be treated with 14.4 Gy and the initially involved nodes should be treated with 30.6 Gy.

**V. Axillary region**

The ipsilateral axillary, infraclavicular and supraclavicular areas are treated when the axilla is involved. CT-based planning should ideally be used.

Upper border: C5-C6 interspace.

Lower border: The lower of (i) the tip of the scapula or (ii) 2 cm below the lowest axillary node.

Medial border: Ipsilateral cervical transverse process. Include the vertebral bodies only if the SCL are involved.

**VI. Spleen**

The spleen is treated only if abnormal imaging was suggestive of involvement. The post-chemotherapy volume is treated with 1.5 cm margins. CT-based planning should be used.

**VII.Abdomen (para-aortic nodes)**

Upper border: Top of T11 and at least 2 cm above pre-chemotherapy volume.

Lower border: Bottom of L4 and at least 2 cm below pre-chemotherapy volume.

Lateral borders: The edge of the transverse processes and at least 2 cm from the post-chemotherapy volume.

Note: The kidneys should be outlined and considered when designing the blocks.

The porta-hepatis region should be included if originally involved (this should be identified with CT-based planning).

**VIII. Inguinal/femoral/external iliac region**

These ipsilateral lymph node groups are treated together if any of the nodes are involved.

Upper border: Middle of the sacro-iliac joint.

Lower border: 5 cm below the lesser trochanter.

Lateral border: The greater trochanter and 2 cm lateral to initially involved nodes.

Medial border: Medial border of the obturator foramen with at least 2 cm medial to involved nodes.

Note: If common iliac nodes are involved the field should extend to the L4-5 inter-space and at least 2cm above the initially involved nodal border.



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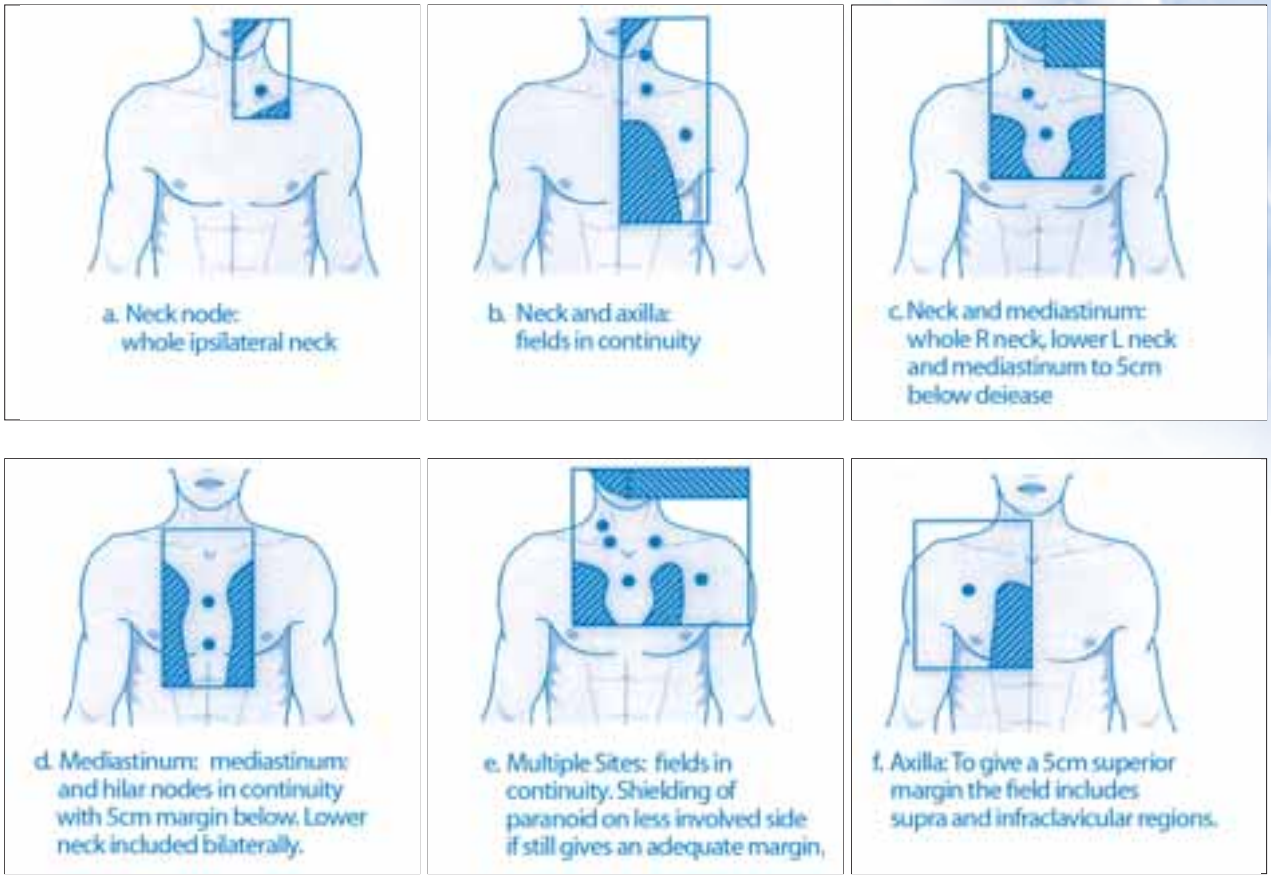

a. Neck node: whole ipsilateral neck

b. Neck and axilla: fields in continuity

c. Neck and mediastinum: whole R neck, lower L neck and mediastinum to 5cm below deiease

d. Mediastinum: mediastinum: and hilar nodes in continuity with 5cm margin below. Lower neck included bilaterally.

e. Multiple Sites: fields in continuity. Shielding of paranoid on less involved side if still gives an adequate margin.

f. Axilla: To give a 5cm superior margin the field includes supra and infraclavicular regions.



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# Glossary of treatment regimens



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## Glossary of Treatment Regimens

Chlorambucil
Rituximab

| | |
|---|---|
| FC: | Fludarabine, Cyclophosphamide |
| FCM: | Fludarabine, Cyclophosphamide, Mitoxantrone |
| FCR: | Fludarabine, Cyclophosphamide, Rituximab |
| FCMR: | Fludarabine, Cyclophosphamide, Mitoxantrone, Rituximab |
| CVP: | Cyclophosphamide, Vincristine, Prednisolone |
| R-CVP: | Rituximab, Cyclophosphamide, Vincristine, Prednisolone |
| CHOP: | Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone |
| R-CHOP: | Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone |
| R-HCVAD: | Rituximab, Cyclophosphamide, Vincristine, Doxorubicin, Dexamethasone |
| DHAP: | Dexamethasone, Cytarabine, Cisplatin |
| ESHAP: | Etoposide, Methylprednisolone, Cytarabine, Cisplatin |
| IEV: | Ifosfamide, Epirubicin, Etoposide (VP16) |
| ICE: | Ifosfamide, Cisplatin, Etoposide |
| CODOX-M: | Cyclophosphamide, Doxorubicin, Vincristine, Methotrexate |
| IVAC: | Ifosfamide, Etoposide, Cytosine Arabinoside, Methotraxate (intrathecal) |
| ABVD: | Doxorubicin, Bleomycin, Vinblastine, Dacarbazine |
| BEACOPP: | Bleomycin, Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, Procarbazine, Prednisolone |
| R-EPOCH: | Rituximab, Etoposide, Prednisolone, Vincristine, Cyclophosphamide, Doxorubicin (infusional). |

*Dosing schedules of agents used in cancer therapy are constantly being revised and new side-effects recognised. The Lymphoma Forum of Ireland makes no representation, express or implied, that any drug dosages in this document are correct. For these reasons the reader is strongly urged to consult the pharmaceutical company's printed instructions before administering any drug recommended in this guide.*

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