

British Committee for Standards in Haematology

Guidelines on diagnosis and therapy

Nodal non-Hodgkin's lymphoma

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The evidence base was presented at an open meeting at the Royal College of Pathologists attended by 120 medics in November 2000.

Contributions were also provided by: A K Burnett, C H Poynton, N Steven and N Rooney (Royal College of Pathologists Minimum Dataset for Lymphoma) and the Lymphoma Association.

The contents were peer reviewed by 40 Haematologists, Oncologists and Histopathologists and relevant suggestions incorporated.

The final draft was approved by the BCSH of the British Society for Haematology and the Joint Committee for Clinical Oncology of the Royal College of Physicians, and the Association of Cancer Physicians.

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Level of Evidence

Level	Type of evidence
Ia	Evidence obtained from meta-analysis of randomised controlled trials
Ib	Evidence obtained from at least one randomised controlled trial
IIa	Evidence obtained from at least one well-designed controlled study without randomisation
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case control studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities

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Introduction

1. Epidemiology

2. Diagnostic standards

3. Staging system definition and International Prognostic Index (IPI)

4. Clinical work-up

1. Epidemiology

Approximately 5,000 new cases of non-Hodgkin's lymphoma (NHL) are registered in England and Wales every year. In line with the rest of the Western world, the incidence of these tumours is increasing by 3–5% per year, and they continue to attain more prominence in cancer mortality statistics. The reason for the increasing incidence is not known; better diagnosis, an increasing elderly population, and unknown environmental factors may all be relevant. The increase has not occurred in all subgroups. The NHLs are a heterogeneous group of diseases linked only by their origin within the lymphoid subtypes. Over two-thirds of all NHLs are accounted for by two histological subtypes: diffuse large B cell lymphoma (DLBCL), an aggressive lymphoma, and follicle centre cell (or follicular) lymphoma, an indolent (or non-aggressive) lymphoma. Other, more rare subtypes exist, and all display distinct natural histories and require specific management. The accurate diagnosis and treatment of many NHLs, some of which are potentially curable, thus requires access to sophisticated diagnostic and expert clinical opinion. These guidelines aim to summarise current diagnostic and management principles to foster consistent treatment for patients with NHL across the National Cancer Centre/Cancer Unit Network.

The guidance is consistent with the National Cancer Centre Network (NCCN) guidelines in the United States.

Table 1.1 Changes in incidence of NHL in parts of England and Wales 1986–1993

Site of disease	Cases	WSR (cases/10 ⁶ /year)	% Change	p-value
All NHL	11334	62.8	4.95	0.002
Nodal NHL	7229	40.6	4.75	0.003
Extra-nodal NHL	3556	19.1	7.51	0.002
Gastrointestinal tract NHL	1071	5.8	4.21	0.045
Gastric NHL	464	2.4	12.70	0.005
Small bowel NHL	293	1.7	8.50	<i>ns</i>
Large bowel NHL	120	0.6	-2.40	<i>ns</i>
Skin NHL	767	4.2	14.20	0.012
Skin lymphoma	516		23.00	0.008
Central nervous system	164	1.0	10.66	0.040

Definitions

Extra-nodal	Primary extra-nodal NHL was defined as cases where initial symptoms had led to a diagnostic biopsy from tissues other than the lymph nodes, spleen, bone marrow, blood, thymus, Waldeyer's ring or tonsil and at the time of diagnosis disease was absent in these tissues.
WSR	World standardised incidence rate, all ages.
Skin NHL	All skin NHL including mycosis fungoides and Sezary disease.
Skin lymphoma	Skin NHL excluding mycosis fungoides and Sezary disease.

2. Diagnostic standards

2.1 Tissue collection

2.1.1 Investigations prior to biopsy

In all patients, a full blood count (FBC) with film and cell marker studies, where appropriate, should be carried out before a node biopsy. This is to avoid unnecessary node biopsies in patients with B cell chronic lymphocytic leukaemia (B-CLL) and, less commonly, acute leukaemia. A significant number of unnecessary biopsies are carried out in patients who have overt leukaemia.

In all patients < 30 years with an enlarged lymph node, a monospot should be carried out.

In all patients with cervical node disease an ENT examination should be carried out to exclude epithelial malignancy of the head and neck, in patients thought to have carcinoma a fine needle aspirate is the first-line investigation.

2.1.2 A designated surgeon should perform all lymph node biopsies for the diagnosis of lymphoma.

An ENT or Maxillo-facial surgeon should be responsible for cervical node biopsies and a general surgeon for others. The use of designated surgeons ensures adherence to protocols for specimen collection and prompt referral of patients with lymphoma to the Haematological Oncology Clinic. A local agreement should be in place to ensure that the preliminary biopsy report can be available to the multidisciplinary team (MDT) within 2 weeks of the patient's first contact with the MDT (see section 21.2).

Box 2.1

Approach to diagnosis of a patient with lymphadenopathy

- FBC with film and cell marker studies, where appropriate, should be carried out before a node biopsy
- Monospot in patients < 30 years
- If cervical node disease, ENT examination to exclude epithelial malignancy of the head and neck
- Designated surgeon(s) – ENT or Maxillo-facial surgeon for cervical nodes and general surgeon for others
- Excision biopsy preferred method; trucut biopsy if node not accessible: not fine needle aspirate
- Node biopsy – send unfixed to lab

2.1.3 At the time of diagnosis a formal excision biopsy of a node should be carried out, unless there are clinical or technical reasons why this is inappropriate.

An excision biopsy allows more detailed assessment of architecture, which is a key feature in the diagnosis of lymphoma. Needle biopsies are also more prone to artefact and may be too small to permit the full range of investigation required for diagnosis in

many cases. A biopsy of an enlarged node should be taken in preference to a biopsy of an extra-nodal site, when possible.

2.1.4 All lymph node biopsies should be sent unfixed to the laboratory. This requires local arrangements for the prompt and safe transport of specimen.

This is essential for a high standard of diagnosis and is increasing in importance with the introduction of new diagnostic techniques. Readers are referred to the Royal College of Pathologists minimum dataset for lymphoma histopathology reports (Appendix 3).

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 to ensure high-quality morphology and reproducible, reliable results with marker studies performed on paraffin sections. The remaining tissue may be snap frozen or disaggregated into a single-cell suspension according to local diagnostic techniques.

2.2 Laboratory diagnosis

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

Access to a specialist haematopathology laboratory should be available in all cancer centres.

2.2.2 The World Health Organization (WHO) classification of neoplastic diseases of the haematopoietic and lymphoid tissues should be the basis of diagnosis (Appendix 3, Table A3.1).

Each laboratory should produce a standard operating procedure (SOP) to implement the use of this classification. This should specify the precise nomenclature and diagnostic criteria to be used. There may be some variation between laboratories reflecting specialist interests and differences in technical approach. Storage of frozen material is desirable.

2.2.3 A specialist haematopathology laboratory requires access to the following resources.

(a) *Morphological expertise.* It is essential that pathologists/haematologists involved in this process have the necessary additional training and experience to undertake this work.

(b) *Immunophenotyping.* All marker studies should be carried out using panels that are designed to test the validity of the morphological diagnosis and to demonstrate key prognostic variables, e.g. Bcl-2 in diffuse large B cell lymphoma (DLBCL).

Immunological marker studies can be carried out using flow cytometry or immunohistochemistry. Opinions will vary as to the choice of techniques or antibodies to be used, but several effective approaches are possible.

(c) *Molecular techniques.* The main current techniques are polymerase chain reaction (PCR) to detect monoclonality and some translocations, and fluorescence *in situ* hybridisation (FISH) techniques for the detection of translocation and numerical chromosomal abnormalities. These techniques should be used in the same way as immunophenotypic studies to test the validity of the provisional diagnosis and to identify prognostic factors. Formal links with the local molecular-cytogenetics service are required.

(d) *Integrated reporting.* Most patients with lymphoproliferative disorders have multiple specimens taken at presentation and follow-up. It is essential that departments have an effective mechanism to correlate results obtained from lymph node biopsies, bone marrow (BM), etc.

2.2.4 *The results of laboratory investigations must be available before initiation of treatment.*

In general a report should be available 5 working days after the specimen is received, although some molecular techniques may take longer. Where the diagnosis depends on investigations that are outstanding, this should be clearly stated.

Box 2.2

Diagnosis – laboratory procedures and standards

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

2.3 Quality assurance, audit and team working

2.3.1 An effective system of audit and quality assurance should be in place in the laboratory.

The main component of quality assurance lies in the construction of the diagnostic process as detailed above. In addition, a system of audit designed to demonstrate the quality of the service should be in place. This can include verification that reports are being prepared in accordance with the SOP and 'independent re-reporting' of randomly selected specimens.

- Laboratories should provide users of the laboratory with details of their diagnostic criteria and technical methods.
- In addition laboratories involved in this work should participate in the relevant NEQAS schemes for immunocytochemistry, flow cytometry, etc.
- It is considered desirable that individual histopathologists should have access to a review panel where diagnoses can be subject to review.

2.3.2 MDT meetings are an essential component of the diagnosis and management of lymphoma.

The arrangement will vary with local circumstances but MDT meetings should be held before a final management plan is produced. All new and relapsed patients should be reviewed at an MDT meeting.

3. Staging system definition and International Prognostic Index

Table 3.1 Ann Arbor staging classification for NHL ^a

Stage	Area of involvement
I	One lymph node region
I _E	One extralymphatic (E) organ or site
II	Two or more lymph node regions on the same side of the diaphragm
II _E	One extralymphatic organ or site (localised) in addition to criteria for stage II
III	Lymph node regions on both sides of the diaphragm
III _E	One extralymphatic organ or site (localised) in addition to criteria for stage III
III _S	Spleen (S) in addition to criteria for stage III
III _{SE}	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 A = asymptomatic; B = symptomatic (unexplained fever of $\geq 38.6^{\circ}\text{C}$ [101.5°F]; unexplained, drenching night sweats; or loss of $> 10\%$ body weight within the previous 6 months).

Box 3.1

The International Prognostic Index (IPI)

The IPI describes a predictive model for patients with DLBCL based on 5 clinical features at presentation.

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

An age-adjusted index for patients aged < 60 years of age is also described, based on stage, LDH and performance status. Patients can be divided into four prognostic categories based on these factors (Section 5, Table 5.1).

4. Clinical work-up

Box 4.1

Essential

- Physical examination: attention to node-bearing area, including Waldeyer's ring, and size of liver and spleen
- Performance status
- B symptoms
- FBC, differential, platelets
- LDH
- Blood urea nitrogen (BUN), creatinine
- Albumin, aspartate transaminase (AST), bilirubin, alkaline phosphatase
- Serum calcium, uric acid
- Chest X-ray, PA X-ray
- Chest and abdominopelvic computed tomography (CT) (including thoracic inlet and above)
- BM biopsy + aspirate
- HIV test (Burkitt's)

Useful in certain circumstances

- Gallium-67 scan (planar and SPECT) double dose with delayed images (category 2)
UGI/barium enema/endoscopy
- Neck CT
- Head CT or magnetic resonance imaging (MRI)
- Plain bone X-ray and bone scan
- Pregnancy test
- HIV test (lymphoblastic lymphoma)
- Beta-2 microglobulin
- Lumbar puncture if paranasal sinus, testicular, parameningeal, orbit disease or BM involvement in high-grade disease.

Further reading

Cartwright RA, McNally R, Staines A. The increasing incidence of non-Hodgkin's Lymphoma (NHL): the possible role of sunlight. *Leuk Lymph* 1994; 14: 387–394
NCCN Preliminary Non-Hodgkin's Lymphoma Practice Guidelines. *Oncology* 1997; 281–346

Management of aggressive NHL

5. Diffuse large B cell lymphoma
6. Burkitt's lymphoma
7. Lymphoblastic Lymphoma/leukaemia (precursor T or B cell lymphoma/leukaemia)
8. Mantle cell lymphoma
9. Lymphoma associated with HIV infection

Generic management

The diagnosis having been made and the extent of disease having been documented (i.e. DLBCL stage IVa IPI : HI) the situation will be explained to the patient by a consultant, preferably in the presence of a relative or friend and a nurse. The natural history will be presented followed by a discussion of the treatment options and the 'risk/benefit' ratio, and the probability of success, measured by 'improving health' and prolonged survival. Particular attention must be paid to short-term toxicity, potential morbidity and mortality and the long-term risk of infertility, second malignancy and damage to vital organs. While care must be taken to take into account different perceptions in different ethnic groups, and it must be appreciated that many people have a limited grasp of statistics, in general it is much better for most patients to know as much as possible about their situation. Written information must also be available.

5. Diffuse large B cell lymphoma

(Mediastinal large B cell lymphoma, anaplastic large cell lymphoma [ALCL], peripheral T cell lymphoma [excluding cutaneous] and follicular lymphoma, grade 3 also to be treated according to this guideline)

DLBCL comprises approximately 30% of all cases of NHL in the UK. It is characterised by aggressive clinical behaviour, typically presenting with rapidly enlarging lymphadenopathy. Extra-nodal involvement is common. All patients presenting with DLBCL should be treated with curative intent. Cure can be anticipated in 40%–50% of all patients who present with DLBCL.

The IPI describes a predictive model for patients with DLBCL based on 5 clinical features at presentation. These are as follows:

- 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)

An age-adjusted index for patients aged < 60 years is also described, based on stage, LDH and performance status.

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

<i>IPI risk group</i>	Number of risk factors	
	All patients	Age adjusted IPI
Low-risk	0,1	0
Low/intermediate-risk	2	1
High/intermediate-risk	3	2
High-risk	4,5	3

Table 5.1 Patients can be divided into 4 prognostic categories

5.1 Treatment

Although the treatments described in the algorithm are based primarily on anatomical extent of disease according to Ann Arbor stage, these approaches are modified in accordance with the IPI risk category.

Box 5.1

DLBCL													
Incidence:	4 new cases/100,000 population/year												
Median age:	64 years												
Sex ratio:	1:1												
Phenotype:	CD19 ⁺ CD20 ⁺ CD22 ⁺ CD79a ⁺ Slg ^{+/-} CD45 ^{+/-} CD5 ^{-/+} CD10 ^{-/+} Bcl-2 ^{-/+}												
Genetics:	t(14,18) in 30% <i>Bcl-6</i> rearrangements in 30–40%												
Outcome:	<table border="0"> <thead> <tr> <th>IPI score</th> <th></th> <th>5-year overall survival (OS)</th> </tr> </thead> <tbody> <tr> <td>0/1</td> <td>35%</td> <td>75%</td> </tr> <tr> <td>2/3</td> <td>46%</td> <td>40%</td> </tr> <tr> <td>4/5</td> <td>19%</td> <td>20%</td> </tr> </tbody> </table>	IPI score		5-year overall survival (OS)	0/1	35%	75%	2/3	46%	40%	4/5	19%	20%
IPI score		5-year overall survival (OS)											
0/1	35%	75%											
2/3	46%	40%											
4/5	19%	20%											
Clinical:	Widespread nodal or extra-nodal disease BM disease 10%												

Box 5.2

Primary mediastinal DLBCL													
Incidence:	0.24 new cases/100,000 population/year												
Median age:	40 years												
Sex ratio:	Female excess (2–4:1)												
Phenotype:	CD19 ⁺ CD20 ⁺ CD22 ⁺ CD79a ⁺ CD45 ^{+/-} Slg ⁻ CD30 ^{-/+}												
Genetics:	No characteristic lesion <i>Bcl-6</i> rearrangements in 30–40%												
Outcome:	<table border="0"> <thead> <tr> <th>IPI score</th> <th></th> <th>5-year OS</th> </tr> </thead> <tbody> <tr> <td>0/1</td> <td>52%</td> <td>65%</td> </tr> <tr> <td>2/3</td> <td>37%</td> <td>40%</td> </tr> <tr> <td>4/5</td> <td>11%</td> <td>0%</td> </tr> </tbody> </table>	IPI score		5-year OS	0/1	52%	65%	2/3	37%	40%	4/5	11%	0%
IPI score		5-year OS											
0/1	52%	65%											
2/3	37%	40%											
4/5	11%	0%											
Clinical:	Bulky mediastinal mass with vena caval obstruction, pericardial and pleural effusions												

Box 5.3

ALCL	
Incidence:	0.24 new cases/100,000 population/year
Median age:	34 years
Sex ratio:	Female excess (2–4:1)
Phenotype:	CD30 ⁺ CD45 ^{+/-} EMA ^{+/-} ALK ^{+/-} CD3 ^{-/+} CD15 ^{-/+} CD45RO ^{+/-}
Genetics:	t(2,5)
Outcome:	IPI score 5-year OS
	0/1 61% } 75%
	2/3 18% }
	4/5 21% }
	Survival is significantly affected by the presence of the ALK protein (ALK ⁺ 5-year OS 93% vs 37% in ALK ⁻)
Clinical:	Good risk presents in children or young adults and may be localised

Box 5.4

Peripheral T cell lymphoma	
Incidence:	0.72 new cases/100,000 population/year
Median age:	61 years
Sex ratio:	1:1
Phenotype:	CD3 ⁺ CD2 ⁺ CD4 ⁺ >CD8 ⁺ CD45RA ⁺ CD5 ^{+/-} CD7 ^{-/+}
Genetics:	No characteristic lesion <i>Bcl-6</i> rearrangements in 30–40%
Outcome:	IPI score 5-year OS
	0/1 17% 40%
	2/3 52% 20%
	4/5 31% 10%
Clinical:	Disseminated nodal and extra-nodal disease

5.1.1 Localised disease (stage I or II)

Treatment approaches differ according to the following factors:

- Disease bulk (< 10 cm vs > 10 cm)
- IPI risk group
- The presence of primary extra-nodal disease

Recommendation 5a

Patients with non-bulky (< 10 cm nodal disease and/or a mediastinal mass measuring < one-third of the maximum transverse diameter of the chest on plain X-ray) nodal stage I or II disease should receive combined modality therapy comprising 3–4 cycles of anthracycline based chemotherapy (e.g. CHOP [Appendix 1]) followed by involved field radiotherapy to all affected lymph node regions.

Level of evidence – level Ib

Results from the Southwest Oncology Group (SWOG) and Eastern Cooperative Oncology Group (ECOG) randomised trials initially confirmed the superiority of this approach over chemotherapy alone.

The outcome for these patients is excellent, with reported long-term progression-free survival (PFS) rates of 60%–70% and OS rates of approximately 80%.

Recommendation 5b

Patients with bulky (≥ 10 cm) disease should be treated according to their IPI subgroup. Patients with low- or low/intermediate risk disease should receive 6–8 cycles of CHOP chemotherapy. Patients with high/intermediate- or high-risk disease should be treated in the same way as those with advanced disease and similar high-risk features (see below).

Level of evidence – level Ib

Involved field radiotherapy should also be considered in this group.

Recommendation 5c

Involved field radiotherapy is mandatory for patients with mediastinal large B cell lymphoma who achieve a partial response (PR) or complete response (CR) to induction therapy.

Level of evidence – level IIb

5.1.2 Advanced disease (stage III or IV)

IPI risk group should determine treatment of these patients.

Standard treatment for patients with low- or low/intermediate-risk disease is with 6–8 cycles of anthracycline-based chemotherapy such as CHOP. Entry into randomised trials is encouraged in this group. Suitable trials in progress at present include the MINT trial, comparing CHOP with CHOP + Rituximab.

Long-term disease-free and OS rates of 60%–70% should be achieved in this group, according to the number of risk factors. There is no evidence to suggest that second- and third-generation regimens improve response or OS rates compared with CHOP.

Patients with high/intermediate- and high-risk disease have a less than 50% chance of cure with conventional chemotherapy and should therefore be treated in the context of clinical trials. For patients aged below 60 years of age, most trials are assessing the role of high-dose therapy and autologous stem cell transplantation (ASCT) as a component of first-line therapy. Management of these patients, and entry into clinical trials should be discussed with the appropriate cancer centre. The Swiss Group for Clinical Cancer Research (SAKK)/UK Coordinating Committee on Cancer Research (UKCCCR) 'Mistral' trial is now open, and participation is encouraged.

In patients over the age of 60 years the GELA trial has demonstrated the superior overall survival for patients receiving CHOP + Rituximab compared with those receiving CHOP alone. Additional trials are not yet published. No trial evidence is available for younger patients. Readers are referred to the BCSH Position Paper on Rituximab. The BNLI Sixty Plus Trial is currently comparing CHOP vs PMitCeBo +/- G-CSF.

Recommendation 5d

Patients over the age of 60 years should receive CHOP combined with Rituximab.

Level of evidence-level Ib

For patients not eligible for entry into this, or other clinical trials, full course (6 to 8 cycles) anthracycline-based chemotherapy (e.g. CHOP) should be considered as standard, but long-term survival rates are in the region of only 20%–30%.

Routine re-staging of patients mid-way through treatment is not necessary. Re-staging at this point should be reserved for patients in whom there is clinical uncertainty with respect to their response status. This is based on the observation that randomised trials in which high-dose therapy (HDT) and ASCT have been used in patients who are 'slow responders' to first-line chemotherapy (i.e. in PR or less, mid-way through treatment), have not shown a survival improvement.

Patients who have obvious disease progression or who have no response mid-way through induction therapy should be treated with a non-cross-resistant regimen (see below). This should be discussed with the cancer centre. Patients who respond to second-line therapy should then proceed to HDT and ASCT.

For all patients who have clinical evidence of response during therapy, formal re-staging should take place at the completion of induction therapy. Patients whom achieve a CR or unconfirmed CR (CR_u) to induction chemotherapy do not require further therapy, with the exception of those patients with mediastinal large B cell lymphoma, in whom mediastinal irradiation should be considered standard therapy.

Optimal management of patients with a PR, in whom residual radiological abnormalities persist at the completion of therapy, remains uncertain. The role of new imaging techniques such as ⁶⁷Ga scanning and FDG-PET are still under assessment. Residual masses should be monitored clinically and radiologically. If stable or shrinking on follow-up, no further therapy is required. If disease progression is documented, patients should receive salvage therapy as for relapsed disease (see below).

5.2 Management of first relapse/progression and primary refractory disease

Patients who relapse or progress after first-line therapy, or who show no initial response have a very poor prognosis if treated with further conventional dose salvage therapy.

Recommendation 5e

The use of HDT and ASCT is standard therapy for patients who relapse, provided that their disease responds to a conventional dose salvage regimen.

Level of evidence – level Ib

In general, they should initially receive therapy with a non-cross-resistant second-line chemotherapy regimen. At present, there is no evidence from randomised trials to indicate superiority of any specific second-line regimen. Discussion with the cancer centre is therefore recommended at this point. Eligible patients should be entered into randomised clinical trials.

Patients aged < 70 years who respond to second-line therapy should proceed to HDT and ASCT. Multiple high-dose regimens have been used, and there is no current evidence to suggest the superiority of any particular regimen. Approximately 40%–50% of relapsing patients, who respond to second-line chemotherapy, will be cured by HDT and ASCT. The use of HDT and ASCT for primary refractory disease produces lower long-term disease-free survival (DFS) rates, even after response to a second-line regimen. Patients may be ineligible for HDT and ASCT because of age, persistent BM infiltration, or failure to mobilise adequate peripheral blood progenitor cells (PBPCs). An individualised approach should be used, especially for patients aged > 70 years. In selected younger patients with persistent BM infiltration, or inadequate PBPC mobilisation, allogeneic BM transplantation (BMT) or non-intensive allograft procedures may be possible. This should be discussed with the cancer centre.

Patients who do not respond to second-line therapy have a very poor prognosis if treated with further conventional- or high-dose therapy. HDT and ASCT should not be considered in this group. Entry into clinical trials is recommended – this should be discussed with the cancer centre. Individualised therapy should be used in patients who are ineligible for clinical trials.

Patients whose disease relapses after HDT have a very poor prognosis with a median survival of only 3–6 months. Selected younger patients may be eligible for allogeneic BMT or non-intensive allograft protocols. This should be discussed with the cancer centre. Patients not eligible for investigational protocols should be managed in an individualised fashion.

Box 5.5

DLBCL – diagnosis

Essential

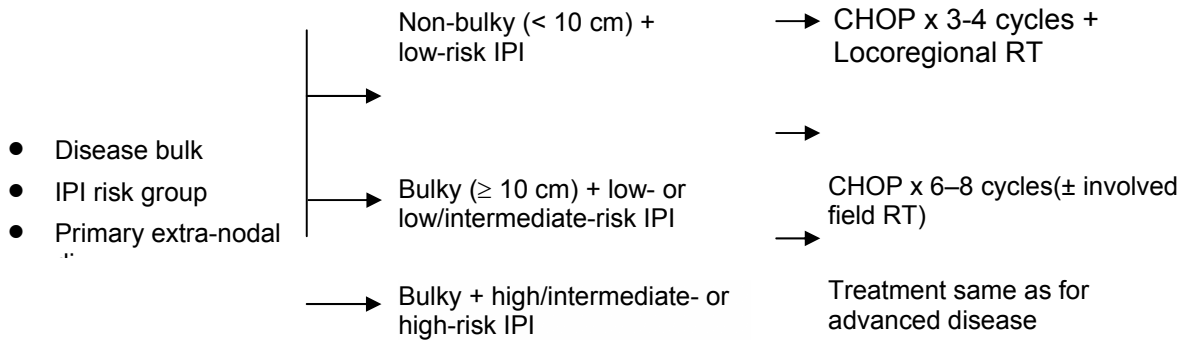
- Haematopathology review of all slides with at least one paraffin block representative of the tumour. Re-biopsy if consult material is non-diagnostic
- Adequate immunophenotyping to establish diagnosis and lineage
- Paraffin panel: CD45 (LCA/Pan T), CD20 (L26/Pan B), CD3 and/or CD45RO (Pan T) and cytokeratin (optional)

Useful in certain circumstances

- Additional immunohistochemical studies to establish lymphoma subtype
- Peripheral T cell lymphoma: CD3, CD43, CD45RO; Hodgkin's disease (HD)/ALCL: CD15, CD30; Lymphoblastic lymphoma: TdT, CD79a; MCL: cyclin D₁, CD5^b, CD43
- Typical immunophenotype: CD45⁺, CD20⁺, CD3⁻, CD45RO⁻
- Cell surface marker analysis by flow cytometry: kappa/lambda, CD45, CD3, CD5, CD19, CD10, TdT, CD14, CD13, CD33, CD20
- Antigen receptor/oncogene rearrangements for clonality, lineage

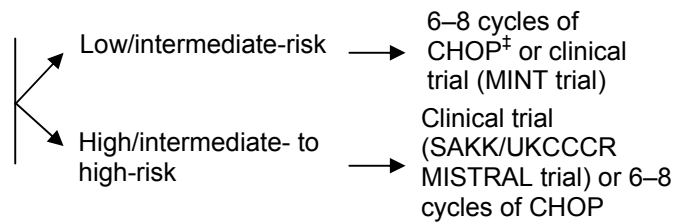
^b Usually requires frozen sections

Figure 5.1 DLBCL – induction therapy*
Localised disease (stage I or II)



Advanced disease

- Local stage with high/intermediate- or high-risk IPI
- Stage III or IV + age-adjusted IPI

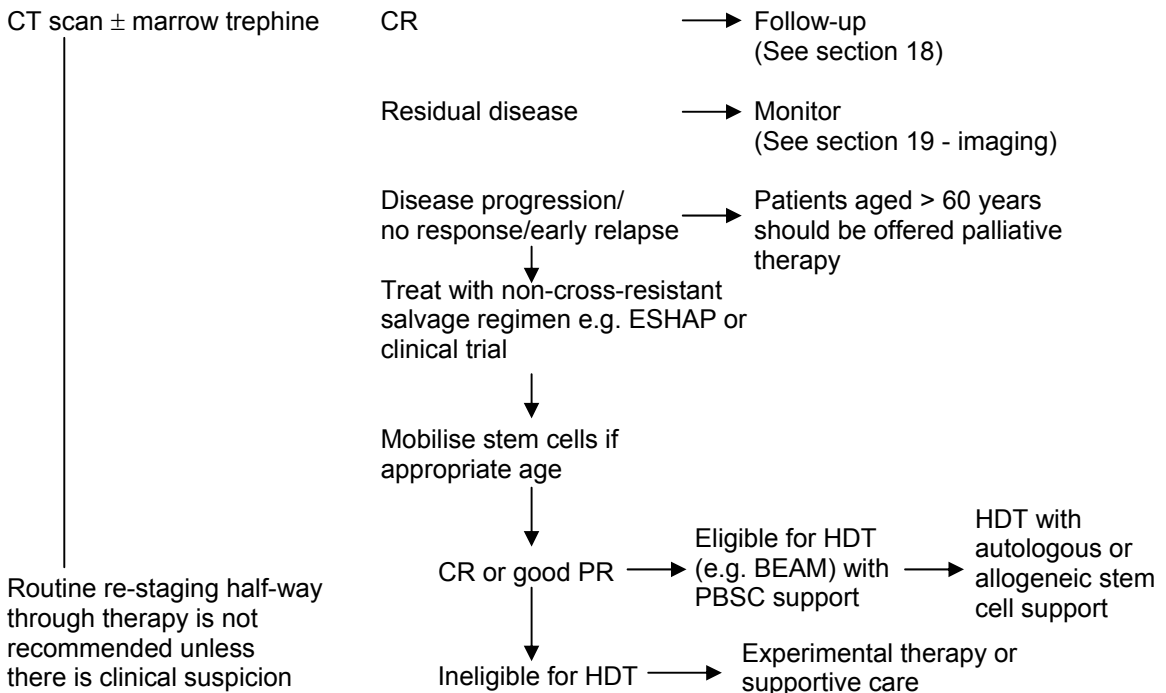


Recommendations are for HIV-negative lymphoma only
 †Recent trial data does not show a survival difference between full CHOP chemotherapy and CHOP x 3 plus radiotherapy. Limited chemotherapy (CHOP x 3 or 4) maybe suitable for IA disease with no adverse factors (LDH or erythrocyte sedimentation rate [ESR])
 ‡ XRT to primary mediastinal disease
 For CNS prophylaxis see section 15

Figure 5.2 DLBCL- response assessment

Repeat staging

Outcome/action



of response failure

6. Burkitt's Lymphoma

Box 6.1

Burkitt's lymphoma	
Incidence:	Rare (< 0.2 new cases/100,000 population/year)
Median age:	31 years
Sex ratio:	Male excess (2:1)
Phenotype:	CD19 ⁺ CD20 ⁺ CD22 ⁺ CD79a ⁺ SIgM ⁺ CD10 ⁺ CD5 ⁻ CD23 ⁻ TdT ⁻
Genetics:	t(8,14) t(2,8) t(8,22)
Outcome:	Survival > 90% is expected for low-risk disease and > 50% for high-risk disease with disease-tailored therapy
Clinical:	Bulky central nodal disease, BM and CNS

Burkitt's lymphoma is a rare entity and comprises approximately 2%–3% of all NHL. Lymphomas occurring in the context of immunosuppression (e.g. post-organ transplantation or AIDS) are typically of Burkitt's subtype. These are considered separately (see below). This section refers to treatment of Burkitt's lymphoma in immunocompetent patients.

Burkitt's lymphoma is characterised by a very aggressive clinical course, with a propensity for BM and CNS involvement, and for extra-nodal involvement, especially in the abdomen. There is typically ileocaecal involvement.

The outcome for patients treated with standard first-, second- or third-generation NHL regimens is very poor, with only 20%–30% achieving long-term survival. However, recent results with high-intensity chemotherapy regimens such as the NCI 89-C-41 protocol have produced cure rates of 80%–90%. All such patients should therefore be discussed with the cancer centre urgently, and all should enter clinical trials. Patients under 60 years should be entered into the LY10 Trial.

Patients with Burkitt's lymphomas have a high risk of developing acute tumour lysis syndrome (TLS), and prophylaxis against this syndrome is mandatory in all patients, irrespective of disease extent.(see section 17).

Patients with Burkitt's lymphoma can be risk-stratified. Those with completely resected abdominal disease or a single extra-abdominal mass, and a low serum LDH are regarded as having low-risk disease. All other patients have high-risk disease.

There is no evidence to support the use of HDT and ASCT or allogeneic BMT to consolidate first remission in patients who receive appropriate high-intensity induction therapy. In patients who, for whatever reason, receive less intensive induction therapy and achieve a PR or CR, high-dose consolidation should be considered. Long-term survival rates of approximately 70% have been reported with this approach and this should be discussed with the cancer centre.

Patients not eligible for a very intensive approach (e.g. age > 70 years) should be treated in an individualised fashion. However, it should be remembered that patients up to 65 years of age have been successfully treated with attenuated 'high-intensity' regimens such as 89-C-41, and should always be discussed with the cancer centre.

Patients who relapse after induction therapy should be treated with a new non-cross-resistant regimen. Responding patients should then be treated with HDT and ASCT or allogeneic BMT. This should be discussed with the cancer centre. Long-term survival has been reported in up to 20% of these patients. In those not eligible for transplant strategies, the prognosis is very poor. These patients should be considered for phase I or II studies, or offered individualised therapy.

Box 6.2

Burkitt's and lymphoblastic lymphomas – diagnosis

Essential

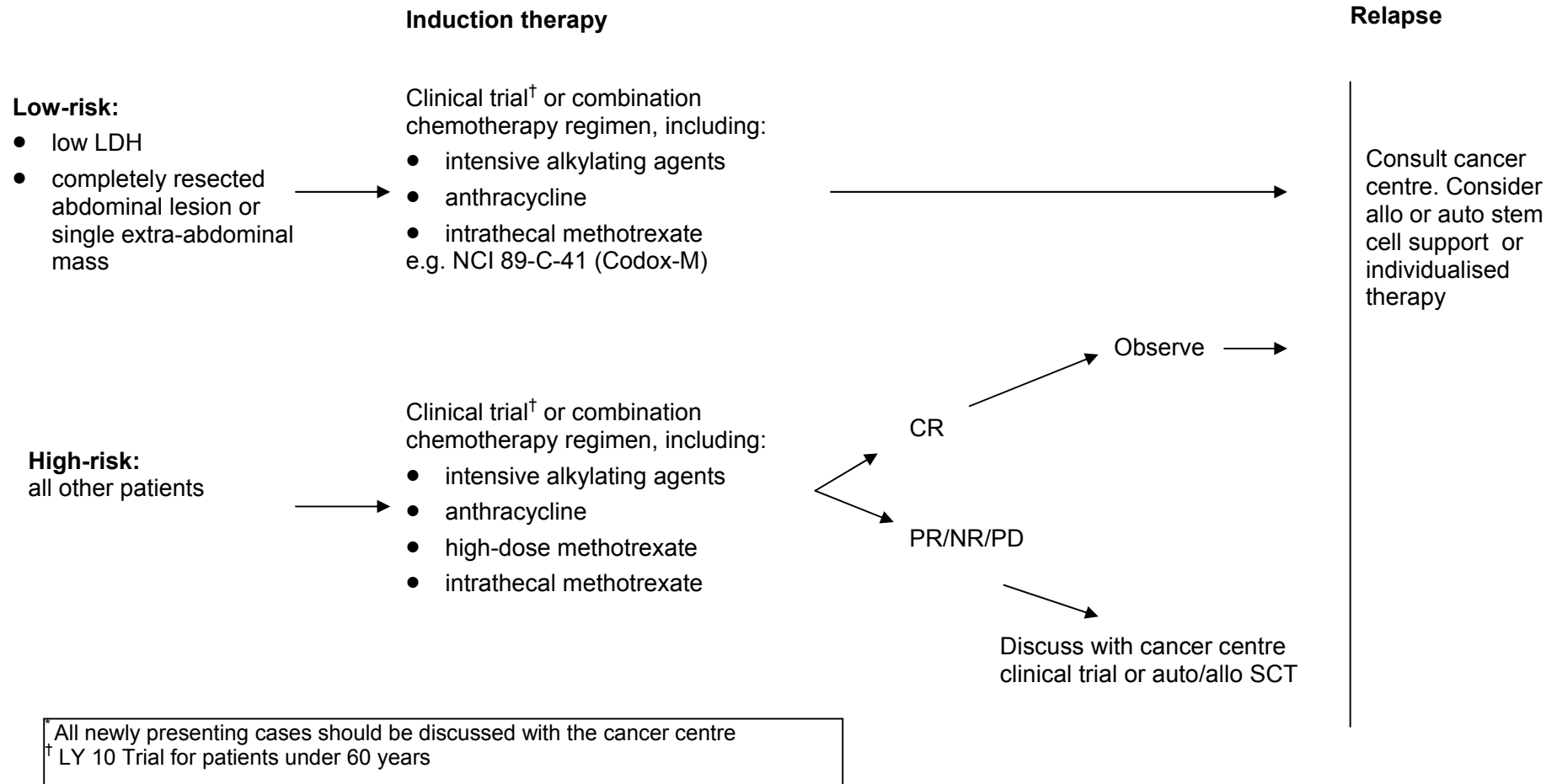
- Haematopathology review of all studies with at least one paraffin block representative of the tumour. Re-biopsy if consult material is non-diagnostic
- Adequate immunophenotyping to establish diagnosis and lineage
 - Paraffin panel: CD45 (LCA/Pan T), CD20 (L26/Pan B), CD3 and/or CD45RO (Pan T), TdT, CD1a and cytokeratin (optional), KI67

Useful in certain circumstances

- Additional immunohistochemical studies to establish lymphoma subtype
 - Typical immunophenotype:
 - Burkitt: slg^+ , CD10^+ , CD20^+ , TdT^-
 - Lymphoblastic B: slg^- , CD10^+ , CD19^+ , $\text{CD20}^{-/+}$, TdT^+
 - Lymphoblastic T: slg^- , CD10^- , CD19/20^- , $\text{CD3}^{-/+}$, $\text{CD4/8}^{+/+}$, $\text{CD1a}^{+/-}$, TdT^+
- Cell surface marker analysis by flow cytometry: kappa/lambda, CD45, CD3, CD5, CD19, CD10, TdT, CD14, CD13, CD33, CD7, CD4, CD8, CD1a
- Antigen receptor gene rearrangements for clonality, lineage

Figure 6.1 Therapy for Burkitt's lymphoma

Burkitt's lymphoma – therapy*



7. Lymphoblastic lymphoma/leukaemia (precursor T or B cell lymphoma/leukaemia)

Box 7.1

Lymphoblastic lymphoma											
Incidence:	0.24 new cases/100,000 population/year										
Median age:	28 years										
Sex ratio:	Male excess (2:1)										
Phenotype:	B cell CD19 ⁺ CD22 ⁺ CD79a ⁺ HLA DR ⁺ TdT ⁺ CD34 ^{+/-} CD10 ^{+/-} CD20 ^{-/+} CD33 ^{-/+} CD13 ^{-/+} SIg ⁻ T cell CD3 ⁺ CD7 ⁺ TdT ⁺ CD4 ^{+/-} CD8 ^{+/-} CD2 ^{-/+} CD5 ^{-/+} CD16 ^{-/+} CD57 ^{-/+}										
Genetics:	No characteristic lesion										
Outcome:	<table border="0"> <tr> <td>IPI score</td> <td></td> <td>5-year OS</td> </tr> <tr> <td>0/1</td> <td>33%</td> <td rowspan="3">} 20–30%</td> </tr> <tr> <td>2/3</td> <td>41%</td> </tr> <tr> <td>4/5</td> <td>26%</td> </tr> </table>	IPI score		5-year OS	0/1	33%	} 20–30%	2/3	41%	4/5	26%
IPI score		5-year OS									
0/1	33%	} 20–30%									
2/3	41%										
4/5	26%										
Clinical:	Nodal, large mediastinal mass, BM, CNS, testis										

Lymphoblastic lymphomas are rare diseases comprising approximately 2%–3% of all NHL. The WHO classification acknowledges that these two conditions are biologically and clinically indistinguishable. In adults, they are typically (> 80%) of T cell lineage, with a propensity for involvement of the mediastinum, BM and meninges. They are characterised by a male predominance, and are most common in adolescents and young adults.

As with Burkitt's lymphoma, patients are at high risk of developing acute TLS, and prophylaxis is mandatory.

All patients with this disease should be discussed with the cancer centre, and all should be entered on clinical trials, or standard protocols designed for the treatment of acute

lymphocytic leukaemia which includes CNS prophylaxis, such as the MRC UKALL 12 Trial. Long-term survival rates of 50%–60% are reported for this disease in young adults.

Recommendation 7a

Patients who achieve CR to induction therapy should be considered for HDT and ASCT.

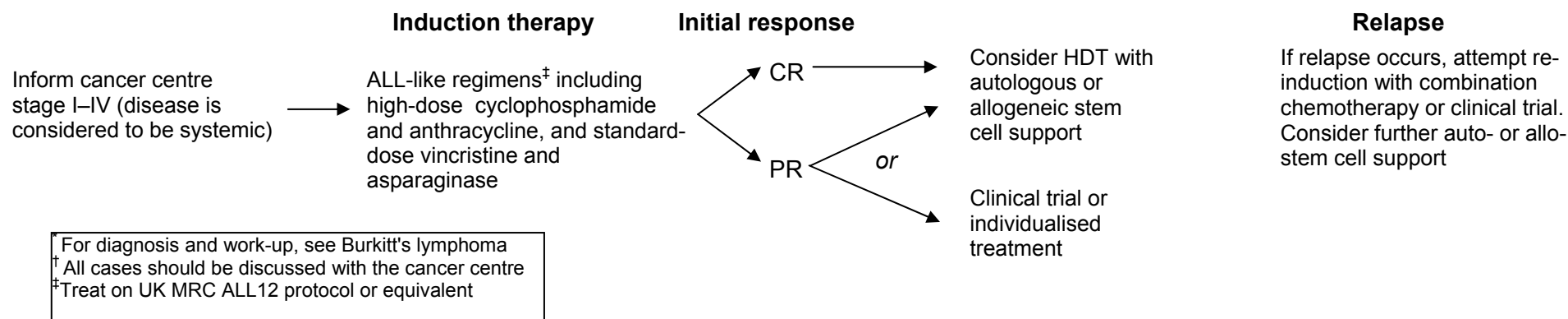
Level of evidence – level Ib.

Although this has not been shown to improve OS, a relapse-free survival advantage has been reported when compared to conventional dose consolidation/maintenance therapy, and the use of ASCT reduces the overall duration of therapy substantially. The role of allogeneic BMT in first remission is unclear. Young patients with suitable HLA-identical sibling donors may be treated with allogeneic BMT, but results do not appear superior to those reported with autologous SCT.

Patients whose disease progresses, or who only achieve a PR to induction therapy should be considered for clinical trials or offered individualised therapy. Patients who relapse after conventional therapy should be discussed with the cancer centre and considered for HDT/ASCT or allogeneic BMT. Patients not eligible for these approaches should be managed in an individualised fashion.

Figure 7.1 Therapy for lymphoblastic lymphoma

Lymphoblastic lymphoma – therapy^{*,†}



8. Mantle cell lymphoma

Box 8.1

Mantle cell lymphoma		
Incidence:	0.72 new cases/100,000 population/year	
Median age:	63 years	
Sex ratio:	Male excess (4:1)	
Phenotype:	CD19 ⁺ CD20 ⁺ CD22 ⁺ CD79a ⁺ CD5 ⁺ CD43 ⁺ Cyclin D1 ⁺ SIgM ⁺ SIgD ⁺ CD23 ⁻ CD11c ⁻	
Genetics:	t(11;14) in 30%	
Outcome:	IPI score	5-year OS
	0/1 23%	45%
	2/3 54%	25%
	4/5 23%	0%
Clinical:	Nodal, BM, blood, Waldeyer's ring and GI tract disease	

Mantle cell lymphoma is an uncommon entity, comprising 3%–4% of all NHL. The median age at presentation is 60–65 years, and it typically presents with stage III or IV disease. BM, peripheral blood (PB) and splenic involvement are common. Optimal treatment for this disease is unknown, and the outlook is poor, with a median survival of only 3–4 years, and long-term survival in only 10%–20% of patients. In view of this, early discussion with the cancer centre, and entry into clinical trials is strongly recommended.

Several approaches to first-line therapy have been used, including single alkylating agents, combination chemotherapy based on alkylating agents (e.g. CVP [Appendix 1]), and anthracycline-based chemotherapy (e.g. CHOP). Although many centres regard anthracycline-based therapies as optimal first-line therapy, there are no data from randomised clinical trials to support this.

Monoclonal antibodies, either alone or in combination with chemotherapy, also have activity in this disease, although they have not been compared with chemotherapy alone in randomised trials. Eligible patients should be entered into the NCRI National Mantle Cell Lymphoma Trial which compares Fludarabine/Cyclophosphamide +/- Rituximab.

The role of HDT and ASCT, either as first-line or salvage therapy is under investigation in clinical trials and should not be regarded as standard.

Box 8.2

Mantle cell lymphoma* – diagnosis

Essential

- Haematopathology review of all slides with at least one paraffin block representative of the tumour. Re-biopsy if consult material is non-diagnostic
- Adequate immunophenotyping to establish lineage and clonality and to identify this specific entity
 - Paraffin panel: CD45 (LCA), CD20 (L26/Pan B), CD3, CD43 or CD45RO (Pan T) and kappa/lambda (optional)
 - Frozen section: kappa/lambda, CD5, CD23, CD10, CD43 and cyclin D₁
 - Typical immunophenotype: CD5⁺, CD43⁺, CD23⁻, cyclin D₁⁺, CD10^{-/+}

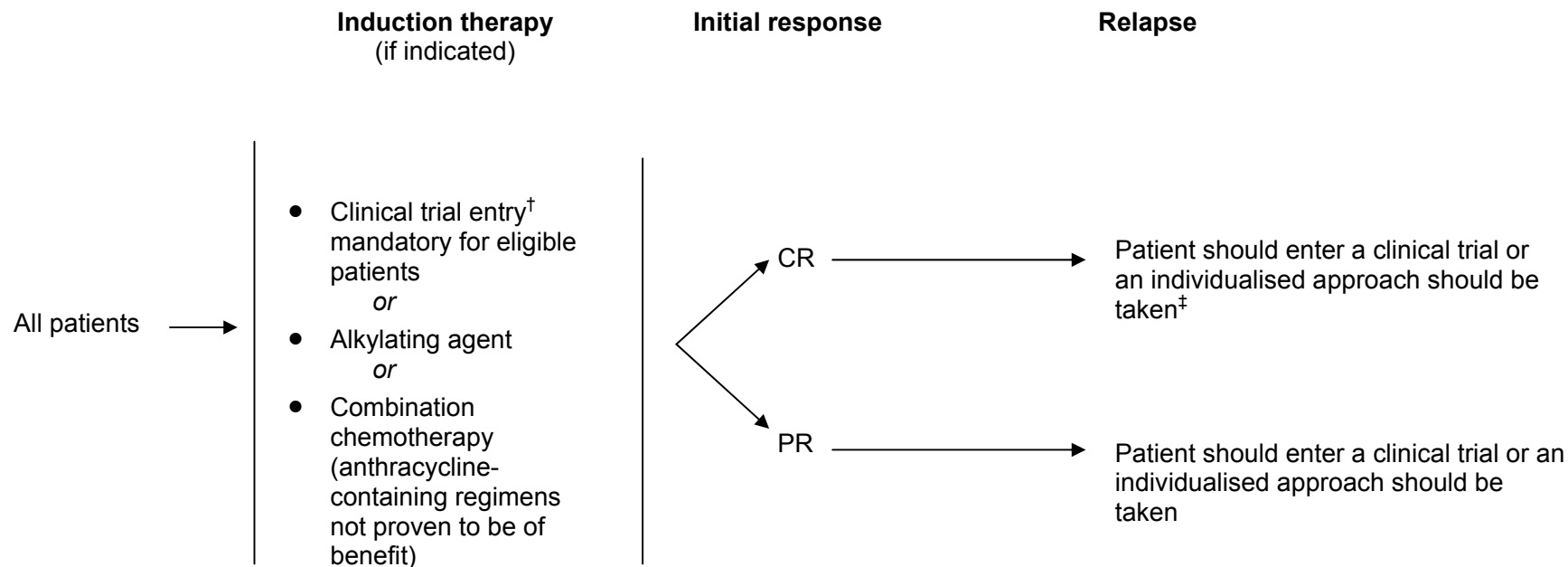
Useful in certain circumstances

- Cell surface marker analysis by flow cytometry: kappa/lambda, CD19, CD20, CD5, CD23, CD43, CD10.
- Antigen receptor/oncogene rearrangements for clonality, lineage

* This is a recently defined entity that is incurable with standard therapies. Optimum curative approach is not known

Figure 8.1 Therapy for mantle cell lymphoma

Mantle cell lymphoma – therapy*



All cases should be discussed with the cancer center
[†]NCRI National Mantle Lymphoma Trial : HTD with autologous or allogeneic source of stem cells is an active area of investigation
[‡]Fludarabine, or other non-cross-resistant regimen may be considered. Chlorambucil may be useful when progression is slow

9. Lymphoma associated with HIV infection

Lymphoma in the context of HIV infection presents particular problems, especially with respect to infection. However, the prognosis of patients with AIDS has improved substantially in recent years, especially with the advent of protease inhibitors. The aim of therapy for patients with lymphoma associated with HIV should therefore be the same as for all other patients.

Treatment of these patients is highly specialised and should always be discussed with the cancer centre.

Treatment should be undertaken by an MDT that includes specialists in NHL and AIDS, and wherever possible, these patients should enter clinical trials. Issues such as the continuation of anti-HIV therapy during lymphoma treatment can only be properly managed in a multidisciplinary context.

In general, the intensity of treatment for these patients is determined using a risk-stratified approach. Good risk features include a normal CD4⁺ count, good performance status, and no prior history of opportunistic infection. Patients with good risk features have a low incidence of treatment-related toxicity and should receive standard treatment. Those with adverse risk factors have an extremely high incidence of treatment-related toxicity, especially infection, and should receive attenuated dose or 'palliative' therapy only.

Box 9.1

HIV-associated NHL

The occurrence of aggressive NHL in HIV infected patients is 60 fold greater than in the general population. The risk is approximately 1.6% per year and for patients surviving 3 years on retroviral therapy the risk is 20%. The lymphomas are EBV-associated with a high incidence of extra-nodal disease (70–90%; CNS 26%, BM 22%, GIT 20%, liver 12%). Histologically the lymphomas are largely DLBCL or Burkitt's/Burkitt's-like; ALCL occurs and a rare entity, body cavity-based NHL affects pleural, pericardial and peritoneal cavities and is HHV8 associated.

Further reading

Pettengell R, Linch D. Position paper on the therapeutic use of Rituximab in CD20-positive Diffuse large B cell Non-Hodgkin's Lymphoma <http://www.BCSHguidelines.com>

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Fisher RI, Gaynor ER, Dahlborg S, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. *New Engl J Med* 1993; 328: 1002–1006

Glick JH, Kim K, Earl J. An ECOG randomised phase III trial of CHOP vs CHOP plus radiotherapy for intermediate grade early stage non-Hodgkin's lymphoma. *Proc Am Soc Clin Oncol* 1995; 14: 391

Magrath I, Adde M, Shad A, et al. Adults and children with small non-cleaved cell lymphoma have a similar excellent outcome when treated with the same chemotherapy regimen. *J Clin Oncol* 1996; 14: 925–934

Martelli M, Vignetti M, Zinzani PL, et al. High-dose chemotherapy followed by autologous bone marrow transplantation versus dexamethasone, cisplatin and cytarabine in aggressive non-Hodgkin's lymphoma with partial response to front-line chemotherapy: a prospective randomised Italian multicenter study. *J Clin Oncol* 1996; 14: 534–542

Miller TP, Dahlborg S, Cassady R, et al. Chemotherapy alone compared with chemotherapy plus radiotherapy for localised intermediate- and high-grade non-Hodgkin's lymphoma. *New Engl J Med* 1998; 339: 21–26

Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. *New Engl J Med* 1995; 333: 1540–1545

Sweetenham JW, Pearce R, Taghipour G, *et al.* Adult Burkitt's and Burkitt-like non-Hodgkin's lymphoma – outcome for patients treated with high-dose therapy and autologous stem cell transplantation in first remission or at relapse: Results from the European Group for Blood and Marrow Transplantation. *J Clin Oncol* 1996; 14: 2465–2472

Sweetenham JW, Santini G, Simnett S, *et al.* Autologous stem cell transplantation (ASCT) in 1st remission improves relapse free survival (RFS) in adult patients with lymphoblastic lymphoma (LBL): Results from a randomised trial of the European Group for Blood and Marrow transplantation and the UK Lymphoma Group. *Proc Am Soc Clin Oncol* 1998; 17: 16a

A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. *New Engl J Med* 1993; 329: 987–994

Verdonck LF, van Putten WL, Hagenbeek A, *et al.* Comparison of CHOP chemotherapy with autologous bone marrow transplantation for slowly responding patients with aggressive non-Hodgkin's lymphoma. *New Engl J Med* 1995; 332: 1045–105

Management of non-aggressive NHL

10. Follicular lymphoma

11. Small lymphocytic lymphoma/chronic lymphocytic leukaemia

12. Marginal zone/gastric MALT lymphoma

10. Follicular lymphoma

Follicular lymphoma is the second most common lymphoma after DLBCL, with an incidence of 4 per 100,000. The median age of patients is around 60 years and approximately 50% of all patients will present with BM involvement (stage IV disease). It is readily treatable but is characterised by a recurring and remitting course over several years with each successive response becoming more difficult to achieve and of shorter duration. Resistant disease or transformation into DLBCL is the usual cause of death. Despite the responsiveness of the disease to chemotherapy, radiotherapy or biological therapy, relapse is usually inevitable even if a CR is obtained, is so the goal of treatment keep the patients symptom free. It is desirable for eligible patients to be recruited to clinical trials.

Table 10.1 Correspondence between International Working Formulary (IWF) and WHO classification systems of NHL

IWF subtype	IWF classification	WHO classification
A	SLL -consistent with CLL -plasmacytoid	B cell CLL*/SLL
B	Follicular small cleaved lymphoma	Follicular lymphoma Grade 1: 0–5 centroblasts/high power field (HPF)
C	Follicular mixed lymphoma	Grade 2: 6–15 centroblasts/HPF
D	Follicular large cell lymphoma	Grade 3a, 3b: > 15 centroblasts/HPF Variants

The Ann Arbor staging classification is not used but advanced stage (III or IV) and symptomatic disease are adverse prognostic factors.

10.1 Investigation

Patients with follicular lymphoma usually present with enlargement of lymph glands. 'B' symptoms are rare. When symptoms are usually present, they are one or more of the B symptoms: fever, night sweats, or weight loss.

Diagnoses based upon histological and clinical criteria are highly accurate for SLL (84%) and follicular lymphoma (93%). Immunophenotyping improves diagnostic accuracy only slightly, to 87% and 94%, respectively. Most patients (> 80%) with SLL or follicular lymphoma present with advanced stage disease (III or IV).

It is now recognised that follicular large cell NHL (grade 3) should not be regarded as a non-aggressive NHL, given its aggressive clinical course and documented response to anthracycline-based chemotherapy, and should be included in the category of aggressive NHL (see section 5).

10.2 Treatment

The clinical course of Follicular Lymphoma differs considerably between individual patients, and several adverse prognostic factors have been identified. The IPI provides an especially comprehensive model. The IPI was originally devised to classify patients with aggressive lymphomas, but has been shown to apply as well to patients with SLL, follicular lymphoma, and low-grade NHL.

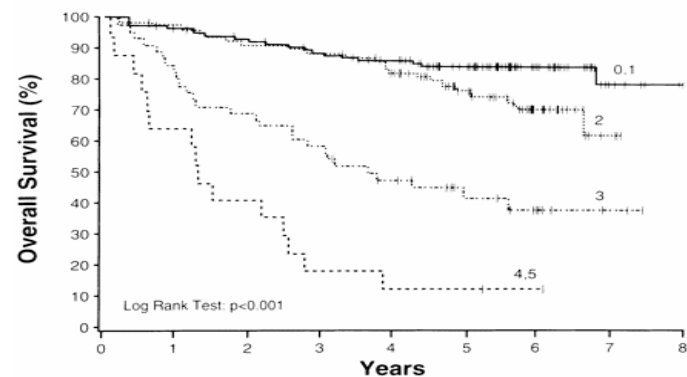


Figure 10.1 Survival of FC according to IPI

The IPI prognostic model was based upon data from newly diagnosed patients. However, a high IPI score is also a useful indicator of poor prognosis in relapsed patients. Additional negative prognostic factors associated with marked reduction in survival for relapsed patients are a poor objective response to initial therapy, or relapse within 12 months after initial response.

10.3 Observation

Since no survival advantage has been shown for immediate treatment compared with expectant management in asymptomatic patients treatment can be delayed until symptoms develop or histological transformation occurs.

10.4 Stage I and II disease

10.4.1 Radiotherapy

For 30% of patients who present with stage I and II disease, involved field irradiation can be curative if the disease is of small volume. At a total dose of 30–40 Gy, 'in-field' relapse is uncommon, and 10-year DFS of 70% can be expected (see section 14). Total nodal irradiation has also been successfully used as initial therapy for patients with stage III disease and as treatment capable of inducing CRs in patients with recurrent or poorly responsive stage III disease. There is no evidence that chemotherapy is better or that its addition to radiotherapy improves survival.

Conclusions and recommendations 10a

- Local radiotherapy remains standard therapy for localised (stage I) follicular lymphoma of small volume
- The toxicity of such treatment should be taken into account when treating completely excised stage I NHL

Level of evidence IV – grade C.

10.5 Standard therapy for stage III/IV disease

Treatment of advanced (stage III or IV) small lymphocytic lymphoma (SLL), follicular lymphoma is palliative, and therapies are usually administered intermittently over a period of several years. This is conventionally managed with the expectation that the illness will pursue a remitting recurring course, death being due to resistant disease (with or without transformation to DLBCL) or the

complications of therapy. Hence it is customary to manage the asymptomatic patient expectantly, until an indication for therapy presents itself. The widely accepted 'indication' for disease is overt progression 'bulk' or compromise of a vital organ, especially the BM. The interpretation of the indications for therapy are influenced by the philosophy of the physician and the preference of the patient. There is little evidence to show whether the choice of initial therapy influences the natural history of indolent NHL, and only limited data showing that patients with a poor prognosis benefit from an aggressive initial treatment. Therefore, except in clinical studies, patients with advanced SLL, follicular lymphoma, or low-grade NHL usually receive a conservative initial therapy such as chlorambucil (e.g. 10 mg/day for 6 weeks followed by 3 two-week cycles separated by 2-week intervals). Steroids and vinca alkaloids are also active with response rates of 60% when used alone. Although widely used, there is no evidence that the addition of steroids and vinca alkaloids to alkylating agents improve response or survival. The addition of an anthracycline (e.g. CHOP) will be more toxic and will improve response though not OS in chemosensitive patients. Including anthracycline in first-line treatment combinations is recommended for histological grade 3 follicular lymphoma, since it achieves a higher response rate, but does not improve survival.

The conventional strategy overall is to treat to 'remission' (variously defined), and then manage by regular surveillance until progression, upon which re-staging and repeat biopsy should be performed and the appropriate intervention undertaken. Such an approach leads to a median survival of about 10 years with the majority of patients receiving 3 therapies at about 3-year intervals. Histological grade 3 disease should be managed as an aggressive lymphoma.

Recommendations 10b

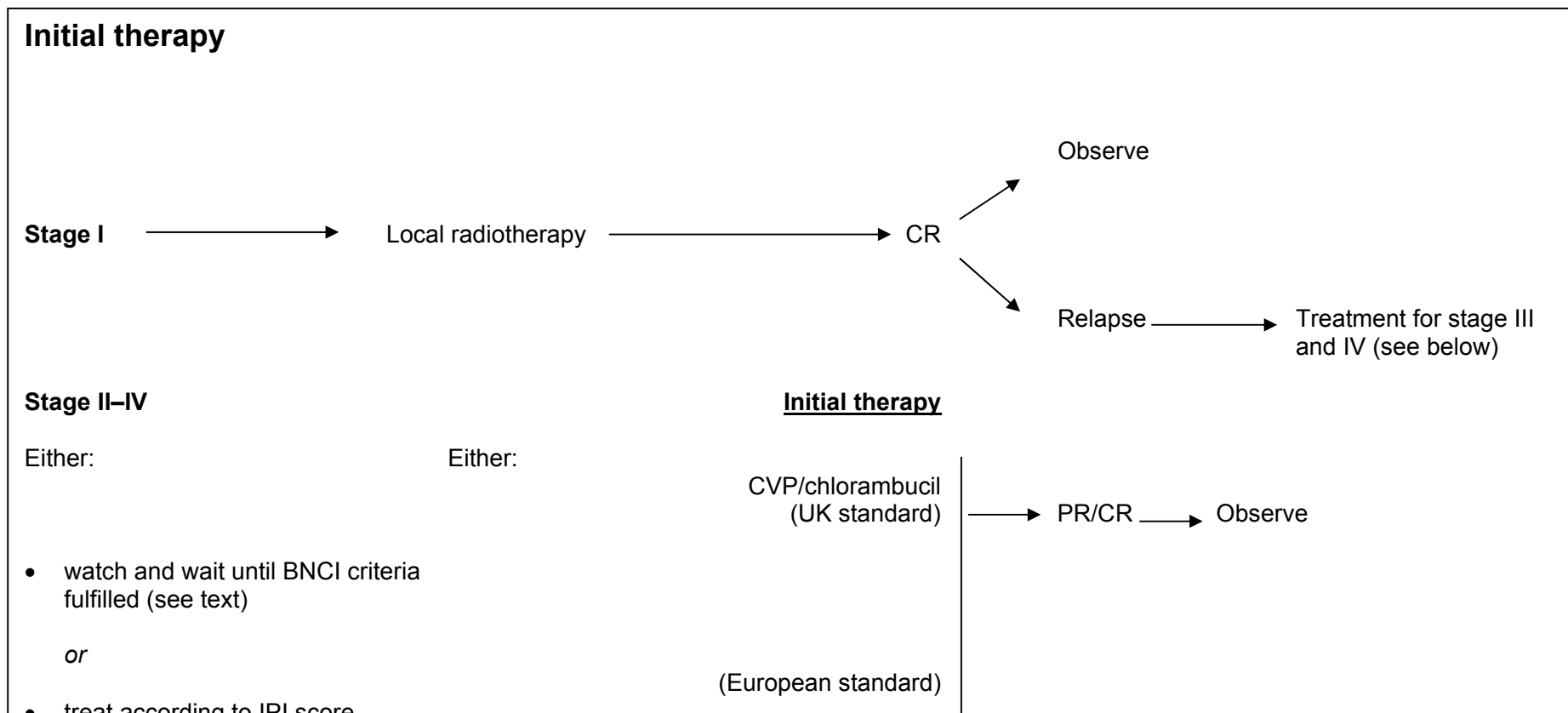
Alkylator-based therapies remain standard treatment in follicular lymphomas grades 1 and 2

Anthracyclines increase CR rates but have no impact on DFS or OS

Level of (negative) evidence IIa, IIb: strength B

10.5.1 Alpha interferon

Randomised trials comparing chemotherapy plus interferon (IFN) to chemotherapy alone suggest that outcome depends upon multiple factors, including patient prognosis, the inclusion of anthracycline as a component of chemotherapy, and the IFN treatment regimen. In some trials carried out in patients with poor prognosis or bulky disease, initial treatment with CHVP plus IFN or COPA plus IFN increased relapse-free and overall survival relative to chemotherapy alone. By comparison, adding IFN to less aggressive chemotherapy such as CVP does not increase OS but may increase relapse-free survival. The recently published SWOG trial showed no benefit from the addition of low-dose IFN at to intensive induction therapy in terms of either DFS or OS. A meta-analysis of all previous studies but excluding this last study suggested both an OS and DFS benefit in patients who received both intensive induction therapy and high α IFN (> 36 mU per month).



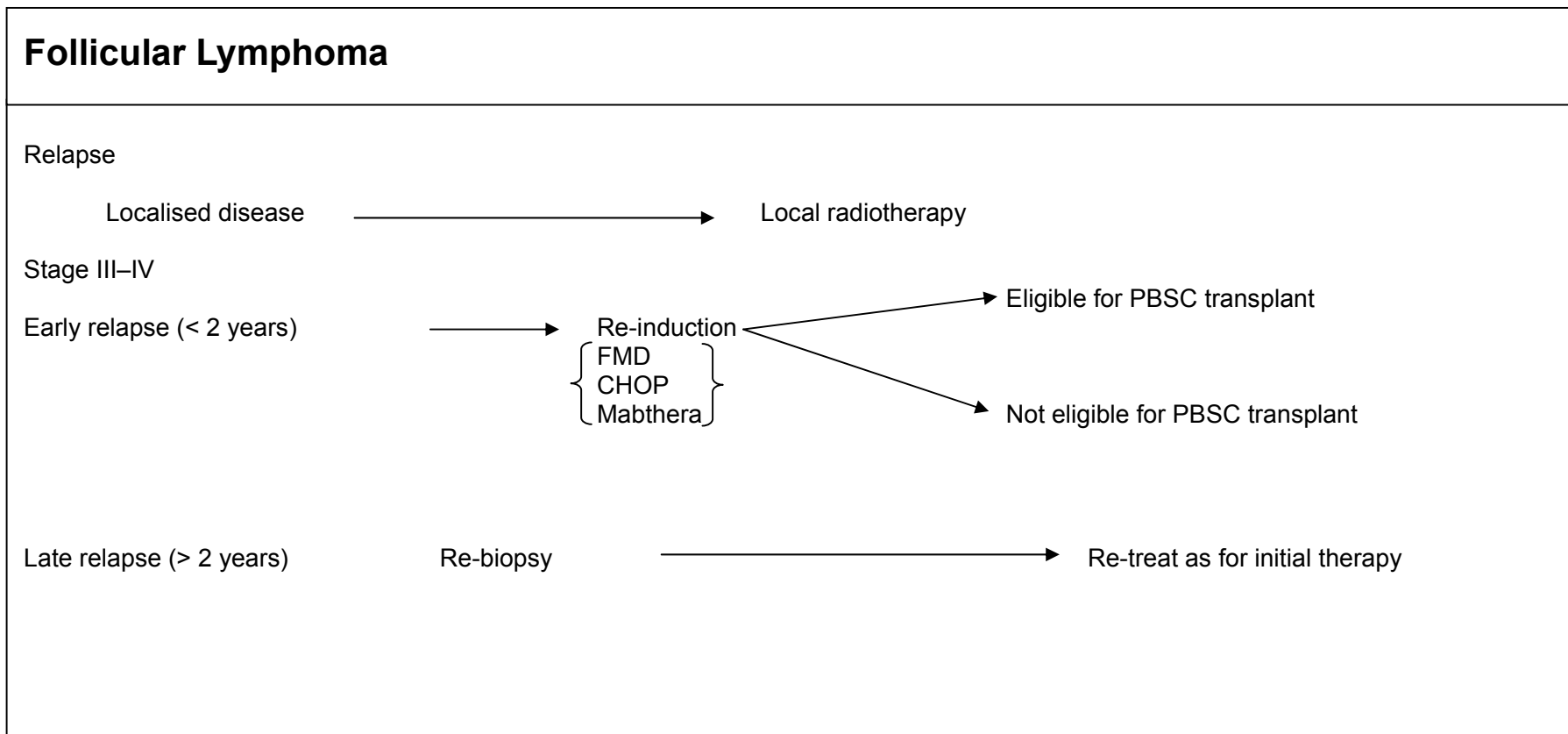


Figure 10.2 Therapy for follicular lymphoma

10.5.2 Stem cell transplantation (SCT) in first CR

A number of phase II studies have reported the use of SCT in patients with responsive follicular lymphoma in first CR. In the largest of these trials, patients entering CR or good PR were treated with a regimen based on total body irradiation (TBI) after CHOP induction therapy. A 3-year DFS of > 60% was observed but longer follow-up suggests continuing recurrence and a significant and as yet unexplained incidence of myelodysplasia.

Recently the German low-grade lymphoma study reported the preliminary results of a prospective randomised trial comparing conventional chemotherapy with myeloablative chemotherapy as first-line therapy in patients with follicular NHL. The 2-year DFS of 70% obtained with this approach compares favourably with the 40% DFS obtained with conventional therapy but longer follow-up will be required to confirm this result.

Conclusion and recommendation 10c

There is insufficient evidence to recommend SCT in first CR.

10.6 Treatment of Relapsed Patients

Response to prior therapy is the most important factor determining subsequent treatment strategy. In general, a short-lived response to treatment requires an increasingly aggressive therapeutic approach although this does not guarantee success. Toxicity, efficacy, and duration of treatment must all be considered as factors in disease palliation.

Prognostic factors are useful as predictors of treatment outcome and the likely evolution of treatment requirements. Many patients with advanced SLL, follicular lymphoma, or low-grade NHL and good IPI scores will respond to repeated courses of CP or CVP therapy with prolonged remission, while patients with poor IPI scores are more likely to have a rapid relapse, and are candidates for early aggressive intervention.

Generally, patients who relapse 2 years or more after treatment with alkylating agents (CP or CVP) will respond to further treatment with the same agents, and there is no

proven need to escalate therapy. Patients whose disease is not well controlled by alkylating agents may respond to single-agent or combination chemotherapies, biological agents, or radiotherapy.

10.6.1 Anthracycline-based chemotherapy

CHOP, or CHOP-like regimens will induce responses in patients with relapsed indolent NHL. Remissions of approximately 12 months duration have been reported.

Administration of multiple courses of anthracycline-based chemotherapy is limited by the cumulative cardiotoxicity.

10.6.2 Purine analogues

Fludarabine phosphate as a single agent, or in combinations such as fludarabine, mitoxantrone, dexamethasone (FMD) may yield beneficial responses in relapsed disease. In several studies, response rates with fludarabine range from 32%–62%. FMD has been reported to induce > 90% response rates, and 47% CRs, in patients with recurrent lymphoma and a good prognosis. Purine analogues are also associated with significant immunosuppression.

10.6.3 Immunotherapy

Rituximab (BCSH Position Paper), a chimeric human/murine IgG₁ monoclonal antibody, is increasingly used in the treatment of patients with relapsed or chemoresistant follicular NHL.

Rituximab has cytolytic activity directed at B cells, in contrast to the more systemic cytotoxicity of chemotherapy. Rituximab effects cell lysis by way of mechanisms that are distinct from those of chemotherapy, a feature that leads to significant activity in chemoresistant patients. The treatment duration of rituximab monotherapy (4 weeks) is considerably shorter than required for most chemotherapy regimens. Rituximab induces remissions in approximately 50% of patients with relapsed or refractory advanced low-grade or follicular NHL, with median PFS of 9 months. Efficacy is highest in patients without bulky tumours. It is recommended for use in patients who are resistant to or intolerant of chemotherapy.

10.6.4 Radiotherapy

Although not widely used in the treatment of disseminated NHL, extended field radiotherapy can induce high response rates in patients with relapsed follicular lymphoma, with DFS rates of 65% at 5 years and 37% at 10 years. Limited field radiation is often used palliatively to relieve local symptoms or mechanical problems, or to treat bulky or persistent lesions (iceberg radiation) as a supplement to chemotherapy.

10.6.5 Ibritumomab tiuxetan

Ibritumomab tiuxetan (Zevalin), a murine monoclonal antibody directed against CD20 and bound to ⁹⁰yttrium, a beta emitter, has been utilised as a single agent in refractory and relapsed low-grade NHL. Recently, results of a randomised prospective clinical trial have been reported where ibritumomab tiuxetan has shown improved response rates when compared to rituximab in patients with relapsed low-grade NHL (78% vs 46%). There is as yet no evidence of any impact on PFS.

10.6.6 Other therapies

Ongoing trials in early stages investigating innovative therapies include studies of anti-idiotypic monoclonal antibodies, vaccines and non-myeloablative allogeneic stem-cell transplantation.

Conclusions and recommendations 10d

- There are no definitive therapies for relapsed Follicular NHL
- Re-biopsy to confirm low-grade histology is recommended
- Entry into clinical trials should be encouraged to define the role of antibody therapy, , and newer combination chemotherapies in this context
- Empirical therapy at relapse should take into account duration of previous response, and agents used previously

11. Small lymphocytic lymphoma/chronic lymphocytic leukaemia

Small lymphocytic lymphoma (SLL) comprises 5–10% of lymphoma and is regarded as the same disease as chronic lymphatic leukaemia. The investigation and management of these entities is the same. The morphological features show a diffuse growth of small lymphocytes with prolymphocytes and paraimmunoblasts.

11.1 Diagnosis

Adequate immunophenotyping is essential. A trephine biopsy will usually show BM involvement and the diffuse or nodular pattern has prognostic significance.

Box 11.1

Small lymphocytic lymphoma	
Incidence:	0.72 new cases/100,000 population/year
Median Age:	65 years
Sex Ratio:	1:1
Phenotype:	CD19 ⁺ CD20 ⁺ CD79a ⁺ CD5 ⁺ CD23 ⁺ CD43 ⁺ SIgM ⁺ (weak) SIgD [±] CD11c [±] CD22 [±] CD10 ⁻
Genetics:	+12 in 30% 13q abnormalities in 25%
Outcome:	5 year OS approximately 50%
Clinical:	Equivalent to advanced stage CLL Blood, BM and nodal disease Small risk (3%) of transformation to DLBCL

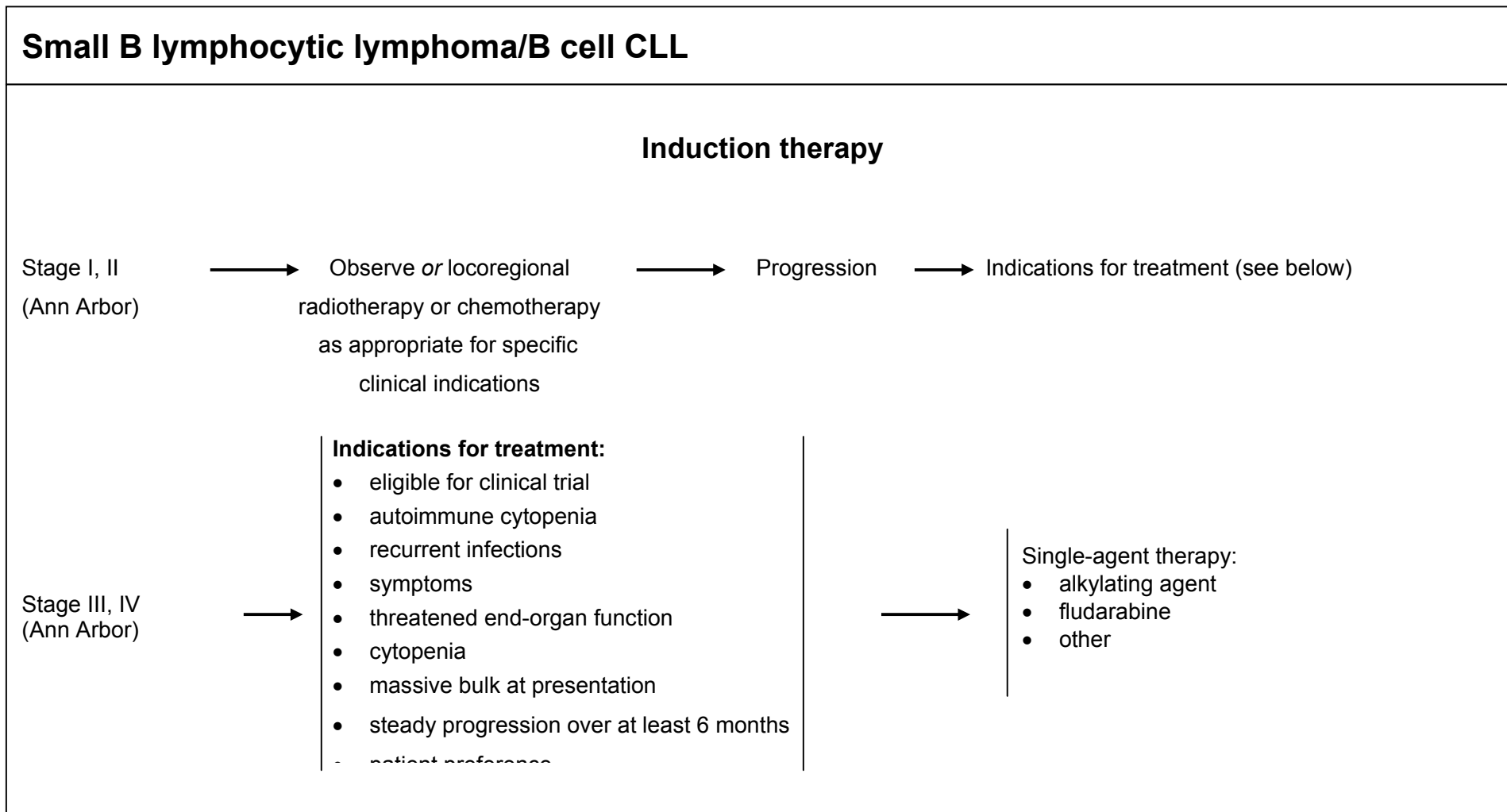
11.2 Work-up

The diagnostic tests are similar to those for other lymphomas, but should include a DAGT (Coombs test) since a small number of patients (< 5%) may develop autoimmune haemolytic anaemia.

11.3 Clinical features and treatment

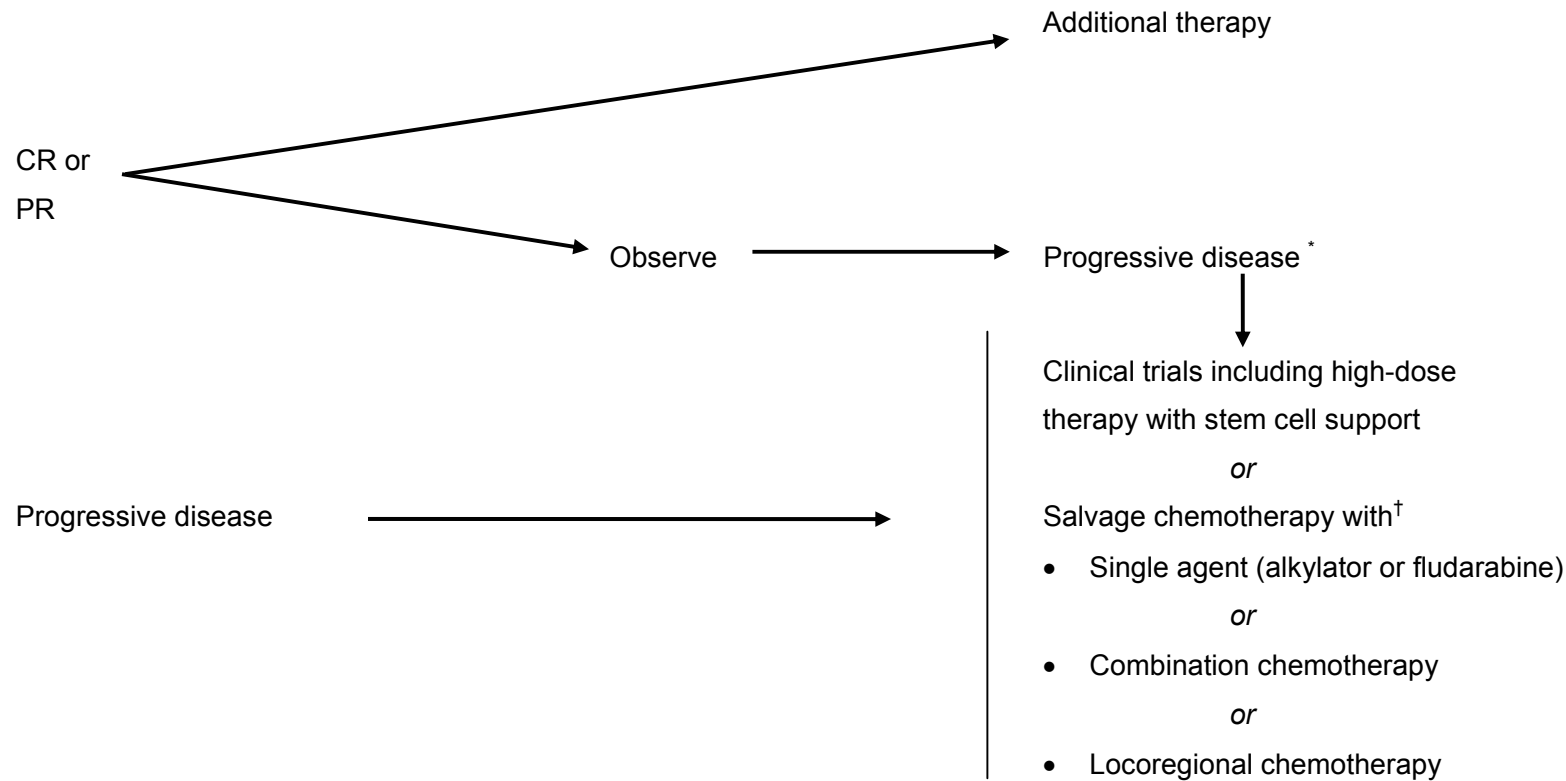
This disease, in common with follicular lymphoma, has a high response rate, but unless truly localised is incurable. Stage I and II disease is uncommon and may have long DFS if amenable to radiotherapy. Alternatively a policy of observation may be undertaken until treatment is indicated. Stage III and IV disease may not need intervention. If treatment is indicated, first-line therapy is usually chlorambucil \pm prednisolone. CVP is an alternative. Fludarabine or 2-chlorodeoxyadenosine (2 CDA) have achieved similar responses as second-line treatment, with CHOP combination therapy usually reserved for third-line treatment. HDT with stem cell rescue or Allogeneic non-intensive transplant remain experimental approaches.

Figure 11.1 Therapy for small lymphocytic/chronic lymphocytic lymphoma



Small B lymphocytic lymphoma/B cell CLL

Initial response



* If progressive disease and systemic symptoms or rapid lymph node enlargement, then rebiopsy; otherwise, rebiopsy if ≥ 2 years since last biopsy.

†Patients who relapse at > 2 years can be given same treatment again without prejudicing survival; those who relapse at < 2 years can proceed to therapy based on fludarabine (or other purine analogues) or anthracyclines.

12. Marginal zone/gastric MALT lymphoma

Three forms of marginal zone lymphoma have been described:

- Extra-nodal – low-grade B cell lymphoma of mucosa associated lymphoid tissue (MALT) – approximately 5% of all lymphomas
- Nodal/marginal zone (monocytoid) – 2% of all lymphomas
- Splenic marginal zone B cell lymphoma < 1% of all lymphomas

12.1 Extra-nodal marginal zone lymphoma (low-grade B cell lymphoma of MALT type).

These are tumours of adults with slight male predominance. Many patients have a history of autoimmune disease or chronic inflammation e.g. Sjögren's syndrome, Hashimoto's thyroiditis or *Helicobacter* gastritis.

Recent studies suggest that proliferation in some early MALT-type lymphomas may be antigen-driven and that therapy directed at the antigen (e.g. *Helicobacter pylori* [*H. pylori*] in gastric lymphoma) may result in regression of early lesion.

12.2 Nodal marginal zone lymphoma (+ monocytoid cells)

The majority of nodal monocytoid B cell lymphoma occur in patients with Sjögren's syndrome or other extra-nodal MALT-type lymphoma. These lymphomas often present with advanced-stage disease and they have a worse survival. These patients should be managed as follicular lymphoma grade 1 and 2.

12.3 Splenic marginal zone lymphoma

This is morphologically distinct from other marginal zone lymphoma, in that the white pulp involvement may show both a marginal and a mantle zone pattern. There is considerable overlap between this entity and splenic lymphoma with villous lymphocyte and the splenic histology is probably identical in both conditions.

Patients typically have BM and PB involvement usually without peripheral lymphadenopathy and may have a small M-component. The course is reported to be indolent and splenectomy may be followed by prolonged survival. Patients who relapse or who have extensive BM or lymph node involvement can be difficult to treat. Chemotherapy with a regimen based on an alkylating agent does not show marked effect.

Box 12.1 and 12.2

Marginal zone lymphoma - nodal	Marginal zone lymphoma - MALT
<p>Incidence: 0.12 new cases/100,000 population/yr</p> <p>Median Age: 60 years</p> <p>Sex Ratio: 1:1</p> <p>Phenotype: CD19⁺CD20⁺ CD22⁺ CD79a⁺ SIg⁺ CD11c[±] CD43[±] CD5⁻ CD10⁻ CD23⁻</p> <p>Genetics: +3 t(11,18)</p> <p>Outcome: 5-year OS 65%</p> <p>Clinical: BM, nodes, spleen May have circulating disease (splenic lymphoma with villous lymphocytes) Associated with Sjögren's disease</p>	<p>Incidence: 0.6 new cases/100,000 population/yr</p> <p>Median Age: 60 years</p> <p>Sex Ratio: slight female excess</p> <p>Phenotype: CD19⁺CD20⁺ CD22⁺ CD79a⁺ SIg⁺ CD11c[±] CD43[±] CD5⁻ CD10⁻ CD23⁻</p> <p>Genetics: +3 t(11,18)</p> <p>Outcome: 5-year OS > 80%</p> <p>Clinical: Usually localised extra-nodal disease associated with autoimmune disease and <i>H. pylori</i> infection. Approximately 30% disseminated. Can transform to DLBCL</p>

12.4 Management

Localised disease may be cured with local treatment (surgery or radiotherapy).

Dissemination occurs in approximately 30% of cases and these patients require chemotherapy similar to that given for other low-grade lymphomas.

Early gastric MALT lymphomas show low regression over 6–18 months following the removal of underlying stimulus i.e. *H. pylori* infections. All patients should have a course of *H. pylori* eradication therapy as part of treatment (see Box 12.3). The need for chemotherapy in patients achieving CR after anti-*H. pylori* therapy has been the subject of a randomised trial (LYO3) set up by the UK Lymphoma Group (UKLG).

Box 12.3

<i>H. pylori</i> eradication: triple therapy		
Omeprazole	20 mg bd [*]	} for 7 days
Metronidazole	400 mg bd [†]	
Amoxicillin	1 g bd [†]	
* Use clarithromycin 500 mg bd if sensitive to omeprazole		
† Continue for 4 weeks for large ulcers		

Outside the trial most clinicians elect to give chlorambucil (e.g. 6 mg/m²/day for 14 days repeated every 28 days for 6 courses) early after anti-*H. pylori* therapy or less commonly radiotherapy (30–36 Gy). Long-term follow-up is mandatory, particularly in patients treated with antibiotic alone since it is not known whether this will definitely cure the lymphoma. Endoscopy is necessary and multiple biopsies should be taken from all areas of the stomach (at least two from each of antrum, body and fundus). Endoscopic ultrasound is considered the optimal method of follow-up surveillance. No evidence exists on the appropriate interval between endoscopy and the length of follow-up, but a reasonable approach might be to repeat endoscopy after 3 months then 6-monthly for 2 years, then annually for 5 years.

Transformation to large cell lymphoma may occur. These patients could receive combination chemotherapy with CHOP or a second-generation regimen. The role of surgery is controversial and it is recommended that it is reserved as salvage therapy in those who do not achieve a CR with chemotherapy alone.

H. pylori eradication should also be given, since this eliminates any residual low-grade component that could result in recurrence if antigen stimulation continued. Non-gastric MALT lymphomas should be treated on the same principles as gastric MALT except for the antibiotics and *H. pylori* treatment.

Stage III/IV – treatments are as for follicular lymphoma with single agent or combination chemotherapy.

Box 12.4

<p>Work-up</p> <ul style="list-style-type: none">- Complete blood count, LDH, BUN- Creatinine, LFT, calcium- Chest X-ray- Abdominopelvic CT- Bone marrow biopsy ± aspirate <p>GI WORK-UP</p> <ul style="list-style-type: none">- Endoscopy~ <i>H. pylori</i> Stain <p>MAY BE USEFUL</p> <ul style="list-style-type: none">~ Endoscopic ultrasound~ <i>H. pylori</i> culture or breath test

Figure 12.1 Three-month re-staging and follow-up for gastric marginal zone lymphoma

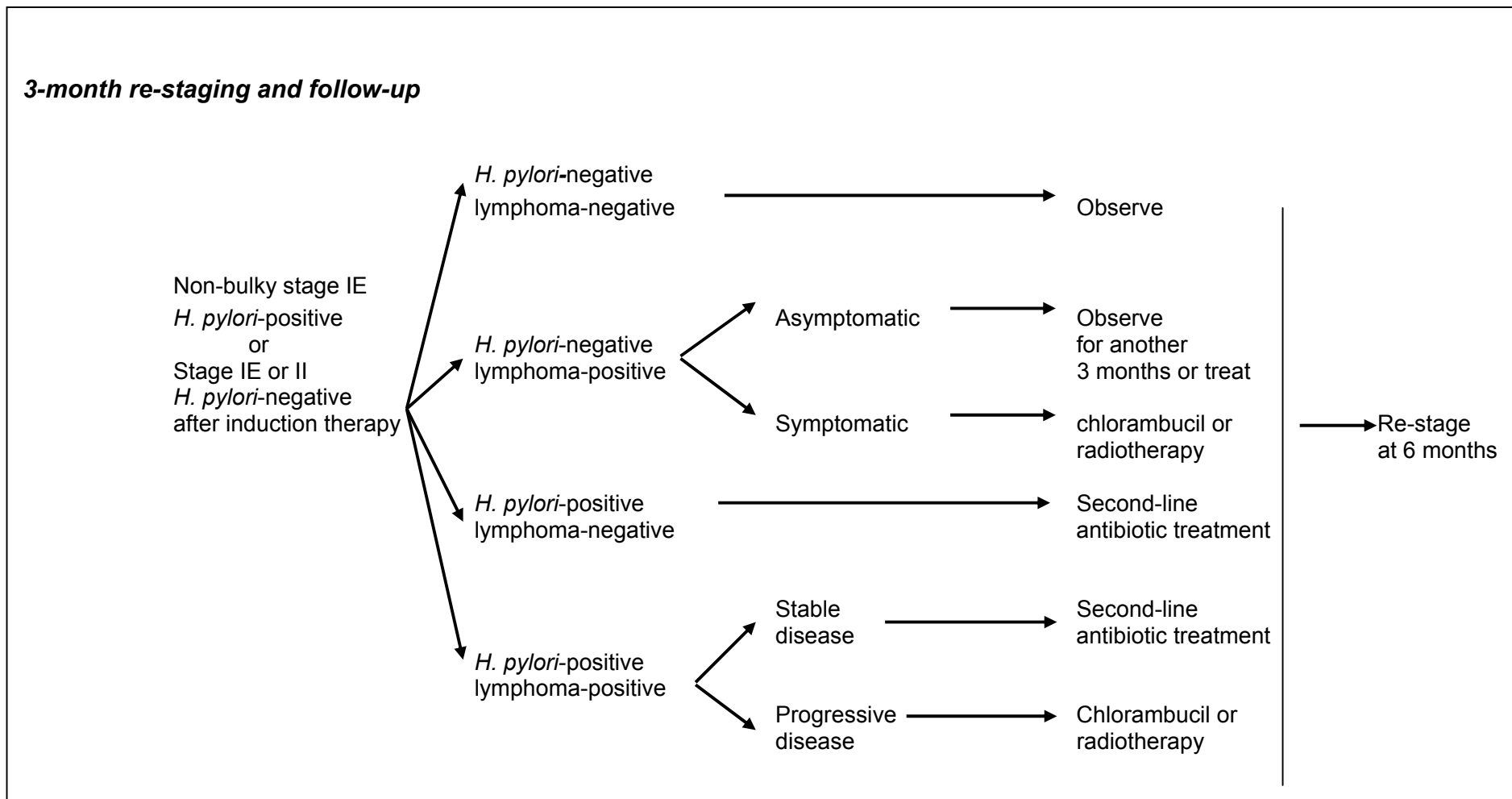
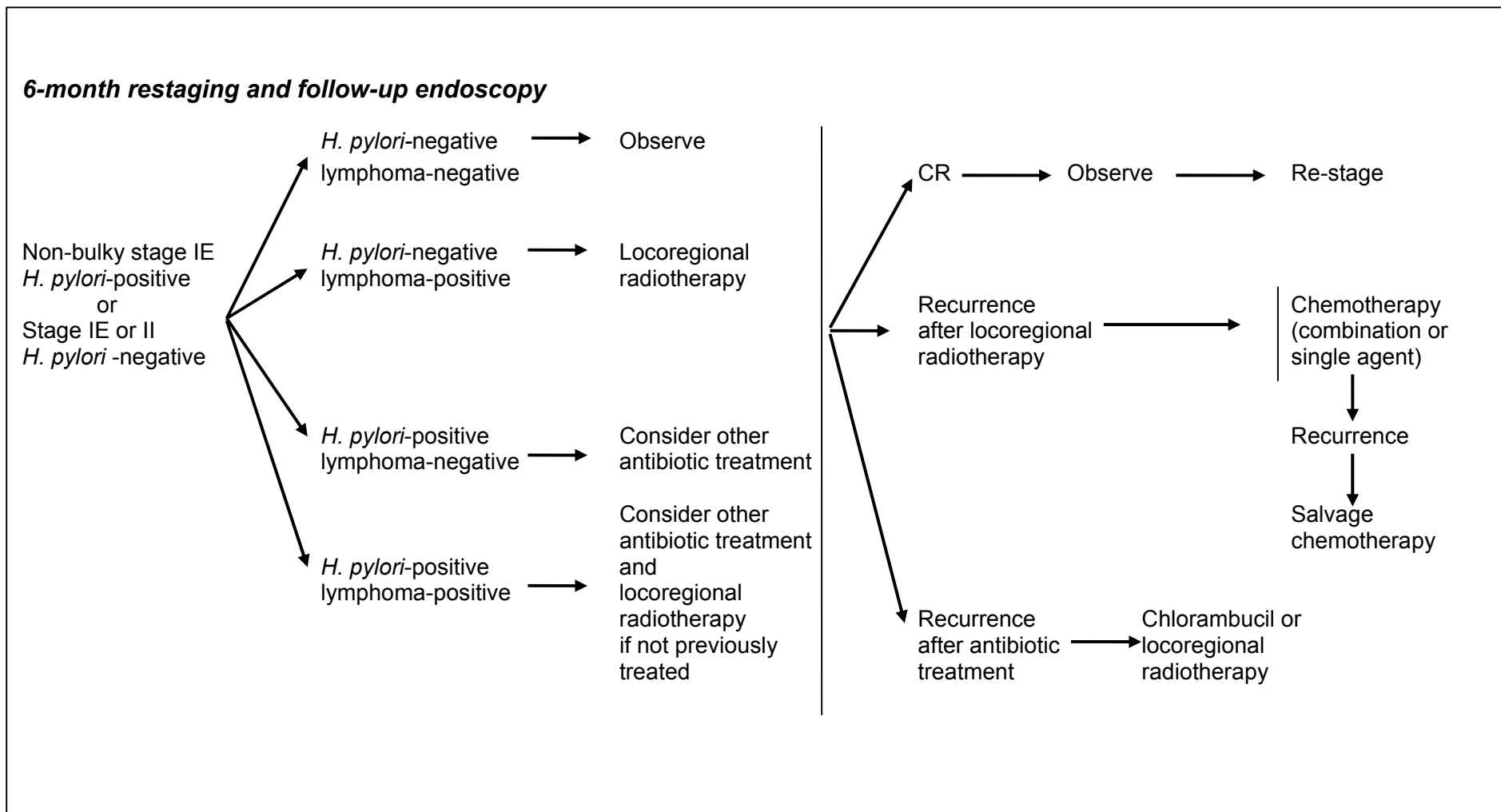


Figure 12.2 Six-month restaging and follow-up for gastric marginal zone lymphoma



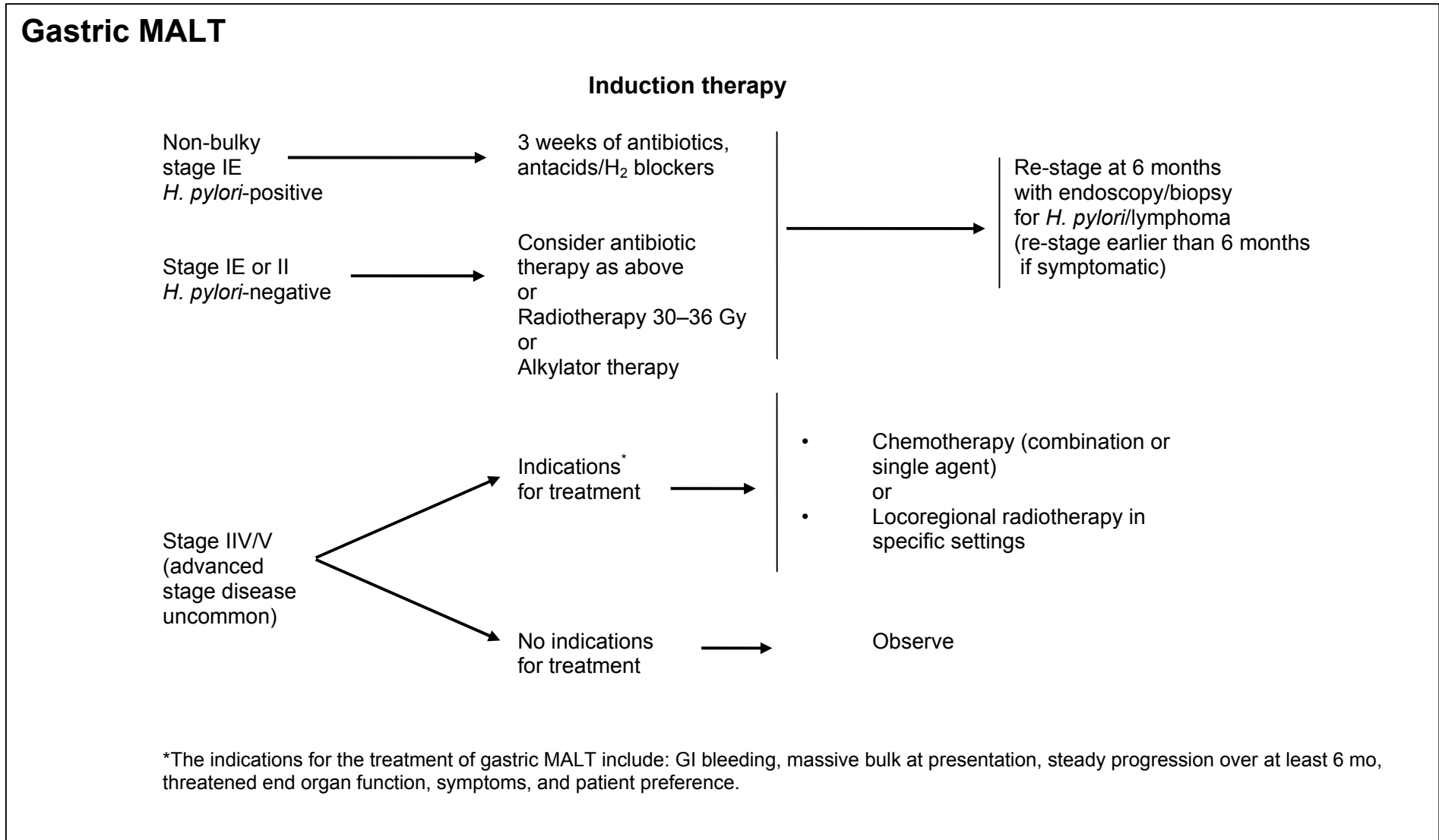
Box 12.5

Treatment of non-gastric MALT

Treat like gastric MALT, except:

- No antibiotics or *H. pylori* treatment
- Stage I/II → locoregional radiotherapy
- Stage III/IV → indications for treatment same as for follicular lymphoma.
Chemotherapy (combination or single agent)

Figure 12.3 Therapy for gastric MALT lymphoma



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General considerations

- 13. Lymphoma and lymphoproliferative disease following transplantation**
- 14. Radiotherapy**
- 15. CNS prophylaxis**
- 16. Haematopoietic growth factors**
- 17. Tumour lysis syndrome**
- 18. Follow-up, late effects and protection of reproductive function**
- 19. Imaging assessments**
- 20. Irradiation of blood products**
- 21. Practice standards**
- 22. Disease registration – template**
- 23. Patient support**

13. Lymphoma and lymphoproliferative disease following transplantation

13.1 Introduction

Lymphoproliferative diseases occur more commonly following allogeneic haematopoietic stem cell transplantation (HSCT) and in recipients of solid organ allografts than in the general population. The incidence ranges from < 1% to > 10% in different series but is generally higher in patients transplanted in childhood, particularly those receiving allogeneic BMT.

The management of post-transplant lymphoproliferative disease (PTLD) represents a particular challenge because of the heterogeneity in pathogenesis, transplant setting and presentation. Furthermore, the evidence supporting management strategies is based almost entirely on case reports and retrospective series. For these reasons, optimal management depends upon close liaison between transplant and oncology/haematology teams and referral to centres experienced in the care of these difficult cases.

The transforming properties of the common human γ -herpes virus, Epstein-Barr virus (EBV), and the level of iatrogenic immune suppression play important roles in the pathogenesis of PTLD. The histological spectrum of resulting disease is wide, ranging from polymorphic polyclonal lymphoid hyperplasia to defined malignant entities such as myeloma and Burkitt's lymphoma. Thus some cases of PTLD are managed successfully as an infectious disease, by reducing immune suppressive dosage and giving anti-viral medication. However, many cases require the use of conventional modalities for treating malignancy, namely surgery, cytotoxic chemotherapy and radiotherapy. The use of additional supportive measures should be considered for immunosuppressed patients undergoing chemotherapy to reduce the risks from myelosuppression and sepsis.

13.2 Pathology and pathogenesis

PTLD is clinically diverse. Clinico-pathological grouping has been attempted in some series.

- Patients present with an IM-like syndrome, including fever, cervical adenitis and splenomegaly. This is typically associated with polymorphic hyperplasia and is more common in paediatric series.
- Patients present with disseminated lymphoma when heavily immunosuppressed within the 6 months following transplantation. They experience rapid progression to multiple organ failure and death. This is associated with either polymorphic or monomorphic lymphoid infiltrates.

- Patients present 6 months to many years post-transplant with less aggressive nodal or extra-nodal disease, which may be focal or multi-focal. The transplanted organ is a common site of disease. Many such are monomorphic and may resemble defined malignancies.

13.3 Management

Management of PTLN is a specialist function and should be only undertaken in close collaboration between the transplant physician or surgeon and oncologists with experience of treating this disorder. This will require knowledge of manipulation of immunosuppression, antiviral therapy, surgical resection, radiotherapy or cytotoxic therapy as appropriate.

14. Radiotherapy

Radiotherapy is the single most effective treatment modality in the management of NHL with single-agent response rates far in excess of those for any chemotherapy agent. It is a locoregional treatment its limitations relating to the extent of disease that can be treated within the limits of normal tissue tolerance. Lymphoma is highly radiosensitive, the dose response reaching a plateau around 30–40 Gy, less than half the dose required for a squamous carcinoma.

In non-aggressive NHL, radiotherapy alone may be curative for limited stage IA or stage IIA disease. High CR rates are reported up to 98% with 10-year relapse-free figures of between 47 and 63%. In stage I and IIA aggressive NHL radiotherapy alone will give lower CR rates around 85% and the treatment of choice for these patients is currently to combine involved field radiotherapy with 3 cycles of CHOP, with a reported 5-year PFS of 77%.

For more advanced disease, primary chemotherapy will be the treatment of choice but radiotherapy to initial sites of bulk disease or residual masses after chemotherapy will prolong PFS although OS may not be influenced.

Other important indications are the role of TBI in conditioning for marrow ablative chemotherapy and prophylactic cranial irradiation of lymphoblastic lymphoma.

For recurrent and chemotherapy-resistant disease palliative radiotherapy is of considerable benefit at symptomatic sites. Sequential hemibody radiotherapy has been shown to produce significant remissions for widespread disease.

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15. CNS prophylaxis

Evidence from observational studies suggest that patients with high-risk IPI scores, sinus or testicular involvement are at higher risk of CNS relapse, which is associated with poor survival.

The overall relapse risk based on high IPI (\uparrow LDH, BM involvement) is around 5%. Where there is involvement of sinus or testis the CNS relapse risk is 20–50%.

Recommendation 15a

CNS prophylaxis should be given to all patients with high IPI or testicular/sinus or BM involvement who are to receive curative treatment approaches

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

- Intrathecal methotrexate (12.5mg)/methotrexate plus cytarabine (50-100mg) with each cycle of CHOP treatment
- CHOP-methotrexate: methotrexate 250 mg/m² IV on day 14 of all cycles or methotrexate 1000 mg/m² on day 14 of first 3 cycles
- Protocol including ifosphamide or high-dose cytarabine systemically

16. Haemopoietic growth factors

The use of growth factors in NHL should in general comply with American Society of Clinical Oncology (ASCO) guidelines and the BCSH Guideline on the use of Colony Stimulating Factors in haematological malignancies.

16.1 Primary prophylaxis

The primary prophylactic use of haemopoietic growth factors (G-CSF and GM-CSF) is likely to reduce the incidence of chemotherapy-induced sepsis. The sepsis rate with most standard first-line lymphoma chemotherapy regimens is, however, too low for this strategy to be cost-effective, and routine use is not recommended unless other high-risk features are present.

Some of the very intensive first-line regimens such as CODOX-M/IVAC, which is used in Burkitt's lymphoma, probably fulfil the ASCO criteria for prophylactic use, and indeed routine G-CSF administration is incorporated into this protocol. The standard dose of G-CSF is 5 µg/kg/day and for GM-CSF is 250 µg/m²/day sc It is reasonable procedure to 'round-off' to whole vials.

16.2 Secondary prophylaxis

This refers to the more selective use of haemopoietic growth factors in patients who have developed sepsis on a previous cycle of chemotherapy. There is a lack of adequate clinical trial data in this situation, and global recommendations cannot be made. In some cases haemopoietic growth factors use is probably justified, but this must be left to the judgement of the clinician viewing all the available information pertaining to an individual case.

16.3 Augmentation of dose delivery

Retrospective analyses of patients receiving standard chemotherapy for histologically aggressive NHL have shown that patients receiving the full dose of chemotherapy on time have a better outcome than those who do not. However, there are many reasons for delaying or reducing chemotherapy other than protracted neutropenia, and it cannot be assumed that routine use of growth factors would result in improved OS due to better disease control. There is also a lack of convincing trial data to support the use of haemopoietic growth factors in this way, and routine use is not therefore recommended.

There may be individuals suffering excessive treatment delays or dose reductions who would benefit from growth factor administration, but it must be borne in mind that cytotoxic drug absorption and metabolism is very variable and some patients develop neutropenia because they have had more drug exposure. Chemotherapy reductions in such patients would be fully appropriate, and administration of growth factors to them without dose reduction would increase

non-haematological toxicity. Any decision to use growth factors to minimise dose reductions must therefore take into account the full range of toxicities experienced in a given patient.

There is at present no evidence that the use of growth factors to increase the relative dose intensity above the standard prescribed dose improves survival, and use of haemopoietic growth factors for this purpose should be limited to clinical trials.

16.4 Adjuncts to progenitor cell mobilisation

Haemopoietic growth factors are indicated for progenitor cell mobilisation. A dose-response has been established for normal individuals receiving G-CSF alone, and the most appropriate dose is probably 10 µg/kg/day. When G-CSF is given after chemotherapy, lower doses of G-CSF may be optimal.

The incidence of febrile neutropenia after HSCT is > 40% and thus falls within the ASCO guidelines for primary prophylaxis. The benefit after autologous PBSC transplantation appears less than after BM transplantation, and a UK randomised trial suggested only marginal cost benefits. Decisions to use growth factors post-transplantation should therefore be based on local resource-utilisation issues.

Box 16.1

Use of haemopoietic growth factors

- Use should comply with ASCO and BCSH guidelines
- Prophylaxis not recommended as routine practice unless high-risk features present
- Prophylaxis is justifiable in patients with previous serious chemotherapy-associated sepsis
- No trial data to support the routine use of growth factors to facilitate full-dose therapy on time or to enable increased dose intensity
- Use of growth factors to accelerate neutrophil recovery after HDT complies with the ASCO guidelines; however, the benefit is less for PBSC than for BM stem cell support

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17. Tumour lysis syndrome

Tumour lysis syndrome (TLS) is a consequence of hyperuricaemia, hyperkalaemia and hyperphosphataemia with hypocalcaemia, which occurs shortly after the initiation of chemotherapy. It is not likely to happen where there is a low tumour burden. Correction of biochemical abnormalities before initiating therapy reduces, but does not eliminate the risk. TLS can cause death within hours of initiating chemotherapy. Recommended measures are:

17.1 Prophylaxis

17.1.1 With no metabolic abnormality

- Allopurinol 500 mg/m²/day. Reduce to 200 mg/m²/day after 3 days of chemotherapy
- Hydration 3 L/m²/day, 1 L N saline, 2 L 5% dextrose
- Chemotherapy initiated with 24–48 hours of admission
- Monitor urine output, blood pressure and CVP at least 4-hourly
- Consider prophylactic bicarbonate, which can be discontinued if the serum urate does not rise
- Monitor electrolytes, urea, creatinine, uric acid, Ca⁺⁺ and PO₄ every 12–24 hours initially

17.1.2 With a metabolic abnormality

- Allopurinol as above. Reduce dose in renal failure
- Hydration as above, add a non-thiazide diuretic as required
- Urinary alkalisation using isotonic sodium bicarbonate (1.4% w/v) adjust rate to maintain urinary pH > 7. Discontinue when serum uric acid normal
- Treat hypocalcaemia if symptomatic or ECG abnormality. Use intravenous Ca⁺⁺ and activated vitamin D
- Treat hyperkalaemia appropriately
- Inform nephrologist at an early stage

17.2 Criteria for dialysis

- Persistent hyperkalaemia despite conventional treatment.
- Rapidly rising serum phosphate or persistent hyperphosphataemia.
- Symptomatic hypocalcaemia despite treatment.
- Fluid overload.
- Hyperuricaemia .

17.3 Rasburicase

This recombinant form of urate oxidase which causes the oxidation of uric acid to allantoin, which is readily excreted in the urine has been shown in early clinical trials to reduce uric acid levels within 4 hours without significant side effects. Paediatric studies have indicated that it is effective prophylaxis against, or treatment of hyperuricaemia in patients with leukaemia or lymphoma. It is contra-indicated in patients who have a hypersensitivity to uricases or have G6PD deficiency or other disorders associated with haemolytic anaemia.

Further reading

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18. Follow-up, late effects and protection of reproductive function

18.1 Follow-up after completion of treatment

At the end of planned treatment and following a full re-staging evaluation to confirm remission status, it is routine for patients to be reviewed in the out-patient clinic on a regular basis. This practice has a number of intended functions including early detection of relapse, patient reassurance, monitoring the long-term effects of treatment on cardiopulmonary, endocrine and reproductive function, and the diagnosis of second malignancy. Very little research has been performed in this area, however, and the frequency of follow-up visits, the duration for which they should be continued, and the type of investigations (if any) to be employed, are not clearly defined. Furthermore, follow-up strategy for patients with HD and aggressive NHL (where cure at relapse is still a realistic proposition) should probably be different from that for patients with indolent NHL, where a chronic relapsing/remitting course is almost inevitable.

Furthermore, the real value of these practices in terms of the number of cases of relapse detected at the routine follow-up visit is likely to be substantially less than many physicians and their patients believe. In a paper published by Weeks and colleagues, 32 of 36 (89%) of relapses occurring in a cohort of patients in CR following treatment for large cell lymphoma, were detected as a result of the investigation of new symptoms rather than by routine screening of asymptomatic patients. Furthermore, all 32 patients with symptoms arranged an earlier clinic visit, suggesting a high degree of motivation in this US population. Very similar results were obtained in a more recent study from the UK in a cohort of 210 patients who achieved a complete or partial remission following primary treatment for HD. Here, 30 of 37 (81%) relapses were detected as a result of the investigation of new symptoms, but only 50% of these individuals had arranged an earlier appointment – presumably because of either a lack of awareness of the importance of symptoms or a reluctance to take the initiative. This suggests the need for better patient education and an information sheet.

Although it would appear therefore that routine follow-up of asymptomatic patients is associated with a very low relapse detection rate, patients themselves value follow-up after completion of treatment of lymphoma and are highly satisfied with current arrangements. In a recent study two thirds of respondents identified reassurance and peace of mind, and one third detection of relapse, as the main functions of follow-up. Seventy-six percent expressed a preference for no change to the current follow-up system, but a significant number of patients (44 of 95, 46%), were prepared to accept fewer routine visits if, when problems arise, rapid clinic access could be guaranteed.

It is, of course, possible that an intensive follow-up protocol employing regular CT and Gallium-67 imaging, for example, might lead to an early detection of relapse and possibly an improved survival. Equally, however, an approach characterised by less-frequent routine visits but early and vigorous investigation of new symptoms reported by the patients may do just as well. An appropriate clinical trial to resolve this issue has not yet been performed; until it is, a pragmatic approach has to be adopted.

Outside clinical trials, it is recommended that patients with HD and aggressive NHL are seen 3-monthly in year 1, 4-monthly in year 2, 6-monthly in year 3, and annually thereafter. At each visit patients are asked about new symptoms and examined for evidence of recurrent disease, and blood is drawn for FBC, ESR and serum biochemical profile (to include LDH). In the case of patients with previous mediastinal, lung or pleural involvement and a complete remission at the end of treatment, a plain chest X-ray should be performed at *alternate visits* in years 1 and 2 then annually until after the fifth anniversary of completion of treatment. For patients with a residual lymph node mass, a chest X-ray should be performed at *every visit* in years 1, 2 and 3 and then annually until year 5.

Box 18.1

Follow-up for patients with aggressive NHL

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

Clinic visits

- 3-monthly in year 1
- 4-monthly in year 2
- 6-monthly in year 3
- annually until year 10, and then alternate years

At each visit

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

Routine investigations

- Blood count and chemistry (to include LDH) and erythrocyte sedimentation rate (ESR) 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)
- Chest X-ray at every visit in years 1, 2 and 3, then annually to year 5 (if residual mass present at end of treatment)

All other investigations arranged in response to new symptoms/signs of disease, abnormal routine investigations or in the context of trial protocols.

For patients with non-aggressive NHL, the suggested frequency of follow-up visits is the same as for aggressive NHL. Routine chest X-ray and measurement of ESR are unnecessary, however, thyroid function tests should be performed annually from year 3 in those who have received a field of radiotherapy that included the thyroid gland (see below).

Box 18.2

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 until year 10, and then alternate years

At each visit

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

Routine investigations

- Blood count and chemistry (to include protein electrophoresis if paraprotein at presentation and LDH)
- Thyroid function tests annually from year 3 after previous radiotherapy to mediastinum/neck

All other investigations arranged in response to new symptoms/signs of disease, abnormal routine investigations or in the context of trial protocols.

With specific regard to patients with NHL in clinical trials, International Workshop recommendations were for 3-monthly review for 2 years, then 6-monthly review for 3 years and then annual review for at least 5 years. Minimum evaluation at each visit should include a history, physical examination (to exclude lymphadenopathy, abdominal masses or organomegaly), an FBC and serum LDH. The authors added that additional blood tests and imaging studies may be required for certain clinical indications but, at present, specific recommendations could not be made.

Although follow-up has traditionally been performed by a physician, appropriately trained specialist nurses are likely to fulfil this role extremely well. This innovation plus a more problem-oriented approach might usefully result in the follow-up visit changing from the frequent, rapid processing of generally fit patients to a less frequent, more extensive consultation designed to optimise detection of recurrent disease and monitor the late effects of treatment. Clearly patients need to be educated as to the limitations of routine investigation and the importance of new symptoms as a possible indicator of recurrent disease. In this regard, patients must also feel confident that they can gain rapid access to a clinic appointment if the need arises, when, even if not due to relapse, their symptoms and concerns will be dealt with sympathetically. The possible use of an information sheet given to patients at the completion of treatment has already been mentioned.

18.2 Management of late treatment effects

Late effects of treatment fall into 3 main groups. These are endocrine dysfunction and infertility (common), second malignancy (less common) and cardiopulmonary dysfunction (rare).

18.2.1 Endocrine dysfunction and infertility

The most commonly seen endocrine complications of treatment for lymphoma are hypothyroidism and hypo-oestrogenic states caused by ovarian ablation. There is an increasing incidence with time of hypothyroidism following incidental exposure of the thyroid gland to radiation, and routine testing of thyroid function is a mandatory part of follow-up in these patients (see above).

Premature menopause due to ovarian ablation caused by either chemotherapy or radiation treatment causes symptoms of oestrogen lack (thinning of the hair, vaginal dryness, depression and reduced libido), reduction in bone mineral density with an increased risk of fracture and a higher incidence of coronary artery disease. For many reasons, therefore, hormone replacement therapy is advisable for these patients, and wherever possible the advice of an endocrinologist should be sought. Although the testis is extremely vulnerable to the effects of chemotherapy in terms of the germinal epithelium's capacity to produce spermatozoa, the interstitial Leydig cell is

significantly more resilient to cytotoxic damage, and overt testosterone deficiency states requiring hormone replacement therapy are only very rarely seen.

The effects on fertility are perhaps the complications of treatment that cause patients the most emotional distress. The testis is far more vulnerable to damage than the ovary, which in young women (< 35 years) can recover after chemotherapy, which would undoubtedly cause permanent sterility in men. It should be remembered, however, that even in patients where ovarian function recovers after treatment, damage has been sustained and a premature menopause is likely. Women should be appropriately advised about this so that attempts at pregnancy, if desired, should not be unduly delayed.

18.2.2 Protection of reproductive function

Attempts at protecting reproductive function from the effects of chemo/radiotherapy using hormonal manipulation have proved largely unsuccessful, and the most effective way of avoiding these late effects is by employing a less-toxic therapy wherever possible. In situations where a more toxic regimen or high-dose chemotherapy is recommended on grounds of efficacy, other strategies designed to preserve fertility have to be considered. For men, semen cryopreservation has been available for some time; this 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.

In any circumstances, cryopreserved semen is a finite resource and is not an option for pre-pubertal boys. In an effort to overcome this and develop a strategy that can reverse treatment-related infertility, research is in progress to see if testicular cells harvested and cryopreserved before the start of chemotherapy, can be reintroduced to the testis after treatment and resume normal spermatogenesis. This has been achieved in a mouse model, and the results of experimental protocols in men are awaited with interest.

Although 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 these circumstances other techniques have to be considered. Unfortunately, *in vitro* fertilisation of thawed, mature eggs harvested and cryopreserved before the start of chemotherapy has resulted in very few pregnancies worldwide, and the technique cannot be recommended. One way of overcoming this is for eggs to be fertilised at the time of harvesting, with subsequent cryopreservation of embryos

(a technique that works well) but this is not possible for women without a partner unless donor sperm are an acceptable option. Furthermore, the harvesting of mature eggs requires several weeks of hormonal stimulation of the ovary, time which is frequently not available for a patient with active disease.

Box 18.3

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

Men

- Semen analysis is the best way of assessing germinal epithelial function. Remember that 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-stimulating hormone (FSH), luteinizing hormone (LH), testosterone or sex hormone binding globulin on a routine basis. Patients with a depressed libido or fatigue should, however, be tested for subnormal levels of serum testosterone. This is rare but, if present, referral to an endocrinologist is indicated. A more common finding is a raised FSH (in keeping with germinal epithelial damage) and a low normal level of testosterone. There is no evidence that testosterone replacement therapy is of benefit for these individuals

Women

- If menstruation is regular and normal (bleeding not unduly heavy or light, no intermenstrual bleeding), sex hormone analysis is unnecessary. If menstruation is irregular or absent, the serum oestrogen, progesterone, FSH, LH and sex hormone binding globulin 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, the use of these should be discussed with the local fertility centre.

An experimental technique of great interest is the harvesting and cryopreservation of ovarian cortex (which contains primordial follicles, the precursor of mature eggs) before the start of sterilising chemotherapy/radiotherapy. In ewes, the reimplantation of autologous ovarian cortical tissue into surgically castrated animals has resulted in a resumption of oestrus cycles, conception after normal matings, and the birth of live offspring. This technique is currently the subject of clinical trials in women, although there is the added concern about possible reintroduction of disease when the cryopreserved graft is reimplanted. Nevertheless, the possibility of reversing treatment-related infertility now exists, and intense research activity in this area is currently underway.

National guidelines for the management of gonadal toxicity after treatment of adult cancer have been published, and these are recommended reading.

18.2.3 Second malignancy

The diagnosis of a second tumour following apparent cure of the first is devastating news for the patient and, unfortunately, one that is often associated with a poor prognosis. Chemotherapy for lymphoma is associated with an increased risk of myelodysplasia and acute myeloid leukaemia (AML) some 4–6 years later, when karyotyping of bone marrow frequently reveals abnormalities of chromosomes 5, 7 or 12. 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 for this type of tumour. 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 the early diagnosis of second tumours, a recommendation that is entirely consistent with that likely to be associated with the optimal detection of recurrent lymphoma (see above).

It has recently been shown that young women (≤ 30 years old) whose breasts have been incidentally irradiated have a greatly increased relative risk of developing breast cancer 10-15 years later. This experience is primarily in patients with HD receiving mantle field irradiation, but there may also be a risk associated with radiotherapy to the lower neck, supraclavicular fossa and axillae as well which result in scattered radiation to the breast. Strategies to reduce this effect depend on a reduction in radiotherapy field sizes and utilising combined modality treatment wherever possible to minimise the late effects of both treatments. The possible role of breast screening in this population is unknown, but is recommended, and the potential benefits of therapeutic interventions (e.g. using anti-oestrogens in prevention) are currently being investigated.

18.2.4 Cardiopulmonary dysfunction

Cardiac function can be affected by the anthracycline class of drugs (typically doxorubicin), which can cause a cardiomyopathy with heart failure. Although the risk is greatest at large cumulative doses (a total dose of no more than 450 mg/m² of doxorubicin is usually recommended), there is no threshold dose, below which cardiomyopathy does not occur, and patients rarely develop this serious complication after only limited exposure. In patients < 70 years of age with no history of cardiorespiratory disease, one approach is to administer anthracyclines up to the previously stated maximum without formal assessment of cardiac function. 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 echocardiology) is mandatory, and doxorubicin could be substituted by arguably less cardiotoxic analogue (e.g. epirubicin or mitoxantrone) if there is evidence of impaired cardiac

function. Assessment of cardiac function is also important in patients being considered for high-dose chemotherapy; many of these will already have received an anthracycline drug and/or radiotherapy, and the stress of major sepsis sometimes associated with severe myelosuppression can precipitate acute and severe cardiac failure in some patients.

Radiotherapy damages small blood vessels and when the heart is included in a radiotherapy field there is an increased risk of coronary artery disease and its complications (angina, myocardial infarction, sudden death). Drugs that act as free-radical scavengers are thought to reduce cardiac damage caused by radiotherapy, but these agents are not generally used and the move is towards a reduction in radiotherapy field sizes.

Both drugs (bleomycin, busulfan, cyclophosphamide and BCNU) and radiotherapy can cause lung fibrosis with a cough, exertional dyspnoea and a restricted pattern of lung function abnormalities. The effect of bleomycin is exacerbated by larger doses, advanced age, pre-existing lung disease, previous radiotherapy and smoking, but the overall impact of lung dysfunction on quality of life and survival is less than the late effects of treatment on the heart. In severe cases of cardiopulmonary dysfunction where a patient is considered cured of lymphoma, heart, lung or heart/lung transplantation should, of course, be considered.

Further reading

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Weeks JC, Yeap BY, Canellos GP, Shipp MA. Value of follow-up procedures with patients with large cell lymphoma who achieve a complete remission. *J Clin Oncol* 1991; 9: 1196–1203

19. Imaging assessments

19.1 Routine management

Initial work-up requires conventional X-ray and CT as part of the staging process. There is no need for this to be repeated unless there is a clinical suspicion of disease progression or failure of response. CT (or MRI) of chest, abdomen and pelvis should be carried out around 6 weeks from the end of treatment; this provides evidence of response and provides baseline data for comparative review if the patient develops new or recurrent symptoms.

Where a CR is confirmed, there is little or no evidence to support the cost-effectiveness of 'routine' review imaging if the patient is asymptomatic. If a residual mass is seen, one further limited CT (or MRI) examination is advised 3 months later to ensure that the mass is unchanged or smaller. In selected cases, particularly those at high risk of relapse, more complex imaging of residual masses (e.g. positron emission tomography [PET]) may assist in management decisions. At present, PET imaging is available in only a limited number of centres, and its precise role is still unclear.

19.2 Selected patient imaging

19.2.1 Head and neck imaging

Depending on the site of the presenting disease it is often important to evaluate the neck (US, CT or MRI) and head (ideally MRI, alternatively CT).

19.2.2 Bone imaging

Skeletal scintigraphy is the mainstay of assessing possible bone involvement, coupled with correlative plain X-ray or MRI of foci showing abnormal tracer uptake.

19.2.3 Functional studies of residual masses

Gallium-67 studies can provide useful information but they can usually only be easily reported in the light of a pre-treatment gallium study. Hence the current interest in PET and functional CT/MRI. It is likely that the indications for PET will widen over the next few years; a residual mass in a symptomatic patient is a recognised indication at this time.

19.2.4 Lymphangiography

This should no longer be performed for lymphoma. Few UK radiologists have the necessary skills to perform this investigation or interpret the resulting images.

Imaging should generally comply with the schematic protocols listed in:

Husband JES, Johnson RJ, Reznick RH. *A guide to the practical use of MRI in oncology*. Royal College of Radiologists, London, 1999

BCSH guidelines on nodal non-Hodgkin's lymphoma – draft 2, August 2002

The use of computed tomography in the initial investigation of common malignancies. Royal College of Radiologists, London, 1994

20. Irradiation of blood products

The occurrence of transfusion-associated graft-versus-host disease has been reported in lymphoma patients. This is a rare occurrence, which took place before the introduction of universal leucodepletion. Consideration should be given to irradiation of blood products for patients treated with fludarabine who have low CD4 counts (e.g. < 200/ μ l), or who will receive a stem cell transplant. (BCSH Guidelines on the gamma irradiation of blood components for the prevention of transfusion-associated graft-versus-host disease, *Transfusion Medicine* 1996: 6; 261-271).

21. Practice standards

2.1 Clinical dataset

In order to facilitate outcome assessment of treatment, it is considered that clinical teams should record a minimum amount of diagnostic and clinical information at the start of treatment. It is suggested that this include

- patient demographics
- histological diagnosis using the WHO-REAL classification (Appendix 3, Table A3.1)
- the histopathology laboratory reference number to enable future review
- date of diagnosis
- clinical stage I to IV according to the Ann Arbor scoring system (see Section 3)
- the presence or absence of B symptoms
- the dimension of largest tumour (< or > 10 cm)
- site of extra-nodal involvement
- performance status 0–4
- LDH normal or above normal range
- serum albumin normal or reduced IPI: L, LI, HI, H (see Section 3).

Each team should have the capacity to collect treatment details and follow-up all patients to monitor disease response.

21.2 Organisational standards

All lymphomas should be managed by a MDT lead by a named haemato-oncologist with demonstrable experience. All consultant team members should be known and include a haemato-oncologist, clinical oncologist, histopathologist, radiologist, nurses qualified in haemato-oncology,

and pharmacist. In addition a named surgeon should be responsible for invasive biopsy (an ENT or facio-maxillary surgeon for neck nodes and a general surgeon for other).

21a Practice Standards

General practitioners and hospital specialists should be aware of the MDT, and lines of access should be clear

Any patient with suspected lymphoma should be seen by a member of the MDT within 10 working days from referral

A biopsy should be completed and a preliminary report available to the MDT within 2 weeks of the patient's first contact with the MDT

Diagnostic procedures should be in accordance with Section 2 of this guideline

A management plan should be in place within 4 weeks of the patient's first attendance, and treatment should commence within 2 weeks of the plan date

The management plan must be recorded in the clinical notes, and must be available to the patient and the general practitioner

The MDT should record a minimum clinical dataset pre-treatment (see above and Appendix 3) and have the capacity to record treatment intentions and disease response. It should be noted that national minimum datasets for England and Wales will be available in 2004 and will augment the clinical data which is outlined in Appendix 3

Educational information should be available for patients

Patients should have access to counselling, psychological support and support groups

Patients should have the opportunity to enter ethically approved trials

22. Disease registration

Date of diagnosis: Unit number: Surname: First name: Address:		Hospital: Consultant:	
Sex: DoB:		GP details Name: Address:	
Histology:			
– Lab No:.....			
– Specimen (lymph nodes, skin etc.):.....			
– Diagnosis:.....			
– Supplementary report of histological type:.....			
Clinical Stage:			
– I II III IV			
– B symptoms:		Loss of $\geq 10\%$ of weight over last 6 months	
		Night sweats Fever	
– Dimensions of largest tumour:		< 10 cm ≥ 10 cm	
– Site of extra nodal involvement:			
Bone marrow	Liver	Skin	Other Please state.....
GIT	Spleen	CNS
– Performance status:		0 = no symptoms 1 = ambulatory	
2 = bedridden < 50% time		3 = bedridden $\geq 50\%$ time 4 = completely bedridden	
– Serum LDH:	within normal	raised	ND
– Serum albumin:	normal	reduced	ND
– Serum B2 microglobulin:	within normal	raised	ND
– International Prognostic Index (IPI):	L LI HI H		

Patient Information

A substantial amount of information for patients can be made available for patients. Included in these are several from the Lymphoma Association.

The Lymphoma Association

PO Box 386

Aylesbury

Bucks

HP20 2GA

Tel: 01296 619400

Helpline: 0808 808555

General Booklets:

Lymphomas

A booklet for patients who have Hodgkin's disease or non-Hodgkin's Lymphoma. Designed to help patients with the illness and treatment.

Young Person's Guide

This booklet deals with issues of particular concern to young people with lymphoma.

Materials available from libraries:

Videos and cassettes:

Non-Hodgkin's Lymphomas and their treatments.

Fact files, including:

- Cancer-related fatigue
- Chemotherapy
- Complementary therapy
- Coping with stress
- Fertility issues
- Herbal medicine
- High-dose therapy and stem cell transplant
- Hormones
- Low-grade lymphoma
- Lymphoma classification

- Minigrafting
- Monoclonal antibodies as treatment for non-Hodgkin's lymphoma
- Neutropenia
- Nutrition and lymphoma
- Oral problems associated with chemotherapy and radiotherapy
- PET scans
- Radiotherapy

Websites

UK Websites

Lymphoma Association	http://www.lymphoma.org.uk
CancerBACUP	http://www.cancerhelp.org.uk
Cancer Research UK	http://www.cancerresearchuk.org
Leukaemia Research Fund	http://www.leukaemia-research.org.uk

Overseas Websites

Lymphoma Research Foundation	http://www.lymphoma.org
Lymphoma Foundation Canada	http://www.lymphoma.ca
NHLBCELL	http://www.NHLBCELL.org
Lymphoma Information Network	http://www.lymphomainfo.net
Oncolink	http://www.oncolink.com

BNLI Details

BNLI CRC and UCL Cancer Trials Centre
222 Euston Road
London
NW1 2DA

Tel: 020 7679 8060
Fax: 020 7679 8061

Contact person: Paul Smith
Tel: 020 7679 8062

NCRI Trials; <http://www.ncrn.org.uk>

BCSH Guidelines:

<http://wwwBCSHguidelines.com>

Appendices

- 1. Treatment regimens**
- 2. Available trials**
- 3. Royal College of Pathologists minimum data set for lymphoma histopathology reports**
- 4. Abbreviations**

Appendix 1: Treatment regimens**CHOP**

Cyclophosphamide	750 mg/m ² IV day 1
Doxorubicin	50 mg/m ² IV day 1
Vincristine	1.4 mg/m ² IV day 1 (max 2 mg)
Prednisolone	40 mg/m ² oral days 1–5
Repeat 3 weekly for 6–8 cycles. Mitoxantrone (10–12 mg/m ²) may be substituted if cardiotoxicity likely to be a problem.	

CVP

Cyclophosphamide	600 mg/m ² IV day 1
Vincristine	1.4 mg/m ² IV day 1 (max 2mg)
Prednisolone	40 mg/m ² oral day 1–5
Repeat 3 weekly for 6–8 cycles	

ESHAP

Etoposide	40 mg/m ² /day	IV over 60 minutes days 1–4
Methylprednisolone	500 mg/day	IV days 1–5
Cytarabine	2 g/m ² /day	IV over 3 hours day 1
Cis-platin	25mg/m ² /day	IV continuous infusion days 1-4
Apart from the administration of the chemotherapy, most patients can remain as out-patients even though this regimen is quite myelosuppressive.		

BEAM

BCNU	300 mg/m ²	day –6
Etoposide	200 mg/m ²	day –5 to –2
Cytarabine	200 mg/m ²	Twice daily day –5 to –2
Melphalan	140 mg/m ²	day –1

CODOX-M

Vincristine	1.5 mg/m ²	day 1 and day 5
Cyclophosphamide	800 mg/m ²	day 1
Doxorubicin	40 mg/m ²	day 1
AraC	70 mg	intrathecal day 2
Cyclophosphamide	200 mg/m ²	day 2 and 5
Methotrexate	1200 mg/m ²	over 1 hour followed by 5520 mg/m ² over 23 hours day 1
Methotrexate	12.5 mg	intrathecal day 15
Commence G-CSF on day 13		

IVAC

Ifosfamide	1500 mg/m ²	day 1–5
AraC	2 g/m ²	bd day 1–2
Etoposide	60 mg/m ²	day 1–5
Methotrexate	12.5 mg	intrathecal day 5

PMitCeBo

Mitoxantrone	7mg/m ²	day 1 IV
Cyclophosphamide	300mg/m ²	day 1 IV
Etoposide	150mg/m ²	day1 IV
Vincristine	1.4mg/m ² (maximum 2 mg)	day 8 IV
Bleomycin	10mg/m ² (bolus)	day 8

Prednisilone 50mg/day on alt days weeks 5 till treatment end

Appendix 2: Available NCRITrials

Aggressive Lymphomas:

- MISTRAL TRIAL:

A randomised phase III trial of standard chemotherapy (CHOP regimen) versus sequential high dose chemotherapy with autologous stem cell transplantation in patients with newly diagnosed Non-Hodgkin's Lymphomas and poor prognostic factors.

Eligibility Criteria

Inclusion criteria

Definite diagnosis of an aggressive Non-Hodgkin's Lymphoma according to one of the following categories of the REAL classification.

- diffuse large B-cell lymphoma
- primary mediastinal large B-cell lymphoma
- aplastic large cell lymphoma (B-cell, T-cell or null-cell type)
- patients must be <60 and >18 years of age
- at least 2 of the following risk factors (according to the age-adjusted International Prognostic Index)
 - stage III or IV disease (Ann Arbor Staging System; see appendix 3)
 - elevated LDH (>upper limit of normal)
 - ECOG performance status 2, 3 or 4
 - adequate organ function, as defined by the following criteria:
 - Creatinine clearance >60ml/min (unless due to tumour involvement). Creatinine clearance at diagnosis may be calculated from serum Creatinine without collection of 24-hour urine
 - serum bilirubin <40µmol/l (unless due to tumour involvement)
 - AST or ALT <2 x upper limit of normal range (unless due to tumour involvement)
 - no relevant lung disorder
 - no relevant heart failure (normal left ventricular ejection fraction, as assessed by echocardiogram)
 - no history of active angina pectoris or myocardial infarction within the preceding 6 months
 - no major ventricular arrhythmia

Lead Investigator(s)

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- **MINT Trial:**

NHL Good Risk Phase III trial comparing CHOP to PMitCEBO in good risk stage II-IV patients with histologically aggressive non-Hodgkin's lymphoma.

Eligibility Criteria

Inclusion Criteria

- (i) Previously untreated aggressive non-Hodgkin's lymphoma of the following types

Working Formulation:

Follicular large cell lymphoma
Diffuse mixed cell lymphoma
Diffuse large cell lymphoma
Diffuse immunoblastic lymphoma

Or REAL classification

Diffuse large B
Peripheral T cell lymphoma

Pathological material must be available for central review

- (ii) Bulky stage IA and stages IV-IV (Ann Arbor staging system)
- (iii) Age 18-59 years
- (iv) Measurable or evaluable disease
- (v) Good prognosis is defined as the presence of no more than one of the following adverse features:

- i. stage III/IV
ii. LDS > upper limit of normal
iii. Performance status 2-4 (ECOG-WHO)
iv. Adequate bone marrow function, indicated by

Haemoglobin >10g/dl
Neutrophils >2 x 10⁹/l
Platelets >100 x 10⁹/l

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BNLI Sixty Plus Trial

BNLI 60+ A phase III trial comparing CHOP to PMItCEBO with or without G-CSF in patients aged 60 plus with aggressive non-Hodgkin's lymphoma.

Eligibility Criteria

Inclusion:

1. Age =>60 years
2. Newly presenting aggressive non-Hodgkin's lymphoma as defined by the working formulation categories F-H. All histology to be reviewed by central BNLI panel
3. Bulky stage IA and stages IB-IV

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LY10

A clinicopathological study in Burkitt's and Burkitt-like non-Hodgkin's Lymphoma

Eligibility Criteria

Pathology study eligibility:

Diffuse B-cell lymphoma in nodal or extranodal site, CD20+ CD79+ with 100% expression of Ki67 (MIB1) in all of the tumour cells

or

Bone marrow replacement/leukaemia consisting of mature B-cell lymphoma showing slg+, CD19+, CD34-, Tdt-

Clinical Phase II Study Eligibility

- I. Pathology as above
- II. Age at least 16 years
- III. Patient's mental and physical status must be sufficient to withstand the treatment described
- IV. Maximum of 1 cycle of pre-induction chemotherapy
- V. All patients should be HIV negative
- VI. No previous chemotherapy or radiotherapy treatment (other than pre-induction chemotherapy)
- VII. No other disease or previous malignancy likely to interfere with the protocol treatments or comparisons
- VIII. Written informed consent

Lead Investigator(s):

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BNLI Radiation Dose Trial

BNLI Radiation Dose BNLI Randomised trial of radiation dose in non-Hodgkin's Lymphoma.

Eligibility Criteria

Inclusion:

1. Any patient receiving local radiotherapy where the aim of treatment is local control of that lymphoma whether as radical treatment of Stage 1 disease, consolidation therapy after chemotherapy or palliation.
2. Histological diagnosis of non-Hodgkin's Lymphoma reviewed by the BNLI panel.
3. Age over 18 years
4. Able to give informed consent

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NCRI Mantle Cell Lymphoma Trial

NCRI Mantle Cell Lymphoma Trial Phase II randomised study of Fludarabine/Cyclophosphamide combination with or without Rituximab in patients with untreated mantle cell lymphoma.

Eligibility Criteria

Inclusion:

- Age 18 years or older
- Proven Mantle Cell Lymphoma
- Previously untreated disease at any stage requiring therapy
- No previous chemotherapy
- Life expectancy of at least 3 months
- Signed and dated informed consent

Lead Investigator(s):

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Non-Aggressive Lymphoma

EBMT-LYM1 Trial

EBMT-LYM1 Randomised Study of Rituximab (MabThera) in patients with Relapsed or Resistant Follicular Lymphoma prior to High Dose Therapy as in vivo purging and to maintain remission following high dose therapy.

Eligibility Criteria

Inclusion:

- (1) Relapsed/resistant follicular lymphoma
- (2) Patients with minimum one prior chemotherapy regimen
- (3) CD20 positive
- (4) CR or good PR following reinduction chemotherapy
- (5) Adequate bone marrow function (platelets $>100 \times 10^9/l$ following reinduction chemotherapy)
- (6) Age 18 years or older
- (7) Pathological material must be available for review and PCR analysis

Lead Investigator(s):

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EORTC 20981

EORTC 20981 Chimeric anti-CD20 monoclonal antibody (Mabthera*) in remission induction and maintenance treatment of relapsed follicular non-Hodgkin's Lymphoma: a phase III randomised clinical trial – Intergroup Collaborative Study (EORTC 20981) including amendment 4 (28.6.2000).

Eligibility Criteria

Inclusion Criteria

Patients with Ann Arbor (see Appendix A) stages III or IV follicular NHL (at initial diagnosis) who have relapsed after a maximum of two adequate non-anthracycline containing systemic chemotherapy regimens. Patient pre-treated with other chemotherapy regimen are not eligible for this trial.

Patients with either remission (CR,PR) no change (NC) or progression on one of a maximum of 2 prior regimens, ie either on the first or on the second regimen.

To qualify for remission or NC, duration of response c.q NC upon one or the prior regimens should have been at least 4 weeks (with a confirmation).

Previous treatment should have been at least 2 months of single agent therapy (eg Chlorambucil) and/or at least 2 consecutive cycles of polychemotherapy (eg CVP) or purine analogues. Patients treated with chemotherapy not fulfilling these criteria are not eligible.

Follicular NHL according to the REAL classification (19), ie follicle centre lymphoma, follicular provisional cytologic grades: I (small cell); II (mixed small and large cell), III (large cell).

The histopathological classification by the local pathologist of the participating centre will be accepted as diagnosis of entering the study. However, slides will have to be sent the central pathologist and reviewed by the Pathology Panel to decide whether the patient was indeed eligible.

The lymphoma must be CD20 positive

Re-biopsy of lymphnodes is not necessary unless the CD20 expression is not known or in case of clinical suspicion of transformation into an intermediate/high grade lymphoma.

At least one mass should be present measurable by 2 perpendicular diameters by either physical or radiological examination

Age: 18 years or older.

WHO Performance Status 0,1 or 2.

Patient information and written informed consent according to the rules of the respective county c.q institute. There will be one patient information and written informed consent for both randomisations.

Lead Investigator(s):

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Name: Dr Robert Marcus

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BNLI MCD vs FMT (Follicular Lymphoma)

BNLI MCD vs FMD BNLI RCT of MCD vs FMD in follicular NHL

Eligibility Criteria

4.0 Eligibility

- newly diagnosed Follicular lymphoma (REAL classification Follicle Centre Cell Lymphoma, grades I-III)
- age 18-70 years
- physician determined indications to treat:

B symptoms, bone marrow failure, bulky or progressive disease and compression syndromes

- advanced stage III or IV disease

Stratified by international prognostic index score:

Low risk (score 1)

Intermediate low risk (score 2)

Intermediate high risk (score 3)

High risk (score 4 or 5)

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Appendix 3

Royal College of Pathologists minimum data set for lymphoma histopathology reports

Co-ordinators N Rooney, A Ramsay, A Norton, A Wotherspoon, B Wilkins

The proposals for reporting of lymphomas should be implemented for the following reasons:

- 1 The management of lymphomas is dependent on the type of lymphoma, its stage and the clinical status of the patient. The histological basis of the diagnosis was recognised as being important in several studies in both HD and NHL.

The histological diagnosis is therefore important in

- a determining appropriate therapy for the individual patient
 - b providing prognostic information
 - c providing effective groupings for clinical trials
 - d providing accurate data for cancer registration
- 2 New markers and diagnostic techniques appear regularly. Some require fresh or frozen tissue for analysis. Validation of these diagnostic tools requires the availability of appropriately stored samples.
 - 3 The epidemiology of lymphoma is complex. Only by accurate separation of different diseases can the incidence of the disease, and any variation, be studied

However the nomenclature of lymphomas has been a contentious area over the years with pathologists being accused of developing clinically irrelevant classifications and clinicians of lumping different diseases into the same treatment categories. The use of different terminology around the world, (Kiel in European trained pathologists, Lukes-Collins in American trained pathologists) made comparison of epidemiological and outcome data difficult and resulted in the development of the Working Formulation for clinical usage.

In 1994 the International Lymphoma Study Group composed of pathologists from around the world proposed the REAL (Revised European-American Lymphoma) Classification. The basic premise was that the classification should identify disease entities using all available information, morphologic, immunophenotypic, genetic, clinical manifestations and clinical course. The terminology is similar to the Kiel classification but recognises nodal and extra-nodal as an important biological parameter.

To validate the classification a multicentre trial was organised to ensure that it was reproducible, practical and useful for clinical trials. The report published in 1997 by the NHL Classification Project confirmed this. For most entities the reproducibility ranges from 85–95%. For some diseases e.g. peripheral T cell lymphoma, immunophenotype was found to be essential, others e.g. follicle centre cell lymphoma could be recognised by light microscopy alone. This supports what most pathologists already encounter in daily practice.

Clinical factors as measured by the IPI were found to be important within the disease groups. When the lymphomas were grouped by outcome it was evident that each group contained very different diseases that required different management. It was apparent therefore that REAL was both a practical and clinically useful system.

The REAL classification has been adopted by the WHO as the basis of lymphoma classification. It has been developed under the auspices of the European Association of Hematopathology and the Society of Hematopathology and includes lymphoid myeloid and histiocytic neoplasms. A total of 52 pathologists worked on the different disease groups supported by a Clinical Advisory Committee of 35 clinicians. The proposals have been discussed widely and have been accepted by the proponents of other classifications as the new international standard.

The WHO classification has modified some of the entities in REAL based on new data but the basic terminology remains the same. There are a large number of entities but many of these are very rare in the UK. To help in the use of this document a list of entities is supported by their approximate incidence in the NHL classification project. Typical appearances of the common lymphomas in the UK are also given to help the reporting pathologist.

This data set has been prepared in association with the British Lymphoma Pathology Group and in discussion with the authors of the equivalent protocols for the USA. These publications are detailed in the reference list.

Lymphoreticular histopathology minimum data set

Surname..... Forename(s)..... Date of birth..... Sex

Hospital..... Hospital No.....NHS No.....

Date of receipt..... Date of reporting Report No.

Pathologist..... SurgeonOncologist/Radiotherapist.....

Indication for investigation

Primary diagnosis staging relapse/progression re-staging

Specimen type

excision biopsy needle biopsy endoscopic biopsy
 extra-nodal resection splenectomy bone marrow

other biopsy (specify) _____

Lymph node Site _____ Size _____ mm

Spleen Weight _____ g Size _____ mm

Skin Site _____

For other organs (e.g. GI tract and lung) macroscopic description and lymph node dissection should be given in a free text report.

Tumour type (WHO classification, Table A3.1)

Immunostaining cytogenetics and molecular genetic analysis should be requested at the discretion of the reporting pathologist taking into account the immunoprofile of entities in the WHO classification.

Hodgkin's disease (see guidance notes)

Nodular lymphocyte predominance	_____
Classical HD	_____
Nodular sclerosis	_____
Mixed cellularity	_____
Lymphocyte depletion	_____
Lymphocyte-rich classical HD	_____

B cell neoplasm (specify) _____

T/NK cell neoplasm (specify) _____

Histiocytic neoplasm (specify) _____

Bone marrow

Involved yes no

Tumour type _____

Table A3.1 WHO classification of lymphoid neoplasms

	Percentage of NHL *
<i>B cell neoplasms</i>	85.0
<i>Precursor B cell neoplasms</i>	
Precursor B lymphoblastic leukaemia/lymphoma	
<i>Mature B cell neoplasms</i>	
B cell CLL/SLL	6.7
B cell prolymphocytic leukaemia	
Lymphoplasmacytic lymphoma	1.2
Splenic marginal zone lymphoma	< 1.0
Hairy cell leukaemia	
Plasma cell myeloma	
Plasmacytoma	
Marginal zone B cell lymphoma of MALT-type	7.6
Nodal marginal zone B cell lymphoma	1.8
Follicular lymphoma	22.0
MCL	6.0
DLBCL	32.0
Mediastinal (thymic)	2.4
Intravascular large B cell lymphoma	
Primary effusion lymphoma	
Burkitt's lymphoma/leukaemia	1.0
<i>T cell and putative NK cell neoplasms</i>	14.0
<i>Precursor T cell neoplasms</i>	
Precursor T lymphoblastic lymphoma/leukaemia	1.7
Blastic NK cell lymphoma	
<i>Mature T cell and NK cell neoplasms</i>	
T cell prolymphocytic leukaemia	
T cell large granular lymphocytic leukaemia	
Aggressive NK cell leukaemia	
Adult T cell lymphoma/leukaemia (ATL/L)	
Extra-nodal NK/T cell lymphoma nasal type	
Enteropathy-type intestinal T cell lymphoma	1.0
Hepatosplenic T cell lymphoma	
Subcutaneous panniculitis-like T cell lymphoma	
Primary cutaneous CD30 positive T cell lymphoproliferative disorders (cutaneous ALCL)	
Mycosis fungoides	< 1.0
Sezary syndrome	
Angioimmunoblastic T cell lymphoma (AILD)	1.2
Peripheral T cell lymphomas, unspecified	7.0
ALCL	2.4
* approximate incidence – refers mainly to lymph node biopsies in adults	
<i>Hodgkin's disease (HD)</i>	

Nodular lymphocyte predominance HD	
Classical HD	
Nodular sclerosis HD	
Lymphocyte rich classical HD	
Mixed cellularity HD	
Lymphocyte depleted HD	
Histiocytic and dendritic cell neoplasms	<i>Less than 1%</i>
<i>Macrophage/histiocytic neoplasms</i>	
Histiocytic sarcomas	
<i>Dendritic cell neoplasms</i>	
Langerhans' cell histiocytosis	
Langerhans' cell sarcoma	
Interdigitating dendritic cell sarcoma/tumour	
Follicular dendritic cell sarcoma/tumour	
Dendritic cell sarcoma not otherwise specified	
Mastocytosis	
Cutaneous mastocytosis	
Indolent systemic mastocytosis	
Systemic mastocytosis with associated clonal haematological non-mast cell lineage disease	
Aggressive systemic mastocytosis	
Mast cell leukaemia	
Mast cell sarcoma	
Extracutaneous mastocytoma	

Guidance notes for lymphoma reporting

A minimum data set identifies the requirements for reporting but needs to be supported with education and quality assurance. It is recognised that not all cases will be reported by specialists in haematopathology, but many cases will require immunostains not available in every laboratory.

Several studies have shown the value of specialist referral for the diagnosis of lymphoma and this is to be encouraged. In cases where there is any doubt, a second expert opinion is strongly recommended. However it is recognised that, at present, not every region can offer a specialist referral centre for the diagnosis of all cases of lymphoma or indeed all cases of lymphoreticular disease. Most pathologists when supported by appropriate immunochemistry should be capable of reporting the common forms of lymphoma in the WHO classification. However, this requires that the reporting pathologist has access to good immunochemistry, keeps up to date in the developments in the specialty and recognises where there are problems in the differential diagnosis. Each laboratory is encouraged to identify a pathologist to take a special interest in lymphoreticular disease. That individual should establish a referral pattern to an appropriate centre where further expertise and techniques are available. The histological diagnosis must be compared with the clinical information and the BM findings. These components are essential for

staging the disease though they may be outside the control of the pathologist. Clinical liaison is particularly important in the primary skin lymphomas where the differential diagnosis of benign and malignant conditions may depend on the clinical circumstances rather than the histological appearances. Unusual variants of common diseases are more common than usual variants of uncommon disease therefore specifying a list of diseases that can be reported locally is impossible. Areas that frequently cause problems and in which referral should be encouraged are:

1. Florid follicular hyperplasia where follicular lymphoma is a possibility
2. Florid T zone hyperplasia where the differential diagnosis lies between T cell lymphoma and reactive lymphadenopathy
3. Small cell proliferations where the distinction between MCL and lymphocytic lymphoma is not resolved by immunostaining
4. High-grade B cell lymphoma where Burkitt's Lymphoma is a possibility. Usually this will mean in those cases where there is a Ki67 index > 90%
5. Most nodal T cell and histiocytic lymphomas are rare and any individuals experience is likely to be limited
6. Cases of lymphocyte depleted HD where anaplastic large cell lymphoma is considered
7. Lymphoid proliferations in the immunosuppressed
8. Cases that do not fit the typical pattern of disease, an outline of the usual features of the most common lymphomas is set out below
9. All cases of paediatric lymphoma

Specimen type

Macroscopic description

In many cases of lymph node biopsy a brief description of the biopsy site, size and cut surface is sufficient. For splenectomy specimens the spleen weight and presence of macroscopic nodules with an indication of their size should be recorded. For extra-nodal lymphoma the standard protocol for the appropriate organ (e.g. stomach, bowel etc.) should be followed. For primary skin lymphoma it is important to record the biopsy site since that may influence the management and prognosis. In ideal circumstances, where facilities exist for handling fresh specimens, the tissue should be received as soon as possible after surgery. Large lymph nodes and spleens should be sliced for optimal fixation. A consistent fixation time of approximately 24 hours aids reproducibility in immunostaining. Consideration should always be given to taking fresh tissue for microbiology, cytogenetics and for snap freezing for future analysis, particularly for the extraction of mRNA.

Tumour type

The classification of lymphoma

It is recommended that all lymphomas are reported according to the WHO classification of lymphoma. The proponents of the Working Formulation, Kiel and REAL classifications have accepted that this is the logical progression of lymphoma classification. The WHO classification encompasses both HD and NHL as well as myeloid and histiocytic neoplasms. The entities are listed together with their relevant incidence in Western populations in Table 1.1. Some of these entities are rare, others occur in specific situations. The importance of recognising these entities is that they may predict behaviour of the tumour and warrant different treatment and therefore need to be identified before treatment is commenced.

For the NHLs the principles of the REAL classification have been incorporated into the WHO classification with very little change in terminology. The incidence of the different lymphomas varies according to racial group, geographic location, age, site of tumour and clinical circumstances. In otherwise normal patients, the majority of tumours diagnosed in lymph nodes will be of follicular or DLBCL-type. At extra-nodal sites marginal zone lymphoma is more common. In the immunosuppressed, variants of EBV-induced proliferations as well as plasmacytic/plasmablastic lymphomas are commonly encountered. Standardisation of terminology has allowed the identification of important groups. MCL with its characteristic appearance and immunophenotype is an important example. Within the follicular lymphomas the identification of monocytoid differentiation may also be significant though this has yet to be validated in clinical studies.

The complexity of T cell lymphomas is highlighted in the report of the Workshop of the European Association of Haematopathology. Although the appearances of T cell lymphoma are more variable, most pathologists are aware of the importance of recognising ALCL of T or null cell type. Recent data and staining for anaplastic lymphoma kinase (ALK) has further defined this important subgroup.

The growth patterns of the different lymphomas gives rise to a wide range of differential diagnoses both benign and malignant. The recognition of the different subtypes of lymphoma defines clinical behaviour independent of stage and prognostic score and so is a valuable activity. A close working relationship with the haematologists and oncologists and radiotherapists ensures optimum treatment.

Primary skin lymphomas are covered in the WHO classification but it is recognised that there are some differences that may affect clinical management. Of particular note is that primary cutaneous follicular lymphoma may lack *Bcl-2* rearrangement and *Bcl-2* expression is weak or absent. DLBCL

may behave less aggressively when it occurs as a primary cutaneous disorder on the head, neck or trunk as opposed to the legs. Cases of primary skin lymphoma should therefore be discussed at the dermatopathology multidisciplinary meeting to ensure optimum management.

Finally, it is inevitable that the classification of lymphoma will be modified in the future as new techniques are introduced. It is incumbent on those reporting haematopathology to keep up to date in the field.

Microscopy

Good quality thin sections (2–4 µm) are essential for accurate diagnoses. Many diagnoses can be reached on standard haematoxylin and eosin sections aided by reticulin staining for the assessment of architecture and PAS stains to highlight vascular structure. Giemsa is useful for the identification of cytoplasmic basophilia, blast cells and mast cells but many histopathology laboratories find it difficult to achieve reproducible results. Other stains to identify mast cells such as toluidine blue and chloroacetate esterase should be available.

Immunostaining

Reporting of lymphoreticular disease has been aided greatly by the availability of immunostains. However, the range of antibodies available is vast and beyond the scope of most laboratories. A basic panel of antibodies should be available in every laboratory reporting lymphoreticular disease. In some cases, e.g. DLBCL and ALCL, immunostaining is essential but some forms of lymphoma are recognisable on standard sections alone. The value of confirmatory tests should not be underestimated. Discrepancies in immunostaining may expose an erroneous diagnosis and therefore confirmation of a routine diagnosis is encouraged. Immunocytochemistry therefore should be applied according to the judgement of the reporting pathologist. Some laboratories prefer to use flow cytometry to assess immunophenotype, the technique used should follow local preference and experience.

Most laboratories carry a range of antibodies for routine diagnosis. A basic panel is difficult to specify because it depends on the local interest, referral practice and budget. Further antibodies are needed to refine the diagnosis of lymphoma and to differentiate difficult lesions. Most require good technique and careful interpretation with the use of appropriate controls and participation in the NEQAS scheme. Some antibodies only work with appropriate amplification methods. Laboratories should be aware of the staining characteristics and technical limitations of each antibody and the expected frequency of their use before investing in a large panel of antibodies.

Co-operation between laboratories in the same area can economise on the use of selected antibodies.

To help with diagnosis of the common lymphomas the usual immunoprofile of the B cell lymphomas is given in Table A3.3. The staining pattern of T cell lymphomas is more variable and since these tumours are relatively rare in the UK no equivalent table has been given. Advice may be sought from regional centres.

Antibodies useful in the diagnosis of lymphoreticular disease

These are grouped according to their use in identifying B cell or T cell proliferations, HD, NK cells, or Langerhans' Cells. Reference should be made to the descriptions of the diseases and to Table A3.2, which details the usual patterns of staining. A more detailed description of the immunophenotype of lymphomas is given in the review by Chu *et al.*

Table A3.2 Antibodies useful for the diagnosis of lymphoreticular disease

CD79a, CD20	B cell antibodies in widespread use though their pattern of staining is slightly different
CD5, 10, 23	These antibodies are useful in identifying subsets of small B cell lymphoma (lymphocytic - CD5 and CD23 positive; MCL CD5 positive, CD23 negative; follicle centre cell CD5 and CD23 negative, CD10 positive; most lymphoplasmacytic and marginal zone lymphomas are CD5, CD10 and CD23 negative). These antibodies work well in paraffin sections. CD5 is usually a T cell marker and will also stain some T cell lymphomas
Kappa and lambda light chains	Light chain stains are extremely useful in identifying clonality but are technically difficult and must be interpreted with caution. Some laboratories prefer to use <i>in situ</i> hybridisation for kappa and lambda mRNA. Heavy chain staining can also be useful in identifying subgroups of lymphoma.
IgG M A D	
Cyclin D1	Cyclin D1 is expressed in MCLs which carry the t(11:14) translocation. It is useful in identifying this form of lymphoma in conjunction with antibodies to CD5 and 23 but it requires careful technique and amplification for consistent results. Up to 20 % of MCL may be negative and other lymphomas carrying t(11:14) may be positive
CD21 and 23	These antibodies identify follicular dendritic cells (although they show different patterns of staining). Their use can help in the identification of follicular growth patterns and in the diagnosis of angio-immunoblastic T cell lymphoma. CD23 also stains 93% of B CLL
Bcl-2	Expressed in many normal T and B cells and many lymphomas. Not expressed in reactive follicle centre B cells and therefore Bcl-2 immunostaining is useful in distinguishing follicular hyperplasia from follicular lymphoma. Care must be taken not to mistake reactive T cells which are normally Bcl-2 positive for positive follicle centre cells It can not be used to distinguish follicle centre cell lymphomas from

other lymphomas. In DLBCL strong Bcl-2 expression is an adverse prognostic factor

Bcl-6	Expressed in germinal centres and follicular lymphoma. A large proportion of DLBCL express this antigen
Ki67	This nuclear antigen is expressed in cells in cell cycle but not in G0. It can help in identifying highly proliferative lymphomas such as Burkitt's where the Ki67 index approaches 100%
EBV	Anti-LMP1 is a robust stain that identifies EBV in about 20–30% of infected lymphoma cells and in all cells of positive cases of HD. <i>In situ</i> hybridisation for EBV encoded RNA (EBER) gives more consistent results
CD3	A reliable T cell marker available as a polyclonal antibody
CD5	This is a useful T cell marker when used in conjunction with CD3 but note it also stains some variants of B cell lymphoma (see above)
CD4 CD8 CD7 TIA and Granzyme B CD56, 57	Markers of T cell subsets are useful in the differential diagnosis of T cell proliferations and in T cell lymphomas. Their interpretation requires care NK cell markers are essential for the diagnosis of malignancies derived from these cells. CD56 is expressed by many of the NK cell malignancies of the nose and rarely tumours in other sites. CD57 is expressed by germinal centre T cells and is useful in the diagnosis of nodular lymphocyte predominant HD
CD30, CD15	Useful in the diagnosis of HD and ALCL. The specificity of CD30 in particular is dependent on the amplification used, the more sensitive the technique the more B cell blasts detected
ALK 1	This antibody detects the nucleophosmin – ALK fusion protein associated with t(2:5) and variant translocations involving the ALK-1 gene. Positive staining identifies the good prognosis subgroup of ALCL and may be the defining feature of the condition
CD1a	This antibody identifies Langerhans' cells in the skin, in the lymph node in dermatopathic lymphadenopathy and the tumour cells in Langerhans' cell histiocytosis. Most T lymphoblastic lymphomas are positive
TdT	Terminal deoxynucleotidyl transferase identifies precursor T and B cell leukaemias and lymphomas. This is a technically difficult stain and needs careful interpretation. It is also expressed in up to 10% of myeloid leukaemias

Genetic studies, chromosomal analysis and FISH

Clonality studies on the immunoglobulin heavy chain (IgH) and T cell receptor (TcR) by PCR can be very useful in cases where there is diagnostic difficulty but are not necessary in the majority of cases of lymphoma. Chromosomal abnormalities, identified by conventional banding techniques or FISH define many of the subgroups of lymphoma but generally require fresh or frozen tissue. In the future, as new markers are discovered and chemotherapy protocols change, these techniques may become more useful. The use of these techniques should follow local protocols or the

requirements of the relevant clinical trial but preservation of frozen tissue for future analysis and close ties with the regional cytogenetics laboratories is to be encouraged.

Hodgkin's disease

Please indicate which form of HD is present.

B cell neoplasm

Please insert full WHO classification of all lesions present. This includes any pre-existing low-grade component.

E.g. DLBCL with grade 1 follicular lymphoma (follicular)

T cell lymphoma

Please insert full WHO classification of all lesions present

E.g. intestinal type T cell lymphoma with enteropathy

Histiocytic neoplasms

Please insert full WHO classification of all lesions present

E.g. follicular dendritic cell sarcoma.

Bone marrow

Most staging data is radiological but the pathologist may be involved in reporting of the BM trephine. However the lymphoma in the BM may be different particularly if the patient has presented with a high-grade lymphoma on the background of low-grade disease. Therefore it is necessary to specify the tumour type in the BM

Usual features of the common lymphomas

B lymphoblastic lymphoma

- typically presents in childhood with leukaemia
- may rarely present as solid tumours involving the skin, bones or lymph nodes
- usually comprised of cells of intermediate size with round nuclei, small nucleoli and frequent mitoses
- TdT, CD10, CD79a positive (also CD19 and CD22 in frozen sections or flow cytometry), CD20 and immunoglobulin negative
- IgH rearranged, TcR is sometimes also rearranged

Lymphocytic lymphoma/(CLL)

- diffuse growth of small lymphocytes with prolymphocytes and paraimmunoblasts in proliferation centres

- BM and blood involvement
- low density IgM, IgD CD5, CD23 positive, cyclin D1 negative
- immunoglobulin heavy and light chain rearranged
- trisomy 12 (33%), 13q (25%)
- a common tumour in adults
- transformation to large cell lymphoma occurs in approximately 5% of cases

Lymphoplasmacytic lymphoma

- small lymphocytes, plasmacytoid cells and plasma cells
- diagnosis of exclusion, no features of CLL, follicular or other lymphoma
- corresponds to Waldenström's disease and lymphoplasmacytic lymphoma of Kiel
- cytoplasmic Ig, (M not D), CD5 and CD10 negative, *Pax-5* rearrangements present in some cases
- usually elderly patients involving BM, nodes, spleen

MCL

- medium sized irregular nuclei, dispersed chromatin, inconspicuous nucleoli, scant cytoplasm
- centroblasts and immunoblasts absent
- IgM IgD CD5 positive, CD10 and CD23 negative
- t(11:14), cyclin D1 expressed
- M > F, widespread disease especially involving Waldeyer's ring
- bowel involvement is common and manifests as lymphomatous polyposis
- survival 3–5 years

Follicular lymphoma

- predominantly follicular (> 75% follicular), follicular and diffuse (25–75% follicular) and predominantly diffuse (< 25% follicular)
- centroblasts and centrocytes with or without sclerosis
- grade 1, 0–5 centroblasts/HPF; grade 2, 6–15 centroblasts/HPF; grade 3a, > 15 centroblasts/HPF with centrocytes remaining; grade 3b, centroblasts form solid sheets with no residual centrocytes
- CD5⁻, CD21⁺ on follicular dendritic cells, CD10⁺ in 60% of patients
- t(14:18), Bcl-2 expressed inappropriately on germinal centre B cells
- 40% of adult NHL, transformation to DLBCL is common
- concomitant DLBCL should be reported separately

Marginal zone lymphoma of MALT

- frequent tumour at extra-nodal sites associated with autoimmune disease and infections
- mixed infiltrate of centrocyte-like cells, monocytoid B cells, lymphocytes and plasma cells
- reactive germinal centres and "destructive" lymphoepithelial lesions
- cytoplasmic immunoglobulin present in 40%, CD5, CD10, CD23 all negative
- no *Bcl-1* or *-2* rearrangements, trisomy 3 and t(11:18) may be found
- (Splenic and nodal types separately classified)

DLBCL

- centroblasts, immunoblasts and B cell variants of ALCL
- large cells prominent nucleoli; cleaved, multilobated and T cell/histiocyte rich variants
- cytoplasmic immunoglobulin, CD20 and CD79a positive, CD10⁺ in approximately 40% of patients, CD5 and CD23 variably expressed
- Bcl-2 expressed in 30%, a poor prognostic marker
- 30–40% adult NHL, 40% extra-nodal
- mediastinal/thymic, primary effusion and primary CNS subtypes

Burkitt's lymphoma

- monomorphic, medium sized round nuclei, multiple small central nucleoli, basophilic cytoplasm, cytoplasmic lipid droplets on cytology
- abundant mitoses and apoptoses, Ki67 ~100%
- CD10, 20,79a positive (also CD19 and 22), CD5 and CD23 negative; IgM > IgA > IgG
- t(8:14), t(2:8), t(8:22) all involving c-myc
- EBV present in most endemic cases, 25–40% AIDS related lymphomas
- Requires aggressive therapy for successful treatment therefore must be distinguished from DLBCL

T/NK cell lymphoma of nasal type

- broad spectrum of cell sizes
- eosinophils histiocytes large RS-like cells
- CD3 and CD56 CD45RO variable, CD4, CD8, CD5 negative, CD20 rare
- EBV present in all cases but may require *in situ* hybridisation to show it.
- less than 15% of western lymphoma but greater proportion in Asia
- most commonly involves nose and face and is rarely seen elsewhere

ALCL

- large cells pleomorphic nuclei, multiple nucleoli, cohesive or sinusoidal growth pattern, rarely small cells only

- CD30 CD25 EMA positive, CD45 variably expressed
- some t(2;5) or variants, ALK positivity associated with good prognosis
- 50% TcR rearrangement
- 25% occur in age < 20, may follow mycosis fungoides, lymphomatoid papulosis or HD
- primary cutaneous forms are classified separately. Their distinction from lymphomatoid papulosis can be difficult and requires close clinical liaison

HD lymphocyte predominant

- good prognosis, most commonly presents as stage I, rarely involves the mediastinum, therefore may justify less intensive treatment
- large lobulated cells (L&H or popcorn cells), background of small mantle B lymphocytes
- most cases have many background CD57⁺ T cells that form rosettes around the large cells
- CD20, CD79a, EMA and Bcl-6 positive, CD30 weak or negative, CD15⁻
- immunostaining is required in most cases to separate from classical HD

HD Classical

- typical Reed-Sternberg cells, mummified cells may be present
- nodular sclerosing mixed cellularity and lymphocyte depleted variants
- lymphocyte-rich classical HD has a background population that is predominantly small lymphocytes and in its nodular form is similar in appearance to nodular lymphocyte predominant HD
- CD15 and CD30 positive see table 3.4

Table A3.3 Summary of the usual staining 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	+	+	-	-/+	-	-	-	-
MCL	+	+	+	-	-	-	-	+
Follicular lymphoma,	+	+	-	-/+	+	-	-	-
Marginal zone B cell lymphoma of mucosa associated lymphoid tissue type	+	+	-	-	-	-	-	-
Nodal marginal zone lymphoma (+/- monocytoïd B cells)	+	+	-	-	-	-	-	-
Splenic marginal zone lymphoma	+	+	-	-	-	-	-	-
Hairy cell leukaemia	+	+	-	-	-	-	-	-
Plasmacytoma	-	+	-	-	-	-/+	-	-
Plasma cell myeloma	-	+/-	-	-	-	-/+	-	-
DLBCL	+	+	-/+	-/+	-/+	-/+	-	-
Mediastinal (thymic)	+	+	-	+/-	-/+	-/+	-/+	-
Intravascular	+	+	-/+	-	-/+	-/+	-	-
Primary effusion lymphoma	-	+	-	-	-	+	-	-
Burkitt's lymphoma	+	+	-	-	+	-	-	

+/- indicates that the lymphoma cells are commonly but not always positive

-/+ indicates that the lymphoma cells are usually but not always negative

Note: for T cell and putative NK cell neoplasms immunostaining is complex and variable

Table A3.4 Hodgkin's disease and its differential diagnosis (modified from Harris NL *et al. Modern Pathology* 1999)

	CD20	CD79a	T cell antigen	CD4 CD8	CD30	CD15	EMA
Nodular lymphocyte predominant HD	+	+	-	-	-/+	-	+
Classical HD	-/+	-/+	-	-	+	+	+
T cell rich large B cell lymphoma	+	+	-	-	-	-	-
ALCL	-	-	+/-	CD8 > CD4 > CD4&8-	+	-	+

+/- indicates that the lymphoma cells are commonly but not always positive

-/+ indicates that the lymphoma cells are usually but not always negative

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Appendix 5. Abbreviations

AILD	angioimmunoblastic T cell lymphoma
ALCL	anaplastic large cell lymphoma
ALK	anaplastic lymphoma kinase
AML	acute myeloid leukaemia
ASCO	American Society of Clinical Oncology
ASCT	allogeneic stem cell transplantation
AST	aspartate transaminase
ATL	acute T cell lymphoma/leukemia
BM	bone marrow
BNLI	British National Lymphoma Investigation
BUN	blood urea nitrogen
CNS	central nervous system
CR	complete response
DFS	disease-free survival
DLBCL	diffuse large B cell lymphoma
EBV	Epstein-Barr virus
ECOG	Eastern Cooperative Oncology Group
ESR	erythrocyte sedimentation rate
FBC	full blood count
FISH	fluorescence <i>in situ</i> hybridisation
FSH	follicle stimulating hormone
GI	gastro-intestinal
HD	Hodgkin's disease – also Hodgkin's lymphoma (HL)
HDT	high-dose therapy
HIV	human immunodeficiency virus
HSCT	haematopoietic stem cell transplantation
ICSI	intracytoplasmic sperm injection

IFN	interferon
LDH	lactate dehydrogenase
LFT	liver function test
LH	leuteinizing hormone
MCL	mantle cell lymphoma
MDT	multidisciplinary team
NCCN	National Cancer Center Network
NCRI	National Cancer Research Institute
NHL	non-Hodgkin's lymphoma
NR	No response
OS	overall survival
PB	peripheral blood
PBSC	peripheral blood stem cell
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PR	partial response
PTLD	post-transplant lymphoproliferative disease
REAL	Revised European-American Lymphoma
SAKK	Swiss Group for Clinical Cancer Research
SBFT	splenobillary function test
SLL	small lymphocytic leukaemia
SPECT	single photon emission computed tomography
SWOG	Southwest Oncology Group
TBI	total body irradiation
TLS	tumour lysis syndrome
UGI	urinogenital investigation
UKCCCR	UK Coordinating Committee on Cancer Research
UKLG	UK lymphoma group
WHO	World Health Organisation
WSR	World standardised incidence rate