
Pan-London Haemato-Oncology Clinical Guidelines

Lymphoid Malignancies
Part 3: Follicular Lymphoma

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Disclaimer

These guidelines should be read in conjunction with the latest NICE guidance, and all applicable national/international guidance. The prescribing information in these guidelines is for health professionals only. It is not intended to replace consultation with the Haematology Consultant at the patient's specialist centre. For information on cautions, contra-indications and side effects, refer to the up-to-date prescribing information. While great care has been taken to see that the information in these guidelines is accurate, the user is advised to check the doses and regimens carefully and if there is any uncertainty about the guidance provided, you should discuss your queries with a Haematology Consultant or Senior Pharmacist. No set of guidelines can cover all variations required for specific patient circumstances. It is the responsibility of the healthcare practitioners using them to adapt them for safe use within their institutions and for the individual needs of patients.

Contact us

The writing cycle for the guidelines will be from May-July each year. If you wish to be part of the writing group, please contact us through the following link: [Pan London Blood Cancer](#) (or via uclh.panlondonbloodcancer@nhs.net).

If you wish to report errors or omissions that require urgent attention please contact us via the same email addresses.

1 Introduction

Follicular lymphoma (FL) is the most common form of indolent lymphoma and the second most common form of non-Hodgkin lymphoma presenting in ~5/10,000 population/year, with a median age of onset of around 60 years.

It shows a slight male preponderance and the majority (~80–90%) have advanced (stage 3 or 4) disease at presentation, with at least half demonstrating bone marrow involvement.

A proportion of limited stage FL cases may be considered cured after targeted radiotherapy but, for the vast majority of patients with FL, this remains an incurable disease with conventional therapy.

While advanced stage disease may be managed by observation alone at least initially, and some cases never need treatment, most patients will require systemic treatment and FL may follow a pattern of relapsing and remitting disease over several years.

Moreover, therapy resistant disease progression and transformation to aggressive lymphoma are common causes of death. However, overall survival (OS) has improved in recent years¹ in tandem with advances in both treatment and supportive care. Median survival is now expected to be in the region of two decades.

2 Early Diagnosis and Prevention

While certain environmental factors, lifestyle influences and genetic loci are associated with the development of FL, no clear causative factor(s) exist for which screening or prevention of disease could be pursued.

There is no known approach that may help prevent the development of FL and it has not been established that earlier diagnosis will impact the outcome of advanced stage FL. However, early clinical presentation might aid the diagnosis of FL when still at limited stage and enable treatment with just local radiotherapy. Moreover, FL commonly presents as a 'lump' and early presentation by patients for medical review is encouraged as it is certainly the case that early diagnosis of other conditions presenting as a lump may benefit their clinical outcome.

Local community engagement exercises to emphasise and raise awareness in the primary care setting regarding the potential presentation of lymphoma and when to refer for specialist review are encouraged, and all patients should be encouraged to adopt a healthy lifestyle.

3 Referral Pathways from Primary Care

3.1 Presentation

Patients usually present with persistent lymph node enlargement. This may occasionally be accompanied by B symptoms (otherwise unexplained: temperature $>38^{\circ}\text{C}$, drenching night sweats, loss of $>10\%$ body weight over 6 months). Unusual presentations may include the consequences of bone marrow suppression, skin lesions, bowel involvement, and other extra-nodal/organ site involvement.

3.2 Referral

The typical trigger for referral is a persistent (>4 – 6 weeks) suspected enlarged lymph node. In work-up to referral it is recommended that the following blood tests are performed as a minimum in primary care:

- FBC
- LDH
- renal profile
- LFTs
- calcium/bone profile
- HIV.

The urgent/2 week wait referral pathway should be utilised if lymphoma is suspected. Early direct contact is encouraged between the primary care referring team and the receiving lymphoma managing centre as appropriate, particularly in systemically unwell or complex cases.

Similarly, specialist centres may receive internal referrals from other hospital teams (such as head and neck/ENT, breast surgery, general surgery, HIV/infectious disease) regarding suspected or proven lymphoma and organisation specific pathways should be followed.

4 Investigation and Diagnosis

4.1 Diagnosis

Definitive diagnosis requires examination of a tissue biopsy sample from an index lesion (most often an enlarged lymph node).

If a tissue/excision biopsy is not possible, then needle core biopsy can be performed, acknowledging the limits this may impose on assessment of tissue architecture. Adequate material is essential and re-biopsy must be considered if samples are deemed insufficient. (Fine needle aspiration should not be performed as a diagnostic investigation for FL.)

Biopsies should be transferred promptly for initial macroscopic examination and slicing by a histopathologist and immersed in formalin for fixation; where possible, separate fresh frozen storage of part of the biopsy is recommended.

A diagnosis can typically be made through histological examination of adequate tissue samples stained with haematoxylin and eosin (H&E) supported by immuno-staining for:

- CD20
- CD10
- Bcl-2
- CD5
- CD3
- (+/- Bcl-6, cyclin D1, CD43, κ and λ light chains).

While not required in the majority of cases, fluorescent in situ hybridisation (FISH) or cytogenetic analyses may reveal evidence of the t(14;18)(q32;q21) that is present in the majority of FL. Molecular analysis using the polymerase chain reaction (PCR) may identify the corresponding IgH/Bcl-2 rearrangement.

Occasionally, flow cytometry analysis of cellular samples may aid diagnosis while rarely a frozen section panel may be required.

The diagnosis should be reported as per current WHO² requirements.

4.2 Staging and imaging

A fundamental aspect of disease assessment is determining the anatomical extent (stage) of disease. This has direct implication on treatment selection and prognosis.

The staging of FL using positron emission tomography (PET) with low dose computed tomography (CT), as PET/CT imaging, has been adopted as an international standard of care following consensus recommendations (Cheson, *et al.*, 2014³). Subsequent NICE guidance includes recommendations regarding the use of PET/CT imaging in FL (NICE guideline NG52).

If standard CT imaging is performed as staging for FL then this should include the neck, chest, abdomen and pelvis, ideally with both oral and intravenous contrast, and a bone marrow biopsy should also be obtained.

Staging has routinely been documented according to the Ann Arbor system. It is recommended that staging is recorded according to the recent updates to this approach detailed in the Revised Staging System for Primary Nodal Lymphomas³ as indicated in [Table 1](#).

Table 1: Summary of Revised Staging System for Primary Nodal Lymphomas

Stage [^]	Involved sites
1	One node or a group of adjacent nodes*
2	Two or more nodal groups on the same side of the diaphragm [#]
3	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement
4	Additional non-contiguous extra-lymphatic involvement

Staging is according to the modified Ann Arbor system.

Notes: Tonsils, Waldeyer's ring, and spleen are considered nodal tissue.

Bulk:

[^]2 bulky = as stage 2 above with "bulky" disease

Extranodal (E) applies to stages 1 and 2 only:

 *1E = Single extra-nodal lesions without nodal involvement

[#]2E = Stage I or II by nodal extent with limited contiguous extra-nodal involvement

4.3 Baseline investigations

Recommended as mandatory:

- Blood tests
 - FBC, blood film, and consider peripheral blood immunophenotyping if lymphocytosis
 - Renal profile
 - LFTs
 - Bone profile/calcium
 - LDH
 - ESR
 - Immunoglobulins
 - Serum protein electrophoresis
 - Beta-2-microglobulin
 - Virology: HIV/HCV/HBV sAg + cAb (and HBV DNA level if indicated)
- Bone marrow aspirate and trephine biopsy (if staging was not by PET/CT imaging or if there are other concerns regarding marrow)
- ECG
- CXR.

Consider in specific cases:

- Cardiac function and left ventricular ejection fraction determination (for example in patients >65–70 years old +/- cardiac risk factors who are under consideration for anthracycline treatment and patients planned for myeloablative treatment)

- Targeted further organ assessment if indicated by patient review/past medical history/results of other investigations
- Fertility team review, counselling and preservation measures for those of reproductive age (and who meet NHS eligibility criteria)
- Formal ENT assessment
- Pleural fluid/ascitic fluid/CSF for flow cytometry
- In young cases (aged 16–25 years old): Teenage and Young Adult (TYA) review
- Psychology/talking therapy review
- Comprehensive geriatric assessment
- Independent mental capacity advocate.

4.4 Prognosis

While the overall prognosis of FL has improved over recent years, it is also possible to risk stratify affected patients. Multiple clinical, radiological, haematological and biochemical aspects of FL correlate with outcome and these have been incorporated in various clinical risk models.

The Follicular Lymphoma International Prognostic Indices (FLIPI and FLIPI2) each include five parameters, the presence or absence of which contribute to a score that can be used to determine risk categories for progression-free and overall survival (Table 2).

It is recommended that FLIPI scores are recorded at diagnosis as they may both inform patient discussion and influence first-line treatment options.

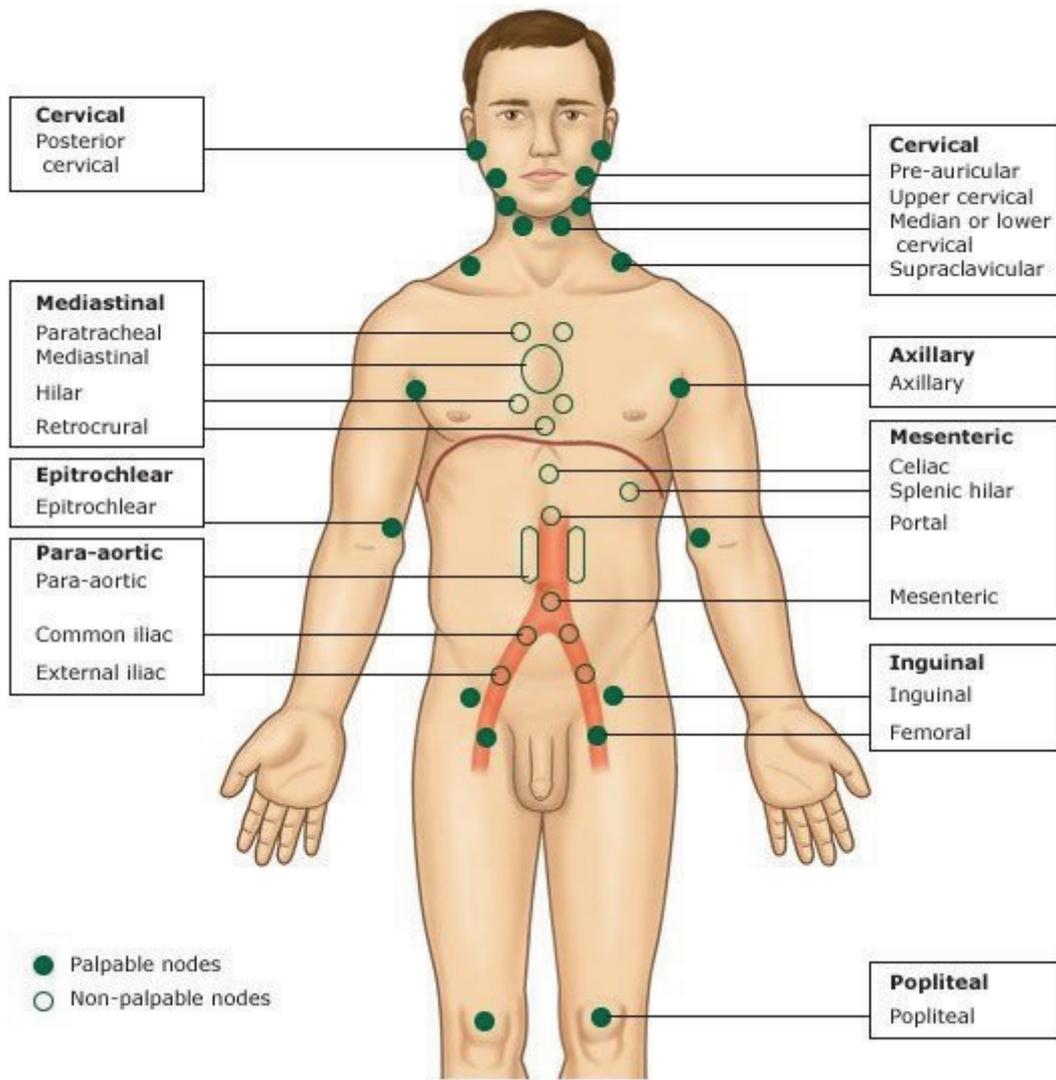
Molecular aspects of both FL tumour cells and the surrounding micro-environment correlate with outcome but at present have no role in routine clinical management.

Table 2: FLIPI and FLIPI2 prognostic systems

FLIPI					FLIPI2					
Parameter	Score = 1	Total score	Risk	OS (%)		Score = 1	Total score	Risk	OS (%)	
				5y	10y				5y	
Age	≥60					Age	>60			
Stage	3 or 4	0–1	low	90.6	70.7	BM	Involved	0	low	98
LDH	>ULN	2	int	77.6	50.9	B2M	>ULN	1–2	int	88
Hb	<120g/L	3–5	high	52.5	35.5	Hb	<120g/L	3–5	high	77
Nodal sites	>4*					Max node	>6cm			

OS, overall survival; ULN, upper limit of normal range; LDH, lactate dehydrogenase; Hb, haemoglobin; Nodal sites, number of lymph node sites involved by lymphoma; int, intermediate; BM, bone marrow; B2M, beta-2-microglobulin; Max node, maximum diameter of largest involved lymph node.

Figure 1: Nodal sites



Reproduced with permission from:

<http://morningreporttgh.blogspot.com/2010/07/lymphadenopathy.html>.

5 Treatment Recommendations

All patients with FL should be considered for entry to clinical trials appropriate to their aspect of disease management.

If not available at the managing centre, then patients should be offered the opportunity to attend other centres where relevant trials may be open for accrual. For clinical trials in FL currently open to recruitment across London go to www.lymphomas.org.uk/lymphoma-trialslink.

Ahead of any treatment, the informed consenting process, including completion of local consent forms, should be completed and documented in the patient's case-notes and communicated to their GP.

Management is critically dependent on FL histological subtype and disease stage.

National and international consensus recommendations for management should be consulted^{5, 6} (NICE guideline NG52).

5.1 Follicular lymphoma: grades 1, 2 and 3a

5.1.1 First-line management

(a) Limited stage disease (Stage 1A or 2A non-bulky)

FL is highly radiosensitive and the minority of cases presenting with limited stage 1 or 2 disease and no adverse factors may be considered for local radiotherapy utilising 24Gy over 12 fractions with curative potential.

A lower radiation dose of 4Gy split over 2 fractions may be appropriate in cases where a palliative approach is pursued or radiation toxicity requires particular consideration.

Expectant management ("watch and wait"/"watchful waiting") may also be pursued in selected cases after taking into consideration patient preferences, the potential for spontaneous remissions in FL, and the sometimes waxing and waning nature of the disease.

A progression-free survival (PFS) benefit has been demonstrated by the addition of rituximab with chemotherapy to radiotherapy. Such an approach is **not** recommended in this context due to the potential increased toxicity associated with chemotherapy. However, the addition of single agent rituximab to radiotherapy may yield additional benefit with a favourable toxicity profile.

(b) Advanced stage disease

The fundamental aspect of managing advanced disease is determining whether treatment is indicated. There is no overall survival benefit to initiation of anti-lymphoma therapy in advanced stage disease based solely on the presence of FL in the absence of other adverse factors.

The presence of the following are indications for treatment:

- rapidly progressive disease
- vital organ compression/compromise
- significant bone marrow infiltration/disease mediated haematopoietic suppression (including haemoglobin <100g/L and/or neutrophils <1.0 x 10⁹/L and/or platelets <100 x 10⁹/L)

- ascites
- pleural effusion (but not if small and clinically insignificant)
- B symptoms
- bulky disease including multiple (>3LN sites each >3cm in diameter) or single (>7cm in diameter) sites.

Reference should be made to treatment indicators from the EORTC and GELA (including the modified GELF criteria that consist of:

- high tumour burden (as evidenced by any of: bulky tumour with a greatest dimension of at least 7cm, splenomegaly with cranio-caudal dimension >20cm, 3 lymph node sites with a greatest dimension at each site of 3 cm in 3 distinct lymph node areas, organ compression, pleural effusion or ascites)
- B symptoms
- LDH level > ULN
- elevated beta-2-microglobulin level).

In the absence of these signs/symptoms then “watch and wait” expectant management can safely be pursued, while treatment of patients with advanced stage, low-tumour burden FL with single agent rituximab is an alternative option that should be considered given its favourable impact on disease progression (however, it is acknowledged that there may not be commissioning arrangements in place for rituximab induction monotherapy).

In contrast, some patients with bulky disease may be managed by watch and wait but are likely to have a shorter duration until progression that requires treatment.

Moreover, patients without any clear indication for treatment may prefer to be treated. Such cases should be counselled carefully regarding the lack of evidence for an overall survival benefit to initiation of treatment in this situation and their understandable concerns or worries regarding the “watch and wait” approach addressed as far as possible.

Similarly, patients with indications to recommend treatment may opt not to have treatment. They should be counselled and supported following their decision and closely monitored for evidence of disease progression.

(c) Systemic treatment regimens

Patients should be managed with combination immuno-chemotherapy. Immunotherapy options include:

- Obinutuzumab in combination with chemotherapy (for patients with FLIPI scores 2-5; NICE TA513)
- Rituximab in combination with chemotherapy (NICE TA243⁸) for all patients with FLIPI scores 0-1 or for patients with FLIPI scores 2-5, including if obinutuzumab is not considered appropriate or declined by patient.

No overall survival difference was demonstrated in the GALLIUM study that compared these two approaches, but a PFS improvement at 3 years was demonstrated in favour of obinutuzumab.

Chemotherapy options for use with either obinutuzumab or rituximab include:

- Bendamustine
- Cyclophosphamide, doxorubicin (hydroxydaunorubicin), vincristine (oncovin), prednisolone (CHOP), which should particularly be considered for FL that demonstrates clinically aggressive behaviour (or where transformation is suspected but unable to be proven)
- Cyclophosphamide, vincristine, prednisolone (CVP)
- Other chemotherapy regimens are typically not used first-line and are not recommended here as standard first-line approaches.

In frail patients, single agent rituximab or rituximab + chlorambucil are options.

(d) Consolidation of response

Maintenance options include:

- obinutuzumab following obinutuzumab-based induction treatment

or

- rituximab following rituximab-based induction treatment.

Both are given once every 2 months for 2 years and may be options if adequate response is achieved following respective first-line systemic therapy (NICE TA513 and TA226⁹).

It should be noted that the PRIMA study did not demonstrate an OS benefit for the addition of rituximab maintenance after first-line R-chemo (but did demonstrate a PFS improvement).

Also, the GALLIUM study has since demonstrated no difference in OS between obinutuzumab and rituximab maintenance. So, having considered disease response and patient preferences, not pursuing maintenance may be appropriate.

(e) Toxicity/co-morbidities/dose adjustments

Although these regimens are typically well tolerated, particular attention should be paid to the potential for therapy-related toxicity regarding these or other regimens in this patient population who frequently have additional medical issues. Careful clinical and organ function assessment should be undertaken, dose modifications applied to the treatment regimen as necessary, and appropriate supportive therapy (such as primary prophylactic G-CSF in selected cases) administered. Reference should be made to the MHRA Drug Safety Alert regarding off-licence use of bendamustine published on 20 July 2017. Consideration should also be given to the safety aspects of the GALLIUM study, which included increased frequency of serious adverse events associated with obinutuzumab compared to rituximab, as well as a higher number of non-relapse-related fatal events associated with bendamustine compared to CHOP or CVP chemotherapy.

5.1.2 Second- (and subsequent) line management

FL may relapse/progress and require (further) treatment. At progression or relapse, biopsy of index lesions is strongly recommended particularly to assess the possibility of disease transformation. If there is no evidence for transformation, there are multiple possible management approaches in FL in the second- (or subsequent) line setting. Important aspects to consider include:

- availability of clinical trials
- patient preference

- initial response duration
- previous treatment regimens
- toxicities
- patient fitness and co-morbidities
- emerging evidence supporting novel management approaches.

The stage of disease helps guide management. In selected patients (particularly the less fit) with limited stage disease, a palliative approach with local radiotherapy as 4Gy split in 2 fractions may be appropriate.

In advanced disease, particularly if low bulk and in the absence of other indications for treatment, selected patients may again be appropriate for “watch and wait” with close disease monitoring.

If systemic treatment is indicated at relapse/progression following initial management, an important consideration is whether a patient is a candidate for consolidation of response to second-line treatment by either high-dose chemotherapy with autologous haematopoietic stem cell transplantation (HDT + Auto-HSCT) or allogeneic haematopoietic stem cell transplantation (Allo-HSCT).

In fitter patients demonstrating a sufficient response to second-line therapy, Auto-HSCT should be considered to consolidate response. Rituximab administered following HDT + Auto-HSCT can improve PFS (Pettengell, *et al.*, 2014¹⁰). Occasionally, particularly in young, otherwise fit patients with rapidly progressive/early refractory disease, Allo-HSCT should be considered. Early liaison with the local transplantation centre is recommended.

(a) Systemic treatment regimens

The optimal systemic regimen at second- (or subsequent) line treatment is unknown and, where available, clinical trial enrolment should be considered. In the absence of a trial, determining the approach is particularly dependent on the preceding treatment regimen(s), response duration and patient fitness.

At second-line, an alternative regimen should be considered (particularly if remission duration was less than 12–24 months). Re-treatment with a previous regimen may be appropriate in selected cases who experienced good response duration and lack of significant toxicity, with appropriate consideration of fitness, co-morbidities and patient preference.

Rituximab¹¹ may be used as treatment for relapsed disease (NICE TA137).

Options for rituximab with chemotherapy at second- or subsequent line treatments include:

- BR
- RCHOP
- RCVP
- The purine analogue fludarabine and rituximab are efficacious in combination with cyclophosphamide (FCR), mitoxantrone (RFM), and cyclophosphamide + mitoxantrone (RFCM). These might be considered as possible alternative second-line regimens but may have significant toxicity (full courses are not recommended)^{5,7} and should be avoided where possible in Auto-HSCT candidates due to the potential adverse effect on haematopoietic stem cell harvesting.
- Rituximab monotherapy (NICE TA137)¹¹ or rituximab + chlorambucil may be appropriate in less fit cases.

Obinutuzumab with bendamustine may be used as treatment of patients who are refractory to rituximab-based first-line treatment (NICE TA472) (i.e. those who do not respond or progress within 6 months of treatment with rituximab).

- Other options to consider include early patient access schemes for emerging novel therapies. These typically require direct liaison with a pharmaceutical company.

(b) Consolidation of response

Maintenance of response may be considered with either:

- rituximab (NICE TA137)¹¹ given once every 3 months for 2 years if a complete or partial response is achieved following second-line systemic rituximab-based therapy; or
- obinutuzumab (NICE TA472) given once every 2 months for 2 years if disease responds to second-line systemic treatment with obinutuzumab with bendamustine.

In certain cases, consolidation through a stem cell transplantation approach may be appropriate (as above).

5.2 Follicular lymphoma: grade 3b

This should be managed as per diffuse large B-cell lymphoma (DLBCL) guidance.

5.3 Transformation

FL has a risk of undergoing histological high-grade disease transformation¹² to aggressive lymphoma (typically DLBCL) at a rate of around 3% of cases per year.¹³ If transformation is suspected, biopsy is recommended. Clinical indicators suggestive of possible transformation include:

- sudden rise in LDH to \geq twice upper limit of normal
- rapid discordant localised nodal growth (detected clinically or by imaging)
- new involvement of unusual extra-nodal sites (e.g. liver, bone, muscle, brain)
- new B symptoms
- new hypercalcaemia.

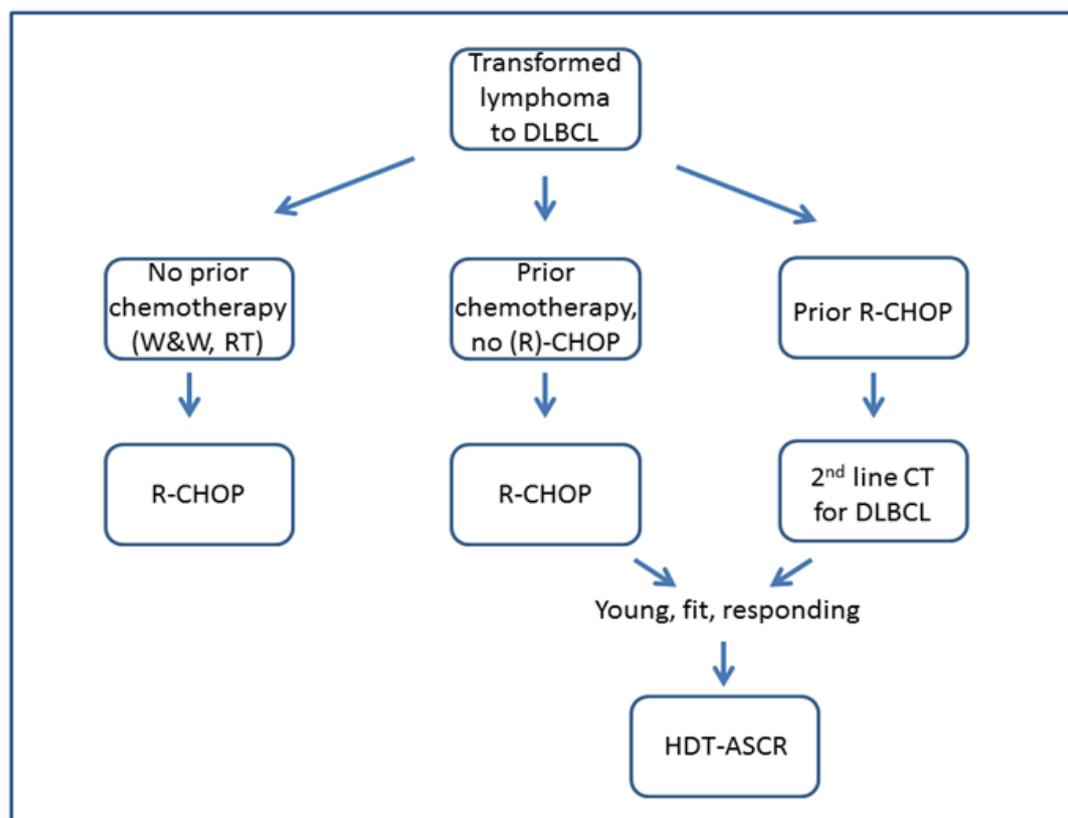
Transformation to DLBCL should initially be managed as per *de novo* DLBCL with the anthracycline containing RCHOP regimen. Consideration of enrolment in an appropriate clinical trial is encouraged.

Previous treatment regimens represent a complicating issue and if transformation develops after anthracycline exposure then alternative regimens should be considered (such as platinum-based combination chemotherapy regimens) as indicated in Figure 2.

Options for subsequent management of transformation to DLBCL that may be considered include:

- in previously treated patients, consolidation of response by HDT + Auto-HSCT in patients fit enough for this approach (early liaison with the local transplantation centre is recommended)
- in previously untreated patients (and in those in whom the disease is localised/limited stage), outcomes are usually better so HDT + Auto-HSCT may be avoided.

Figure 2 Proposed treatment algorithm: W&W, watch and wait; RT, radiotherapy; CT, chemotherapy; HDT-ASCR, high-dose therapy and autologous stem cell rescue.



Source: Silvia Montoto. Treatment of patients with transformed lymphoma. *Hematology*. 2015;2015(1):625–630.

In the rare cases in which FL undergoes transformation to a different high-grade histology, treatment should be specific to the respective aggressive lymphoma, as appropriate.

6 Follow-up Arrangements

The nature and frequency of follow-up review and investigations for patients will be somewhat tailored by their disease presentation, disease-related effects, co-morbidities, treatment type, treatment toxicities, and psycho-social factors.

Follow-up clinical reviews should include history taking and physical examination with particular reference to eliciting any evidence of progression/recurrence of disease (or development of treatment-related toxicities). Blood tests performed at scheduled review visits should include FBC; while LDH, renal, liver and bone profile tests may be indicated.

Given the long-term, ongoing risk of disease relapse, local pathways should be in place to ensure patients can promptly access their local lymphoma service for advice and review. Patients should be counselled as to when to re-present ahead of any scheduled review and should have a keyworker as a focal point of contact.

Patients with early progression of disease within the first 2 years after diagnosis (termed progression of disease at 24 months; POD24) or treatment have inferior outcomes and relatively close follow-up is recommended during these periods (consider reviews 3 to 4 times a year). Subsequent follow-up will typically continue long-term at a frequency of 1 to 3 times a year.

7 Specific or Miscellaneous Considerations

7.1 Follicular lymphoma in situ (FLIS)

This may be identified in excised lymph nodes. While progression to FL is uncommon, it is recommended that patients with FLIS are assessed for evidence elsewhere of overt FL.

7.2 Primary cutaneous follicular cell lymphoma (PCFCL)

PCFCL is a particularly indolent form of lymphoma that has excellent long-term survival and rarely disseminates from the skin.

Localised disease can typically be managed by excision or radiotherapy with curative intent.

For more extensive disease, observation may be appropriate particularly given the slow progression of this entity while radiation, intra-lesional steroids or topical agents may control disease; only rarely is systemic therapy indicated.

7.3 Primary intestinal follicular lymphoma

This most commonly occurs in the small intestine and its clinical course may be particularly indolent. It may be managed with the watch and wait expectant management approach initially and treated only if disease is symptomatic or progresses; survival is very good even without any treatment.

7.4 Irradiated cellular blood products

Patients treated with bendamustine and purine analogues (such as fludarabine) currently have a lifelong requirement to receive irradiated cellular blood products if such transfusions are ever needed.

The proportion of patients this applies to will increase given the incorporation of bendamustine into first-and subsequent line treatment options for FL.

Patients should be counselled and empowered to “check and challenge” regarding blood products if required and be provided with the NHSBT information booklet and wallet card, while the sticker is placed on any paper case-notes. Electronic case records should include notification of this requirement and blood bank systems should incorporate this information.

Local and national policies and procedures regarding the notification, need for and administration of irradiated blood products should be followed when patients have received these agents or haematopoietic stem cell transplantation.

7.5 Paediatric-type follicular lymphoma

Paediatric-type FL may occur in adults as well as children; is more common in males, lacks BCL2 rearrangements and demonstrates large, expansile, highly proliferative follicles. It typically presents as nodal disease of limited stage. Management may include excision alone followed by observation. It has a good prognosis with seemingly limited potential for progression.

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