Lancashire and South Cumbria Haematology CRG Guidelines for Follicular Lymphoma: October 2021

1.0 Scope

- This guideline applies to the management of follicular lymphoma grade 1, 2 and 3a. Grade 3b should be managed as for diffuse large B-cell lymphoma (DLBCL). It does not include primary cutaneous follicular lymphoma.

2.0 Pre-treatment evaluation

The following tests should be performed:

- FBC, U&Es, creat, LFTs, calcium, LDH, Igs/serum electrophoresis
- Beta-2-microglobulin
- Hepatitis B, C, HIV serology
- CT scan neck, thorax and abdomen
- MRI scan for assessment of disease in the oropharynx and Waldeyer's ring, sinuses and nasal cavity, brain and paraspinal areas where there is a suspicion of spinal cord compromise
- Bone marrow aspiration and trephine biopsy where the findings may influence therapy or knowledge of a FLIPI score is important.
- PET-CT scan if CT staging suggests stage I-II disease for which ISRT is being considered. Note PET-CT is able to identify additional sites of nodal and extranodal disease compared to conventional CT and should be considered in selected cases. PET-CT scan should not be performed to assess for high grade transformation.
- Calculate the FLIPI and FLIPI-2 scores - note the nodal groups used to determine the score do not correspond to those used in Ann Arbor staging classification (see appendix 1).

1.1 Post treatment evaluation

- On completion of treatment the patient must be reassessed clinically and abnormal tests at baseline should be repeated, followed by MDT discussion.

2 Treatment

2.1 Stage IA and IIA with contiguous nodal disease

- Standard treatment with ISRT 24Gy should be offered where involved nodes can be safely encompassed within a radiation field.
- Initial observation is an alternative option in asymptomatic patients if there is concern regarding the potential toxicity of RT, where disease appears to have been completely excised or patient choice. It should be noted that treatment-free long-term survival is possible in stage I-II disease with observation alone but also the outcomes after RT appear to have improved where PET has been used to stage.
- Symptomatic stage I-II disease that can not be managed with RT should be treated as for advanced stage disease.

2.2 Advanced stage, asymptomatic low volume disease

- Definitions of low volume disease according to revised GELF and UK criteria are given in appendix 2.
- Standard treatment should be observation. It is recognised that some patients may prefer to have treatment and they should be managed as in 2.3. Observation may also be appropriate for some patients who do not meet the criteria for low volume.

2.3 Advanced stage, symptomatic or non-low volume disease

- This will also apply to asymptomatic patients who do not meet the criteria for low volume disease.
- Initial treatment should be an anti-CD20 monoclonal antibody and chemotherapy. CVP x 6-8 cycles or bendamustine-R x 6 cycles with either rituximab or obinutuzumab will be used. Note obinutuzumab is approved for use only if the FLIPI score is ≥2.
- CHOP-R x 6 cycles may be considered where a clinical suspicion of high grade transformation in the absence of histological confirmation.
- Patients achieving at least PR should be offered maintenance rituximab or obinutuzumab every two months for two years.
- Chlorambucil +/- rituximab or single-agent rituximab are options for older patients and those with poor performance status and comorbidities precluding treatment with CVP or bendamustine.

2.4 Follicular lymphoma grade 3b

- Management as for DLBCL.

2.5 Relapsed and refractory follicular lymphoma

- Re-biopsy should be performed where possible.
- The quality and duration of response to previous treatment should be noted, in particular whether the patient has progressed within 24 months of initiating first line therapy (POD24).
- Patients without symptoms or standard indications for treatment may be observed.
- ISRT should be considered for local disease control where relapse is dominated by disease at one site that can be safely encompassed within a radiotherapy field
- If chemotherapy is required the choice of will depend on several factors including age, FLIPI score at presentation, performance status and cardiac function, comorbidity, initial treatment and duration of response/POD24, potential for high dose therapy at this point or in the future and availability of funding for new agents.
- The initial chemotherapy may be repeated if there was previously a good and prolonged response.
- Treatment will generally be rituximab and chemotherapy. Options are bendamustine-rituximab, CHOP/CVP-rituximab, lenalidomide-rituximab (R-squared regimen), fludarabine combinations e.g F-R, FC-R.
- If the patient did not respond or progressed during or up to 6 months after completing rituximab maintenance or rituximab-based chemotherapy consider bendamustine-obinutuzumab.

- If patients are frail and likely to tolerate chemotherapy poorly options are palliative chlorambucil or low dose etoposide +/- steroids, single agent rituximab.
- Patients achieving a second or third at least partial remission should be offered maintenance rituximab every three months for two years where maintenance rituximab was not given previously, or obinutuzumab maintenance every two months for two years after bendamustine-obinutuzumab.
- An intensive treatment approach involving consolidation with autologous or allogeneic stem cell transplantation should be considered for younger patients e.g <65-70 years, without significant comorbidity in second or later response, particularly with short initial remission duration e.g progression within 24 months of starting first-line treatment (POD24).
- Where transplantation is planned treatment at relapse should be an anthracycline-based regimen e.g R-CHOP, R-IVE, or other salvage regimens as used for relapsed DLBCL, e.g R-GDP, R-ICE, R-DHAP. Treatment with fludarabine should be avoided where autologous stem cell collection is planned.

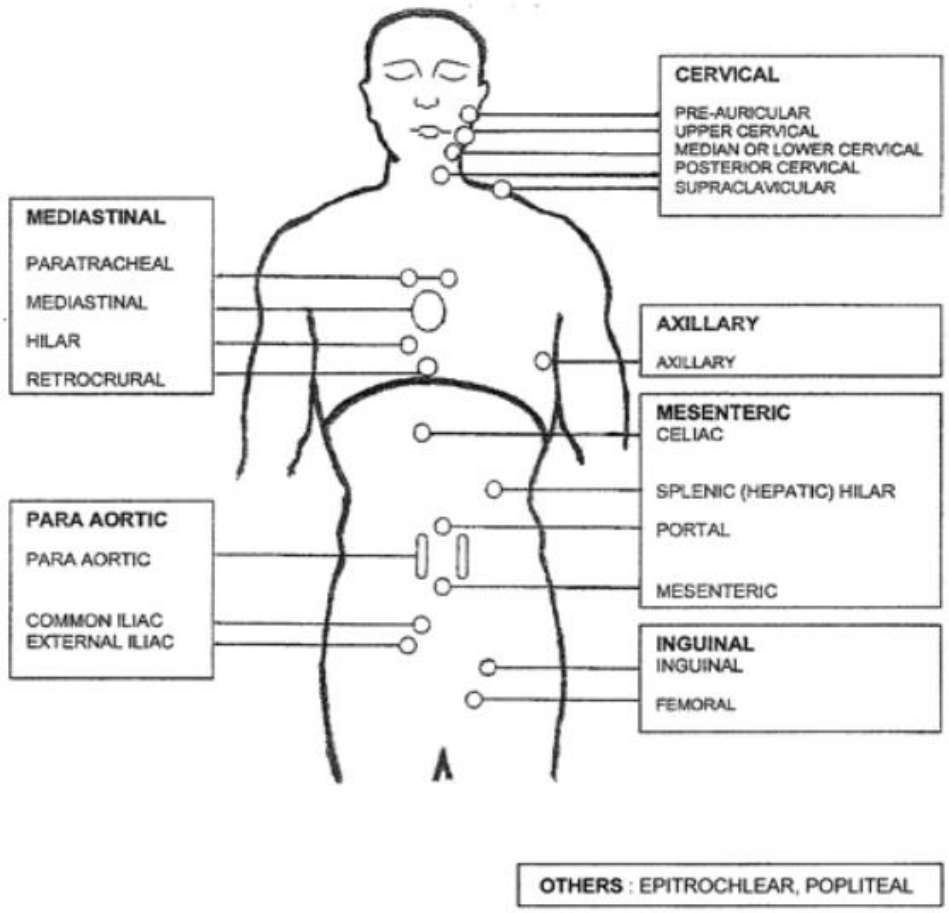
2.6 Transformed follicular lymphoma

- Patients with high-grade transformation at first diagnosis of follicular lymphoma, or who have received no prior chemotherapy for follicular lymphoma, should be managed as for a first presentation of de novo DLBCL.
- Anthracycline-naïve patients should receive R-CHOP x 6 cycles.
- Patients with prior anthracycline exposure who are candidates for autologous or allogeneic transplantation should receive other salvage regimens as used in relapsed DLBCL, e.g R-GDP, R-ICE. Where transplantation is not an option these regimens may be also be used but less intensive gemcitabine-based options e.g gemcitabine+/-rituximab, R-Gem-Ox, are alternatives.
- Consolidation with high dose therapy and autologous or allogeneic stem cell transplantation should be offered to younger patients e.g <65-70 years, without significant comorbidity.

Appendix 1: FLIPI scores in follicular lymphoma

Risk factors: >60yrs, Hb < 12, stage III/IV, >4 nodal sites, raised LDH

Nodal areas in the FLIPI Score (bilateral disease =2 points)	
Cervical:	Preauricular, upper cervical, median or lower cervical, posterior cervical, supraclavicular
Mediastinal:	Paratracheal, mediastinal, hilar, retrocrural
Axillary:	
Mesenteric:	Coeliac, splenic, hepatic, portal, mesenteric
Para-aortic:	Para-aortic, common iliac, external iliac
Inguinal:	Inguinal, femoral
Other:	Epitrochlear, popliteal



FLIPI	% of patients	5yr overall survival	10yr overall survival
Low (0-1 factor)	36%	90.6%	70.7%
Intermediate (2 factors)	37%	77.6%	51%
High (≥ 3 factors)	27%	52.5%	35.5%

FLIPI-2 score (Federico et al, 2009):

827 newly diagnosed patients treated for follicular lymphoma: 559 had rituximab, 49% had CHOP/CHOP-like chemo (73% of these with R), 8% had CVP (40% of these with R), 25% had fludarabine-based (71% with R), 4% had HD therapy.
Excluded patients managed with 'watchful waiting'

Risk factors: High beta-2 micrglobulin, BM involvement, longest diameter of involved node >6cm, Hb <12, age > 60yrs

FLIPI-2 (all)	N %	PFS 5yrs	OS 3yrs
Low risk (0 factors) 20%	20%	69%	99%
Intermediate risk (1-2 factors)	53%	55%	96%
High risk (3-5 factors)	27%	37%	84%
FLIPI -2 (treated with R)			
Low risk (O factors)		89%	
Intermediate risk (1 factor)		73%	
High risk (3-5 factors)		57%	

Appendix 2: Definitions of low volume disease in advanced follicular lymphoma

1. By revised GELF criteria low volume excluded if any of these are present:
    - B symptoms
    - ECOG performance status >1
    - Raised LDH
    - B_2 microglobulin >3ug/ml
    - Any nodal or extranodal mass with diameter ≥7cm
    - Involvement of ≥3 nodal sites each with a diameter of >3cm
    - Significant splenomegaly
    - Organ failure
    - Pleural effusions or ascites
    - Orbital or epidural involvement
    - Peripheral blood infiltration
    - Cytopenias i.e WBC <1.0, platelets < 100

2. NCRI criteria in the 'watch and wait' trial:
    - Normal LDH
    - Largest nodal mass < 7cm
    - No more than 3 nodal sites with a diameter of 3cm or more
    - No significant serous effusions clinically or on CT scan
    - Splenomegaly ≤16cm on CT scan

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