clinical practice guidelines

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Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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incidence and epidemiology

Follicular lymphomas (FLs) are the second most frequent subtype of nodal lymphoid malignancies in Western Europe. The annual incidence of this disease has rapidly increased during recent decades and has risen from 2–3/100 000 during the 1950s to 5–7/100 000 recently.

diagnosis and pathology/molecular biology

Diagnosis should be based on a surgical specimen/excisional lymph node biopsy. Core biopsies should only be carried out in patients without easily accessible lymph nodes (e.g. retroperitoneal bulk), keeping in mind the possible heterogeneity of FL grading difficult to appreciate on core biopsies. Re-biopsy may be required if material is not appropriate. Fine-needle aspirations are inappropriate for a reliable diagnosis.

The histological report should give the diagnosis according to the World Health Organization (WHO) classification. Grading of lymph node biopsies is carried out according to the number of blasts/high power field (Table 1). FL grade 3B (with sheets of blasts) is considered an aggressive lymphoma and treated accordingly [1], whereas grades 1, 2, and 3A should be treated as indolent disease [2]. Review, especially of grade 3A or 3B, by an expert haematopathologist is advised if the infiltration pattern is unusual (diffuse areas, even with small cells).

Extended ribonucleic acid profiling suggests a more favourable clinical course in cases with infiltrating T cells, in comparison to cases with unspecific macrophage bystander cells [3]; however, this technique is not yet applicable in clinical routine practice. In addition, several recent immunohistochemistry studies have reported conflicting data; hence, biological parameters are still investigational for prognostic assessment and are not yet suitable for clinical decision-making [4, 5]. However, if possible, additional biopsy material should be stored fresh frozen to allow additional molecular (currently still investigational) analyses.

staging and risk assessment

Since treatment substantially depends on the stage of the disease, initial staging should be thorough, particularly in the small proportion of patients with early stages I and II (10%–15%) (Table 2). Initial work-up should include a computed tomography (CT) scan of the neck, thorax, abdomen and pelvis, and a bone marrow aspirate and biopsy (Table 3). Positron emission tomography–computed tomography (PET-CT) scan is not mandatory but may contribute to identify areas with high standardised uptake values suspected of disease transformation [6], and may be used as baseline for response assessment (see below). In rare stage I/II cases, PET-CT scan may be also useful to confirm localised stage I/II disease before localised radiotherapy [IV, C].

A complete blood count, routine blood chemistry including lactate dehydrogenase, β2-microglobulin and uric acid as well as screening tests for human immunodeficiency virus (HIV) and hepatitis B and C are required. The staging is carried out according to the Ann Arbor classification system (Table 2), with mention of bulky disease >5 cm when appropriate.

For prognostic purposes, a 'Follicular Lymphoma-specific International Prognostic Index' (FLIPI, Table 4) has been established [I, A] [7, 8]. A revised FLIPI 2 (incorporating β2-microglobulin, diameter of largest lymph node, bone marrow involvement and haemoglobin level) has been recently suggested for patients requiring treatment [9].

treatment

first line

stage I–II. In the small proportion of patients with limited non-bulky stages I–II, radiotherapy (involved field, 24–36 Gy) is

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Table 1. Grading of follicular lymphoma

Grade	Description
1	≤5 blasts/high power field
2	6–15 blasts/high power field
3A	>15 blasts/high power field, centroblasts with intermingled centrocytes
3B	>15 blasts/high power field, pure sheets of blasts

Table 2. Ann Arbor classification

Stage	Area of involvement
I (I_E)	One lymph node region or extralymphatic site (I_E)
II (II_E)	Two or more lymph node regions or at least one lymph node region plus a single localised extralymphatic site(II_E) on the same side of the diaphragm
III (III_E, III_S)	Lymph node regions or lymphoid structures (e.g. thymus, Waldeyer's ring) on both sides of the diaphragm with optional localised extranodal site (III_E) or spleen (III_S)
IV	Diffuse or disseminated extralymphatic organ involvement
For all stages	
A	no symptoms
B	unexplained fever of >38°C, drenching night sweats; or loss of >10% body weight within 6 months

Table 3. Diagnostic work-up

History	B symptoms
Physical examination	Peripheral lymph nodes, liver, spleen
Laboratory work-up	Blood and differential count
	Optional: FACS, PCR for BCL-2 rearrangement
	LDH (suspected transformation), uric acid
	electrophoresis (optional: immune fixation)
	β2-microglobulin (FLIPI 2)
Serology	Hepatitis B, C and HIV serology
Imaging	Chest X-ray
	Abdominal ultrasound
	CT neck, chest, abdomen, pelvis
	MRT only in selected locations (CNS)
	Optional: PET
Bone marrow	Histology
	Cytology
	Optional: FACS, PCR for BCL-2 rearrangement
Toxicity	Electrocardiogram, cardiac ultrasound (before anthracyclines, ASCT)
	Creatinine clearance
	Optional: reproductive counselling in young patients

FACS, fluorescence-activated cell sorting; PCR, polymerase chain reaction; LDH, lactate dehydrogenase; FLIPI 2, Follicular Lymphoma International Prognostic Index 2; HIV, human immunodeficiency virus; MRT, magnetic resonance tomography; CNS, central nervous system; PET, positron emission tomography; ASCT, autologous stem-cell transplantation; BCL-2, B-cell lymphoma 2.

the preferred treatment having a curative potential, whereas the 2 × 2 Gy schedule is inferior and is merely palliative [II, B] [10]. In selected cases, watchful waiting or rituximab monotherapy may be considered to avoid the side-effects of radiation (e.g. cervical: sicca syndrome; abdominal: myeloablative suppression) [11, 12].

In stage I–II patients with large tumour burden or adverse prognostic features, systemic therapy as indicated for advanced stages should be applied; a radiation consolidation may be considered depending on tumour location and expected side-effects [IV, B] [12].

stages III–IV

induction: In the majority of patients with advanced stage III and IV disease, no curative therapy is yet established. Since the natural course of the disease is characterised by spontaneous regressions in 10%–20% of cases and varies significantly from case to case, therapy should be initiated only upon the occurrence of symptoms including B symptoms, haematopoietic impairment, bulky disease, vital organ compression, ascites, pleural effusion, or rapid lymphoma progression [I, A]. In four randomised trials, an early initiation of therapy in asymptomatic patients did not result in any improvement of disease-specific survival or overall survival (OS) [13]. In a recent study, early initiation of rituximab resulted in improved progression-free survival (PFS) (80% versus 48%, $P < 0.001$), but the benefit on long-term outcome has to be determined [14], and the benefit of rituximab maintenance in this setting appears doubtful [15]. Thus, the current therapeutic approach is based on clinical risk factors, symptoms and patient perspective (Figure 1).

If complete remission and long PFS is to be achieved, rituximab in combination with chemotherapy such as CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) or bendamustine should be used [I, B] [17, 18]. CVP (cyclophosphamide, vincristine and prednisone) combination results in inferior PFS, but no impact on OS was observed between these chemotherapy regimens [19]. Full courses of purine analogue-based schemes [FC (fludarabine and cyclophosphamide) or FM (fludarabine and mitoxantrone)] are not recommended due to higher haematological toxicities [19]. In case of (histological or clinical) characteristics of transformation to aggressive lymphoma, an anthracycline-based regimen should be preferred. Four prospective first-line trials, two salvage trials and a systematic meta-analysis confirmed an improved overall response, PFS and OS if rituximab was added to chemotherapy (Table 5) [20–23, 25].

A brief course of chemoimmunotherapy with full rituximab course is an alternative in elderly patients, with good efficacy and low toxicity [II, B] [24].

Antibody monotherapy (rituximab, radioimmunotherapy) or chlorambucil plus rituximab remains an alternative in patients with a low-risk profile or contraindications for a more intensive chemoimmunotherapy [III, B] [26, 27].

Table 4. 'Follicular Lymphoma-specific International Prognostic Index' (FLIPI) risk factors

Parameter	Definition of risk factors	
	FLIPI 1	FLIPI 2
Nodal sites	>4 lymph node regions (definition in [7])	Long diameter of largest lymph node >6 cm
Age	Above 60 years	Above 60 years
Serum marker	Elevated LDH	Elevated β2-microglobulin
Stage	Advanced (III–IV according to Ann Arbor classification)	Bone marrow involvement
Haemoglobin	<12 g/dl	<12 g/dl

With 0–1 risk factors, low risk; 2, intermediate risk; 3–5, high risk.
LDH, lactate dehydrogenase.

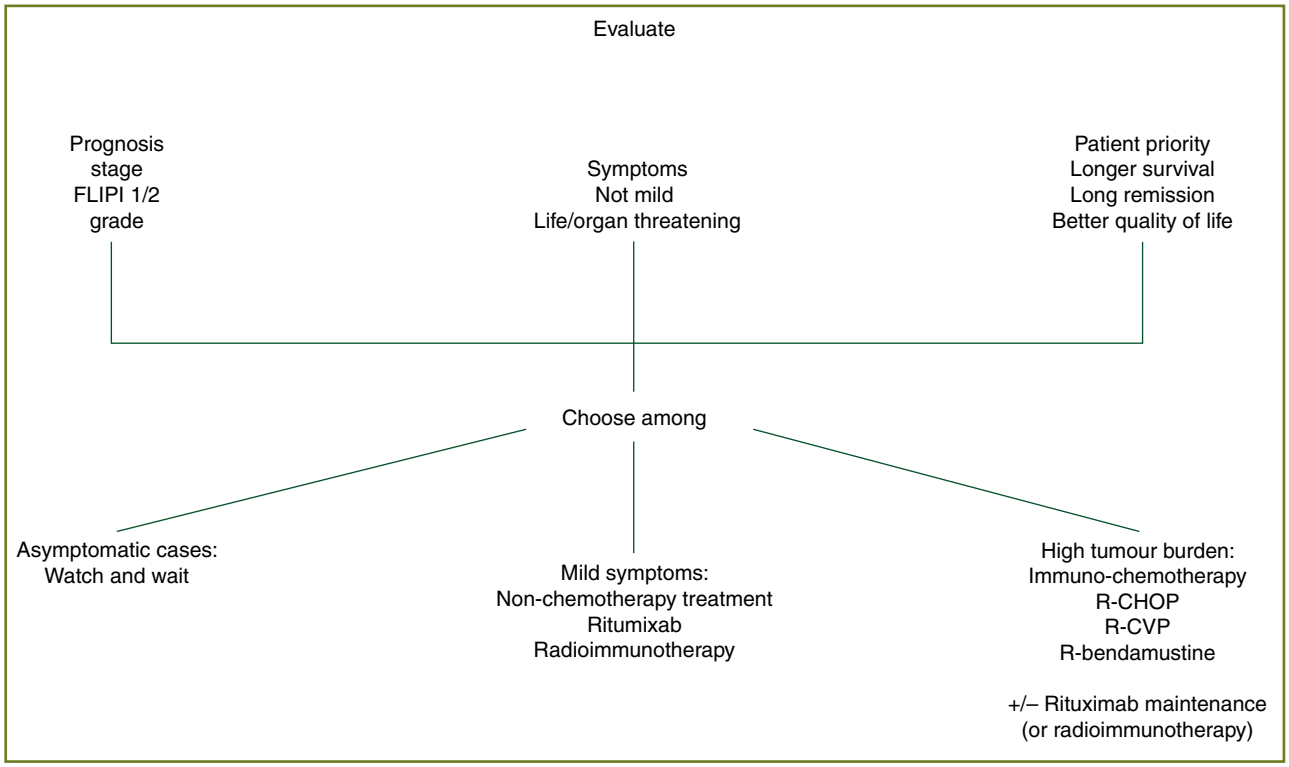

Figure 1. Therapeutic algorithm. Modified from [16]. Reproduced with permission of Informa Healthcare, copyright ©2009, Informa Healthcare.

In patients with positive hepatitis B serology, prophylactic antiviral medication is strongly recommended [I, A] [28].

consolidation/maintenance

Rituximab maintenance for 2 years improves PFS (75% versus 58% after 3 years, $P < 0.0001$) [I, B] [29], whereas a shorter maintenance period results in inferior benefit [29, 30].

Radioimmunotherapy consolidation prolongs PFS after chemotherapy only, but its benefit seems to be inferior in comparison to rituximab maintenance for 2 years [II, B] [31, 32].

Myeloablative consolidation followed by autologous stem-cell transplantation (ASCT) prolongs PFS after chemotherapy only, but its benefit after a rituximab-containing induction is minor and no OS has been observed [33]. Therefore, such an approach is not recommended in first-line therapy of responding patients [I, D].

relapsed disease

A repeated biopsy is strongly recommended with consideration of a PET-guided biopsy to rule out a secondary transformation into aggressive lymphoma.

As at first presentation, observation is an accepted approach in asymptomatic patients with low tumour burden.

Selection of salvage treatment depends on efficacy of prior regimens. In early relapses (<12–24 months), a non-cross-resistant scheme should be preferred (e.g. bendamustine after CHOP or vice versa). Rituximab should be added if the previous

Table 5. Combined chemoimmunotherapy in follicular lymphoma (first line)

Study	Total no. of patients	Median follow-up (months)	Overall response	Time-to-treatment failure (months)	Overall survival
Marcus et al. [20] R-CVP	321	53	81% ($P < 0.0001$)	27 ($P < 0.0001$)	83% (4 years) ($P = 0.029$)
Hiddemann et al. [21] R-CHOP	428	58	96%	NR ($P < 0.001$)	90% (2 years) ($P = 0.0493$)
Herold et al. [22] R-MCP	201	48	92% ($P = 0.0009$)	NR ($P < 0.0001$)	87% ($P = 0.0096$)
Bachy et al. [23] R-CHVP-IFN	358	99	81% ($P = 0.035$)	66 ($P = 0.0004$)	79% (8 years) ($P = 0.076$)
Rummel et al. [17] BR	139	34	93%	NR	84% (4 years)
Vitolo et al. [24] 4x R-FND + 4x R ± R maintenance	234	42	86%	NR	89% (3 years)

P: Significance levels in comparison to chemotherapy only.
R-CVP, cyclophosphamide, vincristine and prednisolone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; R-MCP, methotrexate, procarbazine and lomustine; R-CHVP-IFN, rituximab, cyclophosphamide, doxorubicin, etoposide, prednisone, interferon; BR, bendamustine–rituximab; R-FND, cyclophosphamide, vincristine and prednisolone; NR, no response.

Table 6. Recommended follow-up after end of therapy

Examination	Details	Year 1–2	Year 3–5	Year >5
History	B symptoms	Every 3 months	Twice annually	Annually
Physical examination	Particular: peripheral lymph nodes, liver, spleen	Every 3 months	Twice annually	Annually
Laboratory work-up	Blood and differential count	Every 3 months	Twice annually	Annually
	LDH	Every 3 months	Twice annually	Annually
Imaging	Abdominal ultrasound	Twice annually	Every 12 months	If progress suspected
	CT neck, chest, abdomen, pelvis	Optional: twice annually	Optional: every 12 months	If progress suspected

LDH, lactate dehydrogenase; CT, computed tomography.

antibody-containing scheme achieved >6 months duration of remission [IV, B].

In symptomatic cases with low tumour burden, a rituximab monotherapy may be applied.

Radioimmunotherapy (90yttrium-ibritumomab-tiuxetan) represents an effective therapeutic approach, especially in elderly patients with comorbidities not appropriate for chemotherapy. Otherwise, it should be applied preferably as consolidation [IV, B].

Rituximab maintenance for up to 2 years has a favourable side-effect profile and, based on a systematic meta-analysis, substantially prolongs PFS and OS in relapsed disease even after antibody-containing induction in patients who have not received antibody as first-line therapy [I, A] [34]. A second-line maintenance treatment has not been investigated in the setting of maintenance use in first-line and probably should not be used for those patients who had relapsed during their first maintenance period [IV, D].

High-dose chemotherapy with ASCT prolongs PFS and OS and should be considered, especially in patients with short-lived first remissions after rituximab-containing regimens, but its role has to be redefined in the rituximab era [I, B] [4, 35, 36]. A subsequent rituximab maintenance may achieve some benefit [II, B] [37].

In selected younger patients with high-risk profile or relapse after ASCT, a potentially curative allogeneic stem-cell transplantation (preferably with dose-reduced conditioning) may be discussed in relapsed disease, especially in early relapses and refractory disease [IV, B] [4].

response evaluation

Adequate radiological tests should be carried out midterm and after completion of chemotherapy. Patients with insufficient or lacking response [less than partial response (PR)] should be evaluated for early salvage regimens. PR patients may convert to complete response after post-induction treatment.

No consensus could be reached on the routine application of PET-CT for response evaluation. PET-CT identifies a small group (20%–25%) of patients with a poorer prognosis [38, 39]; however, optimal interventional approaches for this group of patients remain undefined.

Table 7. Consensus-driven recommendations outside clinical studies

Low tumour burden		High tumour burden	
Stage I/II	Stage III/IV	Stage III/IV (<65 years[a])	Stage III/IV (>65 years[a])
Front line			
Radiotherapy (involved field) 24–36 Gy In selected cases, watchful waiting	Watch and wait In symptomatic cases, consider rituximab monotherapy	Chemoimmunotherapy (e.g. R-CHOP, R-CVP, BR) In selected cases, rituximab monotherapy	Chemoimmunotherapy (e.g. R-CVP, BR, R-CHOP) or brief chemoimmunotherapy In selected cases, rituximab–chlorambucil rituximab monotherapy
–	–	CR/PR Rituximab maintenance (every 2 months, up to 2 years)	CR/PR Rituximab maintenance (every 2 months, up to 2 years)
Relapse/progress			
Watch and wait Rituximab monotherapy In selected cases, palliative radiation (e.g. 2 × 2 Gy)	Chemoimmunotherapy (e.g. BR, R-CHOP, R-CVP) In selected cases, rituximab monotherapy	Dependent on first-line regimen and remission duration • Chemoimmunotherapy (e.g. BR, R-CHOP, R-CVP) • Discuss high-dose consolidation with ASCT • Rituximab maintenance (every 3 months, up to 2 years) • Alternatively, radioimmunotherapy • In selected cases, discuss allogeneic transplantation	Dependent on first-line regimen and remission duration • Chemoimmunotherapy (e.g. BR, R-CHOP, R-CVP) • Rituximab maintenance (every 3 months, up to 2 years) • Alternatively, radioimmunotherapy

R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; R-CVP, cyclophosphamide, vincristine and prednisolone; BR, bendamustine–rituximab; CR, complete response; PR, partial response; ASCT, autologous stem-cell transplantation.
[a]According to biological age

Minimal residual disease (MRD) analysis by polymerase chain reaction at the end of the treatment is an independent predictor of long-term outcome, but should not guide therapeutic strategies outside clinical studies.

personalised medicine

As various therapeutic approaches may achieve durable responses in the vast majority of patients, the selection of optimal treatment is mainly based on clinical risk factors, symptoms and patient perspective (Figure 1). PET- and MRD-based tailored treatments are currently evaluated in studies but are not yet routine clinical practice.

Paediatric FL is an FL variant originally described in children, but occurs in adults as well. It is characterised by a localised disease, the absence of B-cell lymphoma 2 aberrations, lack of t(14;18), grade 3 and a high proliferation rate. It shows a much more indolent course and should be managed with less intensity, e.g. local therapy only, despite histologically more aggressive features [40].

New agents (including PI3 kinase inhibitors and Bruton's tyrosine kinase inhibitors) are currently being investigated [41]. Idelalisib has been approved by the United States Food and Drug Administration, and has been recommended for approval by European Medicines Agency for use for adult patients with follicular lymphoma that has not responded to two previous lines of treatments.

Table 8. Summary of recommendations

In localised stages: discuss radiation (24–36 Gy)
In advanced stages: treatment depends on clinical risk factors, symptoms and patient perspective
Standard approach in asymptomatic advanced cases: watch and wait
In advanced symptomatic cases
Combined chemoimmunotherapy for long-term remissions
Rituximab maintenance for consolidation
Relapse is frequently sensitive to conventional approaches
Autologous (and allogeneic) transplantation should be only discussed in relapse

follow-up and long-term implications

The following recommendations are based on consensus rather than on evidence (see Table 6):

- History and physical examination every 3 months for 2 years, every 4–6 months for 3 additional years, and subsequently once a year with special attention to transformation and secondary malignancies including secondary leukaemia [V, C].
- Blood count and routine chemistry every 6 months for 2 years, then only as needed for evaluation of suspicious symptoms.
- Evaluation of thyroid function in patients with irradiation of the neck at 1, 2 and 5 years.

Table 9. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a])

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, …), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a]By permission of the Infectious Diseases Society of America [42].

- Minimal adequate radiological or ultrasound examinations every 6 months for 2 years and annually thereafter. Regular CT scans are not mandatory outside clinical trials, especially if abdominal ultrasound is applicable. PET-CT should not be used for surveillance.
- MRD screening may be carried out in clinical studies but should not guide therapeutic strategies.

note

A summary of recommended treatment strategies outside clinical studies is provided in Table 7, and a summary of recommendations is provided in Table 8. Levels of evidence and grades of recommendation have been applied using the system shown in Table 9. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

conflict of interest

MD has reported scientific advisory board for Bayer, Celgene, Gilead, Janssen and Pfizer; support of academic trials for Celgene, Janssen, Mundipharma, Pfizer and Roche; speaker's honoraria: Celgene, Janssen, Mundipharma, Pfizer and Roche. MG has reported being a member of speaker's bureau for Roche, Mundipharma and Janssen. GS has reported honoraria for advisory board participations or conferences from Roche, Gilead, Celgene, Mundipharma, Amgen and Janssen. UV has reported advisory board for Roche; speakers' bureau for Roche, Mundipharma and Janssen. RM has not reported any potential conflicts of interest.

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