



# Follicular Lymphoma

## Guideline

Recommendations from the society for diagnosis and therapy of haematological and oncological diseases

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## 1 Definition and Basic Information

Follicular lymphomas belong to the indolent lymphomas. Earlier classifications referred to them as centrocytic-centroblastic lymphoma (cb-cc lymphoma), or as Brill-Symmers disease. The most frequent genetic alteration in follicular lymphoma is a balanced translocation  $t(14:18)(q32;q21)$  with deregulation of *BCL2*. This translocation is not found in every patient, and it is not specific for follicular lymphomas.

### 1.1 Epidemiology

Follicular lymphomas are the most common, indolent non-Hodgkin lymphomas (NHL) in Western Europe and the United States. It accounts for 20 - 35% of all patients with newly diagnosed NHL. The median age at diagnosis is 60 to 65 years, displaying a broad range of variation. Females are somewhat more often affected than males.

### 1.2 Factors

Epidemiological studies have identified the following risk factors:

- Exposure to benzene; in Germany, exposure is officially acknowledged as an occupational disease
- Occupational exposure to pesticides
- Smoking, including passive smoking

## 2 Early Detection

There is no evidence for efficient measures of early detection.

## 3 Clinical Picture

In 80% of patients, follicular lymphomas are diagnosed at an advanced stage. Typical features are:

- Persisting and/or progressive, mostly painless lymph node enlargements
- General symptoms (fever, weight loss, night sweats = so called "B symptoms")

- Hematocytopenia:
- Anemia - pallor and fatigue
- Thrombocytopenia - increased risk of bleeding, petechiae
- Granulocytopenia, hypogammaglobulinemia - increased susceptibility to infections

Extralymphatic infiltrations (e.g. ENT regions, gastrointestinal tract) might occur.

Alterations of laboratory values are not characteristic. LDH is within normal range in the majority of patients (approx. 70% of all patients).

## 4 Diagnosis

### 4.1 Diagnostics

The histological diagnosis should be based on the surgical extirpation of a suspicious lymph node. Lymph node biopsy may be taken alternatively in case the lymph nodes are not accessible (e.g. retroperitoneal lymph nodes). A fine-needle aspiration (cytology) is not sufficient. The histology report should state the diagnosis in terms of the WHO classification and specify grading (grade 1-2, 3A or 3B). Grade 3B follicular lymphomas are considered as aggressive lymphomas and treated according to the recommendations for "Diffuse Large B Cell Lymphomas".

As the therapy of indolent lymphomas depends on the stage of disease thorough diagnostics are essential prior to onset of therapy (staging).

Diagnostics include (initial examination):

- Medical history, particularly inquiry about B symptoms
- Physical examination
- Complete blood cell count, including leukocyte count with differential, reticulocytes
- ESR, electrophoresis, total protein
- AST (GOT), ALT (GPT), AP,  $\gamma$ -GT, bilirubin, creatinine, uric acid, blood sugar
- LDH,  $\beta_2$ -microglobulin
- Prothrombin Time (Quick's test), PTT
- Quantitative analysis of immunoglobulins, plus immune electrophoresis in case of suspected paraproteinemia
- Immunophenotyping of cell surface markers based on FACS analysis (only in case of leukemic course)
- Bone-marrow cytology\*, bone-marrow histology\*
- Cytogenetics (FISH, PCR) for (14;18) to distinguish from other indolent NHL\*\*

- CT of the neck/thorax/abdomen  
(alternatively: sonography for follow-up procedures)

\* not mandatory in case of “watch and wait” strategy“ when an advanced stage has already been corroborated by the existence of other lymphoma manifestations.

\*\* not mandatory: supplementary diagnostics if findings are not unambiguous

Positron emission tomography (PET) in the scope of initial staging is only being discussed for the localized Stages I/II, as no therapeutic consequences result in the much more frequent advanced stages of follicular lymphomas [1].

In order to identify patients with an increased risk for acute and/or late complications, tests of lung function, the heart (ECG, cardiac echo) and renal function are mandatory prior to onset of therapy.

## 4.2 Staging

Staging is performed according to the modified Ann Arbor Classification, see [Table 1](#).

**Table 1: Staging according to Ann Arbor Classification**

Stage	Criteria
I	Involvement of a single lymph node region (I/N), or of a single or localized extranodal site (I/E)
II	Involvement of two or more lymph node regions on the same side of the diaphragm (II/N), or involvement of an extranodal site or organ (II/E) and one or more lymph node regions on the same side of the diaphragm (II/N/E)
III	Involvement of two or more lymph node regions on both sides of the diaphragm (III/N), or involvement of localized extranodal foci and affected lymph nodes on both sides of the diaphragm (III/E or III/N/E)
III <sub>1</sub>	Subdiaphragmatic localization, limited to the spleen, celiac and/or portal lymph nodes, either alone or in combination
III <sub>2</sub>	Subdiaphragmatic localization with involvement of paraaortic, mesenteric, iliac, and/or inguinal lymph nodes, either alone or in combination
IV	Diffuse or disseminated involvement of one or more extralymphatic organs, with or without lymph node involvement

Lymphatic tissues include: lymph nodes, spleen, thymus gland, Waldeyer’s tonsillar ring, appendix. Cervical, axillary, or inguinal lymph node enlargements as well as enlargements of liver or spleen are each considered as one region.

Stages are additionally denoted “A” in the absence, and “B” in the presence of

- fever of unknown origin > 38°C
- night sweats
- unintentional weight loss > 10% within a period of 6 months

### 4.3 Risk Groups

The “Follicular Lymphoma International Prognostic Index” (FLIP Index) permits the differentiation of three prognostic subgroups [2], see [Table 2](#). The particular factors are:

**Table 2: Follicular Lymphoma International Prognostic Index (FLIP Index) [2]**

<ul style="list-style-type: none"><li>• &gt;4 affected lymph node regions</li><li>• Lactate dehydrogenase &gt; normal</li><li>• Age &gt; 60 years</li><li>• Stage III or IV</li><li>• Hemoglobin &lt;12g/dl</li></ul>
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One point is assigned to each risk factor. The relative risk is summarized in a score system:

Number of Risk Factors	Risk of Relapse	10-Year Survival Rate [in %]
0 - 1	low	62 - 71
2	intermediate	48 - 51
3 - 5	high	34 - 36

*Legend:  
Solal-Céligny 2004; van de Schans 2009;*

The FLIP Index was originally validated in patients who exclusively received chemotherapy [2]. However, studies revealed that the prognostic significance of the FLIP index also applies to patients treated with rituximab containing combination therapy [3]. At present, FLIPI should only be used for risk assessment, not for indication of therapy.

### 4.4 Differential Diagnosis

All inflammatory lymph node enlargements of bacterial or viral etiology (e.g. tuberculosis, toxoplasmosis, Epstein-Barr virus, cytomegalovirus, HIV) present possible differential diagnoses. In addition, differential diagnostic considerations must include, or if possible exclude, all other malignant lymphomas, lymph node metastases of solid tumors, thymomas, germinal cell tumors, or sarcoidosis.

## 5 Therapy

Patients with indolent lymphomas should be treated, whenever possible, within clinical trials. The selection of treatment depends on the stage of the disease. An algorithm for first-line is depicted in [Figure 1](#).

### 5.1 Stage I and II

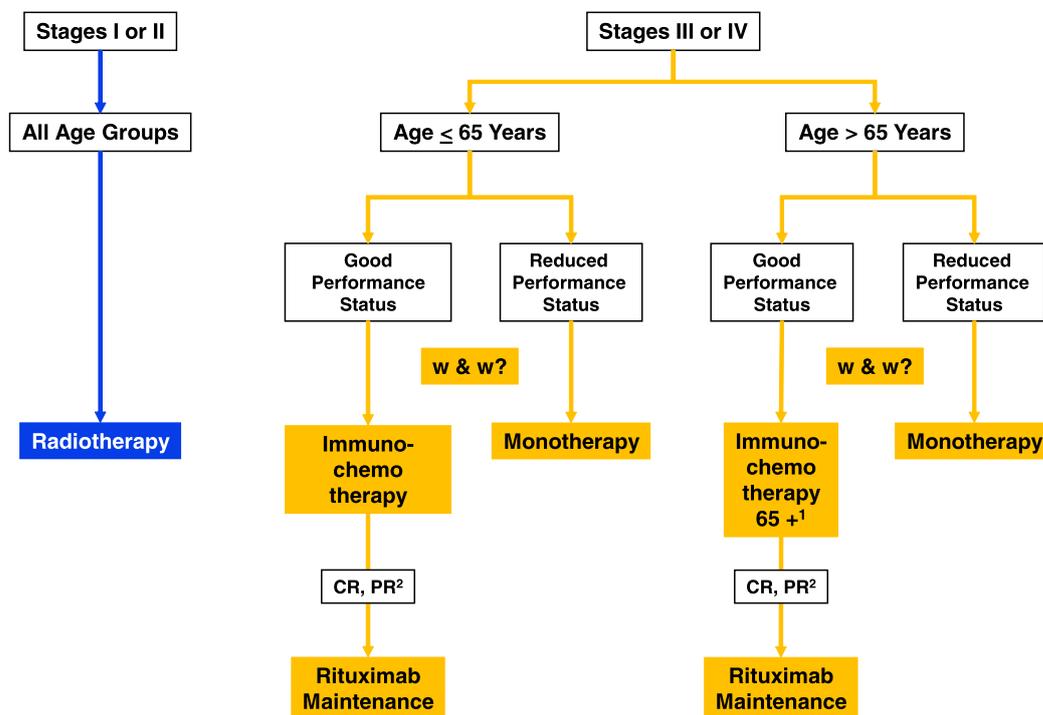
Local radiotherapy (“involved field”) with a total dose of at least 30 Gy is able to induce long term disease-free survival and potentially cure. After 10 years, about

85 percent of patients in Stage I (or LN < 2cm) and merely 35 percent in Stage II (or LN > 3-5 cm) remain disease-free. A current study investigates whether the additional administration of rituximab further improves the therapeutic outcome (*MIR Study of GLSG*).

## 5.2 Stage III and IV

A watch & wait approach is indicated in asymptomatic patients. Therapy should be initiated only in patients with lymphoma-associated symptoms (B symptoms, hematopoietic insufficiency, rapid lymphoma progression, compression of vital organs).

**Figure 1: First-Line Therapy**



Legend:

<sup>1</sup> age adjusted therapy;

<sup>2</sup> CR - complete remission, PR - partial remission

## 5.3 First-Line Therapy in Advanced Stages - Induction

First-line therapy can include the following components: induction, consolidation, and maintenance.

Immunochemotherapy, hence the combination of rituximab and chemotherapy, is the standard for medically fit patients [5].

R-CHOP: Standard therapy with good efficacy and sufficiently good tolerability: low stem-cell toxicity, therefore especially recommended for younger patients [4, 5]; however, risk for cardiotoxicity, neurotoxicity, and alopecia.

R-Bendamustine: Good efficacy combined with very good tolerability, therefore recommended especially to elderly patients [6, 7]; R-bendamustine is at least as effective as R-CHOP in patients with grade I and II follicular lymphomas.

R-MCP: Good efficacy and satisfactory tolerability; please note: high stem-cell toxicity, therefore recommended to elderly patients only [8].

R-FC(M): Only to be considered in case of predominantly leukemic course; increased risk of persistent pancytopenia; stem-cell mobilization may be hampered subsequent to more than 3-4 cycles.

Radioimmunotherapy (RIT): Monotherapy with monoclonal antibodies (rituximab, radioimmunotherapy (RIT) with Yttrium-90- Ibritumomab-Tiuxetan) represents a therapeutic alternative for patients who do not tolerate combined immunochemotherapy.

Different immunochemotherapy protocols are currently compared within active clinical trials.

In addition, oral chemotherapy (e.g. trofosfamide) is a therapeutic option in elderly medically non-fit patients.

Details regarding the therapeutic regimes are summarized in [Systemic Therapy - Protocols](#).

## **5.4 Consolidation / Maintenance**

1. Maintenance with rituximab (every 8 weeks 1 x 375 mg/m<sup>2</sup> over a period of 2 years) in patients responding to first-line immunochemotherapy significantly prolongs progression-free survival [15]. Overall survival was not improved in the most recent evaluation. Unexpected toxicity, in particular an increased rate of grade 3-4 infections, did not occur compared with the observation arm. Considering its high efficacy and low toxicity, maintenance therapy with rituximab is considered standard therapy in patients responding to first-line induction containing rituximab plus chemotherapy.
2. Interferon-alpha is an effective drug in patients with follicular lymphoma. However, these data were obtained prior to the introduction of rituximab into induction therapy. Interferon treatment is associated with severe side effects [16].
3. Consolidation in first remission with means of RIT leads to a significant prolongation of progression-free survival after induction chemotherapy. At present, data on the efficacy of RIT subsequent to initial rituximab-chemotherapy are limited.
4. The benefit of myeloablative high-dose therapy with autologous stem cell transplantation (ASCT) is currently not established in first remission. It is therefore recommended to perform myeloablative therapy with subsequent ASCT only within clinical studies.

More information on the drugs used is summarized in the Section Authorization Status.

## 5.5 Relapse

1. A further lymph node extirpation or biopsy is recommended prior to initiation of relapse therapy, in order to exclude secondary malignant transformation into an aggressive lymphoma. The risk of transformation is at about 3% / year.
2. Immunochemotherapy is the standard for induction also at the time of relapse (duration of remission > 6 months). The selection of the regime depends on primary therapy, e.g. in case of a pretreatment with R-CHOP a therapy with B-R or R-FC will be recommendable, in case of an initial therapy with B-R, for example, a therapy with R-CHOP. If the relapse occurs after initial rituximab/chemotherapy within a period of 6 months, refractoriness to rituximab has to be assumed and treatment with chemotherapy alone is recommended (e.g. bendamustine).

## 5.6 Consolidation / Maintenance after Relapse

1. For consolidation after successful induction, myeloablative high-dose therapy with subsequent autologous stem cell transplantation is an option particularly for younger patients and in cases of early relapses. However, only retrospective data are as yet available to prove the efficacy of ASCT after rituximab-containing salvage therapy [9].
2. Maintenance therapy with rituximab (one infusion every 3 months over a period of 2 years) significantly prolongs progression-free survival and is authorized for application in relapse treatment [10, 11].
3. Alternatively, RIT is to be discussed in this situation [12, 13].
4. Allogenic stem cell transplantation is not a standard for relapsed patients. However, it can be taken into consideration in young chemotherapy-sensitive patients who are in good general condition. Allogenic stem cell transplantation should preferentially be performed within clinical studies [14].

## 6 Follow-Up Proceedings

1. During and immediately after therapy (therapy monitoring, recognition of complications and adverse effects):
  - Medical history and physical examination
  - Complete blood cell count, including leukocyte count with differential, LDH
  - Functional liver and kidney parameters, if necessary, further laboratory diagnostics for therapy monitoring and checkup of adverse events
1. Therapy assessment (lymphoma reduction, adverse effects) after completion of one-half of the therapy cycles and after termination of cytostatic therapy, and in case of suspected progression or complication:
  - Medical history and physical examination

- Imaging of initially involved lymph node regions and extranodal localizations, as far as necessary for decision making
  - Exclusion of adverse events (functional liver and kidney parameters, if clinically suspect cardiac echo, chest x-rays, pulmonary function)
1. Follow-up examinations after termination of therapy in intervals of three months, after the third year in intervals of 6-12 months, as long term follow-up (remission surveillance and/or detection of relapse, early recognition of long-term toxicity, e.g. hypothyroidism after cervical radiotherapy, or emergence of secondary neoplasia):
    - Medical case history and physical examination
    - Complete blood cell count, including leukocyte count with differential
    - LDH, functional liver and kidney parameters
    - Imaging of initially involved lymph node regions and extranodal localizations
    - Extended diagnostics depending on initial findings and findings compiled in the course of the disease
  1. PET and/or PET-CT only in case of clinical consequences and/or in clinical studies (histological confirmation is mandatory in the event of positive findings!),
  2. Determination of the minimal residual disease (MRD) only within clinical studies.

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## 9 Drug Therapy of Tumors - Protocols

- [Follicular Lymphoma - Systemic Therapy - Protocols](#)

## 11 Links

### **Malignant Lymphoma Competence Network**

[www.kompetenznetz-leukaemie.de](http://www.kompetenznetz-leukaemie.de)

### **Deutsche Leukämie - und Lymphom - Hilfe e. V.**

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