

Follicular Lymphoma: Saudi Lymphoma Group's Clinical Practice Guidelines for Diagnosis, Management and Follow-up

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INTRODUCTION

Follicular lymphoma (FL) is the second most common subtype of non-Hodgkin's lymphoma (NHL) after diffuse large B-cell lymphoma (DLBCL). It accounts for approximately 20.3% of NHL cases among Saudi adults in 2011. It affected 42 (11.0%) males and 27 (9.3%) females out of 744 NHL cases. The annual number of cases of this disease has increased from 34 in 2001 to 69 in 2011.^[1]

METHODS

A committee comprising experts in hematology and medical oncology was established under the supervision of the Saudi Lymphoma Group and in collaboration with the Saudi Oncology Society. For collecting evidence, a literature search was carried out with relevant keywords using online database search engines such as PubMed/Medline, Web of Science and Scopus. In addition, expert opinion was considered when necessary.

The levels of evidence used in developing this guideline were as follows:

- Evidence level (EL)-1 (highest), evidence from Phase III randomized trials or meta-analyses
- EL-2 (intermediate), evidence from well-designed Phase II trials or Phase III trials with limitations
- EL-3 (low), evidence from retrospective or observational studies/reports and/or expert opinion.

This easy-to-follow grading system is convenient for readers to understand and allows an accurate assessment of the guideline's applicability in individual patients.^[2]

1. DIAGNOSIS

1.1. Excisional biopsy is the optimal approach for initial diagnosis of FL. Typically, it has a distinctly nodular growth pattern and is comprised of a mixture of centrocytes and centroblasts. Partially involved lymph nodes can also be seen (EL-1).^[3]

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- 1.2. Tumor grade [Table 1] and Follicular Lymphoma International Prognostic Index (FLIPI) are the best tools to predict the outcome of newly diagnosed patients (EL-1).^[4,5]
- 1.3. Almost all cases are positive for CD19, CD20, CD79a, CD21, and CD10 (60%), but lack expression of CD5, CD43, and CD11c. CD23 expression is variable but typically negative (EL-1).^[3,6,7]
- 1.4. BCL-2 protein is strongly positive in almost all Grades 1 and 2 subtypes. BCL-6 is expressed by at least some of the neoplastic cells in all FL tumors (EL-1).^[8,9]
- 1.5. Fine needle aspiration should be avoided for diagnosing FL, as it does not allow to determine the typical growth pattern and grading of the disease (EL-3).

2. STAGING WORKUP

- 2.1. Pathology review is essential for all referral cases.
- 2.2. Evaluations should include complete history (i.e., age; gender; comorbidities; B-symptoms; Eastern Cooperative Oncology Group performance status; hepatitis or human immunodeficiency virus [HIV] risk factors; medications; allergy to contrast media or drugs as well as social and family history) and physical examination (i.e., of lymph nodes, Waldeyer's ring, spleen, liver, central nervous system, gastrointestinal tract, lung, bone and skin).
- 2.3. Laboratory evaluations of all patients should include complete blood count (CBC) with differential count, liver function test as well as routine blood chemistry including lactate dehydrogenase (LDH), electrolytes and calcium.
- 2.4. Hepatitis serology (hepatitis B surface antigen, core antibody and surface antibody as well as hepatitis C virus), and PCR for hepatitis B surface antigen-positive or core antibody-positive cases.
- 2.5. Screening test for HIV is required
- 2.6. Computed tomography (CT) scan of neck and chest, abdomen and pelvis (CAP) should be performed in all cases.
- 2.7. Bone marrow biopsy is recommended as standard for staging FL patients.
- 2.8. Cardiac function (i.e., left ventricular function) should be assessed by echocardiogram before treatment in all patients receiving anthracycline-based chemotherapy.
- 2.9. Pregnancy test should be done for women of childbearing age.
- 2.10. Infertility and fertility preservation should be discussed depending on the type of treatment.

3. STAGE CLASSIFICATION OF FOLLICULAR LYMPHOMA

Staging of FL is based on imaging results.

- 3.1. Stages: Stages I or II versus Stages III or IV according to Ann Arbor staging system [Table 2] (EL-1).^[10,11]
- 3.2. B-symptoms is defined as recurrent unexplained fever of $>38^{\circ}\text{C}$, recurrent night sweats or unexplained $\geq 10\%$ loss of bodyweight in the past 6 months.
- 3.3. Bulky disease is defined as a tumor of diameter ≥ 10 cm on CT or a mass more than one-third the maximal transthoracic diameter on chest X-ray.
- 3.4. Limited stage is defined as Stages I or II and non-bulky disease, with no B-symptoms.
- 3.5. Advanced stage is defined as Stages III or IV, presence of B-symptoms or bulky disease regardless of the stage, except non-bulky Stage IB where B-symptoms are unlikely to be related to the disease and can be treated as limited stage.

4. MANAGEMENT OF FOLLICULAR LYMPHOMA

The limited stage (I/II) and advanced stage (III/IV) management have been distinguished as follows.

- 4.1. Limited stages
Only 15–30% of patients with FL have limited-stage disease at diagnosis.^[11,12]
 - 4.1.1. Stages I and II: Grades 1, 2 or 3a:
 - 4.1.1.1 A potential curative radiation therapy to all involved tumor sites is the preferred option. With this approach, the 10-year overall survival (OS) is the range of 60–80% (median, about 19 years) (EL-1).^[13]

Table 1: Classification of follicular lymphoma into three histologic grades

Grade	Definitions
Grade 1	0-5 centroblasts per high-power field
Grade 2	6-15 centroblasts per high-power field
Grade 3A	>15 centroblasts per high-power field, centroblasts with intermingled centrocytes
Grade 3B	>15 centroblasts per high-power field, pure sheets of blasts

Table 2: Ann Arbor staging classification

Stage	Definition
Stage I	Involvement of a single lymphatic region (I) or localized involvement of single extralymphatic organ or site (IE)
Stage II	Involvement of two or more lymphatic regions on the same side of the diaphragm (II) or localized involvement of a single extralymphatic organ or site and of one or more lymphatic regions on the same side of the diaphragm (IIE)
Stage III	Involvement of lymphatic regions on both sides of the diaphragm
Stage IV	Diffuse or disseminated involvement of one or more extralymphatic organs with or without lymphatic involvement

- 4.1.1.2 Adding rituximab or chemotherapy to radiation improves progression-free survival (PFS) but not OS (EL-1).^[14,15]
- 4.1.1.3 In patients with the non-bulky disease, if radiation is not feasible (in areas with expected significant radiation-induced morbidity), observation is a reasonable option (EL-3).^[16,17]
- 4.1.1.4 In patients with the bulky (>5 cm) limited stage disease, there is need for systemic treatment with immunochemotherapy used in advanced stages, or immunotherapy with or without radiation (EL-2).^[18]
- 4.1.2. Grade 3b:
- 4.1.2.1 The consensus is to treat this group of patients as those with DLBCL; i.e. combined immunochemotherapy with rituximab plus cyclophosphamide, vincristine, doxorubicin and prednisone (R-CHOP) for six cycles followed by two additional rituximab applications (EL-3).
- 4.1.2.2 Another option is three to four cycles of R-CHOP followed by radiation (EL-3).
- 4.2. Advanced stages
- 4.2.1 In patients with low tumor burden and advanced stages, it is not necessary to initiate chemotherapy. However, these patients need to be followed-up regularly, as some may experience spontaneous remission (EL-1).^[19]
- 4.2.2 In patients with high tumor burden and those fulfilling the GELF (Groupe d-Etude des Lymphomes Folliculaires)^[20] and/or BNLI criteria (British National Lymphoma Investigation),^[21] treatment should be initiated [Table 3] (EL-1).
- 4.2.3 The preferred regimen for advanced stages is combined immunochemotherapy with rituximab and bendamustine (RB) (EL-1).^[22,23] Obinutuzumab-based chemotherapy is another option (EL-1).^[24]
- 4.2.4 R-CHOP is also a viable first-line treatment option (EL-1).^[25]
- 4.2.5 Despite the high efficacy of the above-mentioned conventional first-line regimens, none are curative given that the 10-year OS of FL patients is about 70%.^[26]
- 4.2.6 In patients with significant comorbidities and those who are not candidates for such combination regimens but have slow tumor dynamic, a single agent rituximab is an acceptable option (EL-3). It has been found that patients receiving once-weekly rituximab for four consequent weeks had improved quality of life in asymptomatic, advanced-stage and low-tumor-burden FL patients compared with the observation only group (EL-1).^[19]
- 4.2.7 Similar results were observed when high-dose chemotherapy and autologous stem cell transplantation was performed in the management of newly diagnosed patients with high-risk FL. Prospective randomized and retrospective studies have found that these treatment options do improve the PFS but not OS (EL-1).^[27-30]
- 4.3. Maintenance with rituximab after first-line treatment
- 4.3.1 In the PRIMA trial, as compared with placebo, patients on maintenance with rituximab (375 mg/m² every 2 months for 2 years) after RCHOP and RCVP improved PFS (75% and 58%, respectively) (EL-1).^[31]
- 4.3.2 There are no supportive data from randomized trials to advocate the use of rituximab after RB (EL-3).
- 4.4. Management of relapsed and refractory disease
- 4.4.1 The tools to assess indication for initiating first-line treatment are generally also applicable in relapsed patients (EL-1).^[20,21]
- 4.4.2 Therefore, treatment would not immediately begin for all relapse cases, unless there is an indication [Table 3] (EL-1).^[20,21]
- 4.4.3 Lymph node biopsy should be performed if transformation is suspected. The positron emission tomography-CT may be useful in determining lymph node for biopsy (EL-3).
- 4.4.4 The most widely used regimens are single-agent rituximab, RCHOP,

Table 3: Indication for treatment in follicular lymphoma (any one parameter indicates need for treatment)

High tumor bulk is defined as
A tumor >7 cm in diameter
Three nodes in three distinct areas, each >3 cm in diameter
Symptomatic spleen enlargement
Organ compression
Ascites or pleural effusion
GELF criteria
High tumor bulk
Presence of systemic symptoms
Eastern Cooperative Oncology Group performance status >1
Serum lactate dehydrogenase or beta 2-microglobulin level above normal values

GELF – Groupe d-etude des lymphomes folliculaires

RCVP, rituximab, fludarabine and mitoxantrone (RFM), rituximab and bendamustine (RB) or obinutuzumab plus RB, depending on the first-line therapy and duration of response after the initial treatment (EL-1).^[19,22,25,32-34]

4.4.5 A few studies have found encouraging results with when novel agents such as lenalidomide or bortezomib have been used in combination with rituximab or immunochemotherapy (EL-2).^[35,36]

4.4.6 Radiation is also an option in selected patients with localized relapse (EL-3).

4.4.7 The role of maintenance therapy with rituximab in relapsed patients who had received rituximab as first-line therapy is unclear.^[37]

4.4.8. The role of autologous stem cell transplantation in relapsed patient is unclear.^[38]

4.4.9. Allogeneic transplantation should be limited to selected young patients. Non-myeloablative approach is preferred over myeloablative regimens, which should be limited to highly selected young patients with relapsed FL.^[39,40]

4.5. Follow-up

4.6.1. Every 3 months for 2 years, then every 6 months for 3 years, and then annually.

4.6.2. History and physical examination should be documented in each visit.

4.6.3. CBC with differential count and LDH evaluations should be requested in each visit.

4.6.4. Thyroid-stimulating hormone (TSH) test should be carried out at least once annually if the patient had received radiotherapy to the neck.

4.6.5. CT of neck and CAP is required after completion of therapy, and if the findings are normal, no further routine imaging is required.

4.6.6. Mammogram should be done for women who received chest radiotherapy, beginning 10 years after the diagnosis of FL or at the age of 40 years, whichever comes first.

4.6.7. Annual influenza immunization is recommended (EL-3).

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Conflicts of interest

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