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SPECIAL ARTICLE

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 lymphoid malignancies in Western Europe. The annual incidence of this disease has risen from 2-3/100 000 during the 1950s to 5/100 000 recently, without clear explanation.[1]

DIAGNOSIS AND PATHOLOGY/MOLECULAR BIOLOGY

Diagnosis should be based on a surgical specimen/excisional lymph node (LN) biopsy. Core biopsies should only be carried out in patients without easily accessible LNs (e.g. retroperitoneal), to evaluate possible transformation at such sites. Keeping in mind the possible heterogeneity of FL, histological grading can be difficult to appreciate on core biopsies and rebiopsy may be required if the material is not adequate. Fine-needle aspirations are insufficient for a reliable primary diagnosis.

The histological report should give the diagnosis according to the current World Health Organization classification.[2] Histological grading of LN biopsies is carried out according to average number of centroblasts/high-power field (Table 1). FL grade IIIb (with sheets of centroblasts) is considered an aggressive lymphoma and treated as such,[3] whereas grades 1, 2 and 3A should be treated as indolent disease.[4] Pathological review, especially of grade 3A or 3B, by an expert hematopathologist is advised.

Recommendations

- Diagnosis should be based on a surgical specimen/excisional LN biopsy. Core biopsies should only be carried out in patients without easily accessible LNs.
- Pathological review by an expert hematopathologist, especially for grade 3A or 3B, is advised.
- FL grade IIIb should be treated as an aggressive lymphoma, whereas grades 1, 2 and 3A should be treated as indolent disease.

STAGING AND RISK ASSESSMENT

Because treatment largely depends on the stage of the disease, initial staging should be thorough, particularly in the small proportion of patients with apparent early stages I and II (10%-15%) (Table 2). Initial work-up should include a bone marrow (BM) aspirate and biopsy of sufficient size (at least 20 mm), and a computed tomography (CT) scan of the neck, thorax and abdomen (Table 3). Positron emission tomography (PET)—CT improves the accuracy of staging for nodal and extranodal sites and thus is recommended for routine staging in FL [IV, C] (in such instances a separate diagnostic CT scan is not required).[5] A PET-CT scan is mandatory to confirm localised stage I/II disease before involved-site radiotherapy (ISRT).

A complete blood count, routine blood chemistry including immunoglobulin (Ig) levels, lactate dehydrogenase (LDH), β2-microglobulin (B2M) and uric acid as well as

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screening tests for human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) are required. Staging is carried out according to the Ann Arbor classification system (Table 2), with mention of bulky disease (>6 cm) when applicable.[6]

For prognostic purposes, a 'Follicular Lymphoma International Prognostic Index' (FLIPI; Table 4) has been established [I, A].[7] A revised FLIPI 2 (incorporating B2M, diameter of largest LN, BM involvement and haemoglobin level) and a simplified PRIMA FLIPI have been suggested for patients requiring treatment.[6,8]

Recently, a clinicogenetic risk score (m7-FLIPI) has been proposed based on the FLIPI score and mutation status of seven candidate genes (*EZH2, ARID1A, MEF2B, EP300, FOXO1, CREBBP* and *CARD11*)[9]; similarly, a 23-gene expression panel is also a reliable prognostic predictor.[10] Nevertheless, none of the techniques are as yet established in routine clinical practice. In addition, several recent immunohistochemical studies have reported conflicting data; hence, these biological parameters are not yet suitable for clinical decision making.[11] If possible, additional biopsy material should be stored (fresh frozen and paraffin fixed) to allow for future application of additional molecular analyses.

Recommendations

- Initial staging should be carried out according to the Ann Arbor classification system.
- Initial work-up should include a BM aspirate and biopsy and a CT scan of the neck, thorax and abdomen.
- A PET-CT scan is recommended for routine staging [IV, C] and is mandatory to confirm localised stage I/II disease before ISRT.
- A complete blood count, routine blood chemistry including Ig levels, LDH, B2M and uric acid as well as screening tests for HIV, HBV and HCV are required.
- FLIPI 1/2 and PRIMA prognostic index risk factors can be used for prognostic purposes.

TREATMENT OF LOCALISED FL (STAGES I-II)

In the small proportion of patients with limited low tumour burden stages I-II, radiotherapy (RT)-based treatment (ISRT, 24-30 Gy) is the preferred approach with a curative intent, whereas the 2 × 2 Gy schedule is less durably effective but might be used in special situations to minimise side-effects (e.g. lacrimal gland, parotid glands) [II, B].[12,13] Combination of RT with rituximab chemotherapy (ChT) improved progression-free survival (PFS) compared with RT alone [II, C].[14] A combination of localised irradiation with single-agent rituximab may potentially provide the best balance between efficacy and side-effects [III, B].[15] In selected cases (e.g. limited life expectancy, large abdominal fields), watch-and-wait or rituximab monotherapy may be considered [IV, B].[16,17]

In stage I-II patients with a high tumour burden, adverse clinical prognostic features or in cases where ISRT is not feasible (e.g. lung, liver), systemic therapy as indicated for advanced stages should be applied [IV, B].[17]

Recommendations

- In localised stages, 24-30 Gy ISRT is the preferred approach [II, B] and can be combined with single-agent rituximab [III, B].

Table 1. Grading of FL

Grade	Description
1	≤5 blasts/HPF
2	6-15 blasts/HPF
3A	>15 blasts/HPF, centroblasts with intermingled centrocytes
3B	>15 blasts/HPF, pure sheets of blasts

FL, follicular lymphoma; HPF, high-power field.

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Table 2. Ann Arbor classification

Stage	Area of involvement
I (I_E)	One LN region or extralymphatic site (I_E)
II (II_E)	Two or more LN regions or at least one LN region plus a localised extralymphatic site (II_E) on the same side of the diaphragm
III (III_E, III_S)	LN 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

Ann Arbor staging further classifies patients with lymphoma into A or B categories.
A: without symptoms.
B: with symptoms including unexplained fever of >38°C, drenching night sweats or loss of >10% body weight within 6 months.
E, extranodal; LN, lymph node; S, spleen.

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Table 3. Diagnostic work-up

History	B symptoms (see Table 2)
Physical examination	Peripheral LNs, liver, spleen
Laboratory work-up	Blood and differential count Optional: immunophenotyping of peripheral blood Coombs test (DAT) LDH, uric acid Electrophoresis (optional: immune fixation) B2M (FLIPI 2)
Serology	Hepatitis B, C and HIV serology
Imaging	CT neck, chest, abdomen Optional: PET-CT[a] Optional: abdominal ultrasound
Bone marrow[b]	Histology Cytology Optional: immunophenotyping
Toxicity	Creatinine clearance Electrocardiogram, cardiac ultrasound (before anthracyclines), pulmonary function (ASCT) Reproductive counselling in young patients

ASCT, autologous stem cell transplantation; B2M, β2-microglobulin; CT, computed tomography; DAT, direct antiglobulin test or direct Coombs test; FLIPI 2, Follicular Lymphoma International Prognostic Index 2; HIV, human immunodeficiency virus; LDH, lactate dehydrogenase; LN, lymph node; PET-CT, positron emission tomography-computed tomography.
[a] To confirm localised disease or in case of suspected transformation.
[b] In advanced stages: if clinically indicated.

Table 4. FLIPI and PRIMA-PI risk factors

Parameter	Definition of risk factors		
	FLIPI 1	FLIPI 2	PRIMA-PI
Nodal sites	>4 LN regions (definition in[6])	Long diameter of largest LN >6 cm	—
Age	>60 years	>60 years	—
Serum marker	Elevated LDH	Elevated B2M	Elevated B2M
Stage	Advanced stage III-IV (Ann Arbor classification)	Bone marrow involvement	Bone marrow involvement
Haemoglobin	<12 g/dl	<12 g/dl	—

FLIPI:
- low risk: 0-1 risk factor.
- intermediate risk: 2 risk factors.
- high risk: 3-5 risk factors.

PRIMA-PI:
- low risk: B2M normal and bone marrow not involved.
- intermediate risk: B2M normal and bone marrow involved.
- high risk: B2M elevated.

B2M, β2-microglobulin; FLIPI, Follicular Lymphoma International Prognostic Index; LDH, lactate dehydrogenase; LN, lymph node; PRIMA-PI, PRIMA prognostic index.

- In selected cases, watch-and-wait or rituximab monotherapy may be considered [IV, B].
- In stage I-II patients with a high tumour burden, adverse clinical prognostic features or in cases where ISRT is not feasible, systemic therapy as indicated for advanced stages should be applied [IV, B].

TREATMENT OF ADVANCED FL (STAGE III-IV)

First-line treatment

Induction. In the majority of patients with advanced stage III and IV disease, no curative therapy is yet established. Because 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 development of symptoms, including B symptoms (unexplained fever >38°C, drenching night sweats or loss of >10% body weight within 6 months), hematopoietic impairment, bulky disease, vital organ compression, ascites, pleural effusion or rapid lymphoma progression (Table 5) [I, A].

In three randomised trials conducted before the rituximab era, early initiation of therapy in asymptomatic patients did not result in any improvement in disease-specific survival or overall survival (OS) [I, D].[18] In a more recent study, early initiation of rituximab resulted in improved PFS (82% versus 36% at 3 years, $P < 0.0001$), but no survival benefit has been demonstrated to date,[19] and the benefit of rituximab maintenance in this setting appears doubtful.[20] Thus, the currently recommended therapeutic approach is based on clinical risk factors, symptoms and patient perspective (Figure 1).

Four prospective first-line trials, two salvage trials and a systematic meta-analysis confirmed an improved overall response rate, PFS and OS if rituximab was added to ChT (Table 6) [I, A].[21-25] If complete remission and long PFS are the therapeutic goals, rituximab in combination with ChT such as cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) or bendamustine should be used [I, B].[22,26] Cyclophosphamide, vincristine and prednisone (CVP) is inferior to these two regimens in terms of PFS but similar in OS.[27] If there is evidence (histological grade 3B or clinical signs of transformation) of more aggressive lymphoma, an anthracycline-based regimen (rituximab-CHOP) should be applied.

Extended anti-infectious prophylaxis should be considered, especially after bendamustine-containing induction therapy, as long-term CD4-positive T lymphocytopaenia has been observed [IV, B].[28] Awareness of a potential adverse impact on future cellular immunotherapeutic options, such as chimeric antigen receptor T-cell (CAR-T) treatment (see below), is important.

In a large randomised trial, the anti-CD20 antibody obinutuzumab (immunochemotherapy and maintenance for 2 years) resulted in significantly prolonged PFS in comparison with rituximab and, therefore, is considered as an additional, potentially more efficacious option, although no OS benefit was observed [I, B].[29] In another international phase III trial, lenalidomide—rituximab appeared to have a similar efficacy as immunochemotherapy [I, C].[30] Similarly, lenalidomide—rituximab achieve a longer PFS in comparison to rituximab monotherapy.[31]

Antibody monotherapy (rituximab, radioimmunotherapy) or chlorambucil plus rituximab remain alternatives for patients with a low-risk profile or when conventional ChT is contraindicated [III, C].[32,33]

Table 5. High tumour burden criteria in FL [modified from Groupe d'Etude des Lymphomes Folliculaires (GELF)[59] and British National Lymphoma Investigation (BNLI)][60]

Parameter	High tumour burden criteria
LNs	Bulk (>7 cm) or 3 LNs in distinct areas >3 cm
Spleen	Symptomatic splenic enlargement
(Potential) complication	Organ compression by tumour, pleural or peritoneal effusion
Serum markers	Elevated LDH or elevated B2M
Blood count	Leukaemic phase ($>5 \times 10^9$/l) Cytopaenia (neutrophils $<1 \times 10^9$/l, platelets $<100 \times 10^9$/l)
Clinical presentation	B symptoms (see Table 2)

B2M, β2-microglobulin; FL, follicular lymphoma; LDH, lactate dehydrogenase; LN, lymph node.

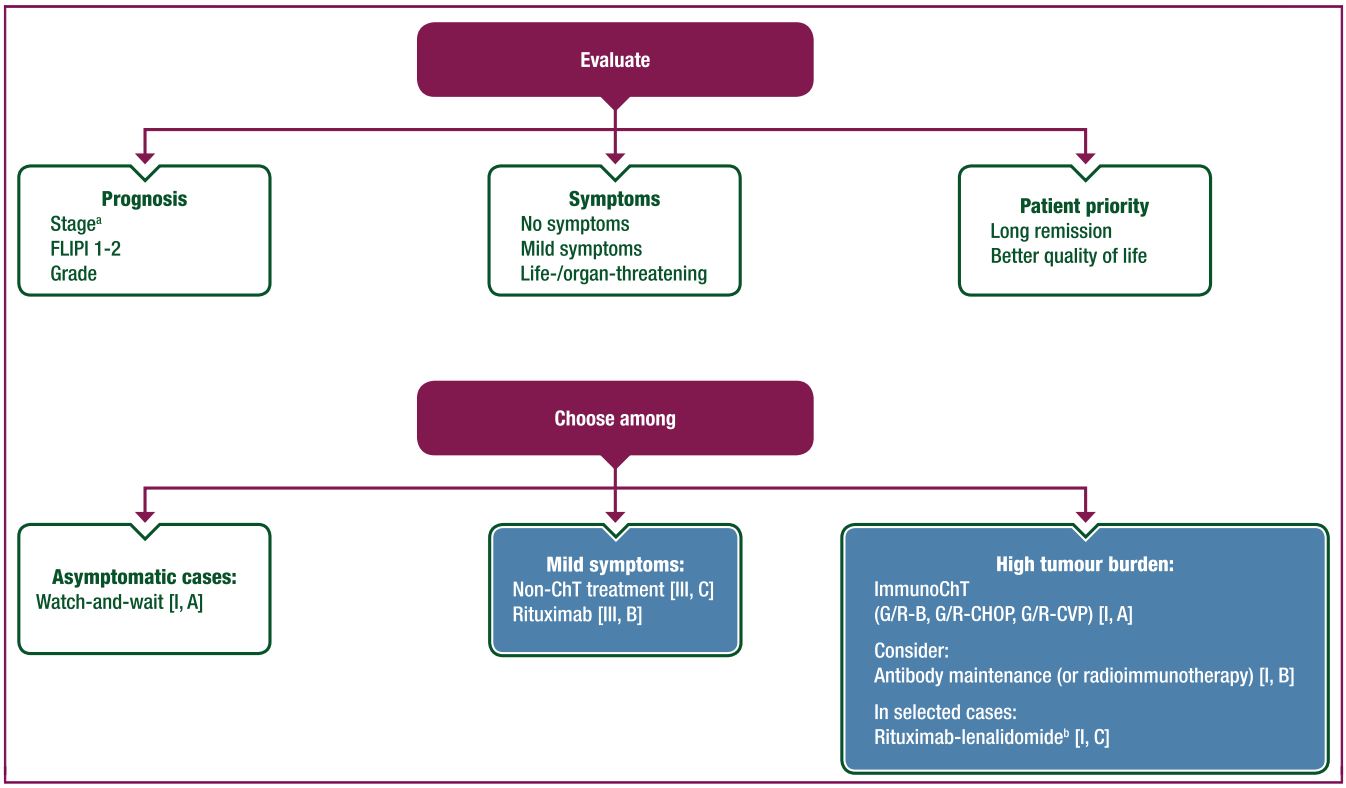

Figure 1. Therapeutic treatment algorithm for FL.
B, bendamustine; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; ChT, chemotherapy; CVP, cyclophosphamide, vincristine, prednisolone; FL, follicular lymphoma; FLIPI 1-2, Follicular Lymphoma International Prognostic Index 1-2; G, obinutuzumab; R, rituximab.
[a] According to the Ann Arbor classification system (Table 2).
[b] Off-label.

In patients with positive hepatitis B serology including occult carrier (hepatitis B surface antigen negative and anti-core antibody positive), prophylactic antiviral medication up to 2 years beyond the last rituximab exposure is strongly recommended, although strict monitoring of HBV, DNA and liver enzymes represents another option in regions where HBV infection is endemic [I, A].[34]

Consolidation/maintenance. Rituximab maintenance every 2 months for 2 years improves PFS after various induction regimens (median PFS 10.5 years versus 4.1, $P < 0.0001$), but there is no impact on OS [I, B],[35-37] whereas a shorter maintenance period results in inferior benefit.[32]

Radioimmunotherapy consolidation also prolongs PFS after ChT, but its benefit seems to be inferior in comparison to rituximab maintenance for 2 years [II, B].[38,39] However, a recent study showed an improved PFS but no difference in OS and an increased cumulative risk of myeloid malignancies after iodine-131 (^{131}I)—tositumomab radioimmunotherapy consolidation in comparison to rituximab in combination with ChT.[40]

Myeloablative consolidation followed by autologous stem-cell transplantation (ASCT) prolongs PFS after ChT, but its benefit after a rituximab-containing induction is minor and no OS advantage has been observed.[41] Therefore, such an approach is not recommended in first-line therapy of responding patients [I, D].

Relapsed disease

At suspected disease relapse or progression, it is strongly recommended to obtain a new confirmatory biopsy in order to exclude transformation to an aggressive lymphoma. It may be useful to perform a PET-guided biopsy of the site with highest tracer intensity uptake (maximum standardised uptake value).

Observation is an accepted approach in asymptomatic patients with low tumour burden and confirmed follicular histology at relapse or progression.

Induction. Selection of the salvage treatment regimen depends on efficacy and duration of response of prior regimens and stage at relapse. Localised symptomatic disease may be managed with low-dose ISRT (2 × 2 Gy). In early systemic relapses (<12-24 months), a noncross-resistant regimen is preferred (e.g. bendamustine after CHOP or vice versa). Other options, including fludarabine-based, platinum-based or alkylating agents-based regimens, could also be useful. Rituximab should be added if the previous antibody-containing scheme achieved >6-12-month duration of remission [IV, B]. In rituximab-refractory cases or remissions lasting <6 months, obinutuzumab—bendamustine (plus obinutuzumab maintenance) has been shown to improve both PFS and OS in comparison with bendamustine only [I, B].[42]

Table 6. Combined immunochemotherapy in FL (first line)

Study	Total number of patients	Median follow-up (months)	Overall response (%)	Time to treatment failure (months)	Overall survival (%)
Marcus et al. 2008[21]					
R-CVP	159	53	81 ($P < 0.0001$)	27 ($P < 0.0001$)	83 (4 years) ($P = 0.029$)
Hiddemann et al. 2005[22]					
R-CHOP	223	58	96	NR ($P < 0.001$)	90 (2 years) ($P = 0.0493$)
Herold et al. 2007[23]					
R-MCP	105	48	92 ($P = 0.0009$)	NR ($P < 0.0001$)	87 (4 years) ($P = 0.0096$)
Bachy et al. 2013[24]					
R-CHVP-IFN	175	99	81 ($P = 0.035$)	66 ($P = 0.0004$)	79 (8 years) ($P = 0.076$)
Rummel et al. 2017[26,37]					
BR	139	34	93	78 (median)	NR (median)
BR + R maintenance	595	34	90	NR (median)	NR (median)
Luminari et al. 2018[27]					
R-CVP	178	84	88	38%	85%
R-CHOP	178	84	93	45% ($P = 0.033$)	83% (n.s.)
R-FM + R maintenance	178	84	91	49% ($P = 0.016$) (8 years)	79% (n.s.) (8 years)
Bachy et al. 2019[35]					
R-CHOP/CVP/FM	1018	118	n/a	35% (10 years)	80 (10 years)
R-CHOP/CVP/FM + R maintenance				51% (10 years) ($P < 0.001$)	80 (10 years) (n.s.)
Marcus et al. 2017[29]					
R-CHOP/CVP/B + R maintenance	601	34	86.9	73.3% (3 years)	92.1 (3 years)
G-CHOP/CVP/B + G maintenance	601	34	88.5	80.0% (3 years) ($P = 0.001$)	94.0 (3 years) (n.s.)
Morschhauser et al. 2018[30]					
R-CHOP/BR + R maintenance	517	38	84	78% (3 years)	94 (3 years)
R-lenalidomide + R maintenance	513	38	89	77% (3 years) (n.s.)	94 (3 years) (n.s.)

P corresponds to significance levels in comparison to ChT only.
B, bendamustine; BR, bendamustine-rituximab; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; ChT, chemotherapy; CHVP, cyclophosphamide, doxorubicin, etoposide, prednisone; CVP, cyclophosphamide, vincristine, prednisolone; FL, follicular lymphoma; FM, fludarabine, mitoxantrone; G, obinutuzumab; IFN, interferon; MCP, mitoxantrone, chlorambucil, prednisone; n/a, not applicable; NR, not reached; n.s., not significant; R, rituximab.

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

In relapsed FL, lenalidomide plus rituximab was superior to rituximab monotherapy in terms of response rates and PFS with a trend towards improved OS[43]; thus, lenalidomide—rituximab may be considered, especially for those patients with short remissions after ChT [II, B].

Radioimmunotherapy [yyttrium-90 (^{90}Y) ibritumomab-tiuxetan] may represent an effective therapeutic approach in elderly patients with comorbidities not appropriate for ChT [IV, B].

In later relapses, monotherapy is an established option with palliative intent, but long-term survival can be achieved [III, C]. The phosphoinositide 3-kinase (PI3K) inhibitor idelalisib has been registered in double-refractory FL, based on a phase II study,[44] but is hampered by infections, late-onset colitis and pulmonary toxicity (atypical pneumonias/pneumonitis); therefore, anti-infectious prophylaxis (co-trimoxazole/acyclovir) and cytomegalovirus (CMV) monitoring are strongly recommended [II, B]. Recent data suggest that other PI3K inhibitors display a more favourable toxicity profile [IV, B].[45]

Consolidation/maintenance. Rituximab maintenance every 3 months 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 salvage [I, A].[46] Nevertheless, second-line maintenance treatment has not been investigated in patients who have received antibody maintenance as part of their first-line therapy and probably should not be used for those patients who have relapsed during their first maintenance period, but is reasonable for other patient subsets [IV, D].

Based on the results of phase II or observational studies, high-dose ChT with ASCT prolongs PFS and potentially OS and should be considered, especially in patients who experience brief first remissions (<2-3

years) after rituximab-containing regimens, which usually have a much worse long-term outcome [II, B].[47-50] Subsequent rituximab maintenance achieves some improvement in PFS [II, B].[51]

In selected younger patients with later relapses with a high-risk profile or relapse after ASCT, a potentially curative allogeneic stem cell transplantation (alloSCT) (preferably with dose-reduced conditioning) may be considered, especially in patients with early relapse and refractory disease, whereas alloSCT in first relapse may worsen OS [IV, B].[52]

Innovative approaches

In recent years, new approaches, including inhibitors of the B-cell signalling pathway and other targeted agents, have shown activity in phase II studies, but to date their benefit has yet to be confirmed in randomised phase III studies. The combination of bortezomib—rituximab has shown only a minor benefit compared with antibody monotherapy and is therefore not recommended [I, D].[53] Treatment with CD19-specific CAR-T can lead to long-term remissions in relapsed FL but this approach currently remains reserved for transformed FL due to toxicities (registered indication), and its use in indolent lymphoma is limited to clinical trials for refractory disease or relapsing patients with poor prognostic features [IV, B].[54]

Response evaluation

Appropriate structural imaging evaluation should be carried out mid-treatment and after completion of ChT. Patients with an inadequate response (less than partial response) should be evaluated for early salvage regimens. Patients with a partial response may convert to complete response under rituximab maintenance.

PET-CT after completion of induction ChT has been recommended for prognostic reasons, as persistent PET positivity (using appropriate Deauville assessment scale) identified a small group (20%-25%) of patients with an adverse prognosis,[55] but therapeutic consequences remain undefined [II, B]. There is no established role for interim PET-CT scan.

Minimal residual disease (MRD) analysis by polymerase chain reaction (PCR) at the end of the treatment and during follow-up is an independent predictor of long-term outcome but should not guide therapeutic strategies outside of clinical studies. Thus far, few data are available on the use of circulating tumour DNA in FL.

Recommendations

- In asymptomatic advanced cases, watch-and-wait is the standard approach [I, A].
- Therapy should be initiated only upon the development of symptoms, including B symptoms, hematopoietic impairment, bulky disease, vital organ compression, ascites, pleural effusion or rapid lymphoma progression [I, A].
- Obinutuzumab or rituximab in combination with CHOP or bendamustine should be used if complete remission and long PFS are the therapeutic goals [I, B]. If there is evidence of more aggressive clinical course, obinutuzumab/rituximab-CHOP should be applied. Extended anti-infectious prophylaxis should be considered after bendamustine-containing induction therapy [IV, B].
- Antibody monotherapy (rituximab, radioimmunotherapy) or chlorambucil plus rituximab remain alternatives for patients with a low-risk profile or when conventional ChT is contraindicated [III, C].
- Rituximab maintenance every 2 months for 2 years is recommended after immunochemotherapy [I, B].
- Alternatively, radioimmunotherapy consolidation may be considered after ChT [II, B].
- Myeloablative consolidation followed by ASCT after ChT is not recommended in first-line therapy of responding patients [I, D].
- In patients with positive hepatitis B serology including occult carrier, prophylactic antiviral medication up to 2 years beyond the last rituximab exposure is strongly recommended [I, A].
- At suspected disease relapse or progression, it is strongly recommended to obtain a new confirmatory biopsy.
- Localised symptomatic disease may be managed with low-dose ISRT (2×2 Gy).
- In early systemic relapses ($<$12-24 months), a noncross-resistant regimen is preferred.
- Rituximab should be added if the previous antibody-containing scheme achieved $>$6-12-month duration of remission [IV, B]. In rituximab-refractory cases or remissions lasting $<$6 months, obinutuzumab—bendamustine (or other ChT regimen) plus obinutuzumab maintenance is recommended [I, B].
- Rituximab maintenance every 3 months for up to 2 years is recommended [I, A].
- High-dose ChT with ASCT should be considered in patients who experience brief first remissions after rituximab-containing regimens [II, B].
- In relapsed FL, lenalidomide plus rituximab may be considered for patients with short remissions after ChT [II, B].
- In symptomatic cases with low tumour burden, rituximab monotherapy may be applied.
- Radioimmunotherapy may be considered in elderly patients with comorbidities [IV, B].
- In later relapses, a non-ChT approach is recommended [III, C]: lenalidomide plus rituximab [II, B]; idelalisib in double-refractory cases only with anti-infectious prophylaxis (co-trimoxazole/acyclovir) and CMV monitoring.
- In selected younger patients with later relapses with a high-risk profile or relapse after ASCT, alloSCT may be considered [IV, B].

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,

Table 7. Recommended follow-up after end of therapy

Examination	Details	Year 1-2	Year 3-5	Year >5
History	B symptoms (see Table 2)	Every 3-6 months	Every 6-12 months	Annually
Physical examination	Particular: peripheral LNs, liver, spleen	Every 3-6 months	Every 6-12 months	Annually
Laboratory work-up	Blood and differential count	Every 3-6 months	Every 6-12 months	Annually
	LDH, IgG levels	Every 3-6 months	Every 6-12 months	If progression suspected
Imaging (optional)	Abdominal ultrasound	Every 6 months	Every 12 months	If progression suspected
	CT neck, chest, abdomen	Every 6-12 months	Every 12-24 months	If progression suspected

CT, computed tomography; IgG, immunoglobulin G; LDH, lactate dehydrogenase; LN, lymph node.

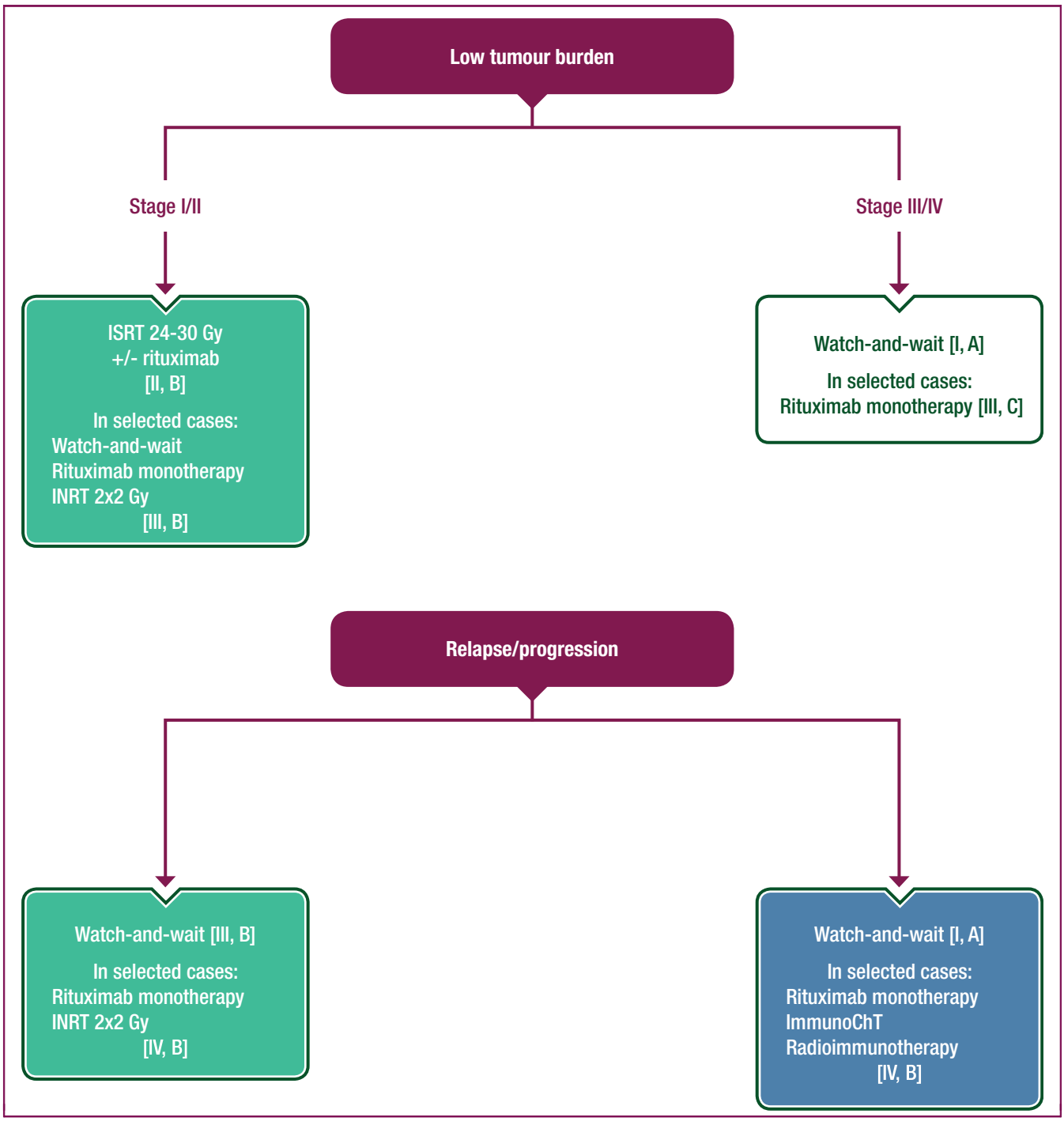

Figure 2. Consensus-driven recommendations—low tumour burden FL.
ChT, chemotherapy; FL, follicular lymphoma; INRT, involved-node radiotherapy; ISRT, involved-site radiotherapy.

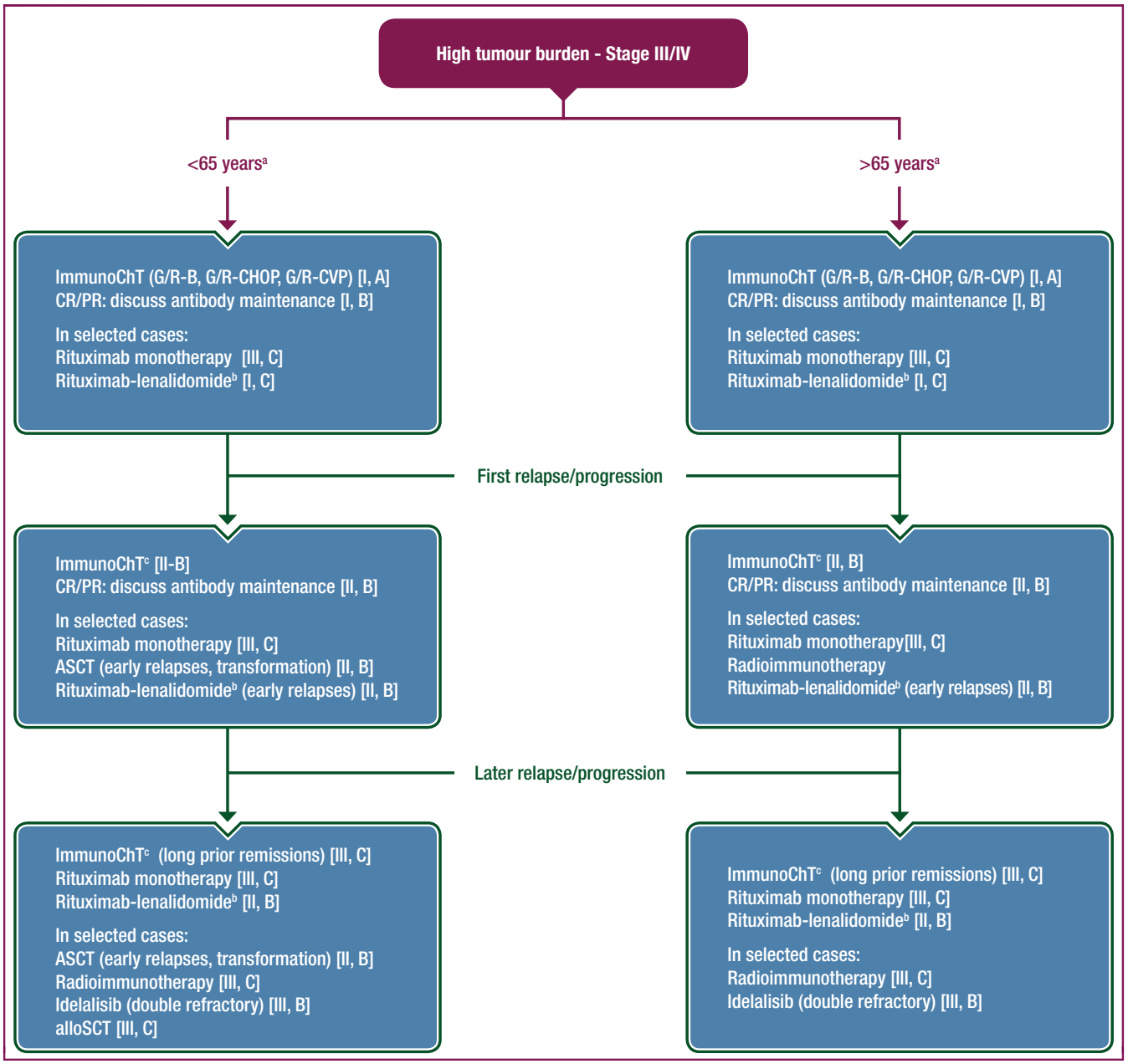

Figure 3. Consensus-driven recommendations—high tumour burden FL.
alloSCT, allogeneic stem cell transplantation; ASCT, autologous stem cell transplantation; B, bendamustine; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; ChT, chemotherapy; CR, complete response; CVP, cyclophosphamide, vincristine, prednisolone; FL, follicular lymphoma; G, obinutuzumab; PR, partial response; R, rituximab.
[a] Biological age (years).
[b] Off-label.
[c] Preferred in rituximab-refractory cases.

symptoms and individual patient priorities (Figure 1). PET- and MRD-based tailored treatments are currently being evaluated in ongoing studies but are not yet routine clinical practice.

Paediatric FL is an FL variant originally described in children, but rarely occurs in adults. It is characterised by typically localised disease, the absence of BCL2 aberrations, lack of *t(14;18)*, grade III histology and a high proliferation rate. It shows a much more indolent disease course and can be managed with local therapy only, despite displaying histologically more aggressive features.[56]

Similarly, duodenal-type FL should be followed with observation only as long as asymptomatic [IV, B].[57]

FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP

The following minimal recommendations are based on consensus rather than on evidence (Table 7):

- After local RT: history and physical examination every 6 months for 2 years, subsequently once a year if clinically indicated.

- Evaluation of thyroid function in patients with irradiation of the neck at 1, 2 and 5 years.
- After (during continuous) systemic treatment: history and physical examination every 3-6 months for 2 years, and every 6-12 months subsequently [V, C].
- Blood count and routine chemistry including IgG levels every 6 months for 2 years, then only as needed for evaluation of suspicious symptoms.
- Minimal adequate radiological or other examinations every 6 months for 2 years and optionally annually up to 5 years. Regular CT scans are not mandatory outside of clinical trials, and PET-CT should not be used for surveillance [V, D].
- MRD screening may be carried out in clinical studies but should not guide therapeutic strategies in clinical practise.
- Adequate prophylaxis (antibiotics and/or IgG supplementation) in patients with symptomatic recurrent infections and based on prior treatment (e.g. with fludarabine or bendamustine). Yearly seasonal flu vaccination may be considered.

METHODOLOGY

These Clinical Practice Guidelines were developed in accordance with the ESMO standard operating procedures for Clinical Practice Guidelines development (http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology). The relevant literature has been selected by the expert authors. A summary of recommended treatment strategies outside of clinical studies is provided in Figures 2 and 3. Levels of evidence and grades of recommendation have been applied using the system shown in Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2020.11.008.[58] Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty. This manuscript has been subjected to an anonymous peer review process.

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