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POSITION PAPER

Diagnosis, management and follow-up of follicular lymphoma: a consensus practice statement from the Australasian Lymphoma Alliance

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Abstract

Follicular lymphoma (FL) is the most common indolent non-Hodgkin lymphoma subtype, accounting for 15–20% of all lymphoma diagnoses. Although typically slow-growing and responsive to frontline therapies, advanced-stage FL remains incurable with current treatments and typically follows a chronic relapsing/remitting course with increasingly shorter responses to subsequent lines of therapy. Outcomes are highly variable; some patients experience prolonged first remissions that may approximate a 'functional cure'. By contrast, a significant minority of patients experience disease progression shortly after frontline treatment resulting in high rates of lymphoma-related mortality. Reflecting on the heterogeneous natural history of FL, clinical practice varies widely, particularly in controversial areas, including appropriate disease staging, selection of management strategies and duration of clinical follow-up. This position statement presents an evidence-based synthesis of the literature for application in Australasian practice.

Introduction

Follicular lymphoma (FL) management remains highly variable and is dictated by stage, tumour burden, toxicities, patient age, comorbidities and preferences. This consensus practice statement addresses the diagnosis, management and follow-up of patients with FL in Australasia.

Methodology

This consensus practice statement was drafted by a lymphoma expert panel under the auspices of the Australasian Lymphoma Alliance (ALA) in accordance with the 'ALA consensus practice statement development policy'. Relevant literature was reviewed by expert authors. Standardised levels of evidence and grades of recommendation have been applied as per Tables S1 and S2. Statements without grading were considered justified standard clinical practice by the experts and ALA members.

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Epidemiology

FL represents the second most common non-Hodgkin lymphoma (NHL) in Australia and New Zealand, comprising 15–25% of cases, with an incidence of 3.1 cases per 100 000 individuals and a marginally higher rate in immunocompromised populations. Globally, this has risen inexplicably by 2.5% annually over the past two decades.[1] The median age of onset is 60–65 years, with a male preponderance (female-to-male ratio = 1:1.7).[2] FL harbours a risk of histological transformation (HT) to a high-grade lymphoma of 1–3% per year and up to 20% overall.[3,4] Transformed FL is treated as an aggressive NHL and is beyond the scope of this practice statement.

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Assessment and diagnosis

An FL diagnosis requires correlation of clinical, pathological and molecular information. Table 1 outlines the recommended work-up of patients with newly diagnosed FL. Excisional biopsy is preferred over core biopsy where feasible,[5] and expert haematopathologist review is recommended.

Histological classification is key to FL diagnosis (Table 2).[6] Nomenclature varies between diagnostic classification schemes[7,8]; however, the diagnostic subgroups correlate directly between the two with similar clinical implications. The main clinically relevant distinction required is that of grade 3B FL (World Health Organization) or follicular large B-cell lymphoma (International Consensus Classification), which is considered an aggressive NHL with corresponding therapeutic implications.[7–9] Atypical or diffuse variants of FL may benefit from extended immunohistochemical staining panels, including germinal centre (CD10, BCL-6 and BCL-2) and follicular dendritic cell markers (CD21).

Table 1 Recommended diagnostic work-up for patients with new and relapsed FL

History	Presence of features of local compression and 'B' symptoms
	ECOG performance status assessment
	Geriatric assessment tool in elderly patients
	Prior/active malignancy and previous chemotherapy exposure
Physical examination	Involved nodal and extranodal sites
	Skin examination (particularly if expected to receive bendamustine)
Laboratory testing[97–99]	Full blood cell count and blood film
	Direct immunoglobulin testing
	Peripheral blood flow cytometry (reserved for patients with lymphocytosis or abnormal blood film findings)
	Electrolytes, renal function and liver function testing
	Calcium, magnesium, phosphate
	Uric acid
	Lactate dehydrogenase
	β2-microglobulin
	Serum protein electrophoresis (±immunofixation)
	HIV, hepatitis B and C serology
	Pregnancy testing in women of child-bearing potential
Cardiac assessment	Consider transthoracic echocardiogram or gated heart pool scan for relevant risk groups expected to receive anthracycline
Imaging[10–13]	FDG-PET + CT staging in accordance with Lugano classification
Bone marrow biopsy[21]	Recommended in early-stage (stages I–II) FL
	In advanced stage FL not generally required where PET assessment of marrow involvement is performed, and clinical treatment is unlikely to be altered based on the result

CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; FDG, ^{18}fludeoxyglucose; FL, follicular lymphoma; PET, positron emission tomography.

Recommendations

- Surgical lymph node biopsy is recommended over core needle biopsy where feasible (III-2, B).
- Multidisciplinary team meeting review, with haematopathologist input, is recommended (IV-B).
- Fluorescence in situ hybridization to detect t(14;18) is encouraged (IV-C).

Staging

Anatomical staging, using Lugano criteria (Table 3), is critical to guiding FL management.[10,11] Staging with ^{18}fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging is more accurate than computed tomography (CT) alone, altering management in 5–25% of patients.[12,13] Although FDG uptake is heterogeneous in FL,[14] data are conflicting regarding the value of maximum standardised uptake value (SUV_{max}) in identifying HT[15–17] and currently no clear evidence supports re-biopsy of lesions to confirm HT based on SUV_{max} alone.[18]

Bone marrow biopsy (BMB) historically formed part of FL staging due to the high rate of marrow involvement. BMB complication rates are low, yet it is invasive, painful and resource intensive.[19] PET-era studies show that imaging plus BMB is superior to either approach alone.[20,21] BMB upstages 14–25% of imaging-detected stage I or II FL with implications for treatment where localised therapy is planned; however, in advanced-stage FL, BMB seldom impacts management, although does comprise a component of validated prognostic scores.[21,22] Omission of BMB is reasonable in imaging-confirmed advanced-stage FL where results will not alter management.

Recommendations

- Baseline PET-CT staging, according to Lugano criteria, should be performed (III-1, A).
- Baseline staging BMB is recommended in all cases where:
  - PET assessment cannot be performed (level III-2, B)
  - limited-stage disease is being considered for local therapy (level III-1, A)
  - clinical suspicion of alternative marrow pathology is present.

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Table 2 Pathological classification systems of FL

Clinical implication	International Consensus Classification		WHO, Fifth Edition	
Indolent NHL	Grade 1	≤5 centroblasts/HPF	cFL or uFL	Composed of small centrocytes and centroblasts and harbour t(14;18)(q32;q21) alteration. Histological grading no longer mandatory. uFL refers to low-grade subsets with blastoid or large centrocye variant cytological features and are frequently possess BCL2 rearrangements than cFL.
	Grade 2	6–15 centroblasts/HPF		
	Grade 3A	>15 blasts/HPF, centroblasts with intermingled centrocytes		
Treated as aggressive NHL	Grade 3B	>15 blasts/HPF, pure sheets of blasts	Follicular large B-cell lymphoma	>15 blasts/HPF, pure sheets of blasts

cFL, classical follicular lymphoma; FL, follicular lymphoma; HPF, high-power field; NHL, non-Hodgkin lymphoma; uFL, follicular lymphoma with unusual cytologic features; WHO, World Health Organization.

Table 3 2014 Lugano staging system

	Stage	Nodal involvement†	Extranodal (E)
Limited/early-stage‡	I	One node or a group of adjacent nodes	Single extranodal lesion without nodal involvement
	II	Two or more nodal groups on the same side of the thoracoabdominal diaphragm	Stage I or II by nodal involvement with contiguous extranodal extension
Advanced-stage	III	Nodal involvement on both sides of the thoracoabdominal diaphragm	Not applicable
	IV	Additional, non-contiguous extranodal involvement	Not applicable

†Nodal involvement includes involvement of spleen (diffuse, solitary or nodular uptake or unexplained splenomegaly >13 cm), liver (diffuse or nodular uptake) and Waldeyer ring/tonsils.
‡Bulky stage II disease as defined by Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria (three or more nodal sites, each measuring ≥3 cm or any mass ≥7 cm) is typically not considered limited-stage and is managed according to advanced-stage FL.
Source: adapted from Cheson *et al.*[11]

• BMB may be omitted where results will not impact the therapeutic approach (level III-2, C).

Clinical risk assessment

The median survival of FL currently exceeds two decades, although the natural disease course is highly variable with up to 10–15% of patients dying within 5 years.[23] Multiple clinical prognostic tools have been developed to improve baseline risk stratification in FL (Table 4).[24–26] However, to date, none has altered therapeutic strategies. Recently, incorporation of biological characteristics, including mutation status[27] or gene expression profiling[28,29] into clinical prognosticators have been evaluated but are yet to be translated into clinical practice.

Another validated clinical prognosticator is the occurrence of disease relapse, or progression, within 24 months of first-line systemic therapy (POD24) in advanced disease,[30] occurring in 20% of patients. POD24 is associated with a 5-year lymphoma-related mortality of approximately 50%.[31,32]

Recommendations

• The use of a validated clinical prognostic tool (e.g. FLIPI, FLIPI-2 and PRIMA-PI) should be calculated in patients at the time of firstline treatment initiation, but there is insufficient evidence to alter treatment based on these results.

Early-stage FL

Approximately one-quarter of patients with FL present with stage I/II FL and are classified as having 'early-stage' FL (ESFL). FL is highly radio-sensitive, and radiotherapy (RT) is potentially curative in patients with ESFL that is encompassable within a single RT field. Curative-intent involved-site RT (ISRT), applying conventional dosimetry to 24–30 Gy in 1.8–2 Gy fractions is minimally toxic yet achieves infield control of ∼100%, and 10-year relapse rates of approximately 50%.[33–40] For uniformity of practice, the principles for ISRT are published by the International Lymphoma Radiation Oncology Group.[41,42]

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Table 4 Commonly used clinical prognostic tools in FL

Clinical tool	Components of score	Risk category	Risk factor	Patients (%)	Rituximab-era outcome[24]
FLIPI	Age >60 years	Low	0–1	36	5-year PFS 68%
	Stage III–IV	Int	2	37	5-year PFS 58%
	Hb level <120 g/L	High	≥3	27	5-year PFS 44%
	Serum LDH >ULN				
	>4 nodal sites				
FLIPI-2	Age >60 years	Low	0	20	5-year PFS 75%
	BM involvement	Int	1–2	53	5-year PFS 60%
	Hb level <120 g/L	High	≥3	27	5-year PFS 41%
	β2M >ULN				
	Lymph node >6 cm				
PRIMA-PI	βM >3.0	Low	BM^- $\beta2M^-$	34	5-year PFS 69%
	BM involvement	Int	BM^+ $\beta2M^-$	34	5-year PFS 55%
		High	$\beta2M^+$	32	5-year PFS 37%

BM, bone marrow; FL, follicular lymphoma; Hb, haemoglobin; Int, intermediate; LDH, lactate dehydrogenase; ULN, upper limit of normal; β2M, beta2-microglobulin.

In a randomised phase 3 trial, combined-modality therapy (R-CVP and RT) improved progression-free survival (PFS), but not overall survival (OS), compared to RT alone.[35] PET staging was not routinely performed, and nonrituximab-containing chemotherapy added no benefit. In a phase 2 study, RT plus adjuvant rituximab was associated with favourable toxicity and quality of life.[37] The absolute benefits of adjuvant therapy should be weighed against the additional risks of toxicities. Adjuvant therapies are not appropriate in patients with reduced life expectancy due to competing risks, those at escalated risk for toxicity from the adjuvant systemic therapy or those with extranodal stage 1AE disease who have an excellent prognosis with RT alone or observation.[35]

For elderly patients or for those with competing risks of mortality in whom long-term disease control is not the primary objective, low-dose RT (4 Gy in 2 Gy per fraction) is exceptionally well tolerated with high response rates.[40] Alternatively, watchful waiting (WW) may be considered, acknowledging that this approach is associated with an inferior PFS to curative-dose RT.[43]

Recommendations

- Patients with ESFL should be offered curative-intent RT to 24–30 Gy total dose in 1.8–2 Gy fractions where feasible (III-2, A).
- Combined RT plus immunochemotherapy with a rituximab-containing regimen may be considered in selected young/fit patients (II, B).
- For elderly or medically unfit patients, low-dose RT or WW may be appropriate (III-2, B).

Advanced-stage FL

WW versus active treatment

In randomised trials, initial clinical surveillance for progression or WW in patients with asymptomatic, low disease burden, advanced-stage FL confers similar OS outcomes compared to upfront treatment, and may lead to deferred treatment commencement by a median of 2–3 years.[44–46] Thus, WW is appropriate for asymptomatic FL in the absence of symptoms, or defined features of high tumour burden (Table 5; i.e. British National Lymphoma (BNLI); Groupe d'Etude des Lymphomes Folliculaires (GELF)). The presence of certain GELF/BNLI characteristics may not warrant treatment initiation in all patients, particularly those with slow disease tempo, where WW does not impact OS.[47]

Recommendations

- WW is an appropriate strategy for patients with low tumour burden asymptomatic disease (II, B).
- Regular clinical assessment is required to monitor for new symptoms of clinically significant progression.

Routine surveillance imaging is not recommended during WW but may be considered to monitor bulky or intra-abdominal disease where relevant complications are anticipated (IV, C).

Induction treatment

Patients with symptomatic and/or high tumour burden FL should be considered for systemic therapy. Anti-CD20 monoclonal antibodies (mAb) (i.e. rituximab and obinutuzumab) are central to first-line FL management;

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Table 5 Criteria for identifying symptomatic or high-tumour burden FL requiring treatment[44,45]

GELF criteria
Three or more nodal sites, each measuring ≥3 cm
Any mass ≥7 cm
B symptoms†
Splenomegaly
Pleural effusions or ascites
Cytopenias (neutrophils <1.0 × 10^9/L and/or platelets <100 × 10^9/L)
Leukaemia (>5.0 × 10^9/L circulating malignant cells)
BNLI criteria
Pruritis or B symptoms
Rapid, generalised progression in the preceding 3 months
Life-endangering organ involvement
Significant bone marrow infiltration (haemoglobin <100 g/L, white cell count <3 × 10^9/L, platelets <100 × 10^9/L)
Bone lesions
Renal infiltration
Significant liver involvement

†Defined as fever >38°C, drenching night sweats, >10% weight loss within 6 months.

BNLI, British National Lymphoma; FL, follicular lymphoma; GELF, Groupe d'Etude des Lymphomes Folliculaires.

either as monotherapy (rituximab 375 mg/m^2 weekly for four cycles)[48] or, more commonly, in combination with chemotherapy.[49–53] Addition of anti-CD20 mAbs to chemotherapy has shown improved survival in randomised trials using CHOP (cyclophosphamide, vincristine, doxorubicin and prednisone), CVP (cyclophosphamide, vincristine and prednisone), bendamustine and chlorambucil.[49,50,54,55] In the phase III GALLIUM study, obinutuzumab-based chemotherapy resulted in a 7-year PFS of 63% versus 55% with rituximab-chemotherapy (hazard ratio = 0.66) and a 46% risk reduction in POD24 events. However, at the cost of higher rates of toxicity in the obinutuzumab arm, including grade ≥3 infection (20% vs 15%) and thrombocytopenia (6% vs 3%) and no impact on OS (88% vs 87%).[56]

The choice of partner chemotherapy should be based on treatment goals and associated toxicities, which vary with age, comorbidities and performance status (PS). Improved PFS is demonstrated with R-CHOP compared to R-CVP, and less toxicity with R-CHOP compared to rituximab-fludarabine-mitoxantrone.[57] Bendamustine with rituximab (B-R) has been compared to other chemotherapy backbones in large, randomised studies demonstrating improved or noninferior PFS outcomes compared with CHOP/CVP.[54,58] No difference in OS between immunochemotherapy arms has been demonstrated. First-line therapy with lenalidomide-rituximab (R^2) is also noninferior to R-CHOP.[59] While not currently reimbursed in Australia or New Zealand, accessibility may increase with the recent availability of generic and biosimilar products.

First-line maintenance therapy

Anti-CD20 mAb maintenance therapy, delivered 2 or 3 times monthly for 2 years after confirmed response to first-line chemoimmunotherapy induction defers recurrence of FL. Landmark randomised trials have consistently demonstrated prolonged PFS and time-to-next-treatment by years and reduced POD24 events[31] but no OS benefit and noteworthy additional toxicities, particularly infection.[56,60] Trials of up to 5 years of maintenance have failed to demonstrate additional PFS benefit but higher infection rates.[61] A recent PET/molecular response-adapted approach to maintenance therapy has demonstrated that the PFS advantage of anti-CD20 mAb maintenance therapy persists in patients who obtain complete metabolic remission but with a similar OS to those without maintenance.[62]

The choice of anti-CD20 mAb requires patient-specific consideration. Obinutuzumab improved PFS over rituximab combinations, albeit with more frequent delivery, and higher rates of grades 3–5 adverse events during induction, maintenance and post-treatment cessation (predominantly neutropenia and infection).[63] Additionally, in nonrandomised data, bendamustine induction given prior to maintenance further increases grades 3–5 infections risk in the maintenance period, most commonly among older (>70 years) patients and/or those with poorer baseline ECOG PS, and/or high comorbidity index. Prolonged antimicrobial prophylaxis was shown to mitigate partially the risk of late infections, particularly in high-risk patients.[64] Hypogammaglobulinaemia is also common after anti-CD20 mAb exposure, and patients with demonstrable low serum immunoglobulin levels and recurrent sinopulmonary infections may benefit from intravenous immunoglobulin.[65]

Recommendations

- First-line regimen choice should consider patient age, comorbidities, ECOG PS, personal preferences, treatment duration, treatment delivery and toxicity profiles.
- Patients with advanced-stage FL who are symptomatic and/or high tumour burden should receive one of the following anti-CD20 mAb-based systemic therapy (I-A).
  - Chemotherapy (bendamustine/CHOP) with obinutuzumab offers superior PFS (II-B).
  - Other acceptable regimens such as R-CHOP, B-R, single-agent rituximab, R-chlorambucil and R-CVP offer inferior disease control rates but potentially more favourable toxicity (II-B).
- Anti-PJP, antiviral prophylaxis may reduce infection risk and are recommended, particularly in patients

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receiving bendamustine and/or maintenance mAb therapy (IV, C).
- Maintenance rituximab or obinutuzumab should be considered in responding patients after induction immunochemotherapy. Discussion regarding benefits versus risks, particularly infection, is required. The same anti-CD20 mAb used during induction is administered every 2–3 months for no more than 2 years maintenance (I, A).
- Anti-CD20 maintenance after bendamustine-based induction regimens should be considered with caution among elderly patients (>70 years) and/or those with high comorbidity indices, at additional risk of infection and/or poor ECOG PS (III, C).
- Low-dose RT (4 Gy in two fractions) should be considered for palliation of local symptoms (II-B).

Management of relapsed/refractory FL

No single treatment paradigm exists for relapsed or refractory FL (R/R-FL). Management is dictated by clinical presentation, prior therapy, treatment delivery, toxicity and patient factors, including age, comorbidities and ECOG PS. At the time of relapse, rebiopsy is essential to exclude HT, particularly among those experiencing POD24.[66,67] Patients with POD24 have inferior outcomes, but treatment for asymptomatic disease is not warranted. The WW approach may be appropriate in asymptomatic or low tumour burden disease at relapse.[68] All patients requiring therapy should be considered for enrolment into clinical trials.

Conventional therapies

Current first-line FL immunochemotherapy regimens are proven in second/later lines noting that availability of bendamustine is restricted in Australia in this context. Noncross-resistant regimens are favoured and additional platinum-based regimens are proven in third or later lines.[69] *Re*-treatment with anti-CD20 mAb is standard, with obinutuzumab-bendamustine benefit proven in rituximab-refractory disease.[70] In those with POD24 events, a major response may be consolidated by high-dose chemotherapy (HDC) and autologous stem cell transplant (AutoSCT) as discussed below.[71]

Single-agent rituximab has response rates of 40–60% and low toxicity, thus may be a suitable option in slowly progressive disease; however, median response duration is less than 2 years.[72] Ultra-low-dose RT remains a valid treatment option to control symptoms related to a localised disease site.[73]

Novel therapies

Lenalidomide-based therapies

Lenalidomide has demonstrated efficacy in R/R-FL in combination with anti-CD20 mAb. Rituximab-lenalidomide (R^2) increased the median PFS from 14 to 39 months over rituximab alone.[74] Neutropenia is the most common grade 3–4 toxicity. Lenalidomide is not reimbursed for FL in Australia or New Zealand but generic brand availability has reduced costs.

Phosphatidylinositol 3-kinase inhibitors

Idelalisib is an oral phosphatidylinositol 3-kinase (PI3K)δ inhibitor with activity in patients exposed to >2 prior treatment lines. Despite high overall response rates, median PFS is modest (11 months) and toxicity including colitis, hepatitis and pneumonitis can be severe.[75] Due to complex but unfavourable benefit-toxicity ratios in combination with antiCD20 mAbs, Food and Drug Administration-approved PI3K inhibitors including idelalisib were voluntarily withdrawn in 2022.

Future approaches

Promising single-agent and combination immunotherapeutics and small molecules are under clinical trial evaluation in R/R-FL. Bispecific T-cell-engaging antibodies, anti-CD19 mAbs, chimeric antigen receptor T-cell therapy and tazemetostat, an oral EZH2 inhibitor, all have demonstrated promising preliminary efficacy with trials ongoing.[76–80]

Stem cell transplantation

HDC and AutoSCT consolidation after first-line rituximab-based therapy yielded improved PFS in randomised studies; however, it is not currently recommended because of the concerning rates of therapy-related malignancies in the absence of OS benefit.[81–83] In R/R-FL, the optimal role and timing of AutoSCT is unclear. Large retrospective analyses have shown that AutoSCT consolidation benefits are dependent on the time from first relapse to transplantation,[84] leading to renewed interest in AutoSCT use for patients with POD24, although no prospective data exist. In POD24 young patients, AutoSCT was retrospectively associated with longer PFS and OS than conventional approaches.[85,86] Subsequent retrospective studies are

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conflicting, with favourable survival associations limited to those receiving transplantation <1 year after POD24 events.[71] In the absence of POD24, AutoSCT consolidation after first relapse has no observed benefit.[85–87]

Beyond second relapse, the role of AutoSCT and allogeneic stem cell transplantation (AlloSCT) has declined as novel therapeutic options proliferate and evolve.[77,78] Historical registry studies of heavily pretreated R/R-FL demonstrated comparable OS and PFS between AutoSCT and AlloSCT, with substantially lower relapse rates seen in AlloSCT balanced by higher nonrelapse mortality despite reduced intensity conditioning (RIC) regimen use.[88,89] Notably, in AlloSCT-treated patients, relapse seldom occurs beyond 2 years, suggesting a potential for cure in the 50% of patients achieving this landmark.[88] Thus, in carefully selected heavily pretreated fit patients, RIC AlloSCT is an option particularly in R/R-FL post-AutoSCT with limited options, or prior ineffective mobilisation of autologous stem cells.[90]

Recommendations

- Repeat biopsy should be performed at relapse to confirm low-grade FL (III, B).
- Asymptomatic relapse with low tumour burden can undergo initial WW, irrespective of POD24 status (IV, C).
- Anatomically limited symptomatic disease should be considered for low-dose RT (III-3, C).
- Where possible, patients requiring systemic treatment should be enrolled in clinical trials.
- Patients experiencing POD24 events typically have an aggressive clinical course (II, B). Fit patients should be considered for immunochemotherapy using agents different from those used in frontline (II, B).
- Other treatment options include:
  - Single-agent rituximab (II, A).
  - Small molecule inhibitors: idelalisib (II, B).
  - Immunomodulators: lenalidomide in combination with rituximab (II, B).
- In young, fit patients AutoSCT may be considered after one or two lines of prior therapy, particularly those experiencing POD24 relapse after frontline immunochemotherapy (III-3, C).
- Fit, heavily pretreated (≥3 lines) patients should be considered for RIC-AlloSCT consolidation where suitable fully matched donors are available. The risk-benefit assessment should be made in conjunction with a specialist stem cell transplant unit (III-2, B).

Response assessment and follow-up

Assessment of FL response at the end of induction (EoI) should be performed using PET-CT using the Lugano criteria, applying the standard five-point scale (Deauville score (DS)) (Table 6).[11,91] Multiple studies have demonstrated that failure to achieve EoI complete metabolic response (DS 1–3) is associated with inferior PFS and OS independent of frontline therapy.[92,93] The role of interim PET-CT (iPET) during induction therapy is not established with an inferior predictive value to EoI PET and the acknowledged deepening of responses during induction and maintenance therapy.[94] On occasion, interim CT may be warranted to confirm response where there is no clear clinical evidence of responding disease. Likewise, in patients with bulky abdominal disease, a CT scan performed in the months after completion of therapy can provide a useful map of any residual lymphadenopathy for comparison in the event of subsequent relapse.

Given the lifelong risk of symptomatic relapse and late treatment-associated adverse events, patients should continue clinical follow-up indefinitely. Clinical review should consist of physical examination and history for symptomatic relapse with haematology and biochemistry testing where clinically indicated.[95] For patients with long treatment-free periods, emphasis should be placed on survivorship interventions, including screening for endocrinopathies, acquired immunodeficiencies and secondary malignancies (particularly skin cancers). Surveillance imaging of

Table 6 PET response assessment of FL according to the Deauville and Lugano response classification[11]

Response	Imaging characteristics
Deauville score (DS)	
1	No uptake
2	≤Mediastinal blood pool
3	>Mediastinal blood pool and ≤ liver
4	Moderately > liver (at any site)
5	Markedly > liver at any site ± new site of disease
X	New areas of uptake unlikely to be related to lymphoma
Lugano criteria	
CMR	DS 1, 2 or 3 in nodal or extranodal sites with or without residual mass
PMR	DS 4 or 5 with reduced uptake compared with baseline and residual mass of any size
SD	DS 4 or 5 with no change in uptake
PD	DS 4 or 5 with increase in intensity of FDG uptake from baseline and/or new FDG-avid foci consistent with lymphoma

CMR, complete metabolic response; FDG, ^{18}fludeoxyglucose; FL, follicular lymphoma; PD, progressive disease; PET, positron emission tomography; PMR, partial metabolic response; SD, stable disease.

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asymptomatic FL is not indicated but may be reasonably considered in patients presenting with symptomatic bulky abdominal disease.[96]

Recommendations

- PET-CT should be performed at EoI where feasible (II-A).
- iPET or CT is not recommended unless clinical suggestion of progressive disease (III-2, B).
- Long-term clinical follow-up is recommended, consisting of targeted clinical history and examination, with laboratory investigations where appropriate.
  - 3–6 monthly reviews for first the 24 months, tailored to remission status.
  - Review intervals after 24 months tailored to patient disease and expectations.
- Additional surveillance imaging of asymptomatic patients is not recommended unless clinical suspicion of symptomatic/bulky relapse is present (III-3, C).

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

Table S1. Levels of evidence.
Table S2. Grades of recommendation.

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