

CHAPTER 12 LOW-GRADE LYMPHOMA

12.1 Introduction

Concepts have changed with the introduction of the WHO classification. While the most common form of ‘low-grade’ lymphoma, follicular lymphoma, remains largely unchanged by this classification system, many other disorders are clearly recognised as distinct clinicopathological entities for the first time (e.g. splenic marginal zone lymphoma).

Many of these entities have a low incidence. Studies utilising the WHO classification are infrequent. A difficulty with treatment recommendations is the ‘relapsing and remitting’ natural history of these malignancies. The overall survival of patients is influenced by the initial therapy used and subsequent therapies given for relapsed or recurrent disease.

The highest priority of treatment is to maximise patients’ overall survival, maintain quality of life and avoid treatment-related morbidity. However, it is difficult to demonstrate any influence of these end-points in a single clinical trial. This reflects the long natural history of these disorders, the effects of sequential therapies, and competing causes of unrelated death in an often elderly population.

Few individual studies have demonstrated an impact on overall survival. There is now evidence that where novel treatment strategies have been serially employed within a single institution, there has been step-wise improvement in overall survival over the decades.¹ It is not clear which components of these therapies are responsible for this improved survival.

Conversely, where initial treatment strategies have remained consistent and utilised therapies based on alkylating agents, there has been no such improvement in survival, demonstrating that the natural history of these disorders has not altered with time, and that supportive care alone does not explain the improvements.² For these reasons, reliable ‘surrogate end-points’ are sometimes used to define treatment recommendations. These include overall response rates, complete remission rates, and ‘molecular’ complete remission rates. Where recommendations have been based upon these ‘surrogate’ end-points, the data supporting their validity are summarised.

The topics included in this chapter are:

- follicular lymphoma (grade 1 and 2)
- small lymphocytic lymphoma
- extranodal marginal zone B-cell lymphoma
- nodal marginal zone B-cell lymphoma
- lymphoplasmacytic lymphoma (Waldenstrom’s macroglobulinaemia)
- splenic marginal zone lymphoma

12.2 Epidemiology

While there are marked variations in the absolute and relative incidence of these disorders in different geographic regions³, the relative proportion of consecutive cases of NHL comprising each of these entities in a Western society has been estimated to be⁴:

- follicular lymphoma — 22%
- small lymphocytic lymphoma — 7%

- extranodal marginal zone B-cell lymphoma — 8%
- nodal marginal zone B-cell lymphoma — 2%
- lymphoplasmacytic lymphoma (Waldenstrom's macroglobulinemia) — 1%
- splenic marginal zone lymphoma — <1%

Unfortunately, there is incomplete population-based incidence data from Australia using the currently recommended histologic classification system.

12.3 Staging

In addition to investigations directed by the history and clinical examination, staging requirements include:

- CT scanning of the chest/abdomen/pelvis
- full blood examination and manual differential with flow cytometry if there is a lymphocytosis or morphologically abnormal lymphocytes present, Coomb's test
- bone marrow aspirate and biopsy, with a minimum total length of 2.0 cm and at least four levels examined^{5,6}
- full biochemical profile including uric acid, LDH, β_2 -microglobulin, and serum protein electrophoresis.

In specific circumstances there may be requirements for other studies, such as hepatitis C serology in patients with splenic marginal zone lymphoma.⁷

In patients with follicular lymphoma, where 'molecular remission' is the therapeutic goal, it is mandatory to establish the presence of a disease-specific molecular marker in the diagnostic tissue, blood and marrow of that patient before the commencement of therapy, for example, *bcl-2* gene rearrangement (see Chapter 7).

12.4 Follicular lymphoma

Summary of representative clinicopathological findings

Clinical	Usually adults >20 years. Often widespread at diagnosis, with splenic and marrow involvement, but often asymptomatic. Rare paediatric variant often localised.
Morphology	<p>Most cases at least partly follicular: >75% follicular — ‘follicular’ 25–75% follicular — ‘follicular and diffuse’ <25% follicular — ‘partly follicular’</p> <p>Diffuse areas may be sclerotic. Cytology: small and large cleaved cells (centrocytes) and large non-cleaved cells (centroblasts).</p> <p>Grade 1: 0–5 centroblasts per hpf Grade 2: 5–15 centroblasts per hpf Grade 3: >15 centroblasts per hpf</p> <p>Grade 3a: centrocytes present Grade 3b: solid sheets of centroblasts</p> <p><i>Variants:</i></p> <p>i. Purely diffuse (grades 1 and 2 only) ii. Cutaneous iii. Marginal zone differentiation (10%). iv. Floral variant versus signet ring cell variant, vi. FL with plasmacytic differentiation vii. Paediatric cases usually grade 2 or 3</p> <p>Any component of diffuse large B-cell lymphoma is reported separately</p>
Immunophenotype	<p>SIg + (occasionally SIg-ve), <i>bcl-2</i> +, CD10+, CD19+, CD20+, CD22+, CD79a+, <i>bcl-6</i>+, CD5-, CD43-, CD21+, CD23+, CD35+ FDC meshworks outline follicles.</p> <p>Rare paediatric cases usually <i>bcl-6</i>+, CD10+ but <i>bcl-2</i> negative.</p>
Cytogenetics	<p>t(14;18)(q32;q21) (<i>BCL2</i>) (except in paediatric cases) Variant: t(2;18)(p12;q21) Many additional abnormalities including 17p13 (<i>TP53</i> gene)</p>

12.4.1 Follicular lymphoma, grade 1 and 2 (‘low-grade’)

Localised disease (stage I and II)

Accurate staging

Patients with stage I–III who are being considered for curative therapy with radiotherapy should undergo staging with either thallium or PET scanning, as up to 70% of patients will have more extensive disease revealed.^{8,9} Gallium scanning is less sensitive.⁹ Attention to the bone marrow biopsy is important, and at times, either repeat biopsy or examination of further levels of the initial biopsy may be necessary to exclude minimal disease infiltration.^{5,6}

Guidelines — Low-grade lymphoma — staging pre-radiotherapy	Level of evidence	Refs
Before embarking on potentially curative radiation therapy for patients with clinical stage I–III ‘low-grade’ lymphoma, staging should include functional imaging with PET or thallium scanning.	III	8, 9
Before embarking on potentially curative radiation therapy for patients with clinical stage I–III ‘low-grade’ lymphoma, staging should include careful examination of multiple levels of a bone marrow biopsy specimen ≥ 2.0 cm in length.	III	5, 6

Involved-field radiotherapy

A recent overview has established that 40–50% of patients with stage I–II disease can obtain durable disease control and likely cure with involved-field radiotherapy.^{10–12} Most of these studies were performed when various types of ‘low-grade’ lymphoma were included without distinction. These results are summarised in Table 12.1.

The radiation doses ranged from 20 Gy to 50 Gy. There are no convincing data for a significant-dose response relationship beyond 30–36 Gy.¹³ However, doses <30 Gy are associated with a higher local recurrence.¹⁴ For patients with tumour masses ≥ 3 cm in size, there is some suggestion that doses of 30–36 Gy resulted in better in-field control compared with doses <30 Gy¹⁵, but with a trend for greater late local toxicity with the higher range of radiation doses.¹⁵ There is now general agreement that doses over 40 Gy are excessive. The dose recommended is 30–36 Gy, with a higher dose range for sites ≥ 3 cm in diameter. The radiation treatment volume remains controversial. There is some evidence that treatment of larger volumes can delay relapse, but it is not clear that this produces a survival benefit^{10,15}. This is partly attributable to a higher rate of second malignancies.¹⁶ Thus the recommended treatment volume is the ‘involved-field’, where known disease with a suitable margin (with or without nearby uninvolved lymph node groups) is irradiated. It is recognised that there will be variability in the definition of the ‘involved field’.¹⁷

The very rare disorder of follicular lymphoma in childhood has distinct molecular and pathological features, typically lacking *bcl-2* gene rearrangements.^{18,19} The childhood form of the disease also has a distinct natural history. It is usually localised at presentation and typically has an indolent clinical course, and a moderate rate of local recurrence or dissemination after adequate local excision.²⁰ For those paediatric patients with more extensive disease or local disease persisting after the diagnostic biopsy, no clear recommendations can be made. However, local irradiation and combination chemotherapy are useful modalities. The specific treatment administered must give adequate consideration to the associated potential late toxicities.

Conversely, for the uncommon group of adult patients with clinical stage I disease, which is apparently completely excised in the process of the diagnostic biopsy, recurrent disease almost inevitably occurs either locally or at distant sites if additional treatment is not administered, although this recurrence can be quite delayed, with a median time to recurrence of ~five years.²¹ There is no evidence that any of these patients initially observed following complete surgical excision are cured of their disease.

Given its established curative potential, and low morbidity when doses are limited to 30–36 Gy delivered to an involved field, IF XRT should be the minimum treatment offered. The exception is patients with complete surgical excision of all evident disease, who have a life expectancy of less than five years from intercurrent disorders or extremely advanced age. In these cases, observation with no further therapy is a reasonable alternative.

Table 12.1 Published studies of patients with indolent, clinically-staged stage I–II lymphoma, treated with involved-field radiation therapy alone

Study	No patients (% stage II)	Median age in yrs (range)	Histology (number of patients)	Radiation dose (Gy)	10-yr results (%)		Comments
					DFS	OS	
BNLI (Kelsey et al. 1994) ²²	82 (57)	60 (30–80)	FSC (46), FM (19), FL (4), DSL (10)	abdomen=25 elsewhere=35	28	52	Prospective radiation arm of randomised multicentre study 1974–81, extent of abdominal staging unclear
BNLI (Vaughan Hudson et al. 1994) ²³	208 (0)	59 (31–86)	FSC (81), FM (72), FL (10), DSL (27), DSC (18)	recommend 35	47	64	Retrospective, multicentre 1974–91, stage I only
PMH, Toronto (Gospodarowicz et al. 1984) ²⁴	190 (45)	56 (18–87)	All follicular	median 30 range 20–35	53 at 12yrs	58 at 12yrs	Retrospective subgroup analysis from 1967–78 among total of 248 stage I/II nodular histology
Stanford University (MacManus & Hoppe 1996) ¹⁰	177 (58)	52 (22–83)	FSC (101), FM (76)	35–50 most ≤ 44	44	64	Retrospective, 1961–94, includes 45 with staging laparotomy and 32 with total-nodal irradiation
MDACC, Houston (Wilder et al. 2001) ¹⁵	80 (59)	54 (24–81)	FSC (50), FM (30)	median 40 range 26–50	41 at 15yrs	43 at 15yrs	Retrospective, 1960–88, includes 23 with diagnostic laparotomy, 37% received extended field radiation
Royal Marsden (Pendlebury et al. 1995) ²⁵	58 (31)	55 (21–82)	FSC (37), FM (12), DSL (9)	median 40 range 30–54	43	79	Retrospective, 1970–89 includes 27% with ultrasound as only abdominal staging and 23 who received extended field radiation

FSC = follicular small cleaved cell, FM = follicular mixed small and large cell, FL = follicular large cell, DSL = diffuse small lymphocytic, DSC = diffuse small cleaved cell, DFS = disease-free survival, OS = overall survival, BNLI = British National Lymphoma Investigation, PMH = Princess Margaret Hospital, MDACC = MD Anderson Cancer Center

Guidelines — Low-grade lymphoma — optimal treatment	Level of evidence	Refs
Treatment for adult patients with clinical stage I or II 'low-grade' follicular lymphoma should include involved-field radiation therapy of 30–36 Gy.	III	12
Patients with stage I 'low-grade' follicular lymphoma who are rendered apparently disease free after the diagnostic biopsy and have a life expectancy of less than five years may be observed without further therapy.	IV	21
Combined modality treatment with both IF XRT and combination chemotherapy based on alkylating agents is a reasonable option for adult patients with clinical stage I or II 'low-grade' follicular lymphoma.	III	26

Addition of chemotherapy to involved-field radiotherapy

There have been phase III studies exploring the benefit of adding chemotherapy to local IF XRT in patients with stage I–II disease. With the exception of the BNLI study of the addition of low-dose oral chlorambucil²², these trials have been of marginal value because of limited power to detect differences in outcomes.^{27–31}

Table 12.2 Results of randomised studies of radiation plus chemotherapy for localised low-grade lymphoma

Centre	Year	No of patients in each arm	Chemo	FFR/RFS	Survival	Comments
Finsen Institute Denmark (Nissen et al. 1983 ²⁹)	1983	11 6 RT + CT	RT only CVP+S	-	-	Included DSL Survival and FFR similar in both arms
BNLI (Kelsey et al. 1994 ²²)	1994	82 RT only 66 RT + CT	Chl	37% @ 10y 43% @ 10 y	52% @ 10y 42% @ 10y	Included DSL and FLC
EORTC* (Carde et al. 1984 ²⁷)	1984	28	CVP	67% 5y RFS 92% 5y RFS	100% @ 5y 100% @ 5y	Follicular lymphomas only
Instituto Nazionale Tumori, Milan (Monfardini et al. 1980 ²⁸)	1980	11 RT only 15 RT + CT	CVP	54.6 5y RFS 63% 5y RFS	61.6 @ 5y 93.3 @ 5y	Follicular lymphomas only
MSKCC (Yahalom 1993 et al. ³¹)	1993	10 RT only 6 RT + CT	CHOP	54% 10y RFS 83% 10y RFS	- -	Included DSL No difference in survival

* Stage I patients only. RT = radiation therapy, CT = chemotherapy, Chl = chlorambucil, CVP = cyclophosphamide, vincristine, prednisolone, CHOP = cyclophosphamide, doxorubicin, vincristine, prednisolone, FFR = freedom from relapse, RFS = relapse-free survival, DSL = diffuse small lymphocytic lymphoma, FLC = follicular large cell, BNLI = British National Lymphoma Investigation, EORTC = European Organisation for Research and Treatment of Cancer, MSKCC = Memorial Sloan Kettering Cancer Centre.

There are phase-II data suggesting that the proportion of patients obtaining durable disease control may increase to 65–70% by the addition of chemotherapy based on alkylating agents (CVP or CHOP).²⁶ This is the basis for the continuing Australian TROG/ALLG study of IF XRT with or

without six cycles of CVP chemotherapy. Outside of clinical trials, either IF XRT alone or combined-modality therapy are reasonable treatment options, depending upon patient age, co-morbidities and preferences.

There are no data to support the use of chemotherapy alone, except with palliative intent. This approach is not recommended where local IF XRT can be safely delivered, and this will be for all but the frailest patients. There are two studies exploring observation alone in patients with stage I–II disease.^{26,32} These establish that the rate of local progression is slow and some of these patients have a long survival, without intervention. However, there is no evidence that any proportion of such patients can sustain long-term freedom from disease progression. This approach is not recommended in patients fit enough to undergo IF XRT.

Relapse after initial stage I–II disease

Patients with stage I–II disease who relapse following either initial XRT or combined-modality therapy still have a reasonable prognosis, with estimated ten-year survival rates of 35%³³ and 46%.²⁶ If disease is limited to stage I–II at recurrence, further radiation can be given, with a median survival of ~six years.³³ More extensive disease should be managed as for advanced-stage follicular lymphoma.

Stage III

Wide-field radiotherapy

Patients with stage III and IV ‘low-grade’ lymphomas are often grouped together and considered to have incurable disease. Management is controversial for the subgroup of patients with definite stage III disease, even after extensive staging with careful examination of the bone marrow biopsy and functional imaging (see above). There have been several studies of wide-field radiotherapy for patients with stage III ‘low-grade’ lymphomas. In the original report of the Stanford series³⁴, 61 patients with FSC or follicular-mixed lymphomas received total lymphatic irradiation or sub-total lymphatic irradiation to a dose of approximately 40 Gy. In addition to this radiotherapy, 13 patients had CVP chemotherapy and a further five patients had total body irradiation with boosts to sites of known disease. For the group as a whole, actuarial survival rates at five, ten and fifteen years were 78%, 50% and 37% respectively. At ten years, 40% of patients were predicted to be free from disease relapse. These data have recently been updated and confirm that a significant proportion of patients achieve long-term disease control and probably derive a major survival benefit from very wide-field radiotherapy.³⁵ Jacobs et al³⁶ reported a series of 34 patients with stage III follicular lymphoma who received comprehensive central lymphatic radiation to doses of 20–30 Gy, with overall survival and disease-free survival rates at fifteen years of 28% and 40% respectively. McLaughlin et al³⁷ reported a seven year survival rate of 52%, and relapse-free survival rate of 52% for 74 patients treated with wide-field radiotherapy and chemotherapy. This does not appear to be substantially different to the rates attained by similar radiation therapy alone.

Longer follow up is required for these studies to determine whether wide-field radiation can achieve indefinite clinical remission (i.e. ‘cure’) for a significant proportion of patients, or whether there is a continuing pattern of relapse beyond 10–15 years that is determined by the intrinsic aggressiveness or indolence of the disease. Comprehensive lymphatic irradiation should be considered for younger patients who are motivated to pursue potentially curative therapy with stage III disease. The single randomised study comparing comprehensive lymphatic irradiation with intensive chemotherapy (12 cycles of alternating CHOD-Bleo/ESHAP/NOPP) in patients with stage I–III follicular NHL has not revealed any difference in progression-free or overall survival, but with a relatively short median follow up in this context of 71 months.³⁸

If such wide-field irradiation is planned, consideration should be given to collection and storage of autologous haematopoietic progenitor cells prior to the delivery of pelvic irradiation, as it may not be feasible to collect adequate numbers of progenitor cells subsequent to pelvic irradiation if relapse occurs and high-dose therapy is considered.

Guideline — Low-grade lymphoma — lymphatic irradiation — haematopoietic progenitor	Level of evidence	Refs
Wide-field 'comprehensive lymphatic irradiation' should be considered for patients with clinical stage III disease after careful and complete staging.	III	35

Key point

Collection and storage of autologous haematopoietic progenitor cells should be considered before the delivery of pelvic irradiation.

If wide-field radiation is not used, patients with stage III disease should be managed as described below for stage IV disease.

Stage IV disease

A recent large multinational collaborative group has defined the clinical parameters that are independently associated with the long-term outcome of patients with follicular lymphoma. The follicular lymphoma international prognostic index (FLIPI) is based on the analysis of more than 4000 patients.³⁹ The following factors at the time of diagnosis were associated with an inferior overall survival:

- age ≥ 60 years,
- haemoglobin ≤ 12 g/dl
- Ann Arbor stage III or IV disease, and
- ≥ 5 nodal sites of disease involvement.

Using these four factors, the distribution of patients and their 5- and 10-year survival rates were:

0–1 risk factors (36% of patients): 5-year survival = 91% 10-year = 71%

2 risk factors (37% of patients): 5-year survival = 78% 10-year = 51%

≥ 3 risk factors (27% of patients): 5-year survival = 53% 10-year = 27%

These parameters should be measured and recorded at the time of diagnosis in all patients to allow estimation of prognosis. This prognostic model has a better predictive capacity in patients with follicular lymphoma than other prognostic models. It is the recommended prognostic system.

Guideline — Low-grade lymphoma FLIPI — measure and record	Level of evidence	Refs
At the time of diagnosis, the factors constituting the follicular lymphoma international prognostic index (FLIPI) should be measured and recorded in all patients.	IV	39

'Watch and wait' versus initial treatment

In general, the approach to patients with stage IV disease is determined by the presence or absence of lymphoma-related symptoms and the age, general condition and preferences of the individual patient. The available evidence base supports two management approaches as reasonable: (1) withholding

treatment until symptoms develop or are imminent, and then using the sequential application of low-morbidity therapies with the aim of ameliorating symptoms, or (2) the initial treatment using optimally effective anti-lymphoma therapy, even if associated with morbidity, aiming to alter the natural history, and potentially overall survival, of the patient.

Key point

All patients with symptomatic advanced-stage follicular lymphoma should be offered therapy.

The first approach of ‘watch and wait’ is based on a number of observations:

- advanced-stage follicular ‘low-grade’ lymphoma is incurable with therapies based on alkylating agents⁴⁰, with a relentless and steady pattern of disease recurrence, albeit over many years
- the overall survival of patients is not influenced by whether such therapies are applied at the time of diagnosis or after an initial period of observation^{41–43}
- a modest proportion of patients may have a very indolent disease course and not develop symptoms related to their lymphoma for a number of years, and can thus be spared the morbidity of initial treatment^{42–44}
- despite the development of an increasing number of therapies with useful overall response rates, the overall survival of patients did not appear to have altered over many decades⁴⁰, and
- moderate intensity combination alkylating agent regimens such as CVP or CHOP did not consistently show any survival advantage over less intensive regimens or single-agent alkylating agents (chlorambucil or cyclophosphamide) for initial therapy.^{45–51}

These observations support an initial ‘watch and wait’ approach in selected asymptomatic patients. The criteria used to select appropriate patients for such an approach have varied between studies and institutions, but all are designed to identify a group of patients with little risk of imminent disease progression or organ impairment. Examples of the criteria used are:

BNLI (Ardeshta et al. 2003) ⁴²	<p>Absence of all of the following:</p> <ul style="list-style-type: none"> • pruritis of B-symptoms • rapid generalised disease progression • ‘life-endangering’ organ involvement • marrow compromise (Haemoglobin \leq100 g/L, WBC $<$3.0, or platelets $<$100) • bone lesions • renal infiltration, and • macroscopic liver involvement.
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GELF (Brice et al. 1997) ⁴³	<p>All of the following:</p> <ul style="list-style-type: none"> • maximum diameter of any site of disease <7 cm • fewer than three nodal sites with a diameter >3 cm • absence of systemic symptoms • no 'substantial' splenic involvement (spleen <16 cm in length based on CT measurement) • no significant serous effusions clinically evident or on chest X-ray • absence of risk of local compressive symptoms (epidural, ureteral, etc.), and • no circulating lymphoma cells or peripheral blood cytopenias (haemoglobin >10 g/dl, neutrophils >1.5 and platelets >100). <p>Using these criteria, 36% of consecutive patients diagnosed with follicular lymphoma were considered to have a 'low' tumour burden.⁴³</p>
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Such a 'watch and wait' approach is still an active form of management that requires patient review, and careful monitoring and assessment of the status of disease or the development of any of the above parameters, which may require the commencement of therapy.

Guidelines — Low-grade lymphoma — 'watch and wait' criteria	Level of evidence	Refs
Where a 'watch and wait' approach is applied in the initial management of a patient with advanced-stage follicular lymphoma, regular monitoring and active surveillance for disease progression is mandatory.	IV	42
Patients who are initially managed by a 'watch and wait' policy and who either develop symptomatic disease, or have disease that progresses beyond the criteria for 'low tumour burden', should commence therapy.	IV	42
Asymptomatic patients who do not fulfil the criteria for 'low tumour burden' follicular lymphoma, using either of the validated criteria, should commence treatment at the time of diagnosis.	IV	42, 43

Where such an approach is used, and patients develop criteria for the initiation of therapy, local external beam irradiation can be used for single disease sites requiring intervention^{41,42}, or systemic chemotherapy may be used. As discussed above, there has been no advantage demonstrated for using more intensive conventional alkylating-agent regimens as the initial therapy for patients with follicular lymphoma. The approaches supported by phase III trial data include:

- Oral chlorambucil 0.2 mg/kg bodyweight (maximum dose 10 mg) daily until three months beyond attainment of maximum response⁴², or

- Oral chlorambucil 0.4 mg/kg on day one and prednisolone 75 mg orally for three days, both given every two weeks, with dose escalation of the chlorambucil until myelosuppression or ‘therapeutic effect’⁴⁹, or
- Oral chlorambucil 10 mg (flat dose) daily for six weeks, then after a two-week gap, three 15-day courses of 10 mg daily, with 15-day intervals between the courses⁴⁷, or
- Cyclophosphamide 600 mg/m² IV on days one and eight, with prednisolone 100 mg/m² on days 1–5, with courses repeated every 28 days for 16 cycles⁴⁶, or
- Cyclophosphamide 100 mg/m² orally daily, with dose modifications for myelosuppression for a total of two years.⁵¹

There are no data to allow a selection among these approaches based on efficacy. Individual patient characteristics and preferences should influence the regimen selected. For example, there are no comparative data to support any benefit for IV compared with oral therapy, nor for the addition of corticosteroids. One feature of all of these established regimens is the requirement for relatively prolonged therapy and relatively slow therapeutic responses. Although there is no greater efficacy associated with the use of intravenous combination regimens (e.g. CVP or CHOP), the requirement for a shorter treatment duration (generally 6–8 cycles) may make them attractive in some circumstances.

Guideline — Low-grade lymphoma — therapy for advanced-stage follicular lymphoma	Level of evidence	Refs
Single-agent alkylating agents with or without corticosteroids (using published schedules) are a suitable treatment for patients with advanced-stage follicular lymphoma.	II	42, 46, 47, 49, 51
Combination chemotherapy regimens (e.g. CVP or CHOP) may be used where a shorter treatment duration or more rapid disease response is desired, although these regimens are not consistently associated with any long-term improvement in quality or duration of disease response, or overall survival.	II	46, 47, 49, 51

Where such therapies are used, two studies have explored the potential value of the addition of wide-field irradiation. Portlock et al⁴⁸ found no benefit in any of complete remission rate, disease-free interval, or overall survival for the addition of total lymphatic irradiation to CVP chemotherapy. A second study⁵² randomising patients who attained a complete remission to chemotherapy to receive 30–40 Gy external beam XRT to sites of initial nodal ‘bulk’ (size criteria not provided) or not, claimed to demonstrate an improvement in overall survival (20 year actuarial rates of 89% versus 71%; $P < 0.01$). However, the innumerable internal inconsistencies evident in this report seriously question the validity of these claims. It would be unwise to base clinical management decisions on this data without independent validation in another trial.

Guideline — Low-grade lymphoma — advanced disease response and radiotherapy (clinical trial)	Level of evidence	Refs
Where a patient with advanced-stage follicular lymphoma has achieved a complete response to initial therapy, irradiation to nodal sites of disease (initially bulky or otherwise) is not recommended outside of the context of a clinical trial.	II	48

In support of the second approach of the initial application of optimally effective therapy, regardless of tumour-burden or symptoms, there are a number of emerging observations:

- some phase III studies have established that the choice of initial therapy can influence overall survival^{53–56}, challenging the dogma that therapeutic intervention cannot alter the natural history of advanced-stage follicular lymphoma
- at institutions where an aggressive approach to initial treatment has been consistently employed, there has been a consistent and step-wise improvement in overall survival for patients with stage IV follicular ‘low-grade’ lymphoma seen in recent years, independent of known prognostic factors. It appears to be restricted to those patients attained a complete remission with initial therapy (1977–82 median survival seven years, 1992–97 seven-year survival of 80%¹), and
- the attainment of a ‘molecular’ complete remission (i.e. eradication of PCR-detectable cells containing the t(14;18) from the peripheral blood or bone marrow) is associated with an remission duration in patients treated with non-myeloablative therapies.^{57,58}

These observations, particularly the potential utility of a ‘molecular remission’ as a surrogate measure of treatment efficacy, have guided the development and exploration of a number of novel regimens that are capable of achieving complete remission rates of 80–90%, and molecular remission rates of 70–90%.

Importantly, the second and third points are indirect, and have not been either reproducibly shown (second point) or validated in prospective studies (third point). Thus these observations, although promising and provocative, do not provide unequivocal proof of a clear survival benefit for patients treated using such approaches. However, it is important that this data be discussed openly and clearly with patients, particularly those patients who are younger, highly motivated and without other medical co-morbidities, as some may quite reasonably wish to pursue such approaches during the time that the required clinical trials are being undertaken.⁵⁹

Guideline — Low-grade lymphoma — ‘aggressive’ treatment	Level of evidence	Refs
Pending the availability of further data from phase III studies, where motivated and informed patients have been made fully aware of the promising but inconclusive data regarding potential overall survival benefits of initial aggressive treatment approaches and wish to pursue such a strategy, initial therapy attempting to achieve maximal cytoreduction (potentially guided by molecular assessment of minimal residual disease) is a reasonable approach in carefully selected cases.	II	60–64

Regimens capable of achieving these levels of cytoreduction include:

- fludarabine 25 mg/m²/day x 3, mitoxantrone 10 mg/m² x 1, dexamethasone 20 mg orally daily x 5, and concomitant rituximab 375 mg/m² for a total of six doses, with cycles given every 28 days for a total of eight cycles^{60,61}
- ‘alternating triple therapy’ (12 cycles of alternating CHOD-Bleo, ESHAP, and NOPP — see references for dosage details)^{60,61}
- CHOP and rituximab^{62,63}
- fludarabine and rituximab⁶³

The only one of the above regimens to have been compared to a ‘standard’ regimen for the initial therapy of patients with stage IV follicular lymphoma is CHOP and rituximab. The German Low-grade Lymphoma Group compared CHOP alone to CHOP plus rituximab and found that the combination was able to achieve superior time to treatment failure ($P < 0.0007$) and overall survival ($P = 0.016$). However, interpretation of the overall survival data from this study is confounded by a second randomisation to high-dose therapy and autologous transplantation or interferon- α maintenance.⁶⁴ The data with the longest follow up using the FND and ATT regimens did not incorporate rituximab⁶⁰. However, a recent phase III study has demonstrated improved TTF with FND and concurrent rituximab, compared to sequential FND followed by rituximab. The mature data from a phase III study in the treatment of patients with relapsed indolent lymphomas (including follicular lymphoma) showing a clear overall survival advantage for the additional of rituximab to the FCM regimen (fludarabine/cyclophosphamide/mitoxantrone)^{65,66}, make the routine addition of rituximab to the above regimens highly justified when they are being utilised with ‘curative’ intent.

Importantly, the use of single-agent fludarabine in the initial treatment of patients with follicular lymphoma has been shown to result in inferior outcomes compared with a ‘CHOP-like’ regimen (CHVP) followed by interferon maintenance.⁶⁷

Use of maintenance therapies

Some^{53–56,68,69} but not all^{70–72} randomised trials have shown a benefit for interferon maintenance following the initial therapy of patients with advanced-stage follicular lymphoma. A meta-analysis of the published trials demonstrated that this benefit was restricted to those patients treated with anthracycline-based therapies.⁷³ With the emergence of newer regimens used for the initial therapy of these patients and increasingly effective salvage therapies, the relative contribution of interferon maintenance is likely to diminish, but remains a reasonable option that should be considered on an individual patient basis.

Guideline — Low-grade lymphoma — criteria for therapy with interferon	Level of evidence	Refs
The use of interferon- α maintenance after anthracycline-based initial therapy (e.g. CHOP) may be considered on an individual patient basis.	II	55, 53, 73

There are retrospective subgroup data from a prospective randomised trial of rituximab maintenance (375 mg/m² every two months for four doses) in a small group of patients who received rituximab alone as their initial therapy, that this ‘maintenance’ schedule may prolong time to disease progression. However, no data on overall survival are yet available.⁷⁴ The more clinically relevant questions of the potential role of rituximab maintenance after either combination chemotherapy or combined chemotherapy and rituximab await the availability of results from current clinical trials. The routine use of rituximab maintenance is not recommended based on currently available data.

Relapsed stage IV disease

Despite the very large number of phase II trials describing the clinical activity of many chemotherapy regimens in patients with relapsed follicular lymphoma, there are very few phase III studies. A proportion of patients have disease that remains sensitive to single-agent alkylating agents, but the proportion of responses and the duration of responses serially decline with each episode of retreatment.⁷⁵

The available phase III trials have compared single-agent fludarabine with CVP⁷⁶ and with the addition of rituximab to the FCM chemotherapy regimen. They have also compared single-agent rituximab with radioimmunotherapy (Zevalin, ibritumomab tiuxetan).

The study comparing single-agent fludarabine with CVP⁷⁶ demonstrated a higher response rate, complete remission rate, and progression-free survival, but not overall survival with the fludarabine treatment.

Guideline — Low-grade lymphoma — recurrent disease and fludarabine	Level of evidence	Refs
Where patients have initially been treated with an alkylating agent and have recurrent disease requiring systemic chemotherapy, therapy containing fludarabine should be considered.	II	76

Dreyling et al⁶⁵ from the German Low Grade Lymphoma Study Group have performed a phase III trial exploring the value of the addition of rituximab (375 mg/m², one dose per cycle) to the intravenous FCM chemotherapy regimen (fludarabine 25 mg/m²/day x 3, cyclophosphamide 200 mg/m²/day x 3 and mitoxantrone 8 mg/m² x 1) given for a maximum of four cycles. This is the first study to demonstrate a clear survival benefit from a specific chemotherapy regimen used in this setting.

Guideline — Low-grade lymphoma — therapy in relapsed follicular lymphoma	Level of evidence	Refs
In patients with relapsed follicular lymphoma, the addition of rituximab to fludarabine-based combination chemotherapy is associated with improved outcomes, including better overall survival.	II	65

Witzig et al⁷⁷ performed a randomised comparison of single-agent rituximab and the radio-immunotherapeutic approach using yttrium-90 labelled ibritumomab tiuxetan (Zevalin) in patients with relapsed or refractory follicular lymphoma who fulfilled the following criteria:

- no prior rituximab therapy
- bidimensionally measurable disease ≥ 2 cm
- WHO performance status of 0–2
- haemoglobin ≥ 8 g/dl, neutrophils ≥ 1.5 , platelets ≥ 150
- adequate hepatic and renal function
- $< 25\%$ bone marrow infiltration
- external beam radiation to $\leq 25\%$ of bone marrow.

Among the specific patient cohort who met these criteria, the radioimmunotherapy was associated with a significantly higher rate of overall response, and complete response, but not time to progression or overall survival. This is consistent with the data showing high response rates using Zevalin (or other radioimmunotherapy strategies) in patients with disease unresponsive or relapsing within six months of previous rituximab therapy.⁷⁷

Guideline — Low-grade lymphoma — radioimmunotherapy criteria	Level of evidence	Refs
For patients who fulfil specific criteria (specifically <25% bone marrow infiltration), the use of radioimmunotherapy is associated with a higher rate of disease control and should be considered in preference to single-agent rituximab.	II	77

In addition to the strategies listed above that have been established as efficacious on the basis of phase III trials, there are numerous regimens or approaches with useful clinical efficacy data in the setting of patients with relapsed follicular lymphoma, based on phase II studies. These studies provide the basis for the use of strategies such as:

- alkylating agent combination therapies (using cyclophosphamide/ifosfamide/prednimustine)
- nucleoside analogue therapy (fludarabine/2-chloro-deoxyadenosine/gemcitabine)
- nucleoside analogue combination therapies
- cytosine-arabinoside
- platinum compounds (cisplatin, carboplatin, oxaliplatin)
- rituximab
- chemo-immunotherapy combinations (alkylating agents or nucleoside analogues)
- radio-immunotherapy (Zevalin/Bexxar/¹³¹I-labeled rituximab)
- external beam irradiation (local or extended fields, including low-dose TBI)
- anthracyclines and analogues
- vinca alkaloids and epipodophyllotoxins
- interferon- α
- topoisomerase-I inhibitors
- taxanes

Given the recurrent relapsing nature of follicular lymphoma, there are circumstances where such approaches will need to be considered. Each of these regimens has specific restrictions in terms of disease characteristics and organ function, as well as specific toxicity profiles. These will influence and guide the appropriate patients and circumstances where these are reasonable choices. There is no survival data to allow selection of any one of these approaches over another.

Histologic transformation

Patients with relapsed or refractory follicular lymphoma are at risk of developing histologic transformation to an aggressive lymphoma (usually diffuse large B-cell lymphoma, but rarely Burkitt's lymphoma). Where it is safe and reasonable, a biopsy of the dominant site of relapsed disease should be obtained to investigate possible histologic transformation. This is particularly so where there are:

- profound B-symptoms

- a disproportionately raised serum LDH level
- rapid or disproportionate growth of one disease site
- unusual areas of disease involvement (CNS, bone lesions, visceral infiltration), or
- the development of hypercalcemia.

Key point

Where it can be safely performed, re-biopsy of the dominant or clinically suspicious disease site should be performed in patients with relapsed or refractory follicular lymphoma to investigate possible histologic transformation to aggressive lymphoma.

Where histologic transformation has occurred, the patient should be managed as for the specific histology of the transformed disease (diffuse large B-cell lymphoma or Burkitt's lymphoma) (refer to Chapter 13).

- Follicular large cell (grade 3) — to be discussed in the chapter on diffuse large B-cell lymphoma (see Chapter 12 — Aggressive lymphoma).

12.4.2 Role of autologous HSCT in the management of follicular NHL

The role of autologous hematopoietic stem cell transplant (auto-HSCT) in the management of advanced-stage follicular lymphoma remains controversial.

As noted in Section 12.4.1, follicular lymphoma is a disease with a long natural history, with a pattern of cyclical response and relapse to non-intensive therapy. Most patients with advanced-stage disease, however, ultimately die from the disease⁷⁸, justifying investigational strategies, particularly in younger patients. This pattern of disease activity and management has made the design of prospective controlled trials difficult, and highlights the critical importance of long follow up.

Most published studies have been single institution phase II studies using historical controls. The largest study with the longest follow up was performed at the Dana-Faber Cancer Institute with patients enrolled between 1985 and 1995.⁷⁹ Patients were eligible if they were less than 65 years of age and had relapsed after at least one standard chemotherapeutic regimen or had sensitive disease but had failed to enter remission after at least one regimen. Autologous marrow was purged using a cocktail of monoclonal antibodies. The disease-free survival and overall survival are estimated at 42% and 66% respectively at eight years, with a twelve-year survival rate of 69%. The best outcomes were seen in those in whom purging was deemed to have been successful (using a PCR-based detection assay). The authors conclude that given that the median survival from first recurrence following conventional therapy is five years (a figure derived from the study of Johnson et al⁷⁸), this strategy may prolong survival. Similar results are reported from a number of other groups^{80–82}, all reaching similar conclusions. There appears, however, to be a pattern of ongoing relapse in these studies.

Three prospective randomised controlled trials investigating the role of auto-HSCT as part of the therapy of follicular NHL have been reported recently. The European CUP trial⁸³ enrolled 140 patients with relapsed follicular lymphoma to initially receive three cycles of conventional salvage chemotherapy (DHAP). Responding patients were randomly assigned to receive three further cycles of conventional chemotherapy, or high-dose therapy followed by purged (P) or unpurged (UP) stem cell support.

Only 89 patients were randomised. With a median follow up of 69 months, there was a significant benefit in terms of progression-free and over-all survival for the high-dose therapy arms. The study was not powered to allow a definitive statement to be made regarding the benefit of purging. Two large studies addressing the role of auto-BMT as part of up-front therapy for follicular NHL have

recently been presented in abstract form. The French study of the GELF (GELF94) and GEOLAMS (GEOLAMS 064)^{84,85} are reported to show conflicting results. GELF94 randomised 401 patients with untreated high tumour burden follicular lymphoma to either 18 months of a CHVP plus interferon alpha regimen, or to four cycles of CHOP followed by a cyclophosphamide/VP16/TBI conditioned autograft. Overall survival was significantly longer at seven years for the transplant arm (86% versus 74%). There was no excess mortality from second malignancies in the transplant arm. GEOLAMS 064 utilised a similar control arm. The transplant arm consisted of three courses of VCAP followed by a purged autograft in responding patients. At a median follow up of five years, overall survival was comparable in both arms, and there was an excess of second malignancies in the transplant arm. The conflicting findings in these studies are difficult to comment on in the absence of peer-reviewed publications, which are awaited. The modest benefits to auto-BMT shown in the GELF94 study may be largely negated by current best-practice conventional regimens that include monoclonal antibodies.

The recent reports of second malignancies complicating auto-HSCT are of concern. The Dana-Faber group has reported an actuarial incidence of MDS at ten years of 19.8% in a series of 552 patients with lymphoma undergoing auto-HSCT following Cy/TBI conditioning.⁷⁹

Guideline — Low-grade lymphoma — auto HCST — indication	Level of evidence	Refs
Auto-HSCT may be indicated in patients who have failed at least one conventional chemotherapeutic regimen.	II	83
The use of auto-HSCT as part of up-front treatment remains controversial.	III,IV	84, 85

12.4.3 Role of allogeneic HSCT in the management of lymphoma

Registry data and a small number of phase II studies suggest that the procedure-related mortality of conventional sibling allo-HSCT in patients with follicular NHL is high, between 30% and 40%. However, relapse rates appear to be lower than those described following auto-HSCT, and there appears to be a plateau on the survival curve not evident following auto-HSCT.⁸⁶⁻⁸⁸

These results, together with recent studies showing convincing disease responses following non-myeloablative stem-cell transplant (NST), suggest that a graft versus follicular lymphoma effect exists, and that some patients may be cured following allo-HSCT.

The role of NST will become clearer as studies with longer follow up are presented. At this time, while significant response rates have been reported and treatment related mortality rates appear to be lower than conventional allo-HSCT, the curative potential of NST in follicular lymphoma is unknown.⁸⁹⁻⁹²

Guidelines — Low-grade lymphoma — auto-HCST and NST considerations	Level of evidence	Refs
Conventional sibling allogeneic HSCT should be limited to young patients with poor prognosis follicular lymphoma who have limited comorbidities.	IV	86-88
NST can be considered in patients with poor prognosis follicular lymphoma, but should optimally be performed in the context of approved clinical trials.	III, IV	89-92

12.5 Small lymphocytic lymphoma

Summary of clinicopathological findings

Clinical	Mostly asymptomatic, fatigue, autoimmune haemolytic anaemia, infections. Lymph nodes liver and spleen commonly involved. Rarely (Richter's) transformation to large B-cell lymphoma or Hodgkin lymphoma.
Morphology	Diffuse involvement with pseudofollicular pattern (proliferation centres containing small lymphocytes, prolymphocytes and para-immunoblasts). Small, round, regular nuclei but variants may have irregular nuclei. Early involvement may be interfollicular or unrecognised without immunophenotyping. White and red pulp involved in spleen. Bone marrow infiltration may be nodular, interstitial, and later, diffuse.
Immunophenotype	Weak SIgM +/- SIgD, CD5+, CD19+, CD20 weak+, CD22 weak+, CD79a+, CD79b usually-ve, CD23+in most but not all cases, CD43+, CD11c weak+, CD10-, cyclinD1-ve. FMC7 usually-ve. SIg often reactive against self antigens.
Genetics	40–50% naïve B-cells with unmutated VH genes 50–60% post-germinal centre cells with somatically mutated VH genes Trisomy 12 (usually naïve, unmutated VH genes) del(13q14) del(11q22–23) del(6q21), del(17p13)

A consequence of the WHO classification system is that 'small lymphocytic lymphoma' has been merged as an entity with chronic lymphocytic leukaemia (CLL). This is a logical extension of the knowledge that small lymphocytic lymphoma is molecularly and immunophenotypically identical to CLL, and for a number of years has been considered to represent the 'tissue manifestation' of CLL. The full management of these patients is beyond the scope of this review. Those rare patients who present with truly localised disease after complete staging should be managed as described for:

- localised nodal marginal zone B-cell lymphoma, if isolated nodal involvement is present
- localised extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue if isolated mucosal involvement is present. Those with advanced-stage disease (stage IV, whether or not leukaemic involvement is present) should be managed according to guidelines for CLL.

The major issue with patients considered to have small lymphocytic lymphoma is the establishment of an accurate definitive diagnosis, as distinction from other diffuse mature B-cell lymphoproliferative disorders (lymphoplasmacytic lymphoma, marginal zone B-cell lymphoma, and mantle-cell lymphoma is critical). (See Chapter 8)

12.6 Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT)

Summary of clinicopathological findings

Clinical	GIT (especially stomach), lung, ocular adnexae, skin, thyroid and breast. May have multiple extranodal sites and/or regional node involvement without dissemination.
Morphology	Small to medium-sized, centrocyte-like or monocytoid cells accumulate outside the follicle mantle, progressively expand to form sheets and migrate into the germinal centre. Lymphoepithelial lesions common in stomach. Zones of plasmacytoid differentiation common.
Immunophenotype	IgM+, +/- IgA or IgG, CD20+, CD79a+, CD21+, CD35+, CD5-, CD10-, CD23-, cyclinD1-, CD43+/-, CD11c +/-.
Genetics	Post germinal centre B-cell Trisomy 3 Disease associated with t(11;18)(q21;q21) (<i>API2/MLT</i> fusion) is resistant to anti <i>Helicobacter</i> therapy

12.6.1 Gastric

The management of gastric marginal zone lymphoma is discussed separately (see Chapter 17).

12.6.2 Non-gastric sites

Extra-nodal marginal zone lymphoma can occur at many non-gastric sites, most commonly conjunctivae, skin, salivary gland, lung or thyroid. Other rare sites such as bladder, prostate and breast, are also reported.^{93,94} In some of these sites, there are known associations with chronic antigenic stimulation (e.g. *Borrellia Burgdorferi* and skin disease⁹⁵, *Chlamydia Psittaci* and conjunctival disease⁹⁶, Sjogren's disease and salivary gland involvement⁹⁷, and Hashimoto's thyroiditis and thyroid disease.⁹⁸ Where an infectious agent is implicated, by analogy, with gastric marginal zone lymphoma and *Helicobacter pylori* infection, eradication of the organism should be considered as the treatment of first choice. It can result in regression of the associated lymphoma, although there are insufficient data on specific organs to accurately determine what proportion of patients may respond to such eradication therapy. Nevertheless, given its low toxicity, this approach is recommended where there is (1) an identified associated pathogen, (2) no critical or impending threat to the organ involved, and (3) no history of kinetically aggressive preceding behaviour of the disease in the local site.

Guideline — Low-grade lymphoma — extra-gastric marginal zone lymphoma — pathogen treatment urgency	Level of evidence	Refs
Where an identified pathogen is associated with extra-gastric marginal zone lymphoma, and there is no clinical urgency to obtain immediate disease regression, eradication therapy directed against the identified pathogen is recommended.	III	95, 96

Localised disease

Approximately 60–75% of these cases of extra-gastric marginal zone lymphoma are anatomically localised (stage I–II disease).^{99,100} Where there is no associated infective agent identified, or successful eradication of an identified agent is not associated with disease regression, or there is clinical urgency to achieve disease regression, localised irradiation using 25–35 Gy is highly effective, depending upon the specific location and the relative risk of adverse effects on surrounding

normal tissues,. There are a number of large retrospective series describing complete remission rates of 95–100% with external beam XRT in this dose range^{93,101,102}, and long-term local disease-control rates of 95–100%. The rate of local relapse appears to be higher with external beam RT doses of <25 Gy.⁹³ Although patients with nodal marginal zone lymphoma will more rarely have localised disease (<30%¹⁰³), the approach to their management should be similar to patients with other stage I–II ‘low-grade’ lymphomas.

Guideline — Low-grade lymphoma — extra-gastric marginal zone lymphoma — durable local control	Level of evidence	Refs
Where there is no associated infective agent identified, successful eradication of the agent is not associated with disease regression, or there is clinical urgency to achieve disease regression, localised irradiation using 25–35 Gy is highly effective in achieving durable local control for extra-gastric marginal zone lymphoma (nodal and non-nodal).	III	93, 101, 102

Depending upon the adequacy of initial staging, length of follow up and patient selection, approximately 20–30% of patients will develop disease recurrence outside the irradiated field, with the contralateral paired organ at moderate risk (~ 10% long-term). The long-term rate of disease-free survival is approximately 75% at 5–10 years.^{93,100}

Disseminated disease

Where disease is disseminated at diagnosis, recurs within prior radiotherapy fields, or radiation cannot be delivered, a range of chemotherapy and immunotherapy strategies have shown activity in phase II studies. However, it should be emphasised that the durability of local control appears to be inferior to that achieved with XRT^{94,104}, and systemic chemotherapy is not recommended in circumstances where local XRT can be safely delivered for the treatment of localised disease. Agents with established activity include rituximab¹⁰⁵, 2-CdA¹⁰⁶, cyclophosphamide¹⁰⁴, and fludarabine.¹⁰⁷ Oral chlorambucil (15 mg/m²/day) and prednisolone (100 mg/day) each given for five days every 28 days also has similar levels of activity to the listed agents, with no evidence of benefit (as measured by either response rate, CR rate, FFS or overall survival) for the addition of epirubicin.¹⁰⁸ With any of these agents, initial response rates are high (50–90%), and there are no comparative data that allow meaningful comparisons of efficacy. Choices for treatment should be based on patient acceptance and tolerance of the anticipated adverse effects of the agents under consideration.

Disseminated disease (stage III or IV) is incurable with available therapies. However, patients with stage IV disease due to the bilateral involvement of paired organs (which is extremely rare) should be treated with local XRT with curative intent. The reported median survival is 7–10 years.^{109,110}

Asymptomatic patients may be observed without therapy, as there is no evidence that this strategy impairs their long-term outcome.¹¹⁰ Similarly, the available non-randomised data^{99,109,110} do not suggest the superiority of combination chemotherapy (e.g. CHOP) over single-agent alkylating agents (cyclophosphamide or chlorambucil). The one available randomised trial of the addition of an anthracycline (epirubicin) to alkylating agent therapy (chlorambucil) did not show any benefit in terms of either overall response rate or overall survival.¹⁰⁸ There is a continuing randomised study by the International Extranodal Lymphoma Study Group (IELSG) of chlorambucil ± concurrent rituximab.

Guideline — Low-grade lymphoma — extra-gastric marginal zone lymphoma — therapeutic options	Level of evidence	Refs
Patients with asymptomatic disseminated marginal zone lymphoma may be observed without initial therapy.	III	110
Patients with symptomatic or progressive disseminated marginal zone lymphoma should be treated with single-agent chemotherapy (alkylating agents/nucleoside analogues/rituximab have similar levels of activity).	III	104–107
There is no apparent benefit from the use of combination chemotherapy regimens (e.g. CHOP) as initial therapy.	III	99, 109, 110
There is no benefit from the addition of anthracyclines to alkylating agents (e.g. chlorambucil).	II	108

Transformation to aggressive lymphoma

The lifetime risk of developing histological transformation to a histologically aggressive NHL is approximately 10–20%, and is influenced by the presence or absence of the t(11;18)(q21;q21) translocation. The relative frequency of this translocation varies according to the organ involved.⁹⁹

12.7 B-cell monoclonal lymphocytosis

There are recent data that a small proportion of elderly patients with normal numerical peripheral blood parameters have a detectable monoclonal B-cell population in the peripheral blood by sensitive flow cytometry, with a phenotype consistent with extra-nodal marginal zone lymphoma.¹¹¹ These patients should not be treated unless symptoms develop, or there is evidence of progressive lymphocytosis with haematopoietic impairment. These disorders have been given the label of B-cell monoclonal lymphocytosis and their clinical significance is yet to be determined, but it appears that the annual risk of progression to a recognisable lymphoproliferative disorder is about 1%.¹¹²

12.8 Nodal marginal zone B-cell lymphoma

Summary of clinicopathological findings

Clinical	Localised or generalised lymphadenopathy, without extranodal or splenic disease.
Morphology	Perifollicular and interfollicular infiltration by centrocyte-like or monocytoid cells. May resemble extranodal marginal zone or splenic marginal zone lymphoma. Plasmacytic differentiation common.
Immunphenotype	Similar to extranodal marginal zone lymphoma, but some cases are IgD+, similar to splenic marginal zone lymphoma.
Genetics	None defined.

This is a very rare disorder. It is managed stage-for-stage in the same way as extranodal marginal zone lymphoma.

12.9 Lymphoplasmacytic lymphoma (Waldenström's macroglobulinemia)

Summary of clinicopathological findings

Clinical	IgM paraprotein >3 g/dl. Hyperviscosity syndrome. Autoimmune disorders. Bone marrow, lymph nodes and spleen involvement.
Morphology	Monomorphous. Small lymphocytes, plasmacytoid cells and plasma cells. No features of marginal zone lymphoma, follicular lymphoma or chronic lymphocytic leukaemia. Dutcher bodies.
Immunophenotype	Surface and cytoplasmic IgM, IgG or IgA. IgD -ve. CD19, CD20, CD22, CD79a and CD38 +ve. CD43+/- . CD5, CD10, CD23 and cyclinD1 -ve.
Genetics	Post follicular, somatically rearranged VH genes. T(9;14)(p13;q32) (<i>PAX-5</i> encodes BSAP).

Waldenström's macroglobulinemia can manifest symptoms through any combination of:

- the physicochemical properties of the IgM paraprotein (hyperviscosity, peripheral neuropathy, cryoglobulinemia, cold-agglutinins, and amyloidosis)
- bone marrow infiltration with haematopoietic compromise
- extra-medullary infiltration (splenomegaly, lymphadenopathy, or rarely other organ infiltration)
- systemic paraneoplastic symptoms (fevers, sweats, weight loss), or
- immunological disturbance or compromise (autoimmune phenomena or immunosuppressive complications).¹¹³

Specific therapies may be employed to manage any of these individual manifestations, distinct from any systemic anti-neoplastic therapy.

12.9.1 Prognostic features

The major adverse prognostic features for overall survival are: age ≥ 65 years, serum albumin < 40 g/L, and the presence of at least one, or two, lineage cytopenias (Hb < 120 g/L, neutrophils $< 1.5 \times 10^9/L$, or platelets $< 150 \times 10^9/L$).¹¹⁴ The five-year actuarial survival rates for patients with 0–1 risk factors is 90%, 2 risk factors 67% and 3–4 risk factors 37%. Patients who are asymptomatic and without evidence of progressive disease may be managed expectantly without therapy. There are no randomised studies evaluating immediate versus delayed therapy.

12.9.2 Hyperviscosity

For patients who present with hyperviscosity, plasmapheresis is an effective form of management, allowing systemic treatments time to control the disease. As well, plasmapheresis may be used in a palliative context in patients with advanced drug-resistant disease.¹¹⁵ The required frequency of plasmapheresis depends on the production rate of the IgM and the threshold at which the individual patient becomes symptomatic, but is usually every three to eight weeks.¹¹⁶

12.9.3 Chemotherapy

Alkylating agents

Traditionally, alkylating agents, most commonly chlorambucil, have been used as the primary therapy for symptomatic patients. In one of the few randomised studies reported in this disease, Kyle

compared continuous chlorambucil 0.1 mg/kg/day with intermittent dosing 0.3 mg/kg/d for seven days every six weeks.¹¹⁷ Based on a reduction in serum paraprotein of $\geq 50\%$, the response rate with continuous therapy was 75%, and for intermittent therapy 64%. These therapies were very prolonged, with a median time to achievement of response of 18 and 21 months, respectively. The median response durations were 26 and 46 months, respectively, and the median overall survival in both treatment arms was 65 months. None of these differences were statistically significant. These characteristics provide a basis for comparison with other therapies.

In the context of sequential studies at a single institution¹¹⁸, there was no difference in response rate, or overall survival between patients treated with chlorambucil and prednisolone (57% response rate), intravenous (IV) CVP (cyclophosphamide/vincristine/prednisolone) (44% response rate) or CHOP (65% response rate). None of these differences were statistically significant, and the median overall survival of these cohorts again did not differ. Thus there is no additional benefit from the addition of corticosteroids to simple alkylating agents, nor are the more aggressive IV alkylating agent regimens, or anthracycline-containing regimens, superior to chlorambucil alone for initial therapy, based on this single institution retrospective comparison.

These and other studies have provided justification for using the attainment of an objective response as a surrogate endpoint for improving overall survival. In three studies, patients attaining an objective response have had greater median overall survival than non-responding patients; 49 months versus 24 months¹¹⁹, 96 months versus 42 months¹²⁰ and 92.4 months versus 30 months.¹¹⁸ Those rare patients attaining a complete response had a median overall survival of eleven years.¹¹⁸

Nucleoside analogues

As initial therapy, the nucleoside analogue class of drugs appear to be at least as effective single agents as alkylating agents, and have the advantage of requiring between three and six months of therapy, albeit parenteral in all published series, although oral fludarabine is now available and is pharmacokinetically equivalent to the IV form.¹²¹ There are no comparative studies of the efficacy of IV versus oral fludarabine in this disease, but they are predicted to have equivalent efficacy. Cladribine (2-chlorodeoxyadenosine; 2-CdA) has achieved an overall response rate of 75% (reported range 44–90%) among previously untreated patients, with 12% attaining CR.¹¹⁸ Fludarabine has achieved an overall response rate of 79%, with 5% attaining CR, and a median response duration of greater than three years for all responding patients.¹⁰⁷ The follow up of these studies at the time of reporting is inadequate as yet to draw any firm conclusion on any impact on overall survival.

Thus either single-agent oral alkylating agents (continuous or intermittent chlorambucil) or a nucleoside analogue (2-CdA or fludarabine) are recommended for the initial therapy of symptomatic patients. The continuing United Kingdom/ALLG randomised study of chlorambucil versus fludarabine in this setting is addressing the highly relevant question of the optimal initial therapy. It should be supported by both patients and clinicians. Combination therapies that are capable of achieving significantly higher rates of true complete remissions are required. This is a reasonable surrogate endpoint for the rapid assessment of efficacy in the context of exploratory phase II studies of novel combinations.

Guideline — Low-grade lymphoma — Waldenstrom's lymphoma — therapeutic options	Level of evidence	Refs
Patients with asymptomatic Waldenstrom's macroglobulinemia may be observed without initial therapy.	IV	113
Patients with symptomatic or progressive Waldenstrom's macroglobulinemia may be treated with plasmapheresis.	III	115, 116

Relapsed or refractory disease

In the context of relapsed/refractory disease, alkylating agent-based therapy (cyclophosphamide, adriamycin, prednisolone) has been compared with single-agent fludarabine.¹²² Using conventional response criteria, the response rates were 11% and 30% respectively ($P = 0.02$), with median response durations of three months and 19 months respectively ($P < 0.01$), and superior event-free survival with fludarabine ($P < 0.01$). In spite of these differences, there was no difference in overall survival ($P = 0.89$). These response rates are supported by previous single-arm phase II studies of the nucleoside analogues in this context, where 2-CdA was able to induce responses in 45% of patients, and fludarabine in 31%.¹¹³ There are no comparative studies of these two nucleoside analogue agents in this setting. Thus in the setting of relapsed or refractory disease, a nucleoside analogue, either fludarabine or 2-CdA, is clearly superior to alkylating agent therapy, and is recommended.

Guideline — Low-grade lymphoma — Waldenstrom's lymphoma — response to therapy	Level of evidence	Refs
In patients with relapsed Waldenstrom's macroglobulinemia, a nucleoside analogue (2-CdA or fludarabine) is associated with a higher response rate and more durable disease control than alkylating agent/anthracycline therapy.	II	122
Rituximab has useful activity as a single-agent in relapsed/refractory Waldenstrom's macroglobulinemia.	III	123–125
The combination of fludarabine and rituximab has high levels of activity in relapsed/refractory Waldenstrom's macroglobulinemia.	III	126

Thalidomide¹²⁷ has attained a response rate of 25%, but with very brief durations of response, making this therapy unattractive as a single-agent. Interferon- α has demonstrated modest activity¹²⁸ and can be considered as a maintenance therapy, provided it is well tolerated.

Monoclonal antibodies — rituximab

In previously untreated patients, MabThera (rituximab) has achieved a response rate of 35%.¹²⁵ In phase II studies in relapsed/refractory patients, MabThera (rituximab), has demonstrated a cumulative response rate of 36% (23/64), with median response durations of 7–15 months.^{124–126} The combination of fludarabine and MabThera has shown marked activity and good tolerance in a phase II study in patients with relapsed/refractory disease, with an overall response rate of 65%.¹²⁶ Based on the established superiority of such combination strategies compared with fludarabine-containing chemotherapy alone in a broad range of indolent lymphoproliferative disorders, including Waldenström's macroglobulinemia, this combination is a very reasonable treatment for patients with relapsed/refractory disease.

Other management issues

Splenectomy can be effective in ameliorating symptomatic splenomegaly and can improve peripheral blood cytopenias due to splenic sequestration or autoimmune phenomena.

For patients with recurrent severe proven infections in the context of established hypogammaglobulinemia, regular replacement therapy with a pooled intravenous immunoglobulin preparation, such as Intragam, is recommended.

In the rare cases where it has been applied, high-dose therapy and either autologous stem-cell transplantation or allogeneic stem-cell transplantation have been able to achieve durable disease control, but with substantial morbidity and some mortality risk in this generally elderly patient group.¹²⁹ There are insufficient data to determine whether allogeneic stem-cell transplantation can

offer the prospect of cure for these patients, as is achievable in other ‘low-grade’ lymphoproliferative disorders.

Approximately 10% of patients ultimately develop a variety of forms of histologic transformation, with a poor outcome with conventional therapies.

12.10 Splenic marginal zone lymphoma

Summary of clinicopathological findings

Clinical	Spleen, splenic hilar nodes, bone marrow and blood. Bone marrow usually involved. Autoimmune thrombocytopaenia or anaemia common.
Morphology	Blood: villous lymphocytes +/- plasmacytoid forms. Spleen: Small round lymphocytes fill splenic marginal zone and replace mantle zone and germinal centres. Peripheral zone of slightly larger and paler cells. +/- plasmacytic differentiation. Red pulp involved. Lymph node: nodular pattern, replacement of follicles but no ‘marginal zone’ pattern. Sinuses dilated.
Immunophenotype	SIgM+ SigD+, CD19+, CD20+, CD79a+, CD5-, CD10-, CD43-, cyclinD1-, CD103-.
Genetics	Allelic loss of 7q21–32 t(11;14) and trisomy three may represent crossover with mantle cell and extranodal marginal zone lymphoma.

The median survival of patients is reported to be about thirteen years¹³⁰. Adverse prognostic factors include: older age, anaemia, thrombocytopenia, and lymphocytosis.

Key points

Splenic marginal zone lymphoma

There are no prospective studies available to guide recommendations in this area. All available data are derived from retrospective cohort series. Within these limitations, the following recommendations can be made:

- 1 It is reasonable to follow, without active intervention, patients who are asymptomatic with stable lymphocytosis and minor, stable and asymptomatic cytopenias.^{130,131}
- 2 It is recommended that patients be screened for hepatitis C. Where active hepatitis C is the underlying immunological precipitant for their lymphoma, specific treatment of the hepatitis C can be associated with significant regression of the lymphoma.⁷
- 3 Where patients have progressive or symptomatic splenomegaly, even in the context of significant marrow infiltration, splenectomy is the preferred therapy, where this can be performed safely.^{130–132} Splenectomy results in favourable clinical response in ~90% of patients. About 50% will never require any further therapy. Patients who are initially treated with splenectomy are reported to have a superior likelihood of survival than those initially treated with chemotherapy, although selection bias cannot be excluded in these retrospective comparisons.¹³⁰

- 4 Where systemic chemotherapy is required for disease progression following splenectomy, or for symptomatic extra-splenic disease, either single-agent alkylating agents such as chlorambucil¹³¹ or fludarabine^{133,134} are reasonable choices, based on limited non-comparative data. CHOP does not appear superior to simpler alkylating agent therapy.¹³²

Approximately 10% of patients ultimately develop various forms of histologic transformation with a poor outcome with conventional therapies.¹³⁵

12.11 References

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