Guidelines on the investigation and management of follicular lymphoma
British Committee for Standards in Haematology

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**METHODOLOGY**

The guideline group was selected to be representative of UK based medical experts. MEDLINE and EMBASE were searched systematically for publications in English from 1980-2010 using key words follicular lymphoma, non-Hodgkin lymphoma and low-grade lymphoma. The writing group produced the draft guideline which was subsequently revised by consensus by members of the Haemato-oncology Task Force of the British Committee for Standards in Haematology. The guideline was then reviewed by a sounding board of approximately 50 UK haematologists, the BCSH (British Committee for Standards in Haematology) and the British Society for Haematology Committee and comments incorporated where appropriate. The objective of this guideline is to provide healthcare professionals with clear guidance on the management of patients with follicular lymphoma. The guidance is not appropriate for patients with other lymphoma subtypes and in all cases individual patient circumstances may dictate an alternative approach.

**GRADING OF EVIDENCE**

These guidelines have used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) nomenclature for assessing levels of evidence and providing recommendations in guidelines. See appendix 2.
SUMMARY OF KEY RECOMMENDATIONS:

- Lymph node excision or adequate core biopsy is required for the diagnosis of follicular lymphoma (FL) - histology enables an assessment of the tumour grade and the exclusion of transformation to a more aggressive histological subtype (1B).

- All cases should be subject to routine central review by an experienced haematopathologist (1B).

- All patients with newly diagnosed FL should undergo a comprehensive clinical, laboratory and imaging assessment to characterise the stage of disease and the physiologic status of the patient, prior to any consideration of therapy (1B).

- The Follicular Lymphoma International Prognostic Index (FLIPI) indices should be recorded for all patients at diagnosis (2B).

- Involved field radiotherapy delivering a dose of 24 Gray (Gy) in 12 daily fractions should be regarded as the standard of care for patients with newly diagnosed, limited stage disease (1A). Outside of a clinical trial, lower doses of radiotherapy can only be recommended for palliation or re-treatment where radiation tolerance may be a concern.

- Observation following total excision of all macroscopic disease may be suggested in selected patients with negative staging after discussion with a radiation oncologist (2C).

- Observation remains an appropriate approach in patients with asymptomatic, advanced stage follicular lymphoma in an attempt to delay the need for chemotherapy. This is particularly the case for patients over 70 years of age (1A).

- Rituximab in combination with chemotherapy should be used in patients with newly diagnosed, symptomatic advanced stage FL (1A). There is currently no strong evidence to support one chemotherapy regimen over another.
• Rituximab maintenance after successful induction therapy prolongs progression-free survival (PFS) and is recommended in patients responding to first-line rituximab-based chemotherapy (1B).

• Patients with Mann and Berard histological grade 3b FL should be treated as if they have diffuse large B-cell lymphoma as there may be important clinical and biologic differences between this group and FL patients with lower grades (2B).

• Autologous stem cell transplantation has no role in first line therapy for FL (which has no evidence of histological transformation) outside the setting of a clinical trial (1B).

• Patients with known FL who present with features of relapsed disease should undergo a biopsy procedure, wherever practicable (1B).

• The combination of chemotherapy with rituximab is the standard for those patients who require treatment at the point of relapse and are rituximab naïve as the combination improves all clinically meaningful outcomes, including overall survival (OS), compared to chemotherapy alone (1A).

• Chemotherapy and rituximab should also be the standard for relapsed FL patients who have received prior rituximab if the patient had previously responded to rituximab (1C).

• Rituximab maintenance prolongs PFS substantially in patients with relapsed/refractory FL who are rituximab-naïve and respond to re-induction therapy with single agent rituximab, chemotherapy or chemotherapy and rituximab and should be offered to all patients in this setting (1A).

• Radioimmunotherapy with $^{90}$Y-Ibritumomab tiuxetan is an active treatment approach in patients with relapsed follicular lymphoma and should be considered in older patients and those that are refractory to or intolerant of chemotherapy and rituximab (2B).

• All patients with FL should be monitored for evidence of disease recurrence and for the late effects of therapy (1C).
1 INTRODUCTION

Follicular Lymphoma (FL) is the most common of the low grade lymphomas in the United Kingdom. Its incidence increases with age, with a median presentation between 60-65 years and a slight female: male predominance (Friedberg et al, 2009).

FL has commonly been seen as a chronic, relapsing, indolent tumour with a median survival of 7-10 years in the pre-rituximab era. Approximately 85% of patients have advanced disease at presentation. Symptoms may include B symptoms, fatigue, the local mass effect of lymph node enlargement, as well as those of bone marrow failure. Many patients, however, are relatively asymptomatic at presentation. The disease has been seen as incurable apart from in the relatively infrequent patient with early stage disease.

The course of the disease is heterogeneous. A minority of patients have indolent disease with little or no progression over several decades. Lymphadenopathy is variable and patients may enter spontaneous and prolonged remissions (Horning and Rosenberg, 1984). Some patients are observed without treatment according to a "Watch & Wait" policy (see section 5) and will never require systemic treatment. In contrast to this, over a period of years, 20-30% of patients will die following transformation of their disease to high grade lymphoma (Montoto et al, 2007). Prognostic indices may help discriminate between risk groups.

Survival of patients with FL has improved over the last 30 years. Single institution series show up to 30% improvement in 5 year OS (Fisher et al, 2005; Liu et al 2006). A United States population-based registry study of over 14000 patients between 1978 and 1999 showed an increase in median survival from 84 to 93 months (Swenson et al, 2005). Improvement in failure-free survival (FFS) was only seen following the introduction of anti-CD20 combinations. The introduction of anti-CD20 antibody therapy in 1997 in the USA and 2004 in the UK, therefore, represents a watershed. Some OS improvement is seen prior to 1997 probably due to the combined effect of different treatment options as well as advances in supportive care.

Treatment plans for an individual patient should be, whenever possible, part of a long term strategy and planned after review of all the evidence at a lymphoma
multidisciplinary team meeting with lymphoma specialists, specialist haematopathologist, radiologists, nuclear medicine physician and radiation oncologist. Many modalities are available for treatment but some of these may compromise future choices e.g. nucleoside analogues and autologous stem cell harvesting. Risk of other long term complications such as myelodysplastic syndromes, other secondary cancers, cardiac toxicity and effects on fertility must also be considered, given the extended and now increasing survival of many patients.

Detailed discussions with the patient of different treatment options are of particular importance in the management of the patient with FL. The relative benefits and objectives of the different treatment options must be clearly presented. The different treatment objectives to be considered include impact on symptoms, attainment of sustained remission, prolongation of survival and, less commonly, the potential for a curative treatment such as allogeneic transplantation. Psychological support from the clinical team and other bodies such as patient groups is particularly important in the face of the chronic relapsing nature of this disease and the multiplicity of treatment choices available to the patient and physician.

2 DIAGNOSIS

(Note: The reader is also referred to the BCSH guideline entitled Best Practice in Lymphoma Diagnosis and Reporting for further information on diagnosis.)

2.1 Morphology

Recognised in the 1920s (Brill et al, 1925; Symmers, 1927), FL is a B-cell neoplasm derived from germinal (follicle) centre cells. Involved nodes show replacement of the normal architecture by closely-packed neoplastic follicles which are uniform in size, lack tingible body macrophages, and possess poorly-formed mantle zones. Reactive germinal centres contain a mixture of centroblasts and centrocytes organised into well-defined zones, whereas germinal centres in FL contain a monomorphic population (usually of centrocytes) and lack any evidence of zonation. FL may be focally follicular, follicular and diffuse, or even completely diffuse (Table 1) (Swerdlow et al, 2008).
The cells between the follicles make up the interfollicular component of FL (Dogan et al., 1998). These cells are normally small centrocytes, and can show phenotypic differences from the cells within the neoplastic follicles (see below).

Approximately half of all FL cases show bone marrow involvement at presentation (Conlan et al., 1990) typically consisting of paratrabecular aggregates of lymphoid cells showing follicle centre cell morphology.

### 2.2 Immunohistochemistry

Follicle centre cells express B-cell lineage markers and the germinal centre cell antigens CD10 and BCL6. The interfollicular component of the FL (Dogan et al., 1998) and bone marrow disease often shows downregulation or loss of these markers. High grade (Grade 3) FL can lose CD10 expression, although BCL6 is often retained (Eshoa et al., 2001). The underlying networks of follicular dendritic cells (FDC) can be shown with CD21.

Normal germinal centre cells are BCL2 negative; in 85% of cases the neoplastic cells in FL are BCL2 positive. At the molecular level FL shows a characteristic t(14;18) translocation which relocates the \textit{BCL2} anti-apoptosis gene so that it is adjacent to an immunoglobulin promoter leading to the over-expression of BCL2 protein. BCL2 staining may be negative in high grade (grade 3) FL and in some cases showing an alternative translocation (see below). The tumour cells in FL will show light chain restriction.

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**Table 1: Architecture patterns in FL**

<table>
<thead>
<tr>
<th>FL Pattern</th>
<th>Architecture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicular</td>
<td>&gt;75% follicular</td>
</tr>
<tr>
<td>Follicular and diffuse</td>
<td>25 – 75% follicular</td>
</tr>
<tr>
<td>Focally follicular</td>
<td>&lt;25% follicular</td>
</tr>
<tr>
<td>Diffuse</td>
<td>0% follicular</td>
</tr>
</tbody>
</table>
All cases of FL require a histological diagnosis. A fine needle aspirate is not appropriate; whilst FL cells can be detected in cytology specimens (Saikia et al, 2002), with confirmation by polymerase chain reaction (PCR) and fluorescent in situ hybridization (FISH), and by flow cytometry in some cases, histology is needed to grade the tumour and to exclude transformation to diffuse large B-cell lymphoma (DLBCL).

2.3 Molecular investigations

The typical IgH/BCL2 translocation can be detected by PCR or by FISH using a break-apart probe for the BCL2 gene (Gu et al, 2008). Some cases, particularly those in the Grade 3 category, can show an alternative translocation involving BCL6 (Katzenberger et al, 2004; Bosga-Bouwer et al, 2005). PCR studies will show a clonal IgH rearrangement.

2.4 Grading of FL

The grading of FL relies on the proportion of centroblasts in neoplastic follicles, but the reproducibility of this method has been questioned (Non-Hodgkin's Lymphoma Classification Project, 1997). This Mann-Berard system defines 3 grades, but the latest World Health Organisation (WHO) classification (Swerdlow et al, 2008) merged grade 1 and 2 into a single low-grade category of grade 1-2 (Table 2). Grade 3 lesions are further subdivided according to the presence or absence of centrocytes, so that Grade 3B FL is composed solely of centroblasts. Grade 3B lymphomas show areas histologically indistinguishable from DLBCL, and a diagnosis of grade 3B FL is clinically regarded as equivalent to a diagnosis of DLBCL (Bosga-Bouwer et al, 2006).
Table 2: Grading of FL (Swerdlow et al, 2008)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1-2 (WHO 2008)</td>
<td>0 – 15 centroblasts per high power field (HPF)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>0 – 5 centroblasts per HPF</td>
</tr>
<tr>
<td>Grade 2</td>
<td>6 – 15 centroblasts per HPF</td>
</tr>
<tr>
<td>Grade 3</td>
<td>&gt; 15 centroblasts per HPF</td>
</tr>
<tr>
<td>Grade 3A</td>
<td>Centrocytes present</td>
</tr>
<tr>
<td>Grade 3B</td>
<td>Centrocytes absent</td>
</tr>
</tbody>
</table>

HPF = high power field

Grading can present problems in some cases. Histological identification of centroblasts is not always straightforward; counting the absolute number of centroblasts in a x40 high power field from 10 follicles is time consuming and prone to error. Small specimens such as needle core biopsies may not be representative. Of interest is a 2007 paper reporting tumour sclerosis to be a more useful prognostic marker than Mann-Berard grading in advanced-stage FL (Klapper et al, 2007).

2.5 Pitfalls and differential diagnosis

Difficult cases include those with atypical morphology, those lacking a follicular architecture, and where BCL2 is negative. Needle core biopsies may consist solely of diffuse areas of FL, or may be composed predominantly of the interfollicular component. With such difficult cases specialist review is mandatory, with addition of PCR and FISH where required.

The differential diagnosis of FL includes nodular lymphocyte predominant Hodgkin lymphoma (NLPHL), chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL), mantle cell lymphoma (MCL) and marginal zone lymphoma (MZL). The nodules of NLPHL contain small lymphocytes and scattered large Error! Bookmark not defined. cells rather than follicle centre cells. CLL shows sheets of small B lymphocytes that are CD5 and CD23 positive and CD10 and BCL6 negative. MCL
has a monomorphic appearance and the cells express CD5 and cyclin-D1. Nodal MZL can colonise pre-existing follicles (Naresh, 2008), and may need FISH to exclude a BCL2 translocation. FL at extra-nodal sites can form lymphoepithelial lesions (Tzankov et al, 2002) and so can mimic mucosa-associated lymphoid tissue (MALT) lymphoma, and MALT lymphoma can show a proliferation of follicular dendritic cells (FDC) that may mimic FL (Fellbaum et al, 1993). However MALT lymphoma is CD10 and BCL6 negative, and FISH will fail to show a BCL2 translocation.

**Recommendations:**

- Biopsy is required for the diagnosis of FL, as histology enables an assessment of the tumour grade and the exclusion of transformation to DLBCL (1B).
- FL is composed of germinal centre B cells that normally express CD10, BCL6 and BCL2. The follicular architecture is confirmed by using CD21 to identify FDC networks (1B).
- All cases should be subject to routine central review, as with any malignant lymphoma, as expert/specialist opinion is required to establish a firm diagnosis (1B).
- Molecular investigations including PCR and FISH are required in cases with atypical clinical and/or pathological features (1B).

3 INITIAL INVESTIGATIONS FOLLOWING A DIAGNOSIS OF FL

Appropriate investigation following diagnostic biopsy in FL serves two purposes. Firstly, staging investigations allow initial assessment of disease extent, including determination of the Ann Arbor stage, identification of sites of bulk disease and derivation of prognostic scoring systems such as the Follicular Lymphoma International Prognostic Index (FLIPI). Staging also provides a rational basis for treatment, allows for appropriate on-going disease monitoring and facilitates comparative post-treatment assessment of disease sites.
3 IMAGING GUIDELINES IN FL

Computed Tomography (CT) is the established technique for assessing FL (Kwee et al., 2008). Functional imaging with 18-F fluoro-deoxy-glucose positron emission tomography computed tomography (FDG PET CT) is an emerging new technique whose precise role is yet to be defined for this patient group. The frequency of follow up imaging which involves radiation exposure needs careful consideration. It must always be justified in terms of likely clinical benefit to avoid unnecessary potential risk due to ionizing radiation exposure.

3.1.2 Use of Imaging at Diagnosis

3.1.2.1 Computed Tomography (CT)

CT should include the neck, thorax, abdomen and pelvis and extend from the skull base to the pubic symphysis. Imaging of the central nervous system is not performed routinely. All studies should be performed with administration of oral contrast to differentiate between loops of bowel and abdominal nodal masses. Intravenous contrast is also recommended, unless there is a contraindication such as renal failure, to distinguish between blood vessels and lymph nodes and to increase sensitivity for detecting extra-nodal disease in the liver and spleen.

CT may be used to identify the most appropriate lesion for biopsy and to assist the radiologist localise lesions during percutaneous needle biopsies.

3.1.2.2 Magnetic Resonance Imaging (MRI)

MR is the imaging of choice in the rare FL patient with suspected lymphoma in the central nervous system including brain, leptomeninges and spinal cord, complimented by examination of CSF. Intravenous gadolinium increases sensitivity and should be considered in patients with a high risk of central nervous system (CNS) disease and a negative MRI.

3.1.2.3 Ultrasonography (USS)

USS is of limited value in the staging of FL. It shows lymphadenopathy in the cervical regions of the neck, around the coeliac axis, splenic hilum, porta hepatis and in the
inguinal regions. It demonstrates disease in the liver and spleen. However, the entire retroperitoneum cannot be assessed and mediastinal and retropharyngeal nodal enlargement cannot be detected.

3.1.2.4 Positron Emission Tomography (PET)

For patients with potentially curable conditions, such as Hodgkin lymphoma, functional imaging with PET utilising the glucose analogue fluoro-deoxyglucose (FDG) has become a routine investigation for the staging and assessment of post-treatment residual masses (Burton et al, 2004; Hutchings and Barrington, 2009). There is substantial evidence that most cases of FL are visualised on FDG-PET, irrespective of grade (Karam et al, 2006; Newman et al, 1994; Moog et al, 1997; Stumpe et al, 1998; Jerusalem et al, 2001; Wöhrer et al, 2006). One of the main factors that influence prognosis in patients with FL is the number of nodal regions containing disease. In the FLIPI involvement of more than 4 nodal areas is an adverse prognostic factor (Solal-Céligny et al, 2004). FDG-PET, compared with CT, more accurately diagnoses nodal disease and detects unexpected sites of extra-nodal disease. However, whether small volume disease detected on PET but not CT is important prognostically is uncertain. The number of patients correctly diagnosed as having limited disease is increased when FDG-PET is included (Jerusalem et al, 2001; Karam et al, 2006; Wirth et al, 2008; Janikova et al, 2008).

FDG-PET is of limited value for the detection of bone marrow disease and is not a substitute for bone marrow biopsy (Jerusalem et al, 2001; Elstrom et al, 2003). Detection of bowel involvement with FDG PET CT is a challenge as normal bowel wall shows FDG uptake (Elstrom et al, 2003).

There is considerable debate about the clinical value of FDG-PET CT in patients with FL; therefore, the results of FDG-PET scanning should not be used to make clinical decisions regarding therapy and the utility of this technique should be further evaluated for FL patients within a prospective clinical trial.

3.2 PATIENT ASSESSMENT

A number of additional investigations may be undertaken to determine disease extent and prognosis in patients with biopsy proven FL. The recommendations below
are based either on the requirements for staging and prognostic scoring (Federico et al, 2009) or as part of good clinical practice allowing the detection of relevant disease-related and patient specific co-morbidities. Some elements are considered core while others are discretionary depending on the clinical context. It should be recognised that specific areas of controversy exist. For example virological testing for hepatitis B and C is recommended before the start of immunotherapy either alone or in combination while HIV testing is subject to local incidence patterns since the incidence of FL does not appear to be increased in patients with HIV infection (Artz et al, 2010; Cave et al, 2009; Vajdic et al, 2010). An assessment of the impact of any proposed therapy on fertility should always be made in younger patients. If clinically appropriate, referral to a specialist in reproductive medicine should be made prior to treatment so that options to preserve fertility can be discussed.

**Recommendations:**

- A full clinical history and examination including determination of performance status and any other relevant co-morbidity scores (1B).
- Full blood count and blood film examination, with immunophenotyping by flow cytometry where there is a peripheral blood lymphocytosis (1B).
- Urea, creatinine and electrolytes (1B).
- Liver function tests, Lactate Dehydrogenase (LDH) and β2 microglobulin (1B).
- Calcium, albumin, urate and phosphate (1B).
- Immunoglobulins and quantitation of monoclonal band if present (1B).
- Bone marrow examination to include aspirate, trephine biopsy and immunophenotyping by flow cytometry and immuno-histochemistry (1B).
- Cytogenetic analysis of involved bone marrow should not be considered routine but may be helpful where there is diagnostic uncertainty (2B).
• Molecular detection of a clonal B-cell population in marrow or blood should not be considered standard but may form part of studies directed specifically at detection of minimal residual disease (2B).

• As part of the staging process of patients with newly diagnosed FL, CT is the established initial imaging investigation and should include the neck, chest, abdomen and pelvis. Oral and intravenous contrast should be administered unless there is a specific contraindication (1B).

• At the current time, FDG-PET is of uncertain value in FL. Routine use should be considered only in the setting of a clinical trial (1B).

• In addition to staging the head and neck, MRI is the diagnostic procedure of choice for rare patients with suspected disease in the central nervous system disease including brain, leptomeninges and spinal cord (1B).

Additional recommended investigations:

• Standard assessment of relevant cardiac, respiratory or other general medical co-morbidities may be required in order to determine patient fitness for particular treatment (1B).

• Pregnancy testing should be undertaken in women of child bearing age prior to administration of relevant treatment (1B).

• Virological testing for hepatitis B and hepatitis C should be undertaken at baseline and in all patients considered at risk of virus reactivation in whom immunotherapy is the treatment of choice (1B).

• Clinical assessment and virological testing for HIV, as indicated by local protocols (2C).

4 PROGNOSTIC SCORING SYSTEMS IN FL

Several prognostic indices or scores, including the International Prognostic Index (IPI) for aggressive lymphoma, have been used to better define risk groups in patients with follicular lymphoma (FL) (Leonard et al, 1991; Cameron et al, 1993;
Romaguera et al, 1991; Lopez-Guillermo et al, 1994; Federico et al, 2000). However, none of these have been adopted into routine clinical practice, either because of being too complicated (Leonard et al, 1991; Cameron et al, 1993; Romaguera et al, 1991), or lacking the ability to identify patients with poor prognosis (Lopez-Guillermo et al, 1994). In 2004 an international collaborative study including 4167 patients resulted in the publication of the Follicular Lymphoma International Prognostic Index (FLIPI) (Solal-Celigny et al, 2004), a prognostic score specifically designed for patients with FL. This index includes the following adverse variables: age ≥60 years, haemoglobin concentration <120 g/l, LDH >upper normal value, stage III-IV, and ≥4 involved nodal areas, and stratifies the patients in 3 groups (low, intermediate and high-risk) well balanced in terms of the proportion of patients in each group and with a clearly different outcome (5-year overall survival: 91%, 78% and 52%, respectively—see table 3). Furthermore, the FLIPI at diagnosis identifies patients with a higher risk of histological transformation (Gine et al, 2006; Montoto et al, 2007b). Although this index was designed in the pre-rituximab era, its prognostic value has recently been confirmed in the rituximab era (Federico et al, 2007) and in patients receiving rituximab as part of the first-line therapy (Buske et al, 2006; Marcus et al, 2008) and its use has spread worldwide. However, at present the FLIPI has not yet been validated prospectively to guide therapeutic decisions for patients with FL and should only be used to guide prognosis and treatment decisions in the setting of clinical trials. Notwithstanding, it is recommended that the FLIPI index should be recorded for all patients at diagnosis.

More recently, another international collaborative study was launched with a two-fold intention: a) to prospectively validate the FLIPI and b) to prospectively design a prognostic index for FL patients treated in the rituximab era. The modified FLIPI2 (Federico et al, 2008; Federico et al, 2009) includes age, serum β2-microglobulin, haemoglobin concentration, bone marrow involvement and tumour burden. Although the latter was calculated using a complex mathematical formula, it correlates with the longest diameter of the largest involved lymph node, which can be used as a surrogate for tumour burden (with one point being scored if this is over 6 cm), making the FLIPI2 relatively easy to calculate. It is recommended that the FLIPI2 index should be recorded in routine clinical practice (see table 3 and appendix 1).
Prognostic indicators at relapse are not established. Data on the value of the FLIPI at the time of relapse is scarce, although its ability to predict survival from progression has been confirmed in retrospective series (Montoto et al, 2004) and in clinical trials (Sacchi et al, 2007).

**Recommendations:**

- FLIPI and FLIPI2 should be recorded at diagnosis (2B).

**Table 3: Prognostic scoring systems in FL- FLIPI and FLIPI2**

<table>
<thead>
<tr>
<th>Variables</th>
<th>FLIPI</th>
<th>FLIPI2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, stage, Hb, LDH, nodal areas</td>
<td></td>
<td>Age, Hb, BM, β2M, nodal size</td>
</tr>
<tr>
<td>Risk groups</td>
<td>Low (0-1)</td>
<td>Low (0-1)</td>
</tr>
<tr>
<td></td>
<td>Intermediate (2)</td>
<td>Intermediate (2)</td>
</tr>
<tr>
<td></td>
<td>High (≥ 3)</td>
<td>High (≥ 3)</td>
</tr>
<tr>
<td>%</td>
<td>36</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>5-yr OS</td>
<td>91</td>
<td>98</td>
</tr>
<tr>
<td></td>
<td>78</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td>52</td>
<td>77</td>
</tr>
</tbody>
</table>

Adverse factors: age >60 years; stage: III-IV; Hb- haemoglobin concentration <120 g/L; LDH elevated above the upper limit of normal; nodal areas ≥ 5; beta 2 microglobulin (β2M) elevated above the upper limit of normal; bone marrow (BM) involvement; longest diameter of largest node > 6 cm (see appendix 1).

**5 MANAGEMENT OF PATIENTS WITH NEWLY DIAGNOSED FL**

**5.1 Guidelines for the management of early stage disease**

It is particularly important in the case of early stage disease to gain as much information as possible to exclude more advanced disease which would result in a change in management. The FLIPI index is also of value in predicting outcome in this group (Plancarte et al, 2006) and should be recorded, as recommended above.
5.1.1 Radiotherapy

Conventionally, early stage follicular lymphoma comprising Ann Arbor stage 1 and stage 2 disease, where the involved nodes are contiguous, has been treated with local radiotherapy. Follicular lymphomas are highly radiosensitive and a number of case series in the literature confirm a high response rates with around 80% of patients having long term disease control at 5 and 10 years (MacManus and Hoppe, 1996; Wilder et al, 2001; Guadnogolo et al, 2006; Pugh et al, 2010). Examination of the patterns of relapse in these patients reveals that the majority relapse outside the irradiated field (Reddy et al, 1989; Eich et al, 2009). Involved field or involved site radiotherapy is the usual management. Conventional doses of 30 to 40 Gy that were used in the past are now recognised to be higher than necessary for local disease control and the current standard dose of 24 Gy in 12 fractions is recommended outside of a clinical trial. Even lower doses have proved to be effective with a schedule of 4 Gy in 2 fractions reported from several centres (Sawyer and Timothy, 1997; Johansson et al, 2002; Haas et al, 2003; Haas et al, 2005; Murthy et al, 2008; Luthy et al, 2008) The largest series from The Netherlands has a total of 98 patients with follicular lymphoma receiving either 4 Gy in 2 fractions or a single fraction of 4 Gy (Haas et al, 2003, 2005). The overall response rate was 92% and complete response rate was achieved in 61% lasting up to 77 months with a median time to local progression 25 months. The comparison of the UK standard dose of 24 Gy in 12 fractions versus 4 Gy in 2 fractions, is now the subject of a randomised trial in the United Kingdom (FORT). At present in the absence of high quality evidence such low doses can only be recommended for palliation or re-treatment where radiation tolerance may be a concern.

5.1.2 Combined modality treatment

Since the majority of relapses occur outside the radiation field and are seen in up to 50% of patients, combined modality treatment may be an alternative approach. There is limited and conflicting data to date. The largest study from Melbourne reported on 102 patients with stage I or stage II “low grade” lymphoma (Seymour et al, 2003). They received 10 cycles of COP-BLEO or CHOP-BLEO with 30 to 40 Gy involved field radiotherapy. Ninety-nine per cent of patients achieved complete remission; in those with follicular lymphoma there was a median follow up of 10
years and the freedom from failure rate was 72% and overall survival 80%. The International Prognostic Index (IPI) was found to be predictive of outcome in this series. This is now the subject of an ongoing phase III randomised trial. Pending the results of this, combined modality treatment cannot be recommended routinely.

5.1.3 Observation alone in early stage FL

There are no randomised studies comparing no initial therapy with immediate treatment in patients with early stage FL. A retrospective analysis of 43 patients with stage 1a and 2a grade 1/2 FL suggests that this is an acceptable approach with 10 year overall survival of 86% which is not inferior to that of patients treated with radiotherapy (Advani et al, 2004). In this study 56% of patients had still not received any therapy by 10 years. Another observation alone study of 26 patients with stage I FL in whom the tumour had been fully excised at biopsy (stage I0) (Soubeyran et al, 1996) had not relapsed with median follow-up of 4.6 years, 6 relapsed in the same site (median 4.2yr (0.6-9y)) and 7 relapsed outside the original site (median 1yr (0.5-5.5yr). Five year overall survival for the 26 patients was 82.5% once again suggesting that an observation policy in patients with stage I0 FL is reasonable.

There may therefore be a case for patients with limited stage FL with no residual disease following excision biopsy to be observed without treatment, especially if there are concerns with regards side effects of involved field radiotherapy e.g. fertility preservation in young women, elderly frail patients where significant morbidity, such as xerostomia, might be expected.

Recommendations:

- Involved field radiotherapy delivering a dose of 24 Gy in 12 daily fractions is the standard of care (1A).

- Observation of patients with early stage disease is acceptable if radiotherapy is thought to be undesirable or due to patient choice. These patients should be discussed with a radiation oncologist (2C).
Combined modality treatment and immunotherapy are at present investigational approaches which should only be considered within a formal clinical trial (2C).

5.2 Treatment of Advanced Stage Disease

5.2.1 Advanced stage, asymptomatic FL

Three randomised studies of varying quality have shown that there is no advantage to immediate treatment in patients with advanced stage asymptomatic FL compared with a watchful waiting approach in terms of overall survival (Ardeshna et al, 2003; Brice et al, 1997; Young et al, 1988) and cause-specific survival (Ardeshna et al, 2003). The majority of patients in these studies had histology which would be classified today as FL grade 1/2. The treatment arm in the studies consisted of chlorambucil (Ardeshna et al, 2003), prednimustine or interferon (IFN) (Brice et al, 1997) and aggressive combined modality therapy with ProMACE-MOPP +total nodal irradiation (Young et al, 1988). In 2 of the studies low dose radiotherapy to symptomatic nodes was allowed in one (Young et al, 1988) or both (Ardeshna et al, 2003) of the arms. In the largest study of 309 patients with a median 16 years of follow up conducted by the British National Lymphoma Investigation (BNLI), the criteria for patients being eligible for a watch and wait approach were defined as the absence of the following:

1) Pruritus or B symptoms
2) Rapid generalised disease progression in the preceding 3 months
3) Life-endangering organ involvement
4) Significant bone marrow infiltration resulting in bone marrow depression sufficient to warrant immediate chemotherapy. This was defined as an haemoglobin concentration <100g/l, a white cell count <3.0 x 10^9/l or a platelet count <100x10^9/l, having excluded other causes of such cytopenias
5) Localised bone lesions detected on X-ray or isotope scan because of concern over the development of pathological fractures
6) Renal infiltration (even if the renal function was well preserved)
7) ‘Macroscopic’ as opposed to ‘microscopic’ liver involvement.
Bulk disease *per se* was not an exclusion criterion.

A more restrictive set of criteria which defined low tumour burden FL were established by the Groupe d’Etude des Lymphomes Folliculaires (GELF), largely as criteria for trial entry. Low tumour burden was defined as:

1) LDH within normal range
2) Largest nodal or extra-nodal mass less than 7cm diameter
3) No more than 3 nodal sites with a diameter more than 3cm
4) No significant serous effusions detectable clinically or on chest radiography (small, clinically non-evident effusions on CT scan are not deemed significant)
5) Spleen enlargement less than or equal to 16 cm by CT.

Normal β2 microglobulin has now been added to the GELF definition of low tumour burden.

In clinical practice a watchful waiting approach does not need to be limited to patients with low tumour burden though it is likely patients with higher tumour burdens will have a shorter interval until disease progression necessitates treatment.

Watchful waiting is able to defer the initiation of systemic therapy by 2-3 years (Ardeshna *et al*, 2003; Brice *et al*, 1997; Young *et al*, 1998). In the BNLI study, 40% of patients over 70 years had not received chemotherapy or died of lymphoma at 10 years after study entry. This fell to 16% in those patients under 70 years. Thus there is little justification for immediate treatment in patients with asymptomatic advanced stage FL. Patients who undergo observation do not have an increased risk of high grade transformation (Brice *et al*, 1997; Horning *et al*, 1984; Al-Tourah *et al*, 2008) compared to those who start treatment immediately.

The presumed advantage of a watchful waiting approach is that patients are spared toxic side effects of chemotherapy. There is anecdotal evidence that at least for some patients this strategy may lead to a worse quality of life as patients can find being diagnosed with a malignant condition and not receiving treatment psychologically distressing. Preliminary results of a three arm international randomised study comparing watchful waiting with immediate treatment with rituximab using the standard 4 week induction with or without maintenance rituximab.
administered 2 monthly for 2 years, in patients with advanced stage asymptomatic FL with low tumour burden have recently been reported after a median follow up of 32 months. The primary endpoint was time to initiation of new therapy. Three years after randomisation 49% of patients in the watch and wait arm had not received further therapy whereas 80% of patient in the rituximab induction arm and 91% of patients in the rituximab induction and maintenance arm had not initiated new therapy. There was no difference in overall survival with 95% of patients alive at 3 years. The quality of life data remains to be analysed but if this does not show a detriment in the rituximab arms, initial treatment with rituximab in asymptomatic patients with advanced stage, low tumour burden FL may be an alternative option especially in patients in whom deferring chemotherapy is thought to be advantageous. Whether early exposure to rituximab will mean responses to chemotherapy combined with rituximab will be inferior will remain to be determined.

5.2.2 Treatment of symptomatic advanced stage FL

Note that patients with grade 3b FL, using the Mann and Berard grading system, may have clinical and biological differences from other grades FL and should be treated as DLBCL (Bosga-Bouwer et al, 2006).

Patients with advanced stage symptomatic FL are treated with the expectation that the disease will pursue a relapsing and remitting course and may require several lines of treatment during the course of the disease. For many years standard first line treatment was alkylator based, frequently in combinations including vinca alkaloids, corticosteroids and anthracyclines.

Attempts to increase the intensity of chemotherapy by addition of an anthracycline failed to show a survival advantage. A study by Kimby randomised 259 patients with untreated, symptomatic low grade NHL between ChP (chlorambucil + prednisolone) and CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) (Kimby et al, 1994). The 5 year overall survival was equivalent in the two arms (54% vs. 59%). Peterson, randomised 228 patients with previously untreated FL to receive either daily oral cyclophosphamide or CHOP-bleomycin; no significant differences in either complete response (CR) (66% vs. 60%), 10 year time to treatment failure (TTF) (25% vs. 33%) or overall survival (OS) (44% vs. 46%) were seen (Peterson et al,
Any improvement in response with anthracycline-containing combinations must be balanced against the inevitable increase in toxicity and the preclusion of anthracycline as a therapeutic agent in the event of subsequent transformation to high grade disease.

The purine analogue fludarabine has activity in follicular lymphoma as first line treatment used as both a single agent and in combination (Velasquez et al., 2003). No trial identified a survival advantage over single agent alkylator therapy: in a prospective randomised trial fludarabine was compared to cyclophosphamide, vincristine and prednisolone (CVP) in 381 previously untreated patients with follicular lymphoma. Although higher responses were observed in the fludarabine arm this did not translate into an improved progression-free or overall survival (Hagenbeek et al., 2006). In the immediate pre-rituximab era fludarabine containing combinations demonstrated high complete remission rates (79%) and PFS rates of 52% at 5 years in younger patients falling to 29% in the over 60s (Tsimberidou et al., 2002).

The first-line use of fludarabine may, however, have a detrimental effect on mobilising haematopoietic stem cells for autologous transplantation. Its use also carries an increased risk of opportunistic infection and it may be associated with an increased risk of secondary AML/MDS. Finally, patients receiving nucleoside analogues require irradiated blood products to avoid the risk of transfusion-associated graft versus host disease.

IFN has also been studied in FL; (Solal-Celigny et al., 1993). In the French pivotal trial 242 patients were randomised between cyclophosphamide, doxorubicin, teniposide (vm 26) and prednisone (CHVP) or CHVP followed by interferon maintenance (CHVPI). The 123 who received interferon had a PFS of 34 compared to 19 months. Consequently CHVP-I was used as the control arm in the later study that compared CHVP-I to CHVP-I with the addition of rituximab (see below).

Ten trials examined the role of IFN either as an adjunct to induction therapy or as maintenance. In a meta-analysis (Rohatiner et al., 2005) a modest improvement in overall survival and remission duration were seen.

Five phase III trials have now confirmed the efficacy of rituximab in combination with an alkylator-containing regimen both with and without the inclusion of anthracycline (table 4).
There is a suggestion in these studies that the duration of response in patients treated with anthracycline-based therapies might be superior to that obtained with less intensive regimens utilising alkylators. This has led to the widespread adoption of R-CHOP as a standard regimen as first line therapy for follicular lymphoma but recent data (Rummel et al, 2009) add to the uncertainty as to the benefits of incorporating anthracyclines into first line therapy. In this study of 513 patients with symptomatic low grade lymphoma, half of whom had FL, were randomized to either 2 doses of bendamustine (see below) and 1 dose of rituximab (BR) every 28 days, or to the standard R-CHOP regimen every 21 days, for a maximum of 6 cycles. BR patients had a PFS of 54.8 months, compared to 34.8 months with R-CHOP.

The survival benefit of combined immunochemotherapy as first line treatment of FL has been confirmed by a Cochrane meta-analysis (Shulz et al, 2007). This combined survival data from the above randomised trials. This analysis favoured immunochemotherapy with a hazard ratio of 0.57 (95% CI: 0.43 – 0.77)

Note that due to the paucity of reports of primary or secondary involvement of the CNS by FL, CNS chemoprophylaxis is not recommended at first presentation or in the setting of disease relapse. Patients who have histological transformation of FL (see section 7.0) may require CNS chemoprophylaxis, according to recommendations for the histological subtype.
### Table 4  First-Line Treatment: Immunochemotherapy Phase III trials

<table>
<thead>
<tr>
<th>FLIPI (LR/IR/HR)</th>
<th>Regimen</th>
<th>Phase</th>
<th>Pts</th>
<th>ORR</th>
<th>Duration</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>14/41/45</td>
<td>R-CHOP</td>
<td>III</td>
<td>428</td>
<td>96%</td>
<td>TTF: (2y85%)</td>
<td>Hiddeman, Blood ‘04</td>
</tr>
<tr>
<td>-/42/46</td>
<td>R-CHOP</td>
<td>III</td>
<td>540</td>
<td>91.3%</td>
<td>PFS: n.r.</td>
<td>Rummel, ASH ‘09</td>
</tr>
<tr>
<td></td>
<td>R-Benda</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7/37/56</td>
<td>R-MCP-&gt;IFN</td>
<td>III</td>
<td>201</td>
<td>92%</td>
<td>PFS:n.r.(4y71%)</td>
<td>Herold, JCO ‘07</td>
</tr>
<tr>
<td>19/41/40</td>
<td>R-CVP</td>
<td>III</td>
<td>331</td>
<td>81%</td>
<td>TTP:34mo</td>
<td>Marcus, Blood ‘05</td>
</tr>
<tr>
<td>19/35/46</td>
<td>R-CHVP+IFN</td>
<td>III</td>
<td>358</td>
<td>85%</td>
<td>PFS: n.r.(5y53%)</td>
<td>Salles, Blood ‘08</td>
</tr>
</tbody>
</table>

n.r., not reached; PFS, progression-free survival; TTF, time to failure; TTP, time to progression; LR/IR/HR, low risk, intermediate risk, high risk.

### 5.2.3 Rituximab maintenance following first line chemo-immunotherapy.

Maintenance therapy with rituximab is aimed at preventing the re-establishment of malignant cells thereby prolonging the time until relapse, improving survival and maximizing the patient’s quality of life (Ardeshna, 2007).

There is evidence from randomised studies that rituximab maintenance significantly prolongs median event-free survival (EFS) in previously untreated patients who respond to single agent rituximab induction (36 months vs 19months p=0.009) (Ghielmini et al, 2004) and significantly improves PFS and OS in patients who respond to CVP chemotherapy without rituximab (4 yr PFS 56% vs 33% p=0.0000003; 4 yr OS 88%vs 72% p=0.03) (Hochster et al, 2005). The current standard induction therapy is chemotherapy combined with rituximab. The PRIMA study randomised patients with high tumour burden FL who achieved at least a
partial response (PR) to R-chemotherapy (R-CVP, R-CHOP or R-FCM) to either observation or rituximab maintenance 375mg/m² every 2 months for 2 years. With a median follow up of 3 years the PFS in those responding to induction was 75% in the rituximab maintenance group and 58% in the observation group (p<0.0001). The time to initiation of next anti lymphoma therapy was also significantly longer in the maintenance arm. There was an increase in grade 2-4 infections in the maintenance group (39% vs 24% p<0.0001). These were mainly bronchitis, upper respiratory tract infections, sinusitis, urinary tract infections and nasopharyngitis. Grade 3-4 infections were 4% in the maintenance arm and 1% in the observation arm. There was no difference in quality of life between the two arms nor was there a difference in overall survival with 95% of patients alive at 3 years. NICE (the National Institute of Clinical Excellence) has recently approved rituximab maintenance as an option for patients responding to induction therapy in the newly diagnosed setting (TA226).

5.2.4 Autologous stem cell transplantation (ASCT) and newly diagnosed FL.

(Please see section 8.0 for a summary of the evidence)

5.2.5 Radioimmunotherapy (RIT) in the newly diagnosed FL patient

A phase II trial has examined the role of ¹³¹I-tositumomab in the treatment of previously untreated FL (Kaminski et al, 2005). 76 patients with stage III/IV FL received a single one week course of ¹³¹I-tositumomab. Overall response rate (ORR) was 95% and CR was 75%. Molecular responses were seen in 80% of patients achieving a complete response. At a median follow-up of 5.1 years the PFS was 59% and median PFS was 6.1 years. Patients tolerated the treatment without problems and no case of therapy related-myelodysplastic syndrome (MDS) was seen. Whilst the ORR and PFS quoted are extremely impressive the study included patients with a very favourable profile; the median age was 49 years and less than 50% of patients had bulky disease. The SWOG studied the use of ¹³¹I-tositumomab as consolidation after CHOP chemotherapy in 90 previously untreated patients with FL (Press et al, 2003). Treatment was well tolerated and myelosuppression was more severe with chemotherapy than the RIT. The ORR was 90% including 67%
complete response. 57% of patients who failed to achieve a CR with CHOP converted to CR after RIT. The two year PFS was estimated to be 81%.

A prospective phase III randomized trial demonstrated that Y90 – ibrutumomab RIT after standard chemotherapy induction prolongs PFS (Morschhausser et al, 2008). The trial compared a single treatment with RIT to observation in 414 patients with advanced (stage 3 or 4) follicular lymphoma who had achieved partial or complete remission after first-line chemotherapy. The choice of which chemotherapy regimen to use for induction was left to the physicians' discretion, and various combinations were used, including CVP, CHP, fludarabine, chlorambucil and rituximab. The primary end point of median progression-free survival was 37 months in the group receiving Y90 – ibrutumomab and 13.5 months in the control group (P < .0001); longer term overall survival advantages remain unproven. This study predated R-chemotherapy becoming established as the “standard” and as result only a small minority of patients received rituximab as part of induction therapy. High conversion rates (77%) from partial to complete response rates were seen in all treatment groups including the rituximab-containing chemotherapy. There is a concern that Y90 – ibrutumomab consolidation may not confer the same improvement in PFS in patients who receive rituximab-based induction.

**Recommendations:**

- Observation remains an appropriate approach in patients with asymptomatic, advanced stage follicular lymphoma in an attempt to delay the need for chemotherapy (1B).

- Rituximab, in combination with chemotherapy, should be used in patients with newly diagnosed, symptomatic advanced stage FL who require therapy (1A). There is no strong evidence to support one regimen over another (1B).

- Rituximab maintenance after successful induction therapy prolongs PFS and is recommended in patients responding to first-line rituximab based chemotherapy (1B).

- Autologous stem cell transplantation has no role in first line therapy for follicular lymphoma outside a clinical trial (1B).
There is no conclusive evidence that radio-immunotherapy prolongs OS in patients and insufficient data to routinely recommend RIT after receiving rituximab based induction therapy (2C).

6 MANAGEMENT OF RELAPSED FOLLICULAR LYMPHOMA

6.1 Aims of therapy

Although chemotherapy in combination with rituximab has improved outcomes in the newly diagnosed setting, patients with FL almost always relapse and require a succession of therapies over many years (Hiddemann et al., 2005; Herold et al., 2007; Marcus et al., 2008). Modalities of therapy for patients with relapsed disease have altered significantly in recent years and are likely to change further with controlled trial data on newer agents becoming available.

The overall aim of therapy is similar to that at diagnosis - to optimise overall survival while at the same time preserving health-related quality of life. In the relapsed setting the cumulative effects of previous therapies are particularly relevant.

6.2 Patient assessment

Before commencing therapy in patients with symptoms or signs consistent with relapsed FL it is strongly recommended that a repeat biopsy and histopathological reassessment be carried out, wherever practicable. This is because of the risk of histological transformation of FL to a more aggressive lymphoma subtype and the adverse prognostic implications of this event (Bastion et al., 1997; Montoto et al., 2007; Al Tourah et al., 2008). If histological transformation has been excluded decisions regarding therapy will depend on a combination of the following factors:

1. The indications for therapy - there is no evidence that intervention will improve outcomes for patients with relapsed but asymptomatic FL. For example, recurrent asymptomatic nodal disease detected on routine clinical examination should not necessarily result in re-treatment

2. Patient fitness for therapy

3. Previous treatments received and the duration of response to these.
6.3 Chemo-immunotherapy

Those patients with relapsed, symptomatic FL who are rituximab naive should always receive rituximab, in combination with chemotherapy, as the combination improves all meaningful outcomes in relapsed FL, compared with chemotherapy alone, including OS (Forstpointner et al, 2006; Van Oers et al, 2006; Shulz et al, 2007). The optimal chemotherapy regimen at the point of relapse has not been determined; options include alkylating agents with or without anthracyclines and nucleoside analogues. The decision to use an anthracycline combination should be based on patient characteristics such as cardiac function and the response duration of previous therapies. For example, patients who have relapsed late following single agent alkylator based treatment administered in the pre-rituximab era may be treated with an alkylator-rituximab based combination (e.g. cyclophosphamide, vincristine, prednisolone, rituximab). This is based on the competitive response rates seen with this regimen in previously untreated patients and the concern about potential cardiotoxicity of anthracycline use and its preclusion from further use due to accumulated dose exposure later in the course of the disease or in disease transformation.

In those patients who are resistant to or who have relapsed early following anthracycline-based chemotherapy or who have contra-indications to their use, alternate agents should be considered. Nucleoside analogues are active in FL patients who have been heavily pre-treated (Bosch, 1997). Fludarabine-based chemotherapy regimens and rituximab produce high response rates and prolong PFS in patients who are refractory to previous therapies. Forstpointner and colleagues randomised 65 patients who had failed to respond to previous chemotherapy (but who were rituximab naïve), including autologous stem cell transplantation (ASCT), to receive fludarabine, cyclophosphamide and mitoxantrone with or without rituximab (R-FCM v FCM) (Forstpointner et al, 2004). The ORR was 94% in the R-FCM group with a CR rate of 40% and the median PFS was not reached after 3 years of follow-up. Grade 3 or 4 infections were seen in less than 2% of R-FCM treated patients; there was no long term follow-up reported in this study that might inform on the risk of secondary myelodysplasia.

Many patients with relapsed FL will have had rituximab containing chemotherapy previously. Re-treatment of patients with rituximab is effective in patients who have

Although rituximab has been used as monotherapy in the relapsed setting (McCloughlin et al, 1998) the response rates and PFS are markedly improved with the addition of chemotherapy. It is therefore recommended that patients who require therapy be treated with the combination of immunotherapy and chemotherapy. For those patients who are intolerant of chemotherapy, due to co-morbidities or other reasons, rituximab monotherapy can be considered.

6.4 Radio-immunotherapy

Most of the data for RIT in the setting of relapsed FL is derived from Phase II studies in patients treated after 2 or more relapses. There are no randomised trials demonstrating the efficacy of RIT compared to R-chemotherapy regimens. Two radioimmunoconjugates, namely $^{131}$I-tositumomab and $^{90}$Y Ibritumomab have been used in relapsed FL. However, only $^{90}$Y-ibritumomab tiuxetan RIT is approved for treatment within the European Union and it is the only drug that can be prescribed in the UK. $^{90}$Y-Ibritumomab has demonstrated clinical activity in heavily pre-treated populations, including disease refractory to both chemotherapy and rituximab (Witzig et al, 2002a, Witzig et al, 2003) leading to durable responses for some patients (Gordon et al, 2004). Around 70 % of patients who have previously failed 2 lines of therapy or one course of anthracycline-containing chemotherapy who achieve a CR following RIT remain in remission for more than 3 years (Gordon et al, 2004; Witzig, 2003). This patient cohort had not received rituximab previously. An analysis of long-term responders, defined as patients who had a PFS of more than 12 months, demonstrated that $^{90}$Y-ibritumomab tiuxetan achieved durable remissions with a median duration of response approaching 2 years and responses lasting over 6 years in some patients. Higher response rates and longer duration of responses were observed when RIT was used earlier in the therapy schedule (Gordon et al, 2004). The only clinical parameter found to correlate to clinical response in RIT is the maximum dimension of the largest tumour. Patients with tumours with a maximum dimension of < 5 cm had an ORR 90% (p<0.001), whereas bulky tumours were less likely to respond (Witzig et al, 2003).
Y-Ibritumomab RIT appears to be safe with manageable and predictable myelotoxicity (Witzig et al, 2003). With more than 10 years of follow-up data there does not appear to be a significant increase in late AML / MDS, although there is a suggestion that this might be increased after previous exposure to fludarabine to around 3.8% (Czuczman et al, 2007). The high response rates achieved with minimal interruption to patient’s lives and associated high quality of life for patients receiving the therapy make RIT an attractive treatment option for patients with relapsed FL especially those who are refractory to rituximab or chemotherapy and for those who are intolerant or unwilling to have further chemotherapy.

6.5 Novel agents

Bendamustine is a DNA alkylating agent with novel properties that has been studied in FL patients who are rituximab refractory (Friedberg et al, 2008). Phase II trials of bendamustine in combination with rituximab in relapsed FL have reported ORRs of 92% and a median PFS of 23 months (Robinson et al, 2008). A recent multi-centre single arm study treated 62 patients with rituximab-refractory FL (Kahl et al, 2010). Patients had between 1 and 3 previous therapies including CVP-R (38%), CHOP-R (37%), purine analogue-based chemotherapy with rituximab (44%) and radioimmunotherapy (24%). Twenty nine percent of patients had a high risk FLIPI. The ORR was 74% with a 15% CRR. The median PFS was 9.3 months. Grade 3 or 4 haematological toxicity was common; neutropenia was seen in 61% and thrombocytopenia in 25 %. The most common non-haematological toxicity was gastro-intestinal. There were seven toxicity-related deaths, many of which were attributable to myelosuppression. There was one case of MDS detected in a patient more than a year following therapy - this patient had also received fludarabine and mitoxantrone previously. Randomised studies of bendamustine and rituximab with or without other novel agents, in comparison with conventional alkylator and anthracycline-based-therapies are ongoing and may further inform decision making.

A range of BCL2 small molecule inhibitors, novel monoclonal antibodies and immunomodulators are being assessed in clinical trials. These therapies are the consequence of a better understanding of the biology of FL and may herald an era where additional therapies extend the duration of remission without adding further toxicity.
6.6 Maintenance therapy in relapsed FL

Two randomised studies of rituximab maintenance following standard rituximab induction in previously treated patients who were rituximab naïve have been reported and both show a PFS/EFS benefit in the maintenance arm. (Ghielmini, et al, 2004; Hainsworth, et al, 2005). Of more relevance are the two randomised studies which demonstrate the benefit of rituximab maintenance following re-induction with chemotherapy combined with rituximab (van Oers, et al, 2006; Forstpointner, et al, 2006).

In the EORTC 20981 Intergroup study, 465 rituximab naive patients with relapsed/refractory FL were reported (van Oers, et al 2006). The study design involved 2 randomisations. Patients were initially randomised to receive CHOP or R-CHOP induction chemotherapy. Response was assessed after 3 courses; patients with progressive disease (PD) or stable disease (SD) went off study and responders went on to receive a further 3 courses of induction therapy. A second randomisation took place at completion of induction therapy between observation and maintenance rituximab (administered once every 3 months for a maximum of 2 years). The primary endpoint of the first randomisation was response whilst that of the second randomisation was PFS.

The ORR was significantly better in the group that received R-CHOP induction (85.1% vs 72.3%, \(P<0.0001\)), as was the CR rate (29.5% vs 15.6%, \(P<0.0001\)); PR rates were similar (55.6% vs 56.7%). With a median follow up of 39.4 months from first randomisation there was a significant increase in median PFS in the R-CHOP group (33.1 vs 20.2 months, \(P=0.003\)) without a significant increase in OS at 3 years (82.5% vs 71.9%, \(P=0.096\)). 334 patients were randomised to receive maintenance rituximab or observation. With a median follow up from second randomisation of 33.3 months, the median PFS was significantly greater in the rituximab maintenance group (51.5 vs 14.9 months, \(P<0.0001\)), equating to a gain of 3 years in PFS. A gain in PFS of approximately 2.5 years was present whether patients received CHOP induction (42.2 vs 11.6 months, \(P<0.0001\)) or R-CHOP induction (51.8 vs 23 months, \(P=0.0043\)), indicating that the anti-lymphoma effect of rituximab is not exhausted during induction. Importantly rituximab maintenance was also found to confer a
significant overall survival benefit at 3 years when compared to observation, with the risk of dying being reduced by one-third (85.1% vs 77.1%, \( P=0.0111 \)). No breakdown of OS benefit conferred by rituximab maintenance according to induction regimen was given as the study was not powered to determine this.

Maintenance rituximab resulted in a non-significant increase in grade 3 and 4 neutropenia (10.8% vs 5.4%) which probably accounted for the significant increase in grade 3 and 4 infections (mainly ear, nose and throat infections) in this group (9% vs 2.4%, \( P=0.009 \)). Six of 167 patients withdrew from the maintenance arm because of toxicity, 4 due to infection.

It thus appears that in patients with relapsed and refractory FL, maintenance rituximab improves median PFS more than 3-fold when compared with observation. This is achieved with minimal increase in toxicity. Even when rituximab maintenance follows R-CHOP induction the median PFS is more than doubled. In addition a significant overall survival benefit to rituximab maintenance is seen at 3 years.

There is currently no evidence from randomised studies that clearly demonstrates the benefit of rituximab maintenance in patients with relapsed/refractory FL who have been exposed to prior rituximab. NICE guidance however recommends the use of rituximab as maintenance treatment in this situation as well as in patients who were previously rituximab naïve.

Many different schedules of rituximab maintenance have been used. It is not clear which schedule is optimal. Gordon et al treated patients with rituximab 375 mg/m\(^2\) weekly for 4 weeks (Gordan, et al, 2005). Further rituximab was administered only when the plasma concentration fell below 25\( \mu \)g/ml (a level which correlated with response in a previous study). The median time to the next infusion to achieve this was 2-5 months, with 50% of patients achieving this level with a dosing interval of 3 months and almost all with a dosing interval of 2 months. This suggests that 2-3 monthly dosing is probably optimal.

The duration of maintenance is also uncertain. Further rituximab benefit has been noticed even after 2 years. However it is worth bearing in mind that in patients with low tumour burden who received rituximab 375mg/m\(^2\) weekly for 4 weeks, 24% of responders maintained their response at 5 years and 15% at 7 years without any further therapy. Of course, the longer the maintenance period the greater the
financial cost and the greater the possibility that continued B-cell depletion will result in significant adverse effects.

Unfortunately none of the randomised studies of maintenance rituximab have measured patient-related quality of life. It is generally assumed that a patient has a better quality of life if periods of remission are prolonged. However, for some patients repeated visits to receive therapy when they are otherwise well can be a constant reminder of their disease and actually have a significant negative impact on their quality of life. If rituximab is given every two or three months the infusion can be given on the same day as a scheduled follow up visit thus minimising the disruption to the patient’s life.

Recommendations:

- Patients who are being reassessed with features of relapsed FL should undergo a biopsy procedure, wherever practicable (1B).

- The combination of chemotherapy with rituximab should become the standard for those patients who require treatment at the point of relapse and are rituximab naïve as the combination improves all clinically meaningful outcomes, including overall survival, compared to chemotherapy alone (1A).

- Chemotherapy and rituximab should also be the standard for relapsed FL patients who have received prior rituximab if the patient had previously responded to rituximab (1C).

- The choice of chemotherapy will depend on characteristics of the patient. Both anthracycline and nucleoside analogue based therapies are active in patients with relapsed and refractory disease (1A).

- Rituximab maintenance prolongs PFS substantially in patients with relapsed/refractory FL who are rituximab-naïve and respond (partial or complete response) to re-induction therapy with single agent rituximab, chemotherapy or chemotherapy and rituximab (1A).
- **\(^{90}\)Y-Ibritumomab tiuxetan** is an active treatment approach in patients with relapsed FL and should be considered in older patients and those that are refractory or intolerant to chemotherapy and rituximab (2B).

- The benefits of high dose therapy with ASCT in relapsed FL need to be balanced against the long term risks of the procedure and considered in the setting of emerging therapies (1B; see section 8.0).

- Patients with localised, symptomatic disease should be considered for palliative radiotherapy, delivering doses of 4 Gy to 24 Gy (1B; see section 5.1.1).

### 7 MANAGEMENT OF PATIENTS WITH TRANSFORMED FL (TFL)

Histological transformation (HT) into an aggressive lymphoma is a frequent event in the natural history and clinical course of patients with FL (Montoto *et al.*, 2007b; Al-Tourah *et al.*, 2008). In general, patients with transformed FL (tFL) have adverse clinical features (i.e. poor performance status, high LDH, low haemoglobin level, high-risk according to both the IPI and the FLIPI), but the relationship between poor clinical characteristics and HT is not absolute, making a tissue biopsy mandatory to diagnose HT. Furthermore, FL occasionally transforms to Burkitt or to lymphoblastic lymphoma which require different treatment protocols. A recent study has demonstrated that the prognosis of patients with adverse clinical characteristics at relapse suggestive of HT (a sudden increase in the LDH level, rapid discordant nodal growth, new extra-nodal sites of disease or hypercalcaemia) but without histological confirmation is as poor as that in patients with biopsy-confirmed HT and, if obtaining a tissue biopsy is not feasible, these patients should be treated as patients with tFL (Al-Tourah *et al.*, 2008).

The outcome following HT is dismal with a median survival from transformation of around 1 year (Montoto *et al.*, 2007b; Al-Tourah *et al.*, 2008). Data regarding the optimal treatment for patients with HT are scarce, as these patients are frequently excluded both from FL and DLBCL trials. Patients with tFL are generally managed with anthracycline-containing regimens, if they have not received them early in the
course of the disease, or with chemotherapy regimens used as salvage therapy in relapsed DLBCL such as ICE, ESHAP or DHAP, co-administered with rituximab.

In patients achieving a response after salvage treatment, this is frequently followed by consolidation with high-dose treatment (HDT) and autologous stem cell rescue. Some studies demonstrate that the outcome of patients with tFL who receive such treatment is similar to that of patients who have HDT with autologous stem cell rescue for either FL or DLBCL (Williams et al, 2001; Foran et al, 1998). Whether this proves the benefit of HDT in tFL or it is only a consequence of the selection of patients that actually get HDT (i.e. those with a good response to salvage treatment) remains to be seen. Nonetheless, it has to be taken into account when considering the outcome after transformation that most of the studies include patients treated in the pre-rituximab era. In this regard, a study by the Stanford University presented in abstract form but not yet published (Tan et al, 2008), suggested that the outcome of patients after transformation has considerably improved in more recent eras, with a median OS of 3.3 years. In that series, patients who had not received any treatment before presenting HT had a significantly better outcome than those previously treated, which has also been reported in other studies (Yuen et al, 1995). The other important variable that predicts outcome after transformation is the stage at the time of HT, so that patients with localised disease (i.e. the transformed component is of limited stage, according to the Ann Arbor classification, after full staging investigations) have a prolonged survival (Gine et al, 2006; Al-Tourah et al, 2008; Yuen et al, 1995) supporting a less intensive treatment (i.e. avoiding HDT) in this population, as well as in those untreated at the time of HT.

**Recommendations:**

- Rituximab-naïve patients with HT of FL should receive rituximab-chemotherapy as treatment of the HT (1B).
- FL patients with HT who have previously been exposed to rituximab should receive rituximab chemotherapy as treatment of the HT (1C).
- Anthracycline-naïve patients should receive a doxorubicin-containing regimen; otherwise, a second-line therapy of the type used for DLBCL is recommended (1B).
- HDT with autologous stem cell rescue should be considered in younger and fit patients responding to salvage therapy for HT (2B).
- Chemotherapy-naïve patients at the time of HT and those with localised/limited stage disease may have better outcomes and may not require intensification with HDT (2B).

8 THE ROLE OF AUTOLOGOUS AND ALLOGENEIC TRANSPLANT IN FL

Three randomised studies have compared HDT (all with cyclophosphamide-total body irradiation as the conditioning regimen) and autologous stem cell rescue with conventional chemotherapy as first-line therapy of FL (Lenz et al, 2004; Deconinck et al, 2005; Sebban et al, 2006). No differences in OS are detected in any of the studies, but two of them (Lenz et al, 2004; Deconinck et al, 2005) show a significant improvement in PFS for patients receiving HDT. However, the long-term toxicity with an increased risk of secondary malignancies is considerable and, as a result, HDT with autologous stem cell rescue is not recommended for FL as first-line therapy outside the setting of a clinical trial.

In contrast, HDT is considered amongst the standard options for patients with relapsed FL. Several studies in the pre-rituximab era have demonstrated an improvement in the outcome of patients treated with HDT in comparison with historical controls treated with conventional chemotherapy (Brice et al, 2000; Apostolidis et al, 2000). This has been confirmed in a randomised study, demonstrating an advantage in terms of OS and PFS for patients with relapsed FL who receive HDT over those treated with conventional chemotherapy (Schouten et al, 2003). Three recent studies with a long follow-up show a plateau in the PFS curve, with around one third of patients being alive without disease 10 years after treatment (Montoto et al, 2007a; Kornacker et al, 2009; Rohatiner et al, 2007). It is likely that HDT remains an effective procedure in the rituximab era; a cohort of relapsed FL patients receiving in vivo rituximab purging and rituximab maintenance reported an overall survival of 80% at 8 years (Pettengell, et al, 2010). The main discrepancy lies in the appropriate timing for this strategy. The toxicity supports reserving HDT for late in the course of the disease. As discussed above, the introduction of maintenance rituximab prolonging PFS in patients with relapsed FL
also favours delaying the use of HDT (van Oers et al, 2006). On the other hand, the prognosis after HDT correlates with the number of lines of treatment before transplant. In addition, the risk of secondary MDS/AML seems to be associated with the use of total-body irradiation in the conditioning regimen (Montoto et al, 2007a) and with the number of previous relapses (Rohatiner et al, 2007). High risk features at relapse may also help in identifying patients with a poor prognosis as candidates for an intensive treatment early in the course of the disease (Montoto et al, 2004).

Historical studies show that myeloablative allogeneic stem cell transplantation is a curative treatment but has a high associated mortality. The advent of reduced-intensity conditioning (RIC) regimens has broadened the use of allogeneic transplant in FL by reducing its toxicity. Thus, RIC-allotransplants are considered a suitable clinical option for relapsed FL in specific circumstances (Ljungman et al, 2006). Most of the published series report a consistent relapse rate of around 20% at 3 years and a 3-year transplant-related mortality ranging from 30 to 40%, resulting in a 3-year OS and PFS of 50-65% and 43-55%, respectively (Table 5) (Robinson et al, 2007; Morris et al, 2004; Vigouroux et al, 2007; Rezvani et al, 2008; Hari et al, 2008; Ingram et al, 2008; Khouri et al, 2008; Thomson et al, 2010). Recently, excellent results have been published following RIC-allotransplants with T-cell depletion with alemtuzumab (Thomson et al, 2010).

The heterogeneity in the outcomes reported account for differences in the populations treated and in the characteristics of the procedures in different studies. The comparison of RIC allogeneic stem cell transplantation with HDT with autologous stem cell rescue is hampered by the fact that these two procedures are normally performed in very different populations; in the absence of the results of any prospective RCTs and given their toxicity, RIC-allotransplants are frequently performed in patients who relapse after HDT with autologous stem cell support (Khouri et al, 2008). However, some studies suggest that having failed a previous autologous transplant increases the mortality of the procedure (Rezvani et al, 2008). Chemo-refractory disease appears consistently in most of series as an adverse prognostic factor (Robinson et al, 2007; Morris et al, 2004; Vigouroux et al, 2007; Rezvani et al, 2008; Hari et al, 2008; Ingram et al, 2008).

There are no definitive trial results supporting either autologous or allogeneic transplant and the decision regarding timing and donor source varies from centre to
centre based on expert opinion, local experience and retrospective registry data. Consideration should be given to high dose therapy with autologous stem cell support or RIC allogeneic transplantation in selected patients in second or later remission. The decision should be based on previous remission duration, patient fitness, FLIPI index at relapse and choice of donor. If the first remission is less than 2 years it is reasonable to proceed to transplant in second remission. If the first remission is over 5 years then further immunochemotherapy is a reasonable option. If first remission is between 2 and 5 years therapeutic options include autologous transplant, especially if the patient has received rituximab maintenance in first remission, or RIC allogeneic transplantation if a sibling or fully matched unrelated donor is available in patients under 60.

**Recommendations:**

- Autologous stem cell transplantation has no role in first line therapy for follicular lymphoma outside the setting of a clinical trial (1B).
- The benefits of HDT with ASCT in relapsed FL need to be balanced against the long term risks of the procedure and considered in the setting of emerging therapies (1B).
- The patients suitable for transplantation with shorter durations of response following first line therapy should be considered for early referral (2C).
- RIC-allogeneic transplants should be considered for younger FL patients with early relapse (1B).
Table 5: Outcomes after RIC-allo transplant for FL

<table>
<thead>
<tr>
<th>Series</th>
<th>3-yr TRM</th>
<th>3-yr RR</th>
<th>3-yr OS</th>
<th>3-yr EFS/PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robinson, 2002*</td>
<td>31%</td>
<td>20%</td>
<td>65%</td>
<td>54%</td>
</tr>
<tr>
<td>Morris, 2004</td>
<td>11%</td>
<td>44%</td>
<td>73%</td>
<td>65/49%</td>
</tr>
<tr>
<td>Vigourox, 2007</td>
<td>40%</td>
<td>10%</td>
<td>56%</td>
<td>51%</td>
</tr>
<tr>
<td>Rezvani, 2007</td>
<td>42%</td>
<td>14%</td>
<td>52%</td>
<td>43%</td>
</tr>
<tr>
<td>Khouri, 2008</td>
<td>NR</td>
<td>NR</td>
<td>85%</td>
<td>83%</td>
</tr>
<tr>
<td>Hari, 2008</td>
<td>28%</td>
<td>17%</td>
<td>62%</td>
<td>55%</td>
</tr>
<tr>
<td>Ingram, 2008</td>
<td>20%</td>
<td>20%</td>
<td>69%</td>
<td>58%</td>
</tr>
<tr>
<td>Thomson, 2010**</td>
<td>15%</td>
<td>26%</td>
<td>76%</td>
<td>76%*</td>
</tr>
</tbody>
</table>

TRM: transplant-related mortality; RR: relapse risk; OS: overall survival; EFS: event-free survival; PFS: progression-free survival; * at 2 years; ** at 4 years; # current PFS.

9 FOLLOW-UP AND MONITORING OF PATIENTS WITH FL

9.1 Use of Imaging to Evaluate Response at the Completion of Treatment

CT is currently the standard imaging tool for assessing treatment response. The role of FDG PET-CT in determining response at the conclusion of treatment in FL is unclear and not routinely recommended (Juweid et al, 2007). A recent study in immunochemotherapy treated patients, presented in abstract form, suggested that a post-treatment FDG PET-CT is a powerful predictor of PFS (Trotman et al, 2010). Although there was no central review of scans carried out in this analysis, the results invite further studies of the utility of functional imaging and assessment of whether this modality can be used to guide therapy in FL based on response quality.

9.2 Follow-up of patients undergoing watchful waiting

There is no agreed follow-up strategy for patients undergoing watchful waiting; follow up is aimed at detecting the development of symptoms or significant disease progression. A follow up appointment 4-6 weeks after initial diagnosis is suggested.
to assess the rate of disease progression. If after several visits there has been no change, the intervals between appointments can be lengthened.

Clinics should be operated to allow patients to be seen at short notice if there is a change in their condition. At each visit an enquiry about symptoms should be made as well as a physical examination being done. Results of full blood count, renal, liver and bone tests should be available. Any concern may warrant a repeat CT scan or other imaging as appropriate. Standard indications for considering therapy are described in section 5.2.1. A rising LDH is not in itself an indication to initiate therapy but may trigger further investigations. What is most difficult to define is what degree of lymph node enlargement would warrant the initiation of therapy if the patient remains asymptomatic. Clearly the rate of nodal growth will be important. For the purpose of clinical trials a lymphoma mass >7 cm is suggested as a threshold for therapy, provided it has increased in size by at least 25% or more than 3 sites with diameter >5 cm, but ultimately the decision will be left to the physician to make in conjunction with the patient.

9.3 Follow-up of previously treated patients, including surveillance for late effects of therapy

Due to considerable variability in the rate of progression of FL, there are no set standard guidelines for routine patient follow-up after therapy. The frequency of follow up visits and the means used to monitor disease progression should therefore be tailored to the individual patient’s disease and expectations, as well as possible subsequent treatment modalities. It is probably necessary to continue to follow up all patients indefinitely.

Most patients with progressive disease will die with uncontrolled FL rather than complications of therapy. Patients receiving chemotherapy regimens or ASCT need to be monitored for the development of MDS and the effects of cardiotoxic agents.

9.4 Molecular monitoring of FL

It is widely assumed that the depth of remission of FL is related to the duration of clinical response; this has been demonstrated in several subtypes of both acute and chronic leukaemia. Similar approaches using either peripheral blood or bone
marrow cells have been designed for FL, but their utility may be limited, firstly by the lymph nodal origin of FL, and secondly by the fact that transformation can occur at any stage in the disease process. A further complication of using molecular methods as a marker of the depth of response to therapy is the lack of reproducibility of PCR reactions between different laboratories. In summary, molecular monitoring of the *BCL2* translocation cannot be currently recommended for routine FL follow-up.

**Recommendations for follow up of FL patients:**

- CT scanning is currently the appropriate method of response assessment following therapy for FL (1B).
- History and clinical examination performed at least 3 monthly for the first year following therapy and then tailored to an individual patient's circumstances e.g. 4 to 6 monthly for 4 years and yearly thereafter (2C).
- A full blood count, urea and creatinine, LFT and LDH at each clinical visit (2C).
- Thyroid function yearly in patients who have undergone irradiation of the neck (1B).
- Cross-sectional imaging following treatment is instigated only on suspicion of relapse requiring therapy. There is no role for routine scanning of patients following therapy (1C).

**For patients on watchful waiting the above may be further modified as follows:**

- History and clinical examination should be performed 3 monthly until disease progression (2C).
- Full blood count, urea and creatinine, liver function tests and LDH should be taken 3 monthly (2C).
- Cross sectional imaging post-treatment is instigated on suspicion of progression requiring therapy (2C).
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### Appendix 1: Method of calculation of FLIPI and FLIPI2 indices

<table>
<thead>
<tr>
<th>Variable</th>
<th>FLIPI</th>
<th>FLIPI2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>$\geq 60$ years</td>
<td>&gt; 60 years</td>
</tr>
<tr>
<td>Ann Arbor stage</td>
<td>III-IV</td>
<td>-</td>
</tr>
<tr>
<td>Haemoglobin level</td>
<td>&lt;120 g/l</td>
<td>&lt;120 g/l</td>
</tr>
<tr>
<td>Serum LDH level</td>
<td>$&gt;$ ULN$^*$</td>
<td>-</td>
</tr>
<tr>
<td>Number of nodal sites</td>
<td>&gt; 4</td>
<td>-</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>B2M</td>
<td>-</td>
<td>$&gt;$ UNL</td>
</tr>
<tr>
<td>LoDLIN$^*$</td>
<td>-</td>
<td>$&gt;$ 6 cm</td>
</tr>
</tbody>
</table>

ULN$^*$—*upper limit of normal

*LoDLIN: longest diameter of the largest involved node
Appendix 2: Strength of recommendations and levels of evidence:

GRADE

GRADE stands for: Grading of Recommendations Assessment, Development and Evaluation (GRADE). Details of the GRADE system are available at the working group website: http://www.gradeworkinggroup.org/index.htm.

STRENGTH OF RECOMMENDATION

Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

QUALITY OF EVIDENCE AND DEFINITIONS

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what we know or our certainty.

(A) High Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

(B) Moderate Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g. inconsistent results, imprecision - wide confidence intervals or methodological flaws - e.g. lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g. large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.
SUGGESTED TOPICS FOR AUDIT

1. What proportion of FL patients have their pathological material reviewed by a specialist haematopathologist?

2. Rituximab use, in combination with chemotherapy, in previously untreated FL patients, with firm indications to commence treatment?

3. Rituximab use, in combination with chemotherapy, in relapsed FL patients with firm indications to commence treatment?

4. Biopsy rate in patients presenting with symptoms and signs suggestive of relapsed FL?

5. What is the current approach to imaging of FL patients, including functional studies, and do they concur with recommendations made?

6. What proportion of patients with relapsed FL, who respond to re-induction therapy, progress to receive two years of rituximab maintenance?
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