Guidelines for the first line management of classical Hodgkin lymphoma

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The guideline group was selected to be representative of UK-based medical experts and patients’ representatives. MEDLINE and EMBASE were searched systematically for publications in English from January 1990 to June 2013 using the key words Hodgkin, Lymphoma, Treatment, Chemotherapy and Radiotherapy. References from relevant publications were also searched. The writing group produced the draft guideline, which was subsequently revised by consensus by members of the Haemat-Oncology Task Force of the British Committee for Standards in Haematology (BCSH). The guideline was then reviewed by a sounding board of approximately 50 UK haematologists and the BCSH and comments incorporated where appropriate. The ‘GRADE’ system was used to quote levels and grades of evidence, details of which can be found in Appendix I. The objective of this guideline is to provide healthcare professionals with clear guidance on the management of patients with classical Hodgkin Lymphoma (HL). The guidance may not be appropriate for all patients with HL and in all cases individual patient circumstances may dictate an alternative approach.

Key recommendations

Pre-treatment evaluation

- Patients require pre-treatment blood evaluation including human immunodeficiency virus (HIV) serology (1A).
- Staging with contrast–enhanced computerized tomography (CT) of the neck to pelvis is required (1A), although positron-emission tomography (PET)/CT is preferable if clinically feasible (1B).
- Early stage patients should be classified as favourable or unfavourable (1A).
- Advanced stage patients should be assessed to define the Hasenclever/International Prognostic Score (IPS) (1A).
- For male patients, pre-treatment semen cryopreservation should be offered where possible (1A).
- For female patients, pre-treatment review of options with a fertility specialist should be considered (1A).

Management of early stage disease

- Prognostic factors should be determined to allocate patients to favourable and unfavourable sub-groups (1A).
- Standard of care for patients with favourable early stage HL is 2 × ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) and 20 Gy radiotherapy (RT) (1A).
- Standard of care for unfavourable early stage HL is 4 × ABVD and 30 Gy RT (1A).
- A treatment option for unfavourable early stage HL is 2 × escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) + 2 × ABVD and 30 Gy RT (1A).
- The decision to omit RT from the management of stage IA/IIA non-bulky patients should involve discussion with a radiation oncologist (1B) and patients choosing to omit RT need to be aware of the balance of risks between RT and additional cycles of chemotherapy (1B).
- RT should not normally be omitted in patients presenting with bulky disease (1B).
- Early stage patients treated without RT should receive at least 3 × ABVD (1B).
- Patients receiving bleomycin should be assessed carefully for signs and symptoms of pulmonary toxicity before each dose. A history of new or worsening dyspnoea or...
Management of advanced stage disease

- Patients aged 16–60 years old with advanced stage HL should receive either 6–8 cycles of ABVD or six cycles of escalated BEACOPP (1A).
- The choice between ABVD and escalated BEACOPP will depend on a range of factors, particularly the patient’s opinion on the toxicity/efficacy balance between the regimens (2B).
- Patients with a higher IPS are at higher risk of relapse, potentially supporting the use of escalated BEACOPP in this higher risk group, although there are no prospective trial data to support a specific IPS cut-off at which escalated BEACOPP may be advantageous (2B).
- Patients treated with escalated BEACOPP who achieve an end-of-treatment PET-negative remission do not require consolidation RT to residual tissue (1A).
- Patients treated with ABVD should be considered for RT to sites of original bulk or residual tissue >1.5 cm. It remains unclear whether RT can be safely omitted in ABVD patients who have residual tissue >1.5 cm on CT that is PET-negative (1A).
- Interim PET (iPET2) is highly predictive of outcome in patients treated with ABVD (1A).
- It remains unclear how iPET2-positive patients are optimally managed in routine practice. Accepting the limitations of small, published datasets, treatment intensification to escalated BEACOPP ± RT appears reasonable (2B).
- Patients who remain PET-positive on completion of therapy require biopsy assessment or close clinical/radiological surveillance for early progression (1B).
- Patients who develop progressive disease on therapy should be considered for treatment intensification with transplantation (see separate guidelines) (1A).

Management of HL in elderly patients

- Elderly patients should be formally assessed for fitness to receive combination chemotherapy with a co-morbidity assessment tool, which should distinguish ‘frail’ from ‘non-frail’ patients (2B).
- Patients considered ‘frail’ should not usually be offered conventional combination chemotherapy (2B).
- ‘Non-frail’ patients should be offered combination chemotherapy and RT with the aim of achieving complete remission (CR), which is associated with better survival (1B).
- Older patients receiving bleomycin must be followed very closely for symptoms and signs of bleomycin lung toxicity (1A).
- Guidance on therapy choice for non-frail patients is hampered by the lack of randomized trial data. Treatment with VEPEMB (vinblastine, cyclophosphamide, prednisolone, procarbazine, etoposide, mitoxantrone) or COPP (cyclophosphamide, vincristin, procarbazine, prednisone)/ABVD appears to have lower treatment-related mortality than ABVD or BEACOPP (2B).

PET/CT in HL

- PET/CT should be reported by PET/CT imaging specialists (1C).
- As pre-treatment staging with PET/CT will upstage a minority of patients and aid the interpretation of subsequent PET/CT, it is recommended when clinically feasible (1B).
- PET/CT response should be reported according to Deauville criteria (2B).
- By Deauville criteria, a score of 1 or 2 should be considered ‘negative’ and 4 or 5 considered ‘positive’. Deauville score 3 should be interpreted according to the clinical context but in many HL patients indicates a good prognosis with standard treatment (1B).
- Biopsy is advised prior to second-line therapy to confirm residual disease with a score of 4 or 5 where possible to exclude false-positive uptake with fluorodeoxyglucose (FDG) (1B).
- The optimal management of iPET2-positive patients remains uncertain. Therefore, at this time, iPET2 remains desirable for ABVD-treated patients but cannot be mandated as a standard of care (2B).
- If a pre-treatment decision has been made to treat an early stage patient with RT following ABVD, then there is no clear role for interim PET/CT (1A).
- End-of-treatment PET/CT is recommended for all patients who have not achieved an interim PET-negative remission as this may directly affect RT planning, biopsy considerations and follow-up strategy (1B).
Radiotherapy strategies in HL

- The evidence for the role of RT in HL is based on involved field RT (IFRT) (1A).
- Reduced volume approaches, involved node (INRT) or involved site (ISRT) are under evaluation in current protocols (2B).
- The dose for favourable early stage disease should be 20 Gy, and 30 Gy for all other patients (1A).

Follow-up, late effects and survivorship

- Patients are usually followed with intermittent outpatient clinical review for 2–5 years following first line therapy (2C).
- There is no proven role for routine surveillance CT or PET/CT imaging in patients who are otherwise well following first line therapy (2B).
- HL patients should be made aware that they are at an increased lifetime risk of second neoplasms, cardiovascular and pulmonary disease and infertility (1A).
- Apart from the current breast cancer-screening programme, there are no national cancer screening programmes tailored for HL survivors. Women treated with mediastinal RT before the age of 35 years should be offered entry into the breast cancer National Notification Risk Assessment and Screening programme (NRASP) (1A).
- Regular lifestyle advice should be offered to reduce secondary neoplasms and cardiovascular risk. There should be complete avoidance of smoking and careful management of cardiovascular risks, such as hypertension, diabetes mellitus and hyperlipidaemia (1B).
- Patients who have had RT to the neck and upper mediastinum should have regular thyroid function checks. Hypothyroidism can occur up to 30 years after RT (1A).
- Patients should receive irradiated blood products for life (1B).

Background

The annual incidence of Hodgkin Lymphoma (HL) in the UK is 2.7/100 000 with approximately 1700 new cases per annum with a slight male predominance (Cancer Research UK, 2010). There is a peak in incidence in young adults aged 20–34 years with a further peak observed >70 years of age. The incidence is currently stable (Morton et al, 2006; Cancer Research UK, 2010; Shenoy et al, 2011).

Hodgkin Lymphoma is characterized by the presence of Hodgkin and Reed-Sternberg (HRS) cells within a cellular infiltrate of non-malignant inflammatory cells that make up the majority of the tumour tissue (Swerdlow et al, 2008). HRS cells have only recently been identified as clonal B cells that lack typical B-cell surface antigens. B cells failing to express surface immunoglobulin usually undergo apoptosis but HRS cells evade cell death through a number of mechanisms, including incorporation of Epstein-Barr virus (EBV) latent membrane proteins (LMP1 and 2), constitutive activation of the transcription factor nuclear factor κB (NFκB), and interaction with components of the microenvironment (Swerdlow et al, 2008; Steidl et al, 2011; Kuppers et al, 2012).

Hodgkin Lymphoma is classified as either nodular lymphocyte predominant (NLPHL) or classical HL. There are four sub-types of classical HL: nodular sclerosis, mixed cellularity, lymphocyte-rich and lymphocyte-depleted; there is no difference in the prognosis or management of the different sub-types of classical HL. In Europe and North America, nodular sclerosis classical HL accounts for 70% of all classical HL. Lymphocyte-depleted classical HL is more prevalent in immunocompromised patients and is seen more commonly in developing countries, where it has a strong association with EBV infection. NLPHL is distinct histologically and HRS cells are not present, it has a risk of transformation to high grade non-Hodgkin lymphoma and is managed differently from classical HL (Swerdlow et al, 2008).

Clinical presentation of classical HL is usually with painless lymphadenopathy, which is most commonly cervical or supraclavicular. Mediastinal disease is identified in 80% of patients and is more common in nodular sclerosis HL, whilst peripheral or sub-diaphragmatic lymphadenopathy is more common in mixed-cellularity classical HL. Bone marrow involvement is detected in only 5–8% of patients with conventional staging (Mauch et al, 1993; Levis et al, 2004a; Swerdlow et al, 2008), but in up to 18% with positron emission tomography (PET)/computed tomography (CT) staging (El-Galaly et al, 2012). Systemic symptoms of drenching night sweats, unexplained fever >38°C, and weight loss of >10% over 6 months are termed B symptoms and are identified in approximately 25% of patients.

Pretreatment evaluation

Blood evaluation should include full blood count, erythrocyte sedimentation rate, renal function, liver function, bone profile, lactate dehydrogenase and testing for human immunodeficiency virus (HIV).

Patients should be staged with a contrast-enhanced CT scan covering the neck, chest, abdomen and pelvis. An initial PET/CT scan is highly recommended as this provides a baseline for interpretation of subsequent scans and, in a minority of cases, it can upstage patients and alter the planned therapy. It is appreciated that a minority of patients may present with very advanced disease and if obtaining a PET/CT scan would result in a treatment delay this may not be clinically appropriate.

It was common practice to limit bone marrow evaluation to patients with advanced stage disease or B symptoms, however, it is now generally accepted that PET/CT can accurately detect marrow involvement and evaluation by biopsy is often unnecessary (El-Galaly et al, 2012). Clinicians should be
aware that diffuse bone marrow uptake on PET may just reflect a reactive process.

Patients with early stage disease should be categorized as having favourable or unfavourable characteristics. Patients with advanced stage disease should have their Hasenclever/International Prognostic Score (IPS) determined (Hasenclever & Diehl, 1998).

Consideration should be given to fertility preservation and semen cryopreservation should be offered routinely before therapy with combination chemotherapy. There is increasing evidence for the effectiveness of oocyte preservation as a fertility-sparing strategy and referral to a fertility specialist should be considered, if treatment delays are acceptable. This is especially important if the plan is to administer escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone). ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) is generally considered to be fertility-sparing, but some patients may need to receive salvage chemotherapy and stem cell transplantation, which can result in a reduction of fertility. The role for prophylactic use of gonadotropin-releasing hormone (GnRH) analogues to preserve female fertility remains uncertain (Behringer et al., 2012; Wong et al., 2013). For women with a stable partner, and in whom a delay of treatment is possible, in vitro fertilization for embryo cryopreservation may be appropriate. However, this may not be widely available at short notice. Ovarian tissue cryopreservation remains experimental and so far has resulted in only a small number of pregnancies and births (Loren et al., 2013). Generally, fertility preservation techniques can only be discussed on a case-by-case basis, involving fertility experts and oncologists who can judge the appropriateness of the techniques and the risks of delaying treatment.

Key recommendations for pre-treatment evaluation

- Patients require pre-treatment blood evaluation including HIV serology (1A).
- Staging with contrast-enhanced CT of the neck to pelvis is required (1A), although PET/CT is preferable if clinically feasible (1B).
- Early stage patients should be classified as favourable or unfavourable (1A).
- Advanced stage patients should be assessed to define the Hasenclever/IPS (1A).
- For male patients, pre-treatment semen cryopreservation should be offered where possible (1A).
- For female patients, pre-treatment review of options with a fertility specialist should be considered (1A).

Management of early stage disease

Randomized trials have shown that combined modality treatment with chemotherapy and radiotherapy (RT) results in superior tumour control compared with RT alone (Noordijk et al., 2006; Engert et al., 2007; Ferme et al., 2007). Clinical trials in patients with Stage I–II disease have increasingly evaluated treatment reduction as a strategy to reduce late morbidity and mortality. These trials have defined and refined prognostic factors for favourable and unfavourable prognosis Stage I–II HL. Traditionally in the UK, patients with early stage HL with B symptoms or bulk disease have been managed with protocols for advanced stage disease. However, long-term follow-up of large trial data sets, such as the German Hodgkin Study Group (GHSG) HD10 trial, have confirmed that these patients generally have excellent outcomes when treated with early stage unfavourable risk protocols. Definition of ‘large mediastinal mass/bulk’ disease varies slightly between study groups: The European Organization for the Research and Treatment of Cancer (EORTC) defines bulk as a mediastinal thoracic ratio >0.35 at T5/6. The UK National Cancer Research Institute (NCRI) and GHSG define a mediastinal mass ratio >0.33 as ‘large’, while the US National Comprehensive Cancer Network (NCCN) and National Cancer Institute of Canada (NCIC) define bulky as a mediastinal mass ratio>0.33 or any mass with maximal diameter >10 cm. Prognostic factors for the EORTC and GHSG are listed in Tables I and II.

Favourable early stage disease

Recent trials have focussed on abbreviating chemotherapy and RT dosages, and assessing RT-free treatment strategies. The GHSG HD10 trial randomized 1190 patients into four treatment arms, which included two cycles of ABVD plus 30 Gy RT, two cycles of ABVD plus 20 Gy of RT, four cycles of ABVD plus 30 Gy of RT and four cycles of ABVD plus 20 Gy of RT. With a 7-6-year median follow up, no difference was observed in freedom from progression (97%) or overall survival (OS, 98%) between the four groups (Engert et al., 2010). Thus, the least toxic approach consisting of two cycles of ABVD followed by 20 Gy RT appears to be sufficient in favourable Stage I–II HL.

The trial with the longest published median follow-up (11-3 years) in early stage HL is the IA/IIA non-bulky NCIC and Eastern Cooperative Oncology Group (ECOG) trial comparing ABVD alone (4–6 cycles) with treatment includ-

Table I. Favourable prognosis Stage I–II Hodgkin Lymphoma.

<table>
<thead>
<tr>
<th>EORTC</th>
<th>GHSG</th>
</tr>
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<tbody>
<tr>
<td>No large mediastinal adenopathy</td>
<td>No large mediastinal adenopathy</td>
</tr>
<tr>
<td>ESR &lt;50 without B symptoms</td>
<td>ESR &lt;50 without B symptoms</td>
</tr>
<tr>
<td>ESR &lt;30 with B symptoms</td>
<td>ESR &lt;30 with B symptoms</td>
</tr>
<tr>
<td>Age ≤ 50 years</td>
<td>No extranodal disease</td>
</tr>
<tr>
<td>1–3 lymph node sites involved</td>
<td>1–2 lymph node sites involved</td>
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</tbody>
</table>

EORTC, European Organization for the Research and Treatment of Cancer; GHSG, German Hodgkin Study Group; ESR, erythrocyte sedimentation rate.
Guideline

Table II. Unfavourable prognosis Stage I–II Hodgkin lymphoma.

<table>
<thead>
<tr>
<th>EORTC presence of one or more of the following</th>
<th>GHSG presence of one or more of the following</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large mediastinal adenopathy</td>
<td>Large mediastinal adenopathy</td>
</tr>
<tr>
<td>ESR ≥50 without B symptoms</td>
<td>ESR ≥50 without B symptoms</td>
</tr>
<tr>
<td>ESR ≥30 with B symptoms</td>
<td>ESR ≥30 with B symptoms</td>
</tr>
<tr>
<td>Age &gt;50 years</td>
<td>Extranodal disease</td>
</tr>
<tr>
<td>≥4 lymph node sites involved</td>
<td>≥3 lymph node sites involved</td>
</tr>
</tbody>
</table>

EORTC, European Organization for the Research and Treatment of Cancer; GHSG, German Hodgkin Study Group; ESR, erythrocyte sedimentation rate.

...omitting RT increases the risk of early relapse, but with longer follow-up does not appear to compromise OS. It is difficult to interpret the comparative aspects of this trial as STNI is no longer used in routine practice, and there were a small number of unusual events in the STNI arm that complicated the interpretation of OS of the RT-arm of the study. However, this trial has shown that treating IA/IIA non-bulky HL patients with ABVD alone delivers long-term OS of 94%.

Data from the UK NCRI trial (RAPID) and the EORTC H10 trial were presented at the annual American Society of Hematology meeting in 2012 (Andre et al., 2012; Radford et al., 2012). In both trials, patients who achieved an early PET-negative remission had a better progression-free survival (PFS) than interim PET-positive patients. Both trials randomized the patients who achieved an early PET-negative remission with ABVD chemotherapy to receive or omit RT. With both trials, there was an early PFS advantage with the inclusion of RT, but no OS advantage had been shown within the limited follow-up periods of both trials. Of note, patients with mediastinal bulk disease were excluded from the RAPID trial. In the RAPID study, patients who were PET-positive after three ABVD cycles received 1 × additional ABVD and RT. This achieved a 3-year PFS of 85-9% and OS of 93-9% (Radford et al., 2012).

With the current available data, the standard of care for treatment of patients with early stage favourable HL (as defined by GHSG criteria) therefore remains ABVD × 2 + RT. However, as there are longer term risks for patients treated with RT, it is recognized that, in some circumstances, clinicians and patients may prefer to treat without RT, particularly as the majority of IA/IIA non-bulky patients will be cured with chemotherapy alone. Indeed, a cross-trial comparative analysis between the German HD10/11 and NCIC HD6, suggested patients who achieve a CT complete remission (CR) after 2 × ABVD, and then complete a total 4 × ABVD with no RT, have the same excellent outcome as 2 × ABVD + RT (Hay et al., 2012). However, the decision to treat early stage good risk patients without RT should involve a radiation oncologist and the patient must be made aware that a number of trials indicate that removing RT probably increases the risk of early relapse by approximately 3–7% (Meyer et al., 2005, 2012; Andre et al., 2012; Radford et al., 2012). If patients are treated without RT, then choosing the optimum number of cycles of ABVD is difficult. The NCIC/ECOG trial, using 4–6 cycles of ABVD, has the longest follow-up, but initial data from 3 × ABVD for PET-negative patients in the RAPID trial are encouraging. A balance therefore needs to be struck between long-term toxicity of RT and the toxicity of the additional ABVD cycles (Swedlow et al., 2011).

Apart from abstract presentations of the UK NCRI trial (RAPID) and the EORTC H10 trial (Andre et al., 2012; Radford et al., 2012), larger randomized trials using PET/CT to guide decision-making in early stage HL have yet to be formally reported. Consensus opinion from all trials groups is that early stage patients with persisting PET-avid disease after chemotherapy should receive RT. At this stage, it remains uncertain whether achieving an interim PET-negative remission after two cycles of ABVD is as predictive for long-term PFS and OS as achieving a CR by established CT criteria.

Unfavourable early stage disease

In the HD11 trial, the GHSG randomly assigned 1395 patients with early unfavourable HL to four cycles of ABVD plus 30 Gy RT, four cycles of ABVD plus 20 Gy RT, four cycles of BEACOPP plus 30 Gy RT and four cycles of BEACOPP plus 20 Gy RT (Eich et al., 2010). With 6-8 years median follow-up, no difference was observed in OS (93–96%) for all four groups. In the arms of the study with 30 Gy of RT, there was no difference in freedom from treatment failure (FFTF) between BEACOPP and ABVD (P = 0.65), but a significant difference in favour of BEACOPP was seen for FFTF when 20 Gy RT was used (P = 0.02) (Eich et al., 2010). The German Hodgkin study Group HD14 Trial randomly assigned early unfavourable HL patients to either four cycles of ABVD or an intensified treatment of two cycles of escalated BEACOPP followed by two cycles of ABVD (2 + 2) (von Tresckow et al., 2012). Chemotherapy was followed by 30 Gy RT in both arms. At 5 years follow-up, the dose-intensified regime resulted in better tumour control with a 6.2% improvement in PFS compared with standard treatment with four cycles of ABVD. However, acute toxicities were significantly higher in the 2 + 2 arm and with no difference in OS, this regimen would be considered a treatment option rather than a standard of care for the majority of patients.

Currently, four cycles of ABVD followed by 30 Gy RT is widely considered the standard of care for unfavourable early stage HL. There is no evidence to support the removal of RT from patients who present with bulky disease, and of note, such patients were excluded from the RAPID and NCIC/ECOG 6 trials.

Infra-diaphragmatic early stage disease

The incidence of infra-diaphragmatic early stage HL is very low and accounts for 4–13% of cases of Stage I–II disease...
(Vasilakopoulos et al, 2006). When results are adjusted for risk factors they appear to have a similar prognosis to patients with supradiaphragmatic disease. Older age, clinical stage II (borderline), involvement of ≥3 sites and higher IPS is more frequent in patients with infradiaphragmatic disease and the previously reported poorer outcome may be explained by the unfavourable profile of the patients. Although this group of patients are under-represented in clinical trials, there is currently no evidence to suggest that they should be treated differently from their supradiaphragmatic counterparts (Darabi et al, 2005; Vasilakopoulos et al, 2006).

**KEY recommendations for management of early stage disease**

- Prognostic factors should be determined to allocate patients to favourable and unfavourable sub-groups (1A).
- Standard of care for patients with favourable early stage HL is 2 × ABVD and 20 Gy RT (1A).
- Standard of care for unfavourable early stage HL is 4 × ABVD and 30 Gy RT (1A).
- A treatment option for unfavourable early stage HL is 2 × escalated BEACOPP + 2 × ABVD and 30 Gy RT (1A).
- The decision to omit RT from the management of stage IA/IIA non-bulky patients should involve discussion with a radiation oncologist (1B) and patients choosing to omit RT need to be aware of the balance of risks between RT and additional cycles of chemotherapy (1B).
- RT should not normally be omitted in patients presenting with bulky disease (1B).
- Early stage patients treated without RT should receive at least 3 × ABVD (1B).
- Patients receiving bleomycin should be assessed carefully for signs and symptoms of pulmonary toxicity before each dose. A history of new or worsening dyspnoea or pulmonary crackles should lead to stopping of bleomycin until an alternative cause is identified (1B).

**Advanced stage disease**

Standard treatment for patients with stage III/IV HL is combination chemotherapy. In the UK, patients with early stage disease but B symptoms or bulky disease have usually been managed with advanced HL protocols, although this is not universal international practice (Townsend & Linch, 2012). There is significant international variation in the use of RT to sites of initial bulk disease or residual masses following chemotherapy.

Over the past three decades of comparative randomized clinical trials in HL, ABVD and escalated BEACOPP have become established international standards of care for advanced HL [reviewed in (Townsend & Linch, 2012)]. ABVD has better outcomes in terms of efficacy and/or toxicity than MOPP (mechlorethamine, vinristine, procarbazine, prednisone), MOPP–ABV (MOPP, doxorubicin, bleomycin, vinblastine) hybrid and CHIVP/PABLOE (chlorambucil, vinblastine, procarbazine, prednisone/doxorubicin, bleomycin, vincristine and etoposide), and similar efficacy, but lower toxicity, than the Stanford V regimen (mechlorethamine, doxorubicin, vinblastine, prednisone, vincristine, bleomycin, etoposide) (Canellos et al, 1992; Duggan et al, 2003; Johnson et al, 2005; Hoskin et al, 2009). From a number of advanced HL trials, failure-free/PFS with ABVD is around 73–78% with OS in the range of 82–90% (Duggan et al, 2003; Johnson et al, 2005; Federico et al, 2009; Hoskin et al, 2009; Viviani et al, 2011). ABVD should be delivered on schedule with infusions given every 14 d irrespective of neutrophil count. Granulocyte colony-stimulating factor (G-CSF) is only required for patients with infectious complications (Evens et al, 2007; Nangalia et al, 2008).

Different HL study groups have followed different strategies for RT following chemotherapy. Patients with bulky advanced stage disease who achieve a CT CR after MOPP/AVD can avoid RT in contrast with patients in partial remission (PR), who did derive benefit from RT (Aleman et al, 2003). It remains unclear as to whether RT to sites of initial bulk disease or residual tissue can be safely omitted in patients treated with ABVD. In the LYO9 trial, 43% of patients received RT following ABVD or CHIVP/PABLOE and, with a median follow-up of 6–9 years, these patients had a PFS and OS advantage compared with patients treated without RT (Johnson et al, 2005). Of note, the ABVD trials with the highest OS rates have used RT for a large proportion of patients (Duggan et al, 2003; Johnson et al, 2005; Hoskin et al, 2009).

Escalated BEACOPP was been developed by the German HL study group (GHLSG). In comparison with COPP–ABVD and standard dose BEACOPP, escalated BEACOPP has demonstrated improved PFS and OS (Engert et al, 2009). Data from 2182 patients randomized from 408 centres in the GHLSG HD15 trial have shown a 5-year failure-free and OS of 89% and 95% respectively, for patients receiving six cycles of escalated BEACOPP (Engert et al, 2012). Patients in this trial who achieved a PET-negative remission (but PR by conventional CT) were not treated with RT consolidation, in contrast with the HD9 trial. The number of patients receiving RT fell from 71% in HD9 to 11% in HD15, with no apparent loss in treatment efficacy (Engert et al, 2012). Although this is not prospective randomized data, it is reasonable to conclude that patients who achieve PET-negative remission following escalated BEACOPP therapy do not require RT to sites of residual tissue (Engert et al, 2012). From HD15, the outcomes for patients treated with escalated BEACOPP × 6 or BEACOPP 14 × 8 were similar and clinicians/patients may prefer to be treated on the latter regimen if appropriate. Escalated BEACOPP-based strategies have also delivered impressive results in high-risk childhood/
adolescent HL [5-year event-free survival (EFS)/OS: 94%/97%] (Kelly et al, 2011), but have shown unacceptable treatment-related toxicity in patients >60 years old (Engert et al, 2009) and the GHLSG no longer recommends this protocol for patients over 60 years of age.

Data directly comparing ABVD with escalated BEACOPP are limited. The EORTC 20012 trial comparing ABVD with BEACOPP (4× escalated, 4× standard) for higher risk HL patients has been presented in abstract form only (Carde et al, 2012). A PFS advantage was found for escalated BEACOPP, but no survival advantage has yet been demonstrated with a median follow-up of 3-8 years. A smaller Italian trial randomized patients to either ABVD or escalated BEACOPP followed by treatment intensification with RT (to sites of initial bulk and residual tissue) then salvage chemotherapy/autologous transplant for all patients failing to achieve a CR (Viviani et al, 2011). Initial treatment with escalated BEACOPP resulted in a 7-year freedom-from-first progression advantage compared with ABVD (85% vs. 73%; \(P=0.004\)), but the 7-year OS was no different, at 89% and 84%, respectively (\(P=0.32\)). Considering the first line intensification strategy given to approximately a quarter of the patients has been presented in abstract form only (Carde et al, 2007). A number of recently closed and ongoing therapeutic trials are assessing whether, in comparison with historical controls, treatment intensification for iPET2 positive patients with escalated BEACOPP can improve patient outcomes (Gallamini et al, 2011, 2012). The UK RATHL trial (http://public.ukcrn.org.uk/search/StudyDetail.aspx?StudyID=4488) chose to intensify therapy with either 4× escalated BEACOPP or 4× BEACOPP-14 with no RT requirement, while the Italian approach has been to use 8 cycles of BEACOPP (4× escalated and 4× standard) and RT to sites of initial bulk disease. Initial reports from the Italian group appear encouraging (Gallamini et al, 2011, 2012).

There is no international consensus on whether patients are best served by starting therapy with either ABVD or escalated BEACOPP and personal priorities for each patient will clearly influence this decision. There are no prospective data to support a specific IPS cut-off when deciding between escalated BEACOPP and ABVD. Patients opting for ABVD will have clear benefits in terms of toxicity, but will have a higher risk of relapse and need for salvage therapy/autologous transplant. With ABVD-treated patients, there is also uncertainty with regards to the need for RT to sites of initial bulky disease/residual tissue and lack of clarity as to the role of iPET2 when treated outside a clinical trial. Patients opting for escalated BEACOPP have clear benefits with regards to EFS and the clarity that RT will be needed in only 10% of patients. They will, however, potentially experience more treatment-related toxicity.

There are no data on the use of escalated BEACOPP in HIV-related HL, where standard management remains ABVD combined with anti-retroviral therapy (Montoto et al, 2012).

**Key recommendations for management of advanced stage disease**

- Patients aged 16–60 years with advanced stage HL should receive either 6–8 cycles of ABVD or 6 cycles of escalated BEACOPP (1A).
- The choice between ABVD and escalated BEACOPP will depend on a range of factors, particularly the patient’s opinion on the toxicity/efficacy balance between the regimens (2B).
• Patients with a higher IPS are at higher risk of relapse, potentially supporting the use of escalated BEACOPP in this higher risk group, although there are no prospective trial data to support a specific IPS cut-off at which escalated BEACOPP may be advantageous (2B).

• Patients treated with escalated BEACOPP who achieve an end of treatment PET-negative remission do not require consolidation RT to residual tissue (1A).

• Patients treated with ABVD should be considered for RT to sites of original bulk or residual tissue >1.5 cm. It remains unclear whether RT can be safely omitted in ABVD patients who have residual tissue >1.5 cm on CT that is PET-negative (1A).

• Interim PET (iPET2) is highly predictive of outcome in patients treated with ABVD (1A).

• It remains unclear how iPET2-positive patients are optimally managed in routine practice. Accepting the limitations of small, published datasets, treatment intensification to escalated BEACOPP ± RT appears reasonable (2B).

• Patients who remain PET-positive on completion of therapy require biopsy assessment or close clinical/radiological surveillance for early progression (1B).

• Patients who develop progressive disease on therapy should be considered for treatment intensification with transplantation (see separate guidelines) (1A).

Management of HL in pregnancy

There are no prospective trials for the management of HL in pregnancy, but a number of published case reports, case series and case cohorts were reviewed by Bachanova and Connors (2008). The priority must be the health of the mother and, ideally, management should be in conjunction with an obstetrician experienced in high-risk pregnancy. While termination of pregnancy may be the most appropriate course of action for certain patients, for many cases, the fetal and maternal outcomes following HL treatment in pregnancy appear excellent (Evens et al, 2011).

Staging and response assessment with magnetic resonance imaging scans and ultrasound may avoid the need for radiation-based imaging and, in certain cases, delaying therapy until post-partum may be possible, although this must be done with caution.

If therapy is required in pregnancy, the general consensus is that ABVD is the regimen of choice if multi-agent chemotherapy is to be used (Bachanova & Connors, 2008). Although ABVD has been used to treat patients in all 3 trimesters (Anselmo et al, 1999; Cardonick & Iacobucci, 2004), the potential risk to fetal development from chemotherapy is likely to be higher in the first trimester and most clinicians would try and avoid exposure to chemotherapy at this time. Wherever possible, RT should be delayed until post-delivery.

Key recommendations for HL in pregnancy

• Patients should be closely co-managed with a specialized obstetric/fetal medicine unit (1B).

• Staging investigations and response evaluation should be tailored to the clinical presentation with radiology input to minimize fetal radiation exposure (1C).

• Delaying commencement of chemotherapy until post-delivery would not be standard practice and should be done with caution (1C).

• ABVD is the regimen of choice unless specifically contraindicated (1B).

• Wherever possible, RT should be delayed until post-delivery (1B).

Management of HL in elderly patients

Population based data suggest that the over-60s age group account for approximately 20% of cases of HL (Stark et al, 2002) and a number of studies have suggested that their outcome is consistently less good than that of younger patients, especially for those with advanced stage disease (Evens et al, 2008, 2012, 2013; Proctor et al, 2009). Older patients are more likely to die from non-HL causes, including bleomycin lung toxicity, which was reported in 24% of patients over 60 years old treated within the North American Intergroup trial E2496 (Evens et al, 2013). Therapy-related toxicity has, therefore, made delivering the ‘gold standard’ chemotherapies, ABVD and BEACOPP, challenging, especially in the over-70s and the major randomized trials contain only small numbers of elderly patients.

Following a number of workshops at international lymphoma meetings in the early 2000s it was decided to pursue a series of non-randomized phase II studies of alternative therapies in elderly HL. The GHSG have developed phase 2 trials with BACOPP (modified and dose-reduced BEACOPP) and PVAG (prednisolone, vincristine, doxorubicin, gemcitabine) (Halbsguth et al, 2010; Boll et al, 2011). BACOPP (bleomycin, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone) was used to treat 65 patients aged 65–70 years, producing a CR rate of 85% but with a 12% treatment-related mortality and 33 month OS of 70%. With PVAG, 59 patients aged 60–75 years were treated for mainly advanced stage disease, producing a 3-year PFS and OS of 58% and 66%.

The GHSG have also analysed the outcomes for early stage elderly patients treated with ABVD within the HD10 and HD11 trials (Boll et al, 2013). They observed excellent response rates (CR of 89%), but a treatment-related mortality of 5%. With 92 months median follow-up, the 5-year PFS was estimated at 75%. With the UK Shield registration study, the CR rate for early stage patients treated with two or more cycles of ABVD and involved field RT (IFRT) was 62% but, for advanced stage ABVD patients, the CR rate was only 46%, and there were 18% treatment-related deaths (Proctor et al, 2012). Of note, within this registration study, no patients
who were classified as ‘frail’ based on a scoring system, completed treatment or achieved a CR. The high treatment-related death rate with ABVD is similar to that described in the ABVD versus Stanford V trial for older patients (Evens et al., 2013). In the German HD9 elderly analysis, acute toxicity led to 21% treatment-related deaths after BEACOPP compared with 8% for COPP/ABVD (Ballova et al., 2005).

UK and Italian groups have both explored a treatment strategy with VEPEMB (vinblastine, cyclophosphamide, prednisolone, procarbazine, etoposide, mitoxantrone). In total, 103 patients were treated with VEPEMB as part of the Shield programme (Proctor et al., 2012), including 31 early stage patients (VEPEMB × 3 followed by involved field RT) with a CR rate of 74% and 3-year PFS and OS of 74% and 81%, respectively. For 72 advanced stage patients treated with VEPEMB × 6 a CR rate of 61% was achieved with 3-year PFS and OS of 58% and 66%, respectively. However, patients classified as ‘frail’ were excluded from the UK VEPEMB trial and this probably improved the results. Nevertheless, similar encouraging data with VEPEMB have been reported from an Italian trial (Levis et al., 2004b). It also remains common practice to treat less fit elderly patients with older non-anthracycline containing regimens, such as ChlVPP, although published outcomes for this regimen in the elderly are generally poor (The International ChlVPP Treatment Group, 1995).

**Key recommendations for management of elderly patients**

- Elderly patients should be formally assessed for fitness to receive combination chemotherapy with a co-morbidity assessment tool, which should identify ‘frail’ from ‘non-frail’ patients (2B).
- Patients considered ‘frail’ should not usually be offered conventional combination chemotherapy (2B).
- ‘Non-frail’ patients should be offered combination chemotherapy and RT with the aim of achieving CR, which is associated with better survival (1B).
- Older patients receiving bleomycin must be followed very closely for symptoms and signs of bleomycin lung toxicity (1A).
- Guidance on therapy choice for non-frail patients is hampered by the lack of randomized trial data. Treatment with VEPEMB or COPP/ABVD appears to have lower treatment-related mortality than ABVD or BEACOPP (2B).

**The use of PET/CT in HL**

Hodgkin Lymphoma is 18FDG avid in 97–100% of cases (Weiler-Sagie et al., 2010). Staging patients with FDG PET-CT is more accurate than CT alone (Cheson et al., 2007) and the availability of a baseline scan increases the reliability of subsequent response assessment (Quarles van Ufford et al., 2010; Barrington et al., 2011). Contrast-enhanced CT may be done as part of the PET-CT examination or at a separate visit, depending on local imaging arrangements.

The five-point scale (5-PS) also referred to as the ‘Deauville criteria’ has been used for reporting in response guided trials and has published high inter-observer agreement (Barrington et al., 2010; Furth et al., 2011; Biggi et al., 2013) and improved predictive value (Le Roux et al., 2011) when compared with earlier International Harmonization criteria (Juweid et al., 2007). The response scan is compared with the baseline scan and scored according to the level of highest residual FDG uptake using the 5-PS as follows:

- Score 1: No uptake.
- Score 2: Uptake less than or equal to the mediastinum.
- Score 3: Uptake greater than the mediastinum but less than the liver.
- Score 4: Uptake moderately higher than the liver.
- Score 5: Uptake markedly higher than the liver.

After chemotherapy, stimulation of normal bone marrow may result in diffusely increased uptake that is higher than normal liver. The uptake in sites of initial marrow involvement should then be compared with uptake within normal marrow to assess the presence/absence of residual disease.

The 5-PS can be used to assess response during treatment (with an interim scan) and at the end of treatment. To avoid the risk of under-treatment, scores 1 and 2 were used to define a ‘negative’ scan in the RAPID study (Radford et al., 2012). The mediastinum was also used as the threshold for satisfactory response in the HD15 study for patients treated with BEACOPP who subsequently did not receive RT (Engert et al., 2012). It is recommended therefore that a score of 1 or 2 is used to define a complete metabolic response (CMR) if omission of ‘standard’ RT treatment is being considered in discussion with patients.

To avoid the risk of over-treatment, scores 4 and 5 were used to define a ‘positive’ scan in the NCRI RATHL study (Barrington et al., 2010) and in the Italian HD0607 study and scores 1, 2, 3 defined a ‘negative’ scan (http://www.clinicaltrials.gov/ct2/show/NCT00795613) with initial reports suggesting satisfactory responses for patients treated with BEACOPP who subsequently did not receive RT (Engert et al., 2012). It is recommended therefore that a score of 1 or 2 is used to define a complete metabolic response (CMR) if omission of ‘standard’ RT treatment is being considered in discussion with patients.
which was previously referred to as ‘minimal residual uptake’, (Hutchings et al, 2005) are likely have good outcomes with standard treatment (Hutchings et al, 2005; Biggi et al, 2013; Johnson et al, 2013), but until more information is available, de-escalation of therapy outside trials in these patients is not advised.

Standardized methods for PET acquisition and quality control have been developed during the conduct of response-guided trials and are recommended for best clinical practice. The reliability of visual and quantitative assessments depends on correct patient preparation, image acquisition and quality assessment of imaging equipment. Therefore, if management changes are considered based on PET findings, guidelines for tumour imaging with FDG standards should be adhered to (Boellaard et al, 2010). Both interim and end-of-treatment scans should be performed as long after the last chemotherapy administration as possible, to avoid false-positive uptake due to inflammation induced by treatment (Spaepen et al, 2003; Boellaard et al, 2010). Therefore, interim scans should be performed as close to the start of the next cycle of chemotherapy as practical. At the end of treatment, a minimum of 10 d following chemotherapy, 2 weeks after granulocyte colony-stimulating factor (G-CSF) treatment and 3 months after RT is recommended to elapse prior to scanning (Boellaard et al, 2010).

Key recommendations for PET/CT in HL

- PET/CT should be reported by PET/CT imaging specialists (1C).
- As pre-treatment staging with PET/CT will upstage a minority of patients and aid the interpretation of subsequent PET/CT, it is recommended when clinically feasible (1A).
- PET/CT response should be reported according to Deauville criteria (2B).
- By Deauville criteria, a score of 1 or 2 should be considered ‘negative’ and 4 or 5 considered ‘positive’. Deauville score 3 should be interpreted according to the clinical context but in many HL patients indicates a good prognosis with standard treatment (1B).
- Biopsy is advised prior to second-line therapy to confirm residual disease with a score of 4 or 5 where possible to exclude false-positive uptake with FDG (1B).
- The optimal management of iPET2 positive patients remains uncertain. Therefore, at this time, iPET2 remains desirable for ABVD-treated patients but cannot be mandated as a standard of care (2B).
- If a pre-treatment decision has been made to treat an early stage patient with RT following ABVD, then there is no clear role for interim PET/CT (1A).
- End-of-treatment PET/CT is recommended for all patients who have not achieved an interim PET negative remission as this may directly affect RT planning, biopsy considerations and follow-up strategy 1B.

Radiotherapy strategies in HL

As chemotherapy has become more effective, the role of RT in HL has diminished, but it is still an essential tool, maximizing local control, allowing fewer cycles of chemotherapy and avoiding intensive chemotherapy in relapse.

The evidence base for RT in both early and advanced HL is based on IFRT. However, concerns regarding the late effects of radiation have led to new protocols using reduced volume treatment. An EORTC consensus led by Groupe d’Etude des Lymphomes de l’Adulte (GELA) is now in favour of involved node RT (INRT) (Girinsky et al, 2008). However, this depends on obtaining pre- and post-treatment PET-CT imaging of the patient in the treatment position (Girinsky et al, 2008; Specht et al, 2013). An alternative approach uses involved site RT (ISRT), which adds a 15 mm safety margin above and below the involved node (Hoskin et al, 2013; Specht et al, 2013). Larger volumes are still preferred in those rare cases where RT alone is recommended.

The dose of RT is now well defined from the GHSG trials HD10 and HD11, which show that 20 Gy is sufficient for favourable early HL, and 30 Gy should be given to all other patients with early or advanced stage disease, where RT is indicated.

Key recommendations for radiotherapy strategies in HL

- The evidence for the role of RT in HL is based on IFRT (1A).
- Reduced volume approaches, INRT or ISRT are under evaluation in current protocols (2B).
- The dose for favourable early stage disease should be 20 Gy, and 30 Gy for all other patients (1A).

Follow-up, late effects and survivorship issues

There is significant variation in follow-up practice with little evidence to support a particular strategy. Clinicians typically keep patients in follow-up clinics for 5 years before discharge with intermittent outpatient review, but follow-up frequency inevitably varies depending on patient requirements. Some patients/clinicians may prefer early discharge from formal follow-up after completion of first line therapy.

Routine CT or PET/CT scans significantly increase radiation exposure and health care costs with no clear evidence of benefit for patients (Voss et al, 2012; Patel et al, 2013). As such, routine CT or PET/CT scanning for otherwise well patients is not normally required.

Despite the high cure rates, long-term survivors of HL have increased mortality compared to the general population (Ng et al, 2002; Favier et al, 2009; Baxi & Matasar, 2010). During the first 5–10 years of follow-up, the lead cause of absolute excess risk (AER) of mortality remains HL, especially in those with unfavourable prognosis. However, the AER for all-cause
mortality remains significantly elevated more than 20 years after treatment (Ng et al, 2002). The major causes of long term, non-relapse morbidity and mortality are second neoplasms and cardiac disease, but also include pulmonary disease and infections. Patients, who have received neck RT, can become hypothyroid and issues relating to reduced fertility and psychosocial problems may significantly affect quality of life. HL patients have also been shown to have long-term anergic immunological responses and measurable defects in T-cell function (Levy & Kaplan, 1974). The clinical implications of this remain unclear. Cases of transfusion-associated graft-versus-host disease have been reported (Baglin et al, 1992). Consequently, all HL patients are recommended to receive lifelong irradiated blood products. There are no data to support the lifelong avoidance of live vaccines in patients who have completed treatment for HL.

Second neoplasms

Several studies, including a Cochrane review, large cohort studies and meta-analyses, have confirmed the increased incidence of secondary neoplasms in long-term survivors of HL (Bhatia et al, 2003; Franklin et al, 2005, 2006; Travis et al, 2005; Hodgson et al, 2007b; Favier et al, 2009; Meadows et al, 2009). A recent large collaborative British Cohort study followed 5798 HL patients treated with chemotherapy between 1963 and 2001 (Swerdlow et al, 2011). Combined modality treatment (CMT) carried a greater relative risk (RR) for secondary neoplasms than chemotherapy alone (CA) [RR CMT 3.9; 95% confidence interval (CI), 3.5–4.4; RR CA 2.0; 95% CI, 1.7–2.4]. The largest AERs related to lung cancer, CMT 14.0, CA 10.7, non-Hodgkin lymphoma, CMT 13.9, CA 11.6 and leukaemia, CMT 11.7, CA 12.8. However, CMT was associated with AERs for a range of additional secondary neoplasms including breast, bowel, non-melanoma skin cancer and unspecified primary.

Depending on the age at treatment and the extent of the radiation field, the 25-year cumulative risk of breast cancer in women treated in childhood or early adulthood with RT is approximately 10–33%, compared with a lifetime risk in the UK of 11% (Taylor et al, 2007; Westlake & Cooper, 2008). Furthermore, survival stage-for-stage with breast cancer after HL is worse than that following de novo breast cancer (Milano et al, 2010). Since 2003, this breast cancer risk has been prospectively managed by a screening programme throughout the UK (Howell et al, 2009).

Cardiovascular disease

Cardiovascular disease is the second most important cause of excess mortality amongst long-term survivors of HL, after secondary neoplasms (Ng et al, 2002; Baxi & Matsasar, 2010). Myocardial infarction (MI) carries the greatest risk and this has been particularly linked to mediastinal RT. The Collaborative British Cohort Study followed 7033 patients treated between 1967 and 2000 and identified 166 deaths from MI (Swerdlow et al, 2007). This represented an absolute excess risk of 126 per 100 000 person-years, and the risk remains high for at least 25 years. Significant and independent increased risk of MI was identified for supradiaphragmatic RT, anthracyclines and vinca-alkaloids. The risk was particularly high for the ABVD regimen and the combination of supradiaphragmatic RT and vincristine without anthracyclines.

Pulmonary toxicity

Shortness of breath is described by as many as 30% of patients treated for HL; bleomycin pulmonary toxicity, acute radiation pneumonitis and late stage pulmonary fibrosis are all implicated. Fatal pulmonary fibrosis following bleomycin is described in 1–2% of bleomycin-treated patients (Williams et al, 1987; Kaye et al, 1998; Nichols et al, 1998; O’Sullivan et al, 2003). Data from HL and germ cell tumour patients have suggested a range of contributing factors including older age, higher doses, pre-existing lung disease, renal impairment and the concomitant use of G-CSF (O’Sullivan et al, 2003; Martin et al, 2005). However, only dose and older age seem to be reliably associated and the risk should be largely considered idiosyncratic. Bleomycin toxicity ranges from a measured decrease in diffusion capacity, lung volumes and vital capacity, to pneumonitis with non-specific patchy opacities to end stage pulmonary fibrosis (http://www.drugs.com). Early symptoms and signs are dyspnoea/dry cough and crackles that occur 1–9 months after starting treatment and should lead to immediate cessation of the drug until another cause has been identified. Anecdotal case reports suggest that steroids might help pre-fibrotic stages (Sleijfer, 2001).

KEY recommendations for follow-up, late effects and survivorship

- Patients are usually followed with intermittent outpatient clinical review for 2–5 years following first line therapy (2C).
- There is no proven role for routine surveillance CT or PET/CT imaging in patients who are otherwise well following first line therapy (2B).
- HL patients should be made aware that they are at an increased lifetime risk of second neoplasms, cardiovascular and pulmonary disease and infertility (1A).
- Apart from the current breast cancer-screening programme, there are no national cancer screening programmes tailored for HL survivors. Women treated with mediastinal RT before the age of 35 years should be offered entry into the breast cancer National Notification Risk Assessment and Screening programme (NRASP) (1A).
- Regular lifestyle advice should be offered to reduce secondary neoplasms and cardiovascular risk. There should
be complete avoidance of smoking and careful management of cardiovascular risks such as hypertension, diabetes mellitus and hyperlipidaemia (1B).

- Patients who have had RT to the neck and upper mediastinum should have regular thyroid function checks. Hypothyroidism can occur up to 30 years after RT (1A).

- Patients should receive irradiated blood products for life (1B).

Disclaimer

While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the British Society for Haematology, nor the publishers accept any legal responsibility for the content of these guidelines. This Guideline is in date at the time of publishing. It will be reviewed at least annually and any updates will be posted on the BCSH website http://www.bcsghguidelines.com.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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Guideline


Appendix I
Grade nomenclature

Strength of recommendations

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

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.