Pan Birmingham NHS
Cancer Network

# Guideline for the Management of Classical Hodgkin's Lymphoma in Adults

## Version History

| Version | Date | Summary of Change/Process |
|---|---|---|
| 2.0 | 24.09.07 | Endorsed by the Governance Committee |
| 2.1 | 22.07.10 | Re-formatted and sent to Haematology NSSG and Andrea Stevens for consultation. |
| 2.2 | 20.08.10 | With comments from Andrea Stevens |
| 2.3 | 15.06.11 | Version update – Fiona Clark<br>With comments from Dr Rudzki, Histopathology<br>Circulated to the Haematology NSSG. |
| 2.4 | 08.07.11 | With changes from Yasmin Hasan (referral\neck lump information). |
| 2.5 | 29.07.11 | Updated and reviewed by Fiona Clark |
| 3.0 | 03.08.11 | Reviewed and endorsed by Guidelines Sub Group |

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| **Date Approved by Network Governance** | **August 2011** |

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| **Date for Review** | **August 2014** |

Changes made during 2011

- Radiotherapy volume definitions have been removed and reference to the NCRI document we now use added to the text.
- The National trials portfolio has been updated.
- Additional sections on follow-up and late effects of treatment have been added.
- Additional section on lymphocyte predominant Hodgkin's lymphoma has been added.

## 1 Scope of the guideline

This guidance has been produced to support:

- The diagnosis and staging of patients with suspected classical Hodgkin's lymphoma.
- The management of patients with classical Hodgkin's lymphoma

## 2 Guideline background

2.1 In Pan Birmingham Cancer Network (PBCN) two hospitals are designated transplant centres for haematological malignancies - University Hospital Birmingham Foundation Trust [UHBfT] and Heartlands Hospital (part of Heart of England Foundation Trust [HEFT]). These two hospitals treat patients with haematological malignancies at the British Committee of Standards in Haematology (BCSH) levels I - IV. In addition to this, Good Hope Hospital (as part of HEFT) practices to level 1 and Worcestershire Hospital NHS Trust and Sandwell and West Birmingham Hospitals NHS Trust [SWBH], Sandwell site, practice to level 2.

2.2 For patients with neck lumps, some of whom may have Hodgkin's lymphoma, rapid diagnosis is required and the Head & Neck Improving Outcomes Guidance requires each site to identify a multidisciplinary neck lump clinic with fast and open referrals between Haematology and Head & Neck teams. Within the Pan Birmingham Cancer Network a local agreement has been reached (http://www.birminghamcancer.nhs.uk/staff/clinical-guidelines/head-and-neck-cancer ) that these patients will be assessed in the first instance by the Ear Nose and Throat team in parallel clinics (SWBH, UHBfT and HEFT) or haematology team with rapid access to surgeons for biopsy (Good Hope Hospital).

## Guideline statements

## 3 Referral

3.1 Patients with a combination of the following should undergo an urgent blood count, film and Erythrocyte sedimentation rate (ESR):

- Fatigue
- Fever
- Generalised itching
- Bruising
- Alcohol-induced pain
- Lymphadnopathy
- Drenching night sweats
- Weight loss
- Breathlessness
- Bone pain
- Abdominal pain
- Splenomegaly

3.2 Please refer to the Network guideline for the management of neck lumps http://www.birminghamcancer.nhs.uk/staff/clinical-guidelines/head-and-neck-cancer.

3.3 Please note: if there are no enlarged nodes/no enlarged spleen a diagnosis of Hodgkin's lymphoma should still be considered in patients with suggestive symptoms - night sweats/weight loss/severe pruritus/alcohol induced pain.

3.4 Patients that present to other teams such as ear, nose and throat (ENT), head and neck, plastics and dermatologists **should have access to the CNS as soon as they are informed of their diagnosis**, and be referred urgently to the haematologists. Local policies should be in place to ensure that the patients are treated within 31 days and that the breaking bad news policy is followed.

3.5 Patients should be referred using in the 2 week wait form (appendix 1) to their local haematology service.

## 4 Diagnosis and staging

4.1 All patients, regardless of route of referral, should receive care within the context of a specialist multidisciplinary team.

4.2 Initial diagnostic tests should be carried out in a manner that ensures minimal hospital visits for the patient and enables the maximum waiting times to be adhered to (usually tests should be completed within 2 weeks of urgent clinic appointment).

4.3 Biopsy

4.3.1 Where the diagnosis is uncertain a fine needle aspiration (FNA) should be carried out for isolated lymphadenopathy. If a node is >1cm diameter or has been present for >6 weeks, it may be preferable to omit the FNA and proceed straight to a biopsy to avoid a delay in diagnosis. For multiple enlarged nodes, excision biopsy should be carried out as the primary investigation, as lymphoma is the most likely diagnosis in this setting.

4.3.2 If lymphoma is suspected from the FNA result, proceed to an excision biopsy as soon as possible. If the FNA result is inconclusive or reactive, and lymphoma is suspected on clinical or radiological grounds, proceed to an excision biopsy as soon as possible.

4.3.3 For neck nodes the lymph node excision should be carried out by a surgeon who specialises in surgery of the neck (e.g. ENT, thyroid, head and neck).

4.3.4 Biopsy for suspected lymphoma should undergo review by a specialist haematopathologist together with immunohistochemistry. The report

should integrate all the component parts of diagnostic testing (as per BCSH: best practice in lymphoma diagnosis and reporting, April 2010,[1]: An update of the 2008 BCSH guideline incorporating the 2008 WHO guidelines), as they apply to lymphoproliferative disorder.

4.4 Diagnostic and staging tests should include the following:

a. CT scan: thorax, abdomen and pelvis.
b. CT neck may be included in some cases where involvement is suspected by the haematologist / radiologist.
c. Chest X-ray (not required for patients that have had a CT thorax)
d. Full Blood Count.
e. Erythrocyte sedimentation rate (ESR).
f. Bone marrow aspirate and trephine biopsy. This is not required for patients with non-bulky stages IA/IIA without adverse prognostic factors. Marrow biopsy is required for full staging where the patient has B symptoms, or a low Hb, WBC or platelet count or a raised ESR. Stage III patients should have a marrow biopsy even if they do not have these abnormalities to ensure that stage IV disease is not missed. If the marrow is involved, it will be re-biopsied after treatment to confirm remission.
g. Biochemical profile including; electrolytes, urea, creatinine, calcium, phosphate, and liver function tests.
h. Lactate dehydrogenase
i. Urate.
j. Echocardiogram and lung function tests for appropriate patients.
k. Note in US/NCCN, PET-CT is viewed as an essential test at diagnosis, interim and at end of treatment for Hodgkins lymphoma. This has not been widely adopted within UK practice as yet.

## Treatment

### 5 All patients

5.1 Treatment options should be discussed and agreed by the multidisciplinary team.

5.2 All patients being offered chemotherapy that can result in fertility problems should be informed about sperm banking / oocyte and ovarian cryopreservation. Those wishing further information/treatment should be referred to the assisted conception unit at Birmingham Women's NHS Foundation Trust Patients should understand that fertility may be preserved or return after treatment has ended, and women should understand that attempts at oocyte harvest can result in delayed treatment with potential detriment to health. There is an NCRN study to assess fertility outcomes for women undergoing chemotherapy using AMH hormone profiling. Within the RATH-L study, there is a fertility substudy assessing ovarian tissue collection for high-risk patients.

5.3 Elderly patients, those with a poor performance status (WHO >2), or those with co-existing diseases not able to undergo the standard treatments may be considered for ChlVPP.

5.4 The response to treatment should be documented. Patients on ABVD will require a CT scan of the affected area after 2-3 and 6 cycles of treatment. Early interim PET-CT scanning has been shown to offer prognostic information and may be appropriate for patients where an interim CT scan suggests a suboptimal response. Early interim PET-CT and adapted therapy is the subject of the national RATH-L trial.

5.5 All patients should be offered treatment in a clinical trial where they are eligible.

5.6 Patient Information and Counselling

5.6.1 All patients, and with their consent, their partners, will be given access to appropriate written information during their investigation and treatment, and on diagnosis will be given the opportunity to discuss their management with a clinical nurse specialist who is a member of the relevant multidisciplinary team (MDT). The patient should have a method of access to the haematology team at all times.

5.6.2 Access to psychological support will be available if required. All patients should undergo an holistic needs assessment and onward referral as required.

## 6 Radiotherapy for Hodgkin's lymphoma

6.1 There are now few indications for the use of extended field radiotherapy (EFRT) in the management of Hodgkin's lymphoma. It should be used only as the primary management of patients in the following situations:

a. Patients not fit for chemotherapy.
b. Patients who have extensive residual disease after chemotherapy who are not a candidate for high dose chemotherapy.

6.2 In all other cases where radiotherapy is indicated involved site radiotherapy (ISRT) is recommended unless pre chemotherapy cross sectional imaging is not available in which case involved field radiotherapy (IFRT) should be used. These volumes are as defined in "Guidelines for the use of radiotherapy in nodal lymphoma" produced on behalf of the NCRI Radiotherapy and Lymphoma Clinical Study groups.

6.3 ISRT (or IFRT if no cross sectional imaging prior to biopsy is available) is only used as primary treatment of Hodgkin's lymphoma in patients with stage IA lymphocyte predominant histology.

6.4 ISRT (or IFRT if no cross sectional imaging available) is used following chemotherapy as a consolidation/adjuvant treatment in the following circumstances:

a. Patients with residual disease post chemotherapy. This should be made on the basis of CT scan and PET scanning information and be discussed for each individual patient at the MDT.
b. Patients with stage 1A disease where 2 – 4 cycles of chemotherapy are being given and treatment is to be completed by ISRT (or IFRT).
c. Patients who have relapsed following ABVD and still have residual disease following high dose chemotherapy or who had bulky disease (>10cm) at presentation of relapse.

6.5 Dose should be limited to 30 Gy in 15 fractions. (If the volume is large then 30 Gy in 17 fractions may be clinically appropriate or 35 Gy in 20 fractions if extended fields are being used). There is no evidence that radiation doses higher than this improve in field disease control.

6.6 Specific risks associated with radiotherapy for Hodgkin's lymphoma:

a. Doses higher than 30Gy to the mediastinum are associated with increased risk of cardiac disease.
b. All patients receiving radiotherapy to the mediastinum must be advised to stop smoking as this further increases cardiac risk. For non-smoking patients receiving less than or equal to 30Gy to the mediastinum any excess cardiac morbidity is minimal.
c. Women under the age of 35 receiving radiotherapy for Hodgkin's lymphoma to any part of the breast have an increased risk of breast cancer. For mantle fields (EFRT) the risk of breast cancer is between 1 in 4 and 1 in 7 for these women. The risk is not yet clear for ISRT or IFRT which usually involves much less breast tissue in the target volume.

6.7 Where radiotherapy to a volume that includes breast tissue is unavoidable in this patient group, then breast screening must be offered. This is best managed by referral to the local breast team and should follow the guidance set down by the national recall exercise for such patients in 2003.

6.7.1 In summary this guidance recommends:

a. Aged under 17 years at time of radiotherapy – start at age 25 years.
b. Aged 17 to 35 years at time of radiotherapy – start at 8 years after radiotherapy.

c. Method:
   i. Aged under 30 years: annual MRI.
   ii. Aged 30 to 50 years – annual mammography (2 view) with annual MRI if dense breast tissue.
   iii. Aged over 50 years – 3 yearly mammograms in the context of the national breast screening programme.

## 7 Favourable Early Stage Disease (stage I / IIA)

7.1 Patients with stage IA **lymphocyte predominant** Hodgkin's lymphoma should be treated by ISRT only, however if cross sectional imaging is not available the patient should have IFRT.

7.2 All other patients who clearly fulfil the criteria for favourable early stage disease, (Table 1 – from Borchmann, ASH Education Haematology 2010) should receive a minimum of 2 - 4 cycles of ABVD followed by ISRT (or IFRT – see above for details).

Table 1. Definition of favorable and unfavorable (intermediate) early stage Hodgkin lymphoma

| | EORTC | GHSG | NCIC/ECOG | NCCN 2010 |
|---|---|---|---|---|
| Risk factors | a) Large mediastinal mass (> 1/3)<br>b) Age ≥50 years<br>c) ESR ≥50 without B-symptoms or ≥30 with B-symptoms<br>d) ≥4 nodal areas | a) Large mediastinal mass<br>b) Extranodal disease<br>c) ESR ≥50 without B-symptoms or ≥30 with B-symptoms<br>d) ≥3 nodal areas | a) Histology other than LP/NS<br>b) Age ≥40 years<br>c) ESR ≥50<br>d) ≥ 4 nodal areas | a) Large mediastinal mass (> 1/3) or > 10 cm<br>b) ESR ≥50 or any B-ysmptoms<br>c) ≥3 nodal areas<br>d) > 1 extranodal lesion |
| Favorable | CS I-II (supradiaphragmatic) without risk factors | CS I-II without risk factors | CS I-II without risk factors | CS I-II without risk factors |
| Unfavorable | CS I-II (supradiaphragmatic) with ≥1 risk factors | CS I or CS IIA with ≥1 risk factors<br>CS IIB with c) or d) but without a) and b) | CS I-II with ≥ 1 risk factors | CS I-II with ≥ 1 risk factors (differentiating between bulky disease and other risk factors for treatment guidelines) |

NCIC indicates the National Cancer Institute of Canada; NCCN, National Comprehensive Cancer Network; LP: lymphocyte predominance; NS: nodular sclerosis.

## 8 Unfavourable early stage disease (stage I/IIA)

8.1 Unfavourable early stage disease should be identified, for example: Patients with bulky disease (>10 cm or >0.33 chronic thoracic diameter CTD), extranodal extension, age>50, >2 nodal sites, poor performance status (WHO >2), or high ESR (>50).

8.2 Patients should be offered treatment with ABVD 4-6 cycles with interim CT-scanning and IFRT. As appropriate, current trials should be discussed with them, many of these patients may eligible for the RATH-L trial.

## 9 Advanced disease (Stage III/IV)

9.1 Outside of a clinical trial, patients should be offered standard treatment with ABVD (6 courses), with interim restaging after 2 - 4 cycles by CT scanning and if appropriate PET-CT scanning to determine disease response.

9.2 All patients should be offered a clinical trial where available. The current national trial is RATH-L, risk adapted therapy in Hodgkins lymphoma, assessing early interim PET-CT after 2 cycles of therapy to direct treatment.

9.3 Note use of growth-factor support with ABVD: there have been reports to suggest that growth factors may accelerate bleomycin associated lung toxicity (26% vs 9%). A recent study confirmed ABVD can be delivered safely at full dose and without GCSF support.

9.4 Radiotherapy may be indicated in patients with bulky disease and/or with a residual mass. See section 10 for the management of patients with a residual mass.

## 10 Patients with a residual mass

10.1 The following are management options:

a. A PET-CT scan to determine the nature of the residual mass, a biopsy is recommended for those who are PET+.
b. Involved Field Radiotherapy.
c. Watch and wait. This option may become less appropriate as PET scanning assists in the treatment planning of these patients.

10.2 For patients with residual masses: discussion should take place at MDT. PET-CT scan should be performed not less than 3 weeks after the end of chemotherapy and preferably 8 - 12 weeks after the end of radiotherapy. This is to minimise the risk of a false positive PET-CT result due to post therapy inflammation, seen particularly after radiotherapy. PET-CT scans should be reported by specialist radiologists trained in interpretation.

10.3 A positive PET-CT scan at the end of treatment indicates high risk of disease progression with specificity 92% and positive predictive value 94%. In early reports, progression free survival for a negative PET-CT scan was excellent at 92% and 0% for patients with positive scan at the end of first line treatment. Recent reports indicate early scans after 2 cycles of treatment predict strongly for outcome however this is yet to be evaluated as a treatment decision in clinical trials.

10.4 A patient with residual mass and a positive PET-CT scan should be considered for further treatment; options include ISRT (or IFRT) for a discrete localised positive focus or to proceed to salvage chemotherapy followed by autograft. A biopsy is recommended for those who are PET-CT+ (NCCN guidelines 2011).

## 11 Patients who progress during treatment or within 3 months of treatment completion (Primary Progressive Disease)

11.1 Salvage chemotherapy and peripheral blood stem cell transplant (PBSCT) can be considered for patients who are fit enough (WHO performance status <2). A number of salvage regimens are used for Hodgkin's lymphoma, there is no randomised data to inform which of these is preferred.

11.2 Those unsuitable for this should be treated palliatively with: low intensity chemotherapy, steroids or radiotherapy where appropriate and offered supportive care.

## 12 Relapsed disease

12.1 Patients who are chemotherapy naïve should undergo standard treatment (i.e. 4 – 6 cycles of ABVD).

12.2 Patients relapsing within 12 - 18 months of completing their first line treatment should be considered for an autologous transplant (depending on age, stage of disease and availability of a donor). In some patients a reduced-intensity allograft may be preferable.

12.3 Patients relapsing after 12 18 months of completing their first line treatment may be considered for either:

a. A repeat of their first line chemotherapy if this is their first relapse.
b. A PBSCT.

12.4 Patients who relapse after PBSCT may be considered for an allogenic procedure and should be discussed with the transplant centre either at UHBfT or Heartlands Hospital (part of HEFT).

12.5 Patients who are unable to undergo a PBSCT (for example due to persistent bone marrow infiltration or a failure to mobilise sufficient stem cells) may be considered for an allogeneic procedure and should be discussed with the transplant centre either at UHBfT or Heartlands Hospital.

## 13 Lymphocyte predominant Hodgkin lymphoma (LPHL)

13.1 This is a distinct subgroup of Hodgkin's lymphoma with unique clinical and histopathological features and should be treated differently to classical Hodgkin's as outlined above. LPHL is characterised by an indolent course and occasional late relapses. The German Hodgkin's Study Group reported outcomes for this group of patients, 63% were early favourable, 16% early unfavourable and 21% advanced stage. Freedom from treatment failure (FFTF) and OS were better for LPHL than classical Hodgkin's lymphoma at 88% FFTF and 96% OS at 50 months.

13.2 IFRT is recommended for all patients with stage IA and IIA disease. Patients with unfavourable features and B symptoms should be considered for combined modality treatment. Patients with advanced stage III and IV disease should receive chemotherapy 4 - 6 cycles. There is no randomised data to inform the preferred chemotherapy, however ABVD or CHOP-like regimens are frequently used.

13.3 LPHL is CD20+. The role of rituximab is this disease is the subject of ongoing clinical trials. LPHL has been shown to have good response rates to rituximab as a single agent both first line and in relapse/refractory setting. It may be a therapeutic option for selected patients.

## 14 Follow-up

14.1 Patients who have been treated in a clinical trial should be followed up in accordance with the trial protocol.

14.2 All other patients should be followed up as follows:

a. 3 monthly for the first year.
b. 3 – 4 monthly for the second year.
c. There is very little data to inform decisions regarding the required length of follow-up.
d. Consider discharge after 2 years follow up, with clear written information as to what to look out for and how to self refer back to the open access service (see point below). Patients with additional risk factors may require follow-up for 5 years.
e. An annual influenza vaccination is recommended for all patients.
f. All patients should be counselled for late effects of treatment. Second malignancies are increased after treatment for Hodgkin's lymphoma. Smoking should be avoided and younger women receiving radiotherapy may require breast cancer screening with annual mammography. Cardiovascular disease is significantly increased in survivors of Hodgkin's lymphoma, particularly relating to radiotherapy to mediastinum and the use of

anthracyclines. Patients should receive life-style advice and undergo annual blood pressure screening and review in primary care. Fertility outcomes may need review and support should be offered for further referral for fertility assessment. Women may experience premature ovarian failure and require assessment and HRT.

g. Patients who receive neck and upper mediastinal radiotherapy will need annual thyroid function monitoring.

14.3 For all patients open access to the service is essential. Patients should be advised to seek advice for symptoms that suggest recurrence including new lymphadenopathy and systemic symptoms (sweats, fatigue and weight loss). Patients who develop signs or symptoms suggestive of relapse should be able to see their specialist within 2 weeks. Patients and GP should be made aware of this open access to the service.

## 15 Clinical trials available

15.1 Wherever possible, patients who are eligible should be offered the opportunity to participate in National Institute for Health Research portfolio clinical trials and other well designed studies.

15.2 Where a study is only open at one Trust in the Network, patients should be referred for trial entry. A list of studies available at each Trust is available from Pan Birmingham Cancer Research Network.
Email: PBCRN@westmidlands.nhs.uk

15.3 Patients who have been recruited into a clinical trial will be followed up as defined in the protocol.

## 16 Palliative care

Early links should be made to the palliative care team where the treatment intent is not curative or where the patient has symptoms that are difficult to manage.

### Monitoring of the Guideline

Implementation of the guidance will be considered as a topic for audit by the NSSG in September 2013.

## References


1. BCSH: Best practice in lymphoma diagnosis and reporting, April 2010.
2. National Comprehensive Cancer Network guidelines : Hodgkins 2011. Version 2.2011
3. "Guidelines for the use of radiotherapy in nodal lymphoma". Paper accepted for publication 2011 in 'Clinical Oncology'


## Original Authors


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## Approval Signatures


## Approval Signatures


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Signature  Date 06 September 2011

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# URGENT REFERRAL FOR SUSPECTED HAEMATOLOGY CANCER

If you wish to include an accompanying letter, please do so. **On completion please FAX to the number below.** (Version 2.0)

These forms should only be used for suspected cancer and in conjunction with the NICE Referral Guidelines for Suspected Cancer, June 2005

| **Patient Details** | **GP Details (inc Fax Number)** |
|---|---|
| Surname<br>Forename<br>D.O.B. Gender<br>Address<br>Postcode<br>Telephone<br>NHS No<br>Hospital No<br>Interpreter? Y / N First Language: | **Date of Decision to Refer**<br>**Date of Referral**<br>**GP Signature** |

**Relevant information:** (Check as appropriate)

**Symptoms/Signs:**

| | | | | | |
|---|---|---|---|---|---|
| Fatigue | ☐ | Drenching night sweats | ☐ | Fever | ☐ |
| Weight Loss | ☐ | Generalised itching | ☐ | Recurrent infections | ☐ |
| Bruising | ☐ | Breathlessness | ☐ | Lymphadenopathy | ☐ |
| Bone Pain | ☐ | Alcohol-induced pain | ☐ | Persistent unexplained splenomegaly | ☐ |

**Additional Lymphadenopathy Features:**

| | | | |
|---|---|---|---|
| Lymph nodes increasing in size | ☐ | Lymph nodes greater than two cm in size | ☐ |
| Persistence for six weeks or more | ☐ | Widespread nature | ☐ |
| Associated splenomegaly, night sweats or weight loss | ☐ | | |

**Investigations:**

| | | | |
|---|---|---|---|
| ESR | _____ | Full Blood Count | _____ |
| Blood film | _____ | Clotting screen | _____ |
| X-ray | _____ | Liver/Bone profile | _____ |
| Urea & Electrolytes | _____ | Immunoglobulin/paraprotein | _____ |

**Clinical Details:**

History/Examination/Investigations……

Medication ……

***For Hospital Use***

Appointment Date Clinic Attending

Was the referral appropriate Yes No (if no please give reason)

**HAEMATOLOGY CLINICS WITH RAPID ACCESS FACILITIES**

| Hospital | Tel | Fax |
|---|---|---|
| ***City and Sandwell*** | **0121 507 5805** | **0121 507 5075** |
| ***Good Hope*** | **0121 424 5000** | **0121 424 8952** |
| ***Heartlands and Solihull*** | **0121 424 5000** | **0121 424 8952** |
| ***Queen Elizabeth (UHBFT)*** | **0121 627 2485** | **0121 460 5800** |
| ***Walsall Manor*** | **01922 721172 ext 7110 or 7785** | **01922 656773** |