Lancashire and South Cumbria Haematology NSSG Guidelines for Hodgkin's lymphoma

1.1 Pre-treatment evaluation

The following tests are to be performed at presentation followed by MDT discussion:

- FBC, ESR, U&Es, creat, LFTs, calcium, LDH, immunoglobulins
- Hepatitis B, C and HIV serology
- Chest X-ray
- PET-CT scan where treatment is with curative intent, or at least a CT scan of neck, thorax and abdomen if PET-CT scan is not possible
- MRI scan if required for assessment of disease in the oropharynx and Waldeyer's ring, sinuses and nasal cavity, CNS and paraspinal areas where there is a suspicion of spinal cord compromise
- Bone marrow trephine biopsy unless stage I/IIA, presence of unequivocal evidence of marrow infiltration on PET-CT scan or when knowledge of marrow infiltration will not affect management e.g an elderly patient with stage III disease, palliative management
- ECG and assessment of cardiac function in patients with a history of or risk factors for cardiac disease or when mediastinal irradiation may be indicated
- Determination of stage, treatment risk group according to the German Hodgkin's Lymphoma Study Group (GHSG) criteria **(appendix 1)** or Hasenclever score (appendix 2) for advanced stage, presence of bulk disease (>0.33 mediastinal ratio or >10cm mass)

1.2 Post-treatment evaluation

- On completion of treatment the patient must be reassessed clinically and where treatment is given with curative intent all abnormal tests at baseline repeated followed by MDT discussion with review of an end of treatment PET-CT scan performed at least 6 weeks after the last dose of chemotherapy (note this interval does not apply to interim PET-CT scans), or three months after the last dose of radiotherapy.

2. Classical Hodgkin's lymphoma

- Note that patients with stage IIB disease with bulk and/or extra-nodal disease will be managed as for advanced stage disease.

2.1 Early stage, no risk factors

Standard treatment options:

1. ABVD x 2 cycles + 20Gy ISRT
2. PET adjusted therapy (as per the RAPID trial)

- The alternative PET response-directed chemotherapy only approach may be considered particularly if the acute or long term effects of radiotherapy are of concern clinically or to

the patient. They must be be appraised of the risks, benefits and uncertainties of this approach.

- Patient must have a baseline PET-CT scan
- ABVD x 3 cycles
- In week 3 of cycle 3 ABVD patients will be assessed clinically and by PET-CT followed by MDT discussion to determine if it safe to omit RT.
- If Deauville score is 0-2 RT may be omitted
- If Deauville score is 3-5 a fourth cycle ABVD must be given followed by 20Gy ISRT followed by another PET-CT scan

2.2 Early stage with risk factor(s)

Standard treatment: ABVD x 4 + 30Gy IFRT

There is no evidence to support the omission of RT in these patients.

Following MDT discussion if there is concern that the required RT field is too extensive or maybe associated with significant early or late toxicity an alternative treatment is ABVD x 6 cycles.

2.3 Advanced stage, ≤ 60 years and fit

Standard initial treatment will be either:

- ABVD x 6 cycles +/- consolidation RT
- escalated BEACOPP x 6 cycles +/- consolidation RT
- PET-response adjusted therapy (as per RATHL trial)

PET response-directed therapy

- Initial ABVD x 2 cycles
- MDT review of interim PET scan in week 3 of cycle 2
- If PET2 –ve (Deauville score 1-3) continue for further four cycles of AVD
- If PET +ve (Deauville score 4-5) continue ABVD x 6 cycles or offer change to escalated BEACOPP x 6 cycles

RT consolidation following escalated BEACOPP:

- in metabolic CR (Deauville score 1-3), RT may be omitted.
- if Deauville score 4-5 give RT 30Gy to residual lesions where possible
- if RT to residual positive lesions is not feasible there must be rebiopsy or at least close follow up of the lesions with repeat a PET-CT scan.

RT consolidation following ABVD:

- if metabolic CR demonstrated on interim PET scan an end of treatment PET scan is not indicated but a CT scan should be performed with MDT review
- it must be noted that it remains unclear whether RT can be safely omitted following ABVD where there are residual lesions >1.5cm on CT that are PET-negative and

decisions relating to consolidation RT should be made on a case by cases basis at the MDT

- following MDT discussion with review of an end of treatment PET-CT scan patients must be considered for consolidation RT to sites of original bulk or residual lesions >1.5cm on CT scan, or residual lesions Deauville score 4-5 on PET-CT scan.
- if RT is not given rebiopsy of residual FDG avid lesions must be considered or at least close follow up with repeat a PET-CT scan.

Following consolidation RT to PET-positive lesions there must be MDT review of a further PET-CT scan performed at least 3 months after the last dose. There must be rebiopsy or at least close follow up by PET-CT scan of any persistently positive lesions.

Patients with progressive disease will be managed as for refractory disease.

2.4 Hodgkin's lymphoma in older patients > 60 years or younger patients with significant comorbidities

Escalated BEACOPP must not be used in patients > 60 years. Otherwise if the patient is considered fit enough for ABVD and radiotherapy if required the approach used above in younger patients should be followed.

If considered unfit for ABVD options are VEPEM-B or ChlVPP x 6 cycles for stage IIB –IVB disease.

For earlier stages a combined –modality approach i.e 3 cycles + 30Gy ISRT is appropriate, or 6 cycles alone if following MDT review there is a concern over the potential toxicity of RT.

Options for patients considered unfit for VEPEM-B or ChlVPP are DECC, single agent etoposide, single agent vinblastine, radiotherapy alone.

2.5 Management of relapsed, refractory and progressive disease

- All patients must be referred to the Haematology MDT for further discussion.
- Rebiopsy must be undertaken where the duration of first remission is > 5 years.

Relapse > 5 years after primary therapy:

- In the absence of B symptoms and if localised relapse and further RT is feasible standard treatment will be combined modality therapy
- if there are B symptoms or more advanced disease or RT is not feasible options are further standard dose chemotherapy or salvage chemotherapy followed by high dose therapy and autologous stem cell transplantation

2.5.1 Candidates for high dose therapy

- Patients must be restaged with PET-CT scan and bone marrow trephine biopsy.
- Prognostic factors prior to salvage chemotherapy in patients undergoing autologous stem cell transplant should be recorded: remission duration < 1 year, extranodal disease, B symptoms (**appendix 3**). However, note that the metabolic remission status following salvage is the best predictive factor.

- The first goal of treatment is a metabolic CR before proceeding to PBSC mobilisation.
- The choice of initial salvage regimen will depend on patient and local factors. Options are ICE, DHAP, GEM-P.
- PET-CT scan will be repeated after two cycles.
- If there is a metabolic CR a third cycle will be given with a view to PBSC mobilisation.
- If the response is < metabolic CR change to an alternative salvage regimen e.g GEM-P, GDCVP, brentuximab, followed by PBSC mobilisation if metabolic CR is achieved.
- Where PBSC mobilisation is successful and the patient maintains sufficient performance status and cardiorespiratory function the response must be consolidated with autograft.
- If the patient has failed to achieve metabolic CR and has undergone an autologous transplant an end of treatment PET-CT scan will be reviewed at the MDT.
- Consolidation RT will be considered to residual FDG-avid lesions and where there was a dominant site of relapse at an initially involved site e.g bulky disease
- If the patient has achieved metabolic CR prior to transplant there may still be case for consolidation RT e.g to a dominant site of relapse at an initially involved site e.g bulky disease and residual abnormalities.

Patients failing to achieve a metabolic CR with salvage therapy:

- autograft may still be offered with curative intent. However, the outcomes are poor.
- younger patients < 50-60 years should be offered referral to an allogeneic stem cell transplant centre to discuss the risks and benefits of allogeneic transplant.

Patients relapsing after autologous transplant:

- Further salvage chemotherapy or brentuximab or and referral for consideration of allogeneic transplantation should be offered for younger i.e <65 years and fit patients relapsing after autologous transplant.
- Repeat autologous transplant may be considered if there is a long duration of remission e.g > 5 years since first transplant. Note this is presently not routinely funded by commissioners.
- For other patients see 2.5.2.

2.5.2 Patients who are not candidates for high dose therapy

- Combined-modality therapy should be considered, especially when there is early stage relapse, patients have not previously received RT or have relapsed outside an initial RT field.
- Salvage radiotherapy alone is an alternative option, especially for older patients with early stage relapse, without B symptoms and good performance status.
- The most appropriate chemotherapy regimen will depend on age, performance status, frailty status, comorbidity and organ function, previous treatment e.g whether has had brentuximab, availability of funding and access to compassionate use programmes.

- Options are: gemcitabine or gemcitabine combinations (Gem-P, GDCVP), ChlVPP, VEPEM-B, brentuximab, nivolumab, single agent vinblastine, DECC, single agent etoposide/steroids.
- Palliative RT for local disease control should be considered.

3 Lymphocyte predominant (LP) Hodgkin's lymphoma

Staging and clinical assessment should be as for Hodgkin's lymphoma.

3.1 Early stage

- For Stage IA disease standard options are observation where there has been complete surgical excision, or ISRT 30Gy
- For stage IIA standard treatment is ISRT 30Gy
- If stage IIA and not suitable for RT manage as for advanced stage disease

3.2 Advanced stage

Note the difficulty distinguishing LP Hodgkin's lymphoma from diffuse large B-cell lymphoma, especially T-cell rich variant. Management should be as for diffuse large B-cell lymphoma with R-CHOP. If the patient is unfit for RCHOP other options are R-CVP or single agent rituximab.

3.3 Relapse

- Repeat biopsy is strongly advised – reactive lymphadenopathy is common and LP Hodgkin's lymphoma may also transform to diffuse large B-cell lymphoma
- Localised relapse outside a previously irradiated area should be treated with ISRT.
- Localised relapse within a previously irradiated area or more advanced disease should be treated with RCHOP x 6
- If not fit for CHOP options are CVP-R or single agent rituximab
- Observation alone is appropriate for asymptomatic patients if their ability to tolerate chemotherapy or RT is a concern

Appendix 1: Early stage Hodgkin's lymphoma

	EORTC	GHSG
Risk factors;	A: Bulky mediastinal mass B: Age >=50yrs C: Raised ESR D: >= 4nodal involved regions	A: Bulky mediastinal mass B: Extranodal disease C: Raised ESR D: >= 3 involved nodal regions
	Raised ESR means >50mm/hr without B symptoms, > 30mm/hr with B symptoms	
	Treatment Groups	
Early favourable	CS I-II, no risk factors	CS I-II with no risk factors
Early unfavourable (intermediate)	CS I-II, ≥1 risk factor	CS I, CS IIA with ≥1 risk factor CS IIB with C/D but without A/B
Advanced	**CS III-IV**	CS IIB with A/B; CS III-IV

Appendix 2: Hasenclever score for advanced Hodgkin's lymphoma

Prognostic factors are: male, >45yrs, stage IV disease, Hb <10.5, albumin<40, lymphs <0.6 or < 8% WBCs, WBC > 15

IPI	% cases	DFS 5yrs	OS 5yrs
0	7	84	89
1	22	77	90
2	29	67	81
3	23	60	78
4	12	51	61
5+	7	42	56
For grouped IPIs			
0 or 1	29	79	90
>=2	72	60	74
0-2	58	74	86
>=3	42	55	70
0-3	81	70	83
>=4	19	47	59

Appendix 3: Predictive factors in Hodgkins' lymphoma at relapse in patients undergoing autologous stem cell transplantation (Moskowitz C et al. Blood 2001)

Risk factors are remission duration < 1 year, extranodal disease, B symptoms

Risk factors	EFS 5yrs
0 - 1	83%
2	27%
3	10%

Author	Dr MP Macheta
Date	21st Sept 18
Ratified by LSCCN Haematology NSSG	11th Dec 2018
Review date:	Dec 2019