Lancashire and South Cumbria Haematology NSSG Clinical Guidelines: 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
- If PET-CT scan is not possible, bone marrow trephine biopsy unless: stage I/IIA non-bulky disease, or if knowledge of marrow infiltration will not affect management e.g an elderly patient with stage III disease, or 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
- Pulmonary function tests and transfer factor in selected patients with pre-existing pulmonary disease or unexplained breathlessness.
- Determination of stage, treatment risk group according to the EORTC criteria **(appendix 1)** or Hasenclever score **(appendix 2)** for advanced stage. The presence of bulk disease – defined as a thoracic ratio >1/3 at T5/6, or mass >10cm - will also be noted
- Referral for fertility preservation where appropriate

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 (and see appendix 3)

2.1.1 Initial treatment will be with ABVD for 2 cycles. All patients should have a PET-CT scan on day 22-25 of cycle 2 with the response reported according to the Deauville Score.

2.1.2 Patients should have an appointment with a clinical oncologist for an individual discussion regarding radiotherapy during cycles 1-2 ABVD.

2.1.3 **Early stage, favourable risk (EORTC) who are PET-2 negative** (Deauville score 1-3) will receive a third cycle of ABVD followed by ISRT 30Gy. If there is a concern regarding the long term toxicity of radiotherapy an alternative is the RAPID approach in eligible patients i.e inclusion criteria for RAPID trial were stage I/IIA disease, no bulk. If a PET scan is negative (Deauville score 1-2) after ABVD x 3 cycles radiotherapy may be omitted if it is accepted this is associated with a reduction in progression-free survival – note this was approximately 5% in RAPID trial and 10% in EORTC H10 trial but with no reduction in overall survival in either. An alternative in patients with favourable risk by GHSG criteria can be treated with ABVD x 2 cycles followed by ISRT 20Gy since this is associated with an excellent prognosis.

2.1.4 **Early stage, unfavourable risk (EORTC) who are PET-2 negative** (Deauville score 1-3) can be treated with a further ABVD x 2 cycles followed by ISRT 30Gy. If there is a concern regarding the toxicity of radiotherapy or extent of the required field, treatment with a further 4 x ABVD alone is appropriate (and as per RATHL trial bleomycin can be omitted). Note that in EORTC H10 trial unfavourable risk patients who were PET2 –ve treated with ABVD x 4 and RT had an improved PFS at 6 years of only 3% compared to those treated with ABVD x 6 without RT. Note that unfavourable risk patients who are stage II with B symptoms or bulk disease would have been eligible for the RATHL trial so it is also appropriate to consider treatment as for advanced stage disease with ABVD x 6 cycles.

2.1.5 **Early stage patients, both favourable and unfavourable, who are PET-2 positive** (Deauville score 4-5) should be assessed for their suitability for treatment intensification to escalated BEACOPDac followed by ISRT 30Gy. If patients are being managed with a RAPID approach and PET scan after cycle 3 ABVD is positive with Deauville score 5, note that the prognosis in the trial remained poor despite a 4th cycle and radiotherapy, therefore treatment intensification should be considered.

2.1.6 End of treatment PET scan is not required if an interim scan was PET-2 negative, unless there is a clinical concern regarding progressive disease.

2.2 Advanced stage, ≤ 60 years and fit

2.2.1 Stage IIB patients with a mediastinal mass or extranodal disease should also be manged as for advanced stage.

2.2.2 There should be discussion with a clinical oncologist at initial MDT or at least early in the treatment course regarding consolidation radiotherapy to bulk disease.

2.2.3 Initial treatment for most patients should be with ABVD x 2 cycles followed by a PET scan on day 22-27 of cycle 2 as per RATHL trial. If PET-2 scan is negative (Deauville score 1-3) bleomycin can be omitted in cycles 3-6. If the PET-2 scan is positive intensification of treatment to escalated BEACOPDac x 4 cycles should be considered and with a further PET scan after two cycles to ensure there is a response.

2.2.4 Initial treatment with escalated BEACOPDac should be considered in cases with a poor risk Hasenclever score ≥ 3 or patients with extensive and/or bulky disease where radiotherapy consolidation may be difficult and after review of the potential

increased late toxic effects and the need to preserve fertility. With this approach a PET scan should also be repeated after cycle 2: if negative (Deauville score 1-3) the number of cycles of escalated BEACOPDac may be reduced to four; if positive give six cycles.

2.2.5 A PET-CT scan six weeks after last chemotherapy must be reviewed at the MDT. In the absence of progressive disease, after discussion with a radiation oncologist and consideration of the potential acute and long term toxicities, consolidation RT should be advised to residual PET positive lesions. Following escalated BEACOPDac and if in metabolic complete remission on end of treatment PET-CT scan (Deauville score 1-3) RT to bulk disease or residual enlarged nodes can be safely omitted. There is now evidence that following ABVD RT to a residual mass or site of bulk disease which is negative (Deauville score 1-3) on end of treatment PET-CT can be safely omitted. Where patients have positive PET-2 but a negative end of treatment PET-CT scan consolidation RT should be considered on a case by case basis. **See appendices 4, 5.**

2.2.6 Note that patients who are positive with a Deauville score 5 on PET-2 scan have a poor outcome, even if treatment is intensified to BEACOPDac, and further management as for relapsed/refractory disease should be considered.

2.2.7 If residual PET-positive lesions cannot be treated with radiotherapy there should be re-biopsy where possible or MDT review of a follow-up PET-CT scan. Patients with progressive disease will be managed as for refractory disease.

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

2.3.1 Escalated BEACOPP must not be used in patients > 60 years.

2.3.2 If the patient is considered sufficiently fit for ABVD (and RT if required), the approach used above in younger patients should be followed. However, the greater risk of toxicity with ABVD, particularly pulmonary, must be noted if more than two cycles are given.

2.3.2 If considered unfit for ABVD, options are VEPEM-B or ChlVPP x 6 cycles for stage IIB–IVB disease. For earlier stage disease options are a combined modality therapy with three cycles chemotherapy followed by ISRT or six cycles of chemotherapy alone, particularly if there is a concern regarding the toxicity of RT.

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

2.4 Management of relapsed, refractory and progressive disease

2.4.1 Rebiopsy must be undertaken where the duration of first remission is > 5 years.

2.4.2 If there is localised relapse > 5 years after primary therapy and without B symptoms standard treatment will be combined modality therapy where RT is feasible.

2.4.3 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.

2.4.3 Patients who are candidates for high dose therapy

Patients must be restaged with PET-CT scan or CT scan and bone marrow trephine biopsy if PET-CT scan is not possible. Prognostic factors at relapse should be noted: remission duration < 1 year, extranodal disease, B symptoms (**appendix 6**). However, note that the metabolic remission status following salvage is the most powerful prognostic factor.

2.4.4 The goal of salvage therapy is to achieve 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 unless there is clearly progressive disease on clinical grounds. If there is a metabolic CR a third cycle will be given followed by PBSC mobilisation and LEAM autologous stem cell transplant.

2.4.5 If the response is < metabolic CR change to an alternative salvage regimen e.g GEM-P, GDCVP followed by PET-CT scan after two cycles, or brentuximab vedotin (+/- bendamustine), pembrolizumab or nivolumab, followed by PET-CT scan after four cycles. If metabolic CR is achieved proceed to PBSC mobilisation and LEAM autologous stem cell transplant.

2.4.6 It is unlcear whether the number of lines of salvage therapy required to achieve CR influences outcome following autologous transplant. However, where > 1 line of therapy was required to achieve CR, and particularly in younger patients or those with disease refractory to primary therapy, the option of allogeneic transplant should be considered and the patient offered an opinion from an allogeneic transplant centre. If the response remains less than CR despite salvage therapy, autologous transplant may still be offered with curative intent although the outcomes are significantly poorer compared to patients in metabolic CR at time of transplant.

2.4.7 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 with a clinical oncologist. Consolidation RT should be considered to residual metabolically active lesions or where there was a dominant site of relapse e.g bulky disease. If the patient has achieved metabolic CR prior to transplant there may still be case for consolidation RT to sites of bulk disease or residual abnormalities on CT scan.

2.4.8 Patients relapsing after autologous transplant. Further salvage chemotherapy, or brentuximab (+/- bendamustine), pembrolizumab or nivolumab, and referral for consideration of allogeneic transplantation should be offered for younger, fit patients.

2.4.9 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.

2.4.10 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 RT 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, bendamustine, brentuximab vedotin, pembrolizumab, nivolumab, single agent vinblastine, DECC, single agent etoposide/steroids. Palliative RT for local disease control should be considered.

3.0 Nodular lymphocyte predominant Hodgkin's lymphoma

3.1 **Early stage disease IA-IIA** If there is localised and completely resected disease management should be observation alone. If there is residual or non-localised disease, treatment ISRT 30Gy should be considered. If not suitable for radiotherapy manage as for advanced stage disease.

3.2 **Advanced stage disease IIB-IV.** Management should be R-CHOP or R-CVP for six cycles. RCHOP is preferred if there is large volume, clinically aggressive disease or a clinical concern regarding possible high grade transformation. It should be noted that histologically a distinction between nodular lymphocyte predominant Hodgkin's lymphoma and histiocyte-rich diffuse large B-cell lymphoma can be difficult. Single agent rituximab is an option if the patient is unfit for chemotherapy.

3.3 **Relapse and refractory disease.** Repeat biopsy is strongly advised – reactive lymphadenopathy is common and nodular lymphocyte-predominant Hodgkin's lymphoma may transform to diffuse large B-cell lymphoma. Observation alone is an option for asymptomatic patients. Localised relapse outside a previously irradiated area or local recurrence at a site of previously excised disease can be treated with ISRT. Localised relapse within a previously irradiated area or more advanced disease can be treated with chemotherapy, either R-CVP again or R-CHOP. If unfit for chemotherapy single agent rituximab is also an option.

Appendix 1: Early stage Hodgkin's lymphoma

EORTC		
Risk factors;	A: Bulky mediastinal mass -mediastinal/thoracic ratio ≥ 0.35 B: Age >=50yrs C: Raised ESR D: ≥ 4nodal involved regions	
German Hodgkin's Study Group (GHSG)		
	A: Bulky mediastinal mass ≥ 1/3 mediastinal diameter B: Extranodal disease C: Raised ESR D: ≥ 3nodal involved regions	
	Raised ESR means >50mm/hr without B symptoms, > 30mm/hr with B symptoms	
	EORTC	**GHSG**
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 risk factor C/D but without A/B
Advanced	**CS III-IV**	CS IIB with A/B; CS III-IV

Lymph node areas as defined by GHSG

Area A: right cervical + right infra-/supra-clavicular/nuchal lymph nodes

Area B: right cervical + right infra-/supra-clavicular/nuchal lymph nodes

Area C: right/left hilar + mediastinal lymph nodes

Area D: right axillary lymph nodes

Area E: left axillary lymph nodes

Area F: lymph nodes of the upper abdomen (spleen hilum, liver hilum, coeliac)

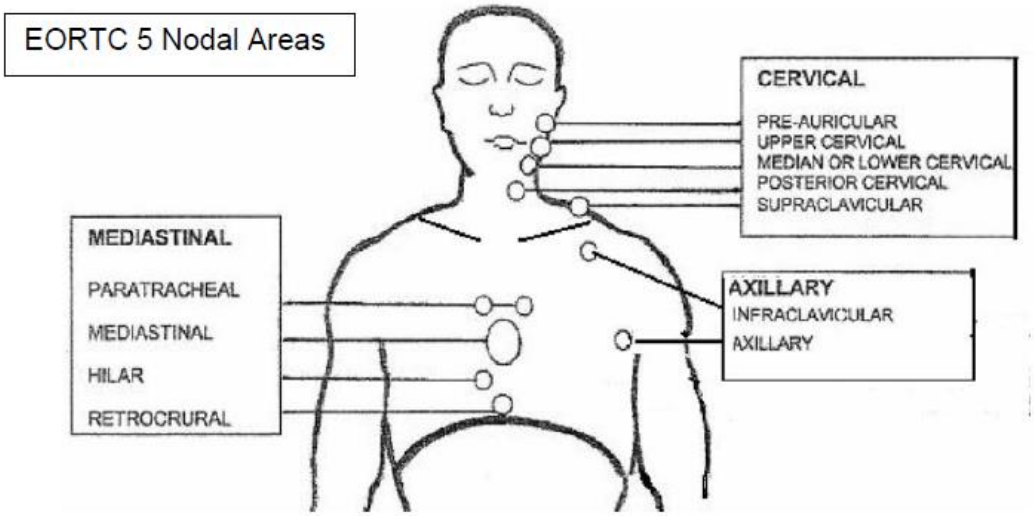
Area G: lymph nodes of the lower abdomen

Area H: right iliac lymph nodes

Area I: left iliac lymph nodes

Area K: right inguinal + femoral lymph nodes

Area L: left inguinal + femoral lymph nodes

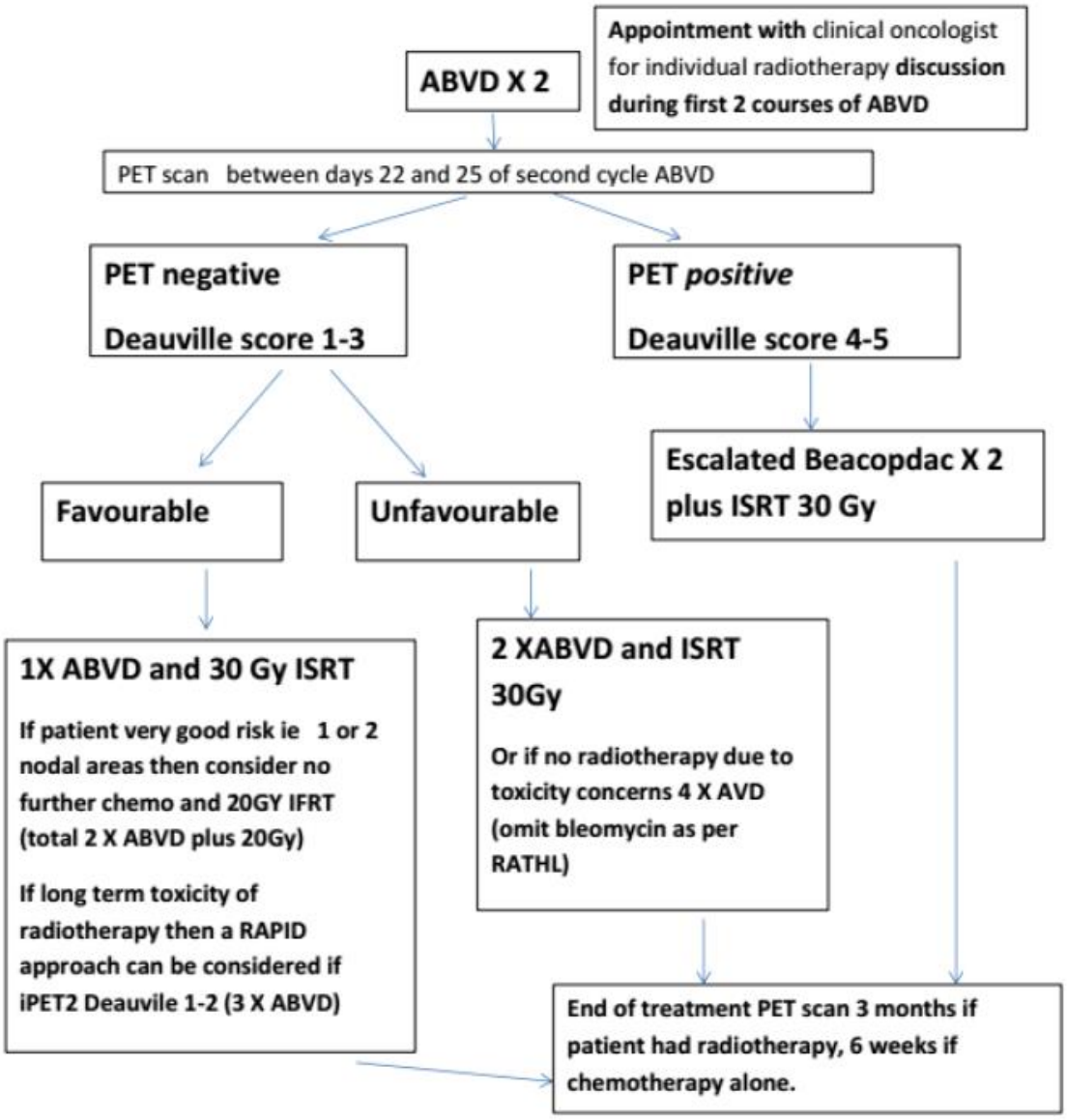


Appendix 2: Hasenclever score for advanced Hodgkin's lymphoma

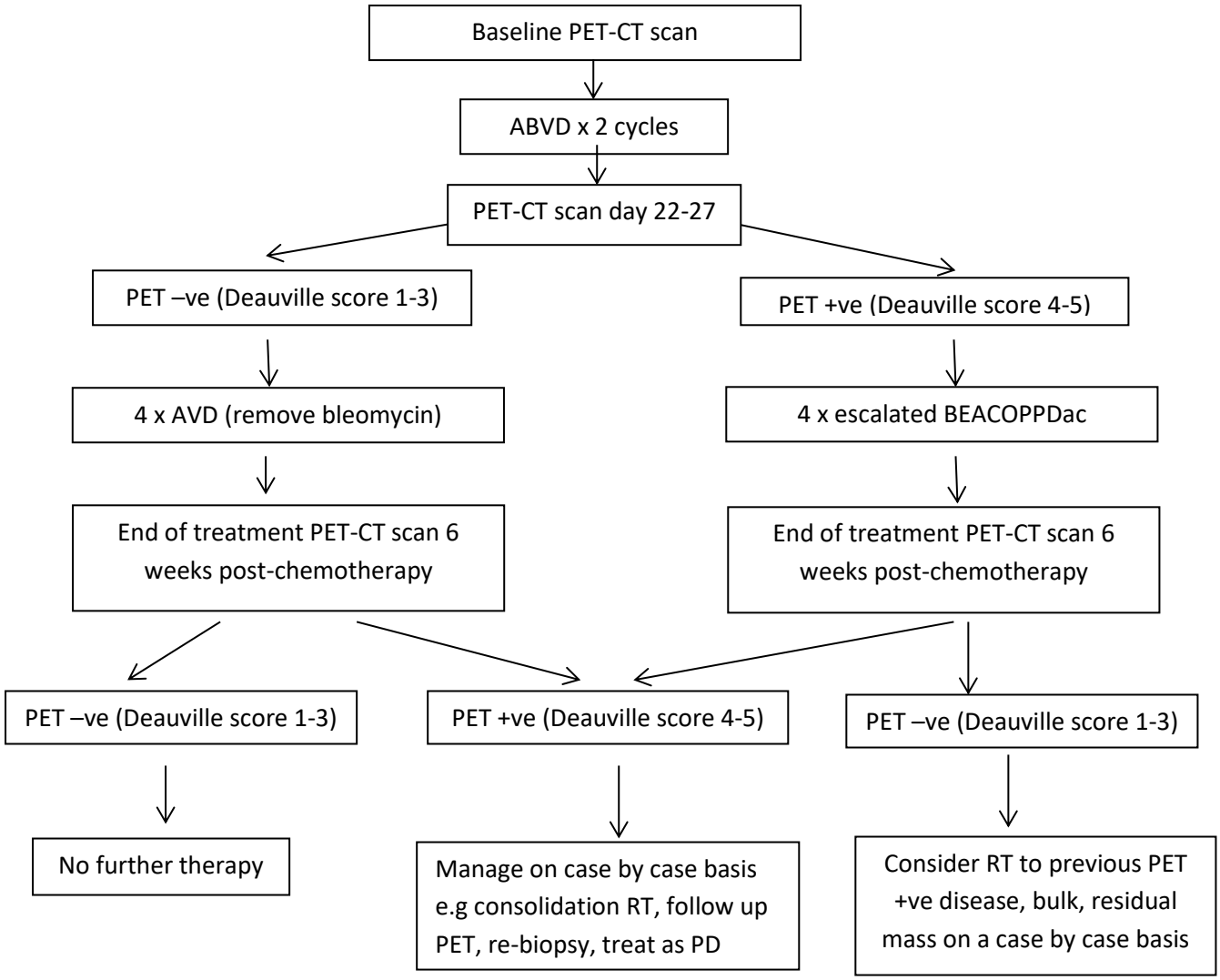
Prognostic factors are: male, >45yrs, stage IV disease, Hb <10.5, albumin<40, lymphs <0.6 or < 8% WBCs, WBC > 15

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

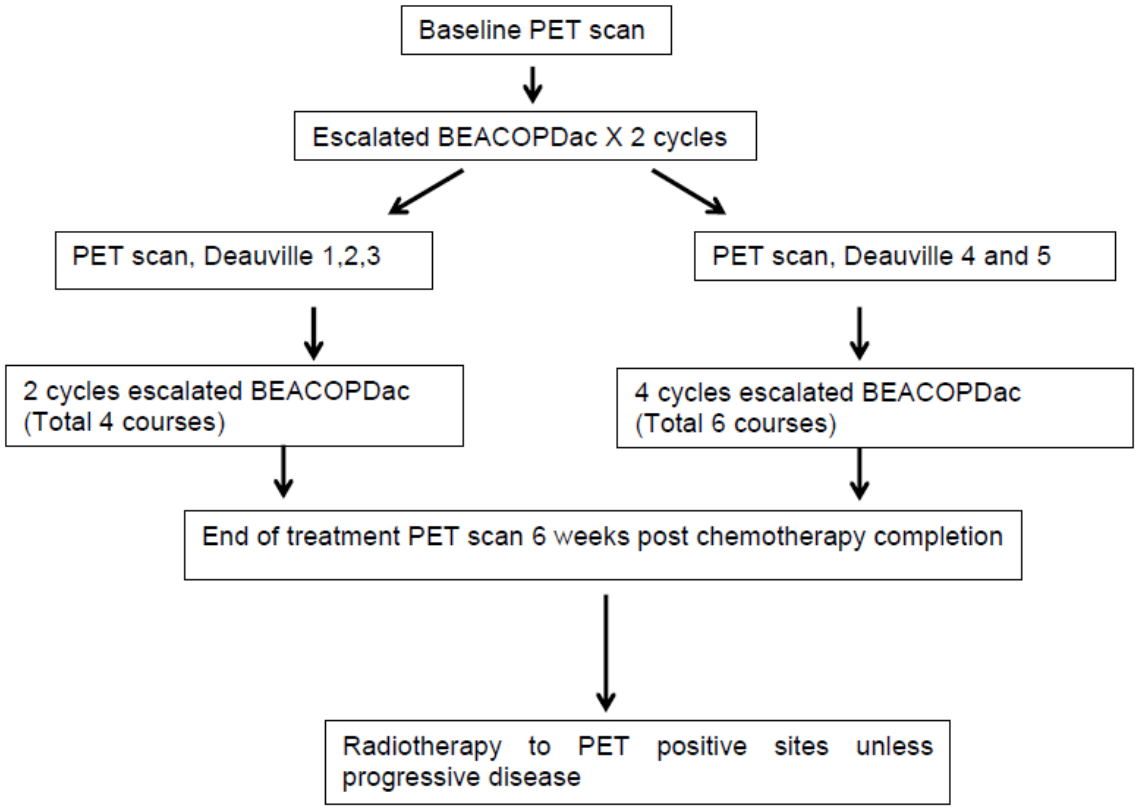
Appendix 3: Guideline for management of early stage Hodgkin's lymphoma (as per Northern Cancer Alliance Haematology Cancer Clinical Guidelines Nov 2019)



Appendix 4: Treatment of advanced stage Hodgkin's lymphoma with initial ABVD chemotherapy (modified from Northern Cancer Alliance Haematology Cancer Clinical Guidelines Nov 2019)



Appendix 5: Treatment of advanced stage Hodgkin's lymphoma with initial escalated BEACOPDac chemotherapy (as per Northern Cancer Alliance Haematology Cancer Clinical Guidelines Nov 2019)



Appendix 6: Predictive factors in Hodgkins' lymphoma at relapse in patients undergoing autologous stem cell transplantation (Moskowitz 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	16th Oct 2020
Ratified by LSCCN Haematology NSSG	
Review date:	Oct 2022