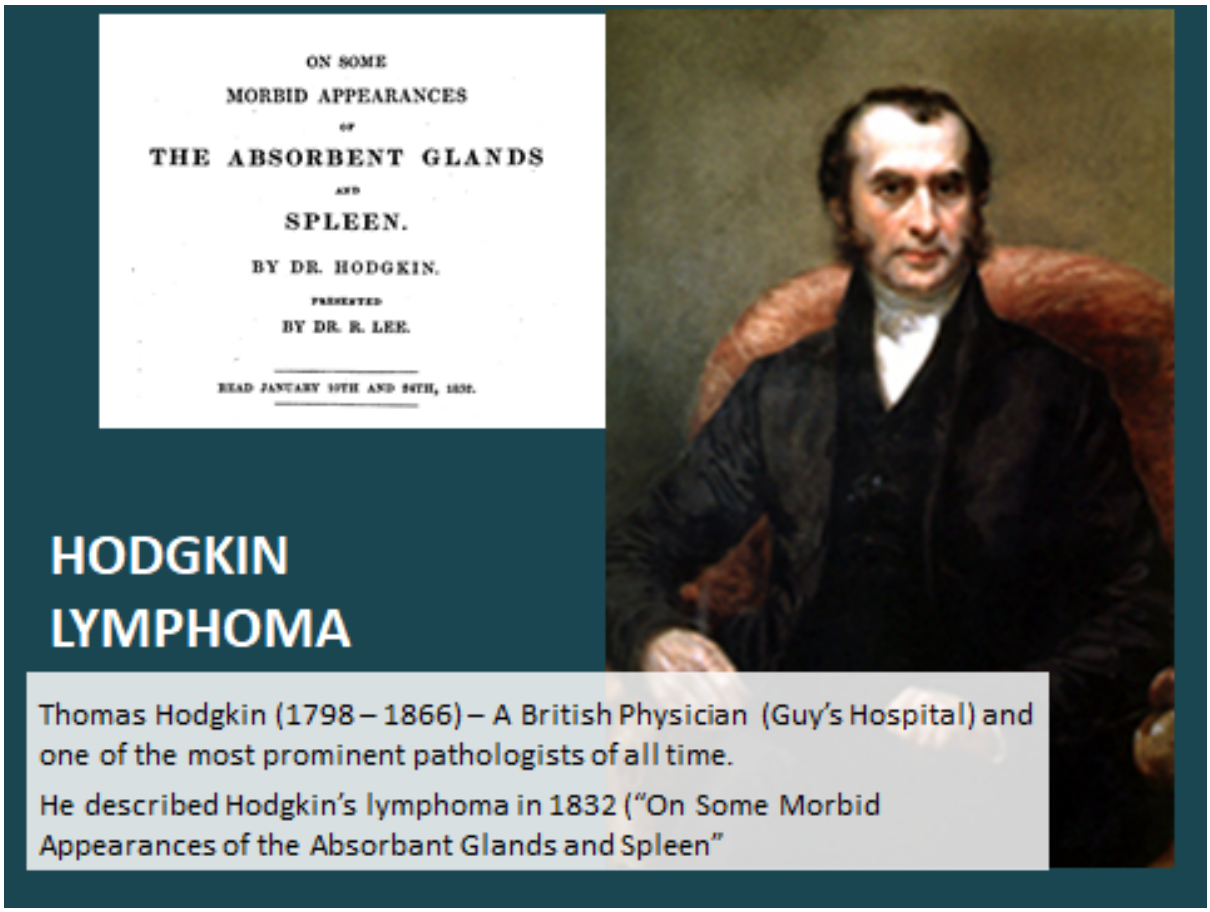
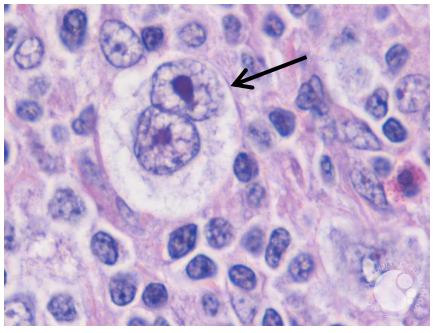
AN INTRODUCTION HODGKIN LYMPHOMA



This is a clinically and pathologically unique, aggressive B-cell lymphoma and one of the most curable haematological cancers. Excellent outcomes are the results of 50 years of refinement of combination chemotherapy and radiotherapy. Despite its relative rarity (20-30 new cases per million per year in the UK), numerous RCTs have contributed to robust treatment evidence and a risk-adapted approach where stage and treatment response after early cycles direct management.

Despite excellent overall outcomes, there are still subgroups whose prognosis remains suboptimal – the elderly and those with relapsed or resistant disease. Many aspects of the pathobiology also remain unclear.



The malignant cell is the **Hodgkin and Reed-Sternberg cell** (HRS) – this is a B cell with germinal centre exposure (somatic hypermutation within the immunoglobulin genes is present) but normal B cell lineage gene expression has been lost.

Aberrent signalling pathways are present in the HRS:

- NF-kB pathway – apoptosis resistance
- JAK-STAT signalling pathway overactive – increased proliferation and growth

HRS cells produce cytokines which attract other immune cells producing a surrounding inflammatory milieu. EBV can be detected in some cases – EBV encoded proteins can increase proliferation and survival of HRS cells.

Dorothy Reed Mendenhall (1874-1964)
Graduate of Johns Hopkins School of medicine.
Discovered the HRS, effectively disproving the common belief that HL was a form of TB

Clinical Features

- Enlarging lymphadenopathy (LAN)
  - Typically painless
  - Variable rate of growth (usually months)
  - Frequently cervical and supraclavicular nodes
- Complications of LAN
  - Compression of vital structures
  - Mild chest pain, cough, SVCO
- Systemic symptoms
  - B symptoms (weight loss >10% in 6 months; drenching night sweats, fevers)
  - Itch
  - Alcohol-induced lymph node pain (uncommon)

The diagnosis is made based on the histological identification of the HRS within the appropriate cellular background.

- The optimal tissue for diagnosis is a complete lymph node. Core biopsies are often adequate but sometimes give false negative results. A fine needle aspiration is inadequate.
- Radiological staging investigations:
  - Either a CT-thorax, abdomen and pelvis (CT-TAP) and a bone marrow biopsy
  - Or, more recently, an FDG-PET with corresponding CT TAP obviates the need for a bone marrow biopsy and is a more sensitive staging investigation.

- Bloods:
  - FBC, renal and liver function (baseline for chemo) HIV serology (sometimes implicated).
- Consider cardiac function assessment
  - Because anthracycline chemotherapy is usually required and this can affect cardiac function.

Treatment of Hodgkin Lymphoma

Treatment is often successful in inducing remission and quite frequently cure in Hodgkin lymphoma. Approximately 75 – 80% of patients diagnosed will require only one course of treatment for lon-term remission. The exact type of treatment depends on the stage and is usually directed by response seen on an interim PET (iPET2) scan after two cycles of chemotherapy (either ABVD or eBEACOPP).

For early stage disease (stage I-II) treatment depends on whether disease is favourable or unfavourable (according to either the EORTC or GHSG criteria which are based around bulky disease, the presence of B-symptoms and the ESR of the blood, the number of nodal sites and age. Once favourable / unfavourable status has been determined, the number of cycles of treatment can be determined.

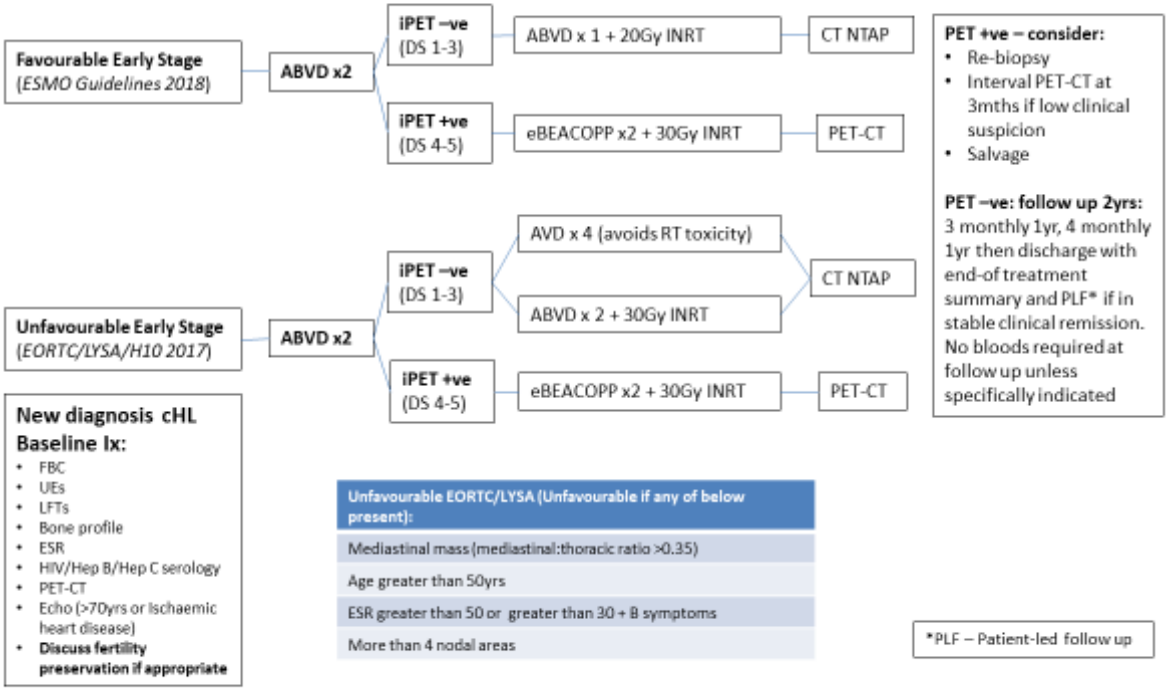
For early stage favourable disease, a RAPID-trial approach is sometimes used (2 ABVD followed by 1 further cycle +/- radiotherapy if iPET2 negative).

For more advanced stage disease, either 6 cycles of ABVD (omitting the bleomycin after cycle 2 if iPET2 negative (the RATHL approach) or using more intensive eBEACOPP / eBEACOPDac for four cycles is sometimes employed. The approach used depends on the international prognostic score system (IPS / Hasenclever Score) and local or regional policy).

Prognosis for early stage disease is often excellent (> 90% 5yr OS). Prognosis for advanced stage disease can be estimated using the Hasenclever index (Hodgkin IPI). Relapse does occur (20% on average) – several novel salvage approaches have shown very good results using agents brentuximab vedotin and subsequently, immune checkpoint inhibitors such as nivolumab. For an outline of treatment pathways, see below. NB. These pathways are guidelines only and are subject to change as more data becomes available.

Pathway for front line treatment of Early Stage (I-IIA) classical Hodgkins Lymphoma *(Hodgkin Lymphoma Updates BJH Jan 2019 Vol 184 No1)*

If available consider clinical trial



PET +ve – consider:

- Re-biopsy
- Interval PET-CT at 3mths if low clinical suspicion
- Salvage

PET –ve: follow up 2yrs: 3 monthly 1yr, 4 monthly 1yr then discharge with end-of treatment summary and PLF* if in stable clinical remission. No bloods required at follow up unless specifically indicated

New diagnosis cHL Baseline Ix:

- FBC
- UEs
- LFTs
- Bone profile
- ESR
- HIV/Hep B/Hep C serology
- PET-CT
- Echo (>70yrs or Ischaemic heart disease)
- **Discuss fertility preservation if appropriate**

Unfavourable EORTC/LYSA (Unfavourable if any of below present):
Mediastinal mass (mediastinal:thoracic ratio >0.35)
Age greater than 50yrs
ESR greater than 50 or greater than 30 + B symptoms
More than 4 nodal areas

*PLF – Patient-led follow up

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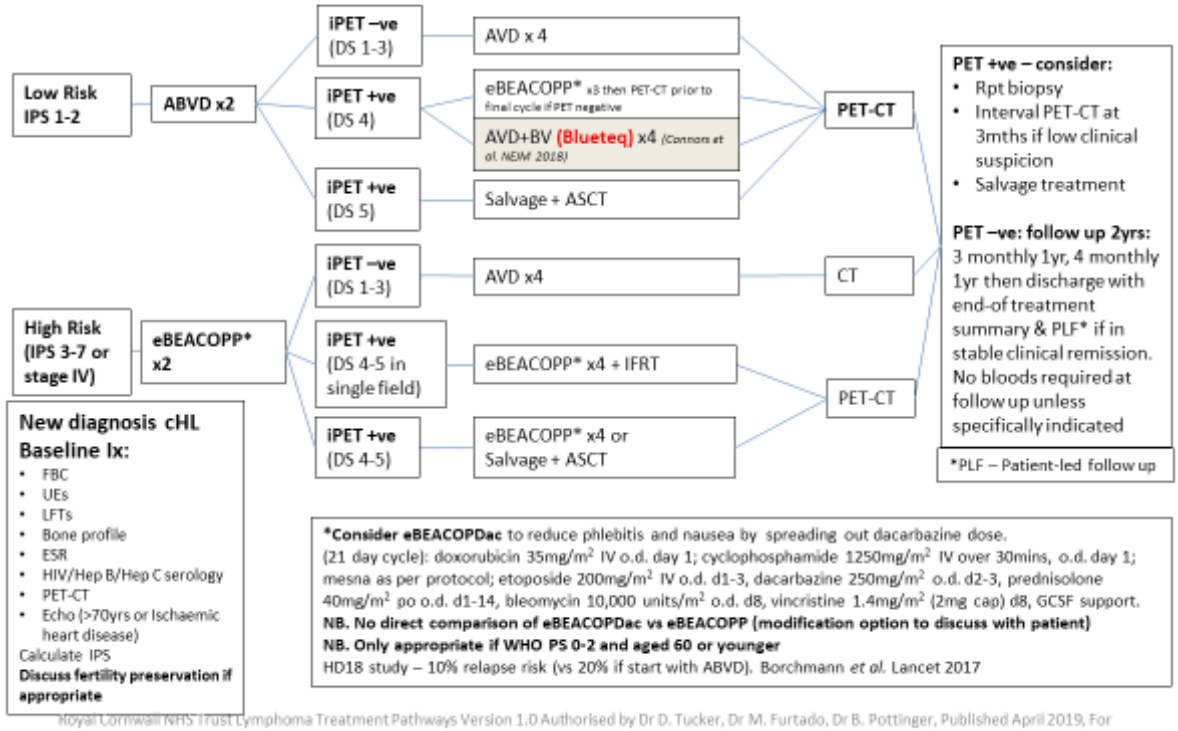
Intensive front line treatment of advanced (stage IIB – IV) classical Hodgkins lymphoma (>60yrs, PS 0-2) *(Hodgkin Lymphoma Update BJH Jan 2019 Vol 184 No1 and Thames Valley SCN, May 2018 – G. Collins)*

If available consider clinical trial



New diagnosis cHL
Baseline Ix:
- FBC
- UEs
- LFTs
- Bone profile
- ESR
- HIV/Hep B/Hep C serology
- PET-CT
- Echo (>70yrs or Ischaemic heart disease)

Calculate IPS
Discuss fertility preservation if appropriate

***Consider eBEACOPDac** to reduce phlebitis and nausea by spreading out dacarbazine dose.
(21 day cycle): doxorubicin 35mg/m^2 IV o.d. day 1; cyclophosphamide 1250mg/m^2 IV over 30mins, o.d. day 1; mesna as per protocol; etoposide 200mg/m^2 IV o.d. d1-3, dacarbazine 250mg/m^2 o.d. d2-3, prednisolone 40mg/m^2 po o.d. d1-14, bleomycin 10,000 units/m^2 o.d. d8, vincristine 1.4mg/m^2 (2mg cap) d8, GCSF support.
NB. No direct comparison of eBEACOPDac vs eBEACOPP (modification option to discuss with patient)
NB. Only appropriate if WHO PS 0-2 and aged 60 or younger
HD18 study – 10% relapse risk (vs 20% if start with ABVD). Borchmann *et al.* Lancet 2017

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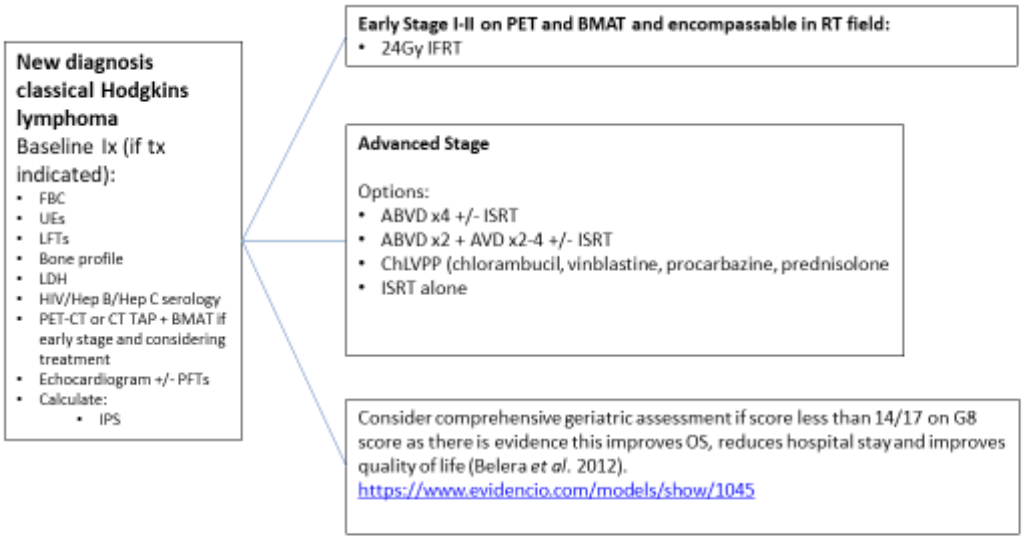
Pathway for front line treatment of classical Hodgkins in Older Patients (>60 / Comorbidities) *(Boll et al. BJH Review 2019 184 pp82-92)*

If available consider clinical trial



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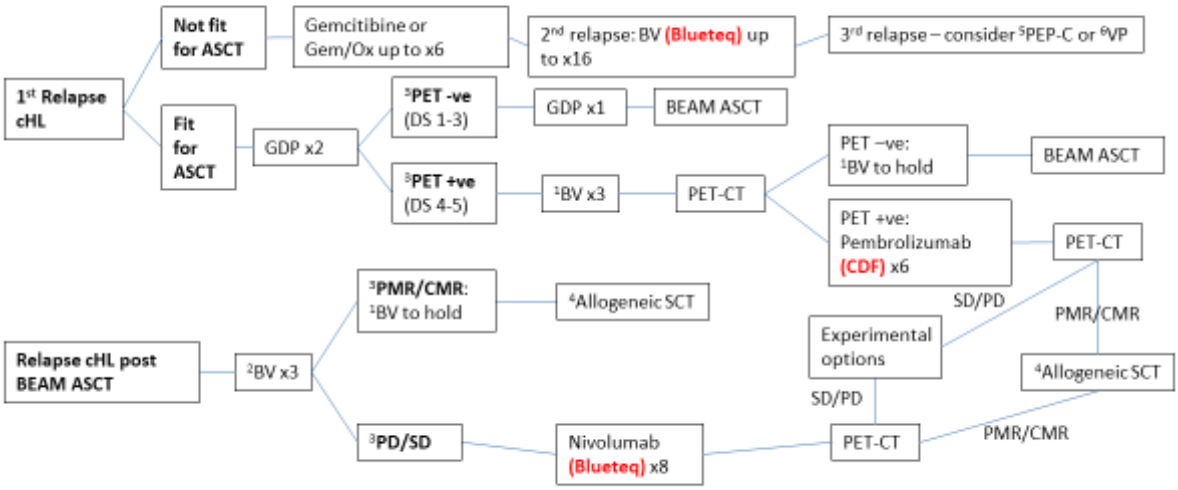
Pathway for treatment of relapsed classical Hodgkins Lymphoma

(Reference: BJH Jan 2019 Vol 184 No1 and Thames Valley SCN, May 2018 – G. Collins)

If available consider clinical trial



Very low risk relapse (early stage at first diagnosis and relapse; >1yr in remission; no radiotherapy given so far) may be treated with either RT alone or combination chemotherpay + RT – SCT may not be needed.

Radiotherapy recommended after systemic tx for bulk at relapse; localised relapse; residual PET avid areas

[1]Aim for SCT promptly; keep administering BV until this is performed

[2]If BV exposed re-treat if prior BV well tolerated and resulted in good remission; up to 16 cycles in total

[3]PET interpretation can be hard; a very good PR but with residual uptake can be treated as negative – discuss at MDT

[4]Allo SCT after PD1 inhibition should always be T-deplete with an 8 week washout

[5]PEP-C – Prednisolone, cyclophosphamide, etoposide, procarbazine (Coleman *et al. Leuk. Lymph.* 2008)

[6]VP – Vinblastine and prednisolone (UCLH protocol)

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