Clinicians' Guides to Radionuclide Hybrid Imaging · PET/CT
Series Editors: Jamshed B. Bomanji · Gopinath Gnanasegaran
Stefano Fanti · Homer A. Macapinlac

Irfan Kayani *Editor*

PET/CT in Hodgkin's Lymphoma

BNMS
BRITISH NUCLEAR MEDICINE SOCIETY

Springer

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PET/CT in Hodgkin's Lymphoma

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PET/CT series is dedicated to Prof Ignac Fogelman, Dr Muriel Buxton-Thomas and Prof Ajit K Padhy

Foreword

Clear and concise clinical indications for PET/CT in the management of oncology patients are presented in this series of 15 separate booklets.

The impact on better staging, tailored management and specific treatment of the patient with cancer has been achieved with the advent of this multimodality imaging technology. Early and accurate diagnosis will always pay, and clear information can be gathered with PET/CT on treatment responses. Prognostic information is gathered and can forward guide additional therapeutic options.

It is a fortunate coincidence that PET/CT was able to derive great benefits from radionuclide-labelled probes, which deliver good and often excellent target to nontarget signals. Whilst labelled glucose remains the cornerstone for the clinical benefit achieved, a number of recent probes are definitely adding benefit. PET/CT is hence an evolving technology, extending its applications and indications. Significant advances in the instrumentation and data processing available have also contributed to this technology, which delivers high throughput and a wealth of data, with good patient tolerance and indeed patient and public acceptance. As an example, the role of PET/CT in the evaluation of cardiac disease is also covered, with emphasis on labelled rubidium and labelled glucose studies.

The novel probes of labelled choline, labelled peptides, such as DOTATATE, and, most recently, labelled PSMA (prostate-specific membrane antigen) have gained rapid clinical utility and acceptance, as significant PET/CT tools for the management of neuroendocrine disease and prostate cancer patients, notwithstanding all the advances achieved with other imaging modalities, such as MRI. Hence, a chapter reviewing novel PET tracers forms part of this series.

The oncological community has recognised the value of PET/CT and has delivered advanced diagnostic criteria for some of the most important indications for PET/CT. This includes the recent Deauville criteria for the classification of PET/CT patients with lymphoma—similar criteria are expected to develop for other malignancies, such as head and neck cancer, melanoma and pelvic malignancies. For completion, a separate section covers the role of PET/CT in radiotherapy planning, discussing the indications for planning biological tumour volumes in relevant cancers.

These booklets offer simple, rapid and concise guidelines on the utility of PET/CT in a range of oncological indications. They also deliver a rapid aide memoire on the merits and appropriate indications for PET/CT in oncology.

London, UK Peter J. Ell, FMedSci, DR HC, AΩA

Preface

Hybrid imaging with PET/CT and SPECT/CT combines best of function and structure to provide accurate localisation, characterisation and diagnosis. There is extensive literature and evidence to support PET/CT, which has made significant impact on oncological imaging and management of patients with cancer. The evidence in favour of SPECT/CT especially in orthopaedic indications is evolving and increasing.

The *Clinicians' Guides to Radionuclide Hybrid Imaging* (PET/CT and SPECT/CT) pocketbook series is specifically aimed at our referring clinicians, nuclear medicine/radiology doctors, radiographers/technologists and nurses who are routinely working in nuclear medicine and participate in multidisciplinary meetings. This series is the joint work of many friends and professionals from different nations who share a common dream and vision towards promoting and supporting nuclear medicine as a useful and important imaging speciality.

We want to thank all those people who have contributed to this work as advisors, authors and reviewers, without whom the book would not have been possible. We want to thank our members from the BNMS (British Nuclear Medicine Society, UK) for their encouragement and support, and we are extremely grateful to Dr Brian Nielly, Charlotte Weston, the BNMS Education Committee and the BNMS council members for their enthusiasm and trust.

Finally, we wish to extend particular gratitude to the industry for their continuous support towards education and training.

London, UK

Gopinath Gnanasegaran
Jamshed Bomanji

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Hodgkin Lymphoma

1

Sajir Mohamedbhai

Contents

Hodgkin lymphoma (HL) is an uncommon B cell lymphoid malignancy. There are two main types of HL—classical Hodgkin lymphoma (cHL) and nodular lymphocyte predominant Hodgkin lymphoma (NLPHL). cHL accounts for 95% and NLPHL for 5% of all HL cases. This chapter will provide a summary of the epidemiology, clinico-pathological features, staging and prognostication of cHL. NLPHL is also discussed briefly.

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1.1 Epidemiology

The incidence of cHL is around three cases per 100,000, with about 1700 new cases diagnosed per year in the UK. It is the third most common cancer in young adults aged between 20–34 years, with a much lower incidence in other age groups. There is a slight male predominance.

1.2 Clinical Presentation

cHL typically presents with painless lymphadenopathy, most often in the neck and supra-clavicular areas. A mediastinal mass is present in over 50% of patients, and this can be asymptomatic or present with dyspnoea, cough, or superior vena cava obstruction (SVCO). Abdominal nodal involvement is less common, often in older patients or when fever or night sweats are present.

A quarter of patients have B symptoms, which include fevers of >38 ºC, drenching night sweats, and loss of more than 10% of body weight over 6 months. Other symptoms such as pruritis, fatigue, and alcohol-related pain may occur but are less specific and are not classified as B symptoms.

About 5–8% of patients with cHL have bone marrow involvement at diagnosis using conventional staging. Rarely, cHL presents with spinal cord compression, central nervous system disease, Waldeyer's ring involvement, testicular masses, or gastro-intestinal masses.

If the disease is left untreated, death usually occurs within 1–2 years, with fewer than 5% of patients alive at 5 years.

Although not an AIDS-defining illness, an association between cHL and HIV infection is well recognised.

1.3 Diagnosis

Surgical excision biopsy of an abnormal node is recommended, although needle core biopsy offers a less invasive alternative, with generally good diagnostic yield. Fine needle aspirate (FNA) is discouraged for lymphoma diagnosis due to poor sample quality for accurate diagnosis.

When the disease is primarily within the chest, involvement of a cardiothoracic team to obtain tissue through mediastinoscopy or by endo-bronchial ultrasound (EBUS) guided biopsy should be considered. Histopathological analysis with immuno-histochemistry is essential for accurate diagnosis, and should be confirmed by an experienced haematopathologist.

1.4 Pathology and Classification

The hallmark of cHL is the presence of malignant Reed-Sternberg (RS) cells scattered within a cellular infiltrate of non-malignant inflammatory cells that make up the majority of the tumour tissue. The RS cells have been shown to be B cells with an altered B-cell programme and, therefore, do not express typical B-cell antigens. They are usually CD15 and CD30 positive. About half of cases harbour Epstein Barr virus (EBV) DNA although the precise role of EBV in the pathogenesis of cHL remains unclear.

cHL is in turn subclassified into four subtypes: nodular sclerosis (70%), mixed cellularity (20%), lymphocyte-rich (5%), and lymphocyte-depleted (rare), according to the cellular background of the RS cells. There are some differences in presentation, sites of involvement, epidemiology, and association with EBV between these four cHL subtypes; however, there are no differences in the prognosis or management of the different subtypes of cHL.

1.5 Staging

Table 1.1 shows the modified Ann Arbor staging system used for HL. The stage highlights the anatomical distribution of the disease but also factors known to be of prognostic significance, such as the absence or presence of B symptoms (A or B), bulky disease (X), and extranodal disease (E). The 2014 Lugano Classification has suggested removing the term X and instead to measure the longest tumour size on CT. It however retains the presence of a single nodal mass of 10 cm or greater than

Table 1.1 Modified Ann Arbor staging criteria for Hodgkin lymphoma

Stage	*Areas involved*
I	**One lymph node region or lymphoid structure**
II	**≥2 lymph node regions on the same side of the diaphragm**
III	**Lymph nodes on both sides of the diaphragm**
IV	**Extranodal sites other than one contiguous or proximal extranodal site or bone marrow**
Qualifier	*Clinical features*
A	No systemic symptoms present
B	Unexplained fevers >38 °C; drenching night sweats; or weight loss >10% of body weight (within 6 months prior to diagnosis)
X	Bulky disease (mediastinal mass larger than a third of thoracic diameter, or any nodal mass >10 cm in diameter)
E	Involvement of one contiguous or proximal extranodal site

a third of the transthoracic diameter at any level of thoracic vertebrae as determined by CT as the definition of bulky disease for cHL.

The Lugano Classification also incorporates CT neck, chest, abdomen, and pelvis combined with functional imaging with ^{18}F-fluorodeoxyglucose-PET (PET/CT) as the optimal staging modality in Hodgkin lymphoma. PET/CT upstages 13–24% of cases compared to CT only. PET/CT may however be positive in sites of infection or inflammation and careful interpretation is required.

PET/CT is highly sensitive for focal bone marrow infiltration, and non-targeted pelvic bone marrow biopsy for staging is now rarely performed. Diffuse bone marrow uptake on PET/CT usually reflects a reactive process, while focal lesions are usually due to disease. Where there is uncertainty, a bone marrow biopsy is advisable.

1.6 Prognostic Factors at Baseline

At diagnosis, cHL is sub-classified into three main prognostic categories (Box 1.1), namely, early favourable, early unfavourable, and advanced, according to the modified Ann-Arbor stage and, for early stage cHL, the presence of clinical risk factors. The treatment and outcomes are in turn influenced by the

Box 1.1 Prognostic Categories in cHL

Early favourable

- Stages I–IIA/B without any risk factors

Early unfavourable

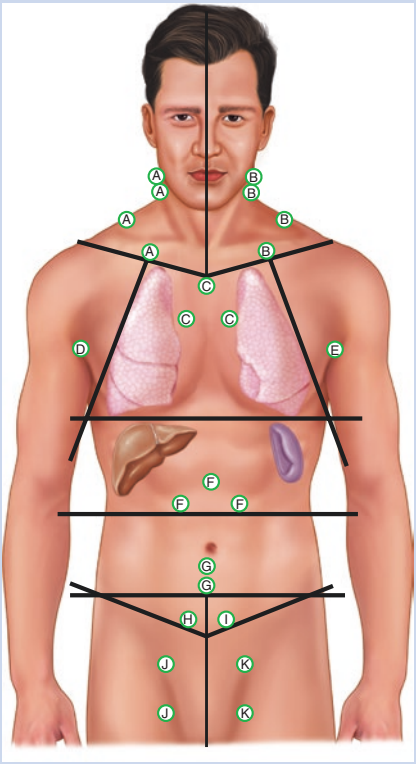
- Stage IA/B and stage IIA with one or more risk factors
- Stage IIB with high ESR and/or involvement of ≥3 lymph node areas as only risk factors

Advanced stages

- Stage IIB with extranodal involvement and/or large mediastinal mass
- Stages III–IV

German Hodgkin Study Group Risk Factors for early stage cHL

- Large mediastinal mass ≥one third of the maximum thorax diameter
- Involvement of one contiguous or proximal extranodal site
- Involvement of three or more nodal areas (see Fig. 1.1)
- Elevated ESR (>50 mm/h in stages I–IIA and >30 mm/h in stages I–IIB)



A: right cervical + infra-/supra-clavicular/nuchal
B: left cervical + infra-/supra-clavicular/nuchal
C: right/left hilar + mediastinal
D: right axillary
E: left axillary
F: upper abdomen (spleen hilum, liver hilum, coeliac)
G: lower abdomen (Para-aortic, iliac, mesenteric)
H: right iliac
I: left iliac
J: right inguinal + femoral
K: left inguinal + femoral

Fig. 1.1 Definition of main lymph node areas (German Hodgkin Study Group)

prognostic category the patient falls into. The precise definition of the risk factors differs somewhat among study groups. The German Hodgkin Study Group risk factors are widely used in early stage disease. Bulky disease has been shown to be an independent adverse prognostic marker in early stage cHL, as is extranodal extension, presence of 3 or more nodal sites (see Fig 1.1) and a raised ESR.

With current treatment regimens, the prognosis of early stage cHL is excellent, with overall 5-year survival approaching 95%. About 10% of early stage patients will experience a relapse or have primary refractory disease.

Box 1.2 IPS/Hasenclever Index Risk Factors in Advanced cHL

1. Serum albumin <40 g/L
2. Haemoglobin <10.5 g/dL
3. Male sex
4. Ann Arbor stage IV
5. Age ≥45 years
6. White cell count ≥15 × 109/L
7. Lymphocyte count <0.6 × 109/L

In advanced cHL, 5-year disease-free survival is variable, between 75 and 90%. A seven-point International Prognostic Score, also known as the Hasenclever Index (Box 1.2), identifies seven risk factors, with each point reducing the 5-year progression-free survival by about 8%. Overall, about 20–30% of advanced stage cHL will experience a relapse or have refractory disease. Unfortunately the baseline IPS is not a very reliable tool in predicting outcome at an individual level.

1.7 Nodular Lymphocyte Predominant Hodgkin Lymphoma

NLPHL is a distinct clinical entity with a histology and clinical course distinct from cHL. NLPHL accounts for about 5% of cases of HL in adults and adolescents and 10–20% of cases in children. Most NLPHL patients (70%) are male. Incidence peaks at 13–14 years in children and 30–35 years in adults. Three-quarter patients present with early-stage disease, often with solitary lymph node involvement. B symptoms are rare in NLPHL.

NLPHL lacks the classical Reed-Sternberg cells but is characterized by the presence of atypical cells, sometimes termed ‘popcorn’ or L&H cells. NLPHL usually displays a nodular growth pattern, which may or may not be accompanied by diffuse areas. L&H cells are typically positive for B-cell-associated antigens such as CD20, unlike cHL cells.

The clinical course in NLPHL is usually indolent and the prognosis is favourable, although late relapses 10–15 years later may occur. Transformation to high-grade B-cell lymphoma is reported in about 12% of patients at 10 years after diagnosis. The risk of transformation increases over time and occurs more frequently in advanced stage disease, especially when disease involves organs such as the spleen and bone and when associated with B symptoms. Histological confirmation at relapse is important to exclude transformation.

Key Points

- Hodgkin lymphoma (HL) is an uncommon cancer of the lymphatic system.
- There are two main types of HL—classical Hodgkin lymphoma (cHL) and nodular lymphocyte predominant Hodgkin lymphoma (NLPHL).
- cHL accounts for 95% and NLPHL for 5% of all HL cases.
- cHL typically presents with painless lymphadenopathy, most often in the neck and supraclavicular areas (mediastinal mass is present in over 50% of patients).
- A quarter of patients have B symptoms.
- About 5–8% of patient with cHL have marrow involvement at diagnosis.
- If the disease is left untreated, death usually occurs within 1–2 years from progression (fewer than 5% of patients alive at 5 years).
- Although not an AIDS-defining illness, an increased incidence of cHL is seen in the setting of HIV infection.
- Surgical excision biopsy of an abnormal node is recommended, although needle core biopsy offers a less invasive alternative, with generally good diagnostic yield.
- Fine needle aspirate (FNA) is discouraged for lymphoma diagnosis due to poor yield.
- When the disease is primarily within the chest, involvement of a cardiothoracic team to obtain tissue through mediastinoscopy should be considered.
- Histopathological analysis with immunohistochemistry is essential for diagnosis, and the diagnosis of HL should be confirmed by an experienced haematopathologist.
- Contrast-enhanced CT neck, chest, abdomen, and pelvis is used for anatomical staging, and this is now often combined with functional imaging with ^{18}F-fluorodeoxyglucose-PET (PET/CT), which upstages 13–24% compared to CT only.
- PET/CT is highly sensitive for focal bone marrow infiltration, and nontargeted pelvic bone marrow biopsy for staging is now performed less often.
- With current treatment regimens, the prognosis of early and intermediate stage cHL is excellent, with overall survival at 5 years approaching 95%.

- In advanced cHL, 5-year disease-free survival is variable, between 75 and 90%.
- NLPHL is a distinct clinical entity characterized by the presence of atypical cells, sometimes termed ‘popcorn’ or L&H cells
- Most NLPHL patients (70%) are male and the disease primarily affects children, adolescents and young adults.
- NLPHL has an excellent prognosis, although late relapses 10–15 years later may occur.

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Pathology of Hodgkin Lymphoma

2

Teresa Marafioti

Contents

Hodgkin lymphoma comprises two disease entities: nodular lymphocyte predominant and classical Hodgkin. The two forms differ in their clinical, biological, morphological and immunophenotipical features [1].

Thomas Hodgkin in 1832 described the disease as Hodgkin's disease [2] although an earlier description was given by Malpighi [3] in the *De viscerum structura exercitatio anatomica*.

In the first histologic classification of Hodgkin's disease [4], three forms were described: paragranuloma, granuloma and sarcoma. Twenty-two years later (1966), the number of described subtypes expanded to six forms: (a) lymphocytic and/or histiocytic (L&H) nodular, (b) L&H diffuse, (c) nodular sclerosis, (d) mixed, (e)

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diffuse fibrosis and (f) reticular. In 1966, a detailed histological description of the tumour cells (i.e. the Hodgkin and Reed-Sternberg (HRS)) and variants was also reported. The current WHO classification (2008) has replaced the term Hodgkin's disease with Hodgkin lymphoma and recognizes two disease entities: the nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) and the classical Hodgkin lymphoma (cHL). The latter includes four histological subtypes (i.e. nodular sclerosis, mixed cellularity, lymphocyte rich and lymphocyte depleted).

2.1 NLPHL: Clinical, Biological, Morphological and Immunophenotipical Features

NLPHL accounts for approx. 3–8% of all Hodgkin lymphoma cases and clinically is regarded as an indolent B-cell neoplasm. The tumour cells are designated as lymphocyte predominant ("LP") or popcorn cells [1, 5]. NLPHL shows male predominance with a ratio of 3:1 male to female in Caucasian individuals and two age peaks, one in children and another in adults of median age (30–35 years).

On morphology, a lymph node involved by NLPHL shows total or partial effacement of the normal architecture replaced by a nodular and/or nodular and diffuse pattern [1].

The nodular pattern is characterized by large lymphoid aggregates composed of small lymphocytes and supported by expanded sphere-shaped meshworks of follicular dendritic cells (FDC). Within and outside the lymphoid aggregates (predominantly B-cells), the "LP" cells show scant cytoplasm, and large vesicular folded or polylobulated nuclei with distinct nucleoli are seen. The LP cells are usually surrounded by small T-cells with the phenotype of follicular helper T-cells (i.e. CD4, CD57, BCL-6 and PD1 positive) [1, 6].

In the diffuse form, the LP cells are embedded in a diffuse background predominantly composed of small follicular helper T-lymphocytes [6], sparse small B-cells and some histiocytes. FDC meshworks are absent. The diffuse areas are rarely completely diffuse, and at least one nodular lymphoid aggregate showing the characteristic features of NLPHL (e.g. mixture of LP cells and small reactive B-cells) is required to exclude the diagnosis of an aggressive B-cell lymphoma, i.e. the T-cell-/histiocyte-rich large B-cell lymphoma (THRLBCL) [1].

Polyclonal plasma cells and collections of histiocytes with only rare neutrophils and eosinophils are other morphological features seen in NLPHL. Follicular hyperplasia with progressive transformation of germinal centres (PTGC) is a finding that may coexist or precede the manifestation of NLPHL. To note is that in contrast to classical Hodgkin lymphoma, sclerosis is not a frequent feature at least in primary biopsies, but it can be seen in relapses.

Six histologic variant patterns of NLPHL [7] have been recently described: "classic nodular (B-cell rich)", "serpiginous/interconnected nodular", "prominent extranodular LP cells with T-cell-rich background", "diffuse pattern (T-cell-rich large B-cell-like)" and "diffuse "moth eaten" with B-cell-rich background".

An analysis from the German Hodgkin Lymphoma Study Group (GHLSG) carried out on more than 400 LPHL cases showed that identification of the histologic patterns is relevant for prognosis. NLPHL patients presenting with histopathologic variants have a poorer outcome compared to those showing the typical nodular histology [8].

LP cells, unlike HRS in cHL, retain their B-cell signature. LP cells are commonly positive for B-cell markers such as CD20, CD74, CD79a, J-chain, PAX-5, OCT-2 and BOB-1, and they express CD45 and immunoglobulin light and/or heavy chains [1].

Markers characteristic of Hodgkin and Reed-Sternberg cells, i.e. CD15-, CD30- and Epstein-Barr virus (EBV)-associated molecules, are commonly negative in LP cells [1] (Fig. 2.1).

2.2 cHL: Clinical, Biological, Morphological and Immunophenotipical Features

The diagnosis of cHL is based on the identification of the characteristic Hodgkin and Reed-Sternberg (HRS) which represent 1–3% of all cell and are immersed in a background of small lymphocytes, histiocytes, epithelioid histiocytes, neutrophils, eosinophils, plasma cells, fibroblasts and vessels. The neoplastic cell population include (a) the Reed-Sternberg cells with large cytoplasm, two to multiple nuclei and acidophilic or amphophilic nucleoli and the Hodgkin cells with a large single nuclei and prominent eosinophilic nucleoli. The development of HRS is obscure. It has been postulated that these cells arise from mononucleated Hodgkin cells via endomitosis; however, recently Rengstl et al. [9] by tracking the cells and their progeny for multiple generations demonstrated that the fusion of daughter cells, called re-fusion, plays an essential role in the formation of HRS cells.

Based on the characteristics of the reactive infiltrate and the morphology of HRS cells, four histological subtypes are described: nodular sclerosis, mixed cellularity, lymphocyte rich and lymphocyte depleted.

The immunophenotype of cHL cells is characterized by the expression of CD30 (in more than 98% of cases) and CD15 (in about 75–80% of cHLs) and lack of CD45. Despite their B-cell genotype, cHL cells are negative for B-cell molecules (i.e. CD19, CD20, CD22), but PAX-5 is generally weaker than in normal B-cells. EBV infection is found in a variable percentage of cHL patients, and it is reported in approx. 20–40% of nodular sclerosis and lymphocyte depleted and 50–75% of mixed cellularity.

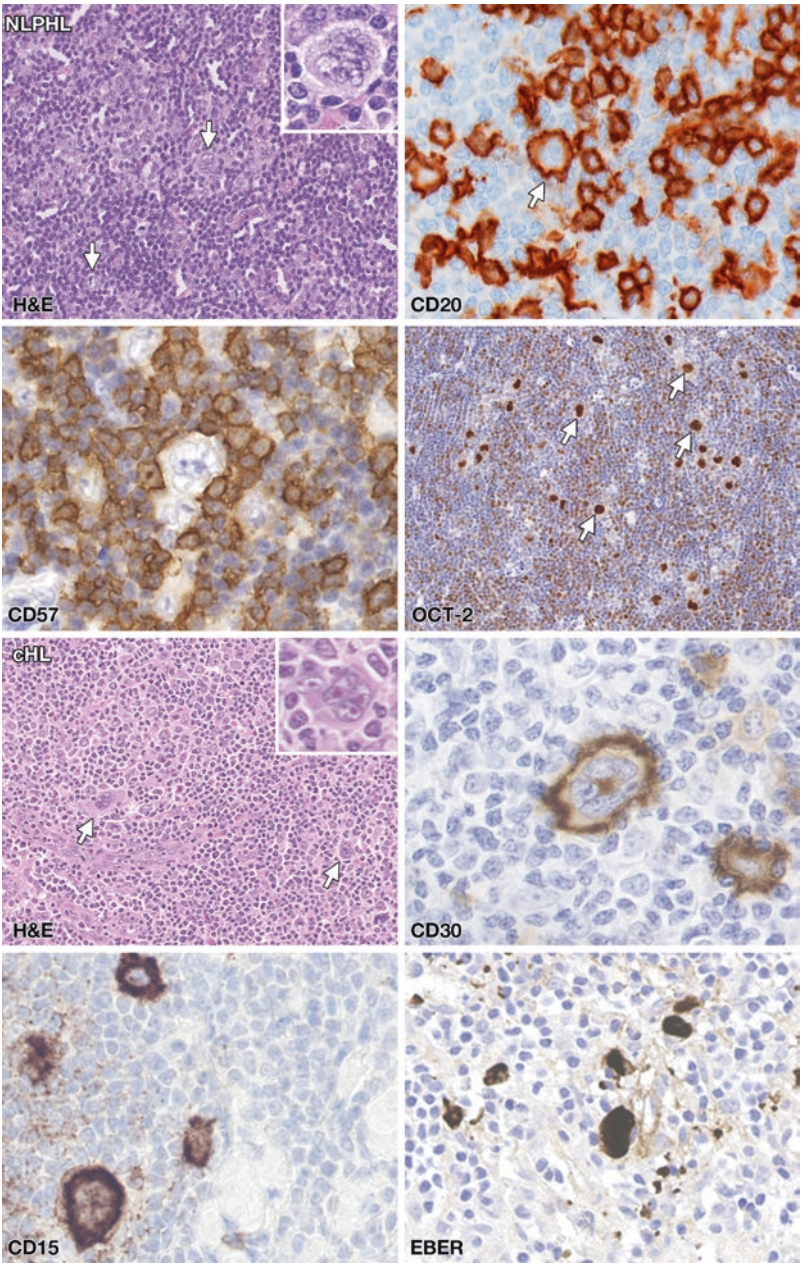

Fig. 2.1 Lymphocyte predominant (LP) cells in nodular lymphocyte predominant Hodgkin lymphoma (LPHL) show the typical popcorn morphology (*arrows and inset*; ×400 and ×600) (haematoxylin and eosin (H&E) stain). The LP cells express CD20 (*arrow*; ×400) and are surrounded by CD57-positive T-cells (×400). LP cells show a strong expression of OCT-2 (*arrows*; ×400). Hodgkin and Reed-Sternberg cells (HRS; *arrows*) lie in a background of small lymphocytes in a typical case of mixed cellularity classical Hodgkin lymphoma (cHL) (×200, haematoxylin-eosin). HRS cells show the typical membranous and dot-like (in Golgi area) CD30 positivity (×400) and express CD15 (×400). HRS cells are EBV positive as revealed by in situ hybridization technique using anti-EBER probes (×400)

2.3 cHL Variants

2.3.1 Nodular Sclerosis

It represents the most frequent subtype of classical HL in Western countries and the USA and corresponds to 75% of all cHL cases. Broad collagen bands originating from a thickened lymph node capsule subdivide the parenchyma into large nodules containing great variability of inflammatory cells. A morphological variant of HRS cells are seen in this cHL subtype, i.e. the lacunar cells so defined because of a condensation of their cytoplasm that is connected to the membrane via narrow filaments giving the effect of a "lacunar" space.

2.3.2 Mixed Cellularity

About 15–25% of cHL cases belong to this group. The histological picture is characterized by a diffuse growth in which a pabulum of plasma cells, epithelioid histiocytes, eosinophils and T-cell surrounding HRS cells are seen.

2.3.3 Lymphocyte Rich

It accounts for about 6% of all HL cases. Morphologically, most cases show a vague nodularity resembling to NLPHL. Conversely to NLPHL, the nodular structures contain small germinal centres and an expanded mantle zone in which the tumour cells with morphologic features of HRS cells are embedded.

2.3.4 Lymphocyte Depleted

It is rare, presents the worst clinical behaviour and prognosis and accounts for about 1% of HL cases. Two subtypes of LD-cHL can be distinguished: fibrotic and reticular/sarcomatous. In the former, a low cellular density with small amounts of lymphocytes, variable number of HRS cells and prominent diffuse reticulin fibre formation is seen. In the latter form, diffuse effacement of the lymph node, increased numbers of HRS cells, some of which appear "mummified", and scanty inflammatory cells are seen.

Key Points

- Hodgkin lymphoma comprises two disease entities: nodular lymphocyte predominant and classical Hodgkin.
- The current WHO classification (2008) has replaced the term Hodgkin's disease with Hodgkin lymphoma and recognizes two disease entities: the nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) and the classical Hodgkin lymphoma (cHL).
- Classical Hodgkin lymphoma includes four histological subtypes (i.e. nodular sclerosis, mixed cellularity, lymphocyte rich and lymphocyte depleted).
- NLPHL accounts for approx. 3–8% of all Hodgkin lymphoma cases and clinically is regarded as an indolent B-cell neoplasm (the tumour cells are designated as lymphocyte predominant ("LP") or popcorn cells).
- On morphology, a lymph node involved by NLPHL shows total or partial effacement of the normal architecture replaced by a nodular and/or nodular and diffuse pattern [1].
- The nodular pattern is characterized by large lymphoid aggregates composed of small lymphocytes and supported by expanded sphere-shaped meshworks of follicular dendritic cells (FDC).
- In the diffuse form, the LP cells are embedded in a diffuse background predominantly composed of small follicular helper T-lymphocytes [6], sparse small B-cells and some histiocytes. FDC meshworks are absent.
- Polyclonal plasma cells and collections of histiocytes with only rare neutrophils and eosinophils are other morphological features seen in NLPHL.
- Follicular hyperplasia with progressive transformation of germinal centres (PTGC) is a finding that may coexist or precede the manifestation of NLPHL.
- Six histologic variant patterns of NLPHL have been described.
- NLPHL patients presenting with histopathologic variants have a poorer outcome compared to those showing the typical nodular histology.
- The diagnosis of cHL is based on the identification of the characteristic Hodgkin and Reed-Sternberg (HRS).
- Based on the characteristics of the reactive infiltrate and the morphology of HRS cells, four histological subtypes are described (nodular sclerosis, mixed cellularity, lymphocyte rich and lymphocyte depleted).
- The immunophenotype of cHL cells is characterized by the expression of CD30 (in more than 98% of cases) and CD15 (in about 75–80% of cHLs) and lack of CD45.

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Management of Hodgkin Lymphoma

3

Sajir Mohamedbhai

Contents

Hodgkin lymphoma (HL) was one of the first solid malignancies in adults to be cured by chemotherapy. The stepwise improvement in HL treatment outcomes over the last 50 years stands as a model of successful cross-specialty collaboration in oncology.

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3.1 Baseline Evaluation

Once the diagnosis of HL is confirmed histologically, a detailed clinical history and physical examination is essential to assess for symptoms, comorbidities, size and distribution of palpable lymphadenopathy and organomegaly. If the patient is unwell or if obstruction of the superior vena cava is suspected, urgent imaging and hospitalisation are needed. A pre-treatment staging PET/CT is recommended wherever possible. Essential laboratory evaluation includes full blood counts, ESR, renal and liver function, bone profile, lactate dehydrogenase (a marker of cell turnover) and HIV serology. There is no role for routine staging bone marrow aspiration and biopsy when staging PET/CT is used.

Males should be offered semen cryopreservation. For females, pretreatment assessment by a fertility specialist should be considered where treatment is not urgent. Baseline assessment of cardiac and lung function is recommended in selected patients such as those with pre-existing cardiovascular or pulmonary comorbidities, smokers and patients older than 50.

3.2 Historical overview of HL treatment

The dramatic improvement in outcomes in HL over the previous century is hailed one of the paradigms of progress in oncology. The early medical application of X-rays in the early 1900s led to significant tumour reductions. Further refinement of radiotherapy during the early to mid-twentieth century cured a proportion of early stage HL patients, albeit with significant toxicity.

The advent of chemotherapy drugs eventually led to the MOPP (mustard, vincristine, procarbazine and prednisolone) regimen, which resulted in the first chemotherapy-based cures in HL, as reported in 1964. The combination of chemotherapy and radiotherapy was highly effective at curing HL, however, adverse effects of treatment, sometimes only apparent until decades later, impacted on long term morbidity and survival. The ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) regimen, developed in the 1970s, was superior but less toxic than MOPP, resulting in cures in up to 70% of patients with HL. The German seven-drug BEACOPP (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone) regimen was developed in an attempt to improve on ABVD in the 1990s. High dose (escalated) BEACOPP produced even higher remission rates, but at the price of greater toxicity and infertility rates than ABVD. These two regimens are currently widely used in HL, with much debate over their relative merits and drawbacks.

Alongside improvements in chemotherapy, refinement of radiotherapy fields and dosing and their optimal combination with chemotherapy has led to our modern strategies in treating HL. A key finding was that less radiotherapy does not necessarily equate to poorer outcomes, especially in early stage disease.

Another milestone has been the incorportation of PET/CT (discussed in chapter 4 and 5) in staging and response assessment, with studies reporting the feasibility of a risk-adapted approach, sparing good early metabolic responders from more intensive and toxic treatments and intensifying treatment in poor responders.

The use of high dose therapy and autologous stem cell transplantation in the 1980s and 1990s provided a curative option for patients with relapsed or refractory

disease. The role of allogeneic stem cell transplantation is still being explored, with strong evidence for a graft-versus-lymphoma effect in HL. Several active novel agents in the last decade hold great promise for the future and are the subject of intensive research.

3.3 Upfront Treatment Modalities

cHL is sensitive both to radiotherapy and chemotherapy. The aim of combined modality treatment is to obtain an optimum balance between the high remission rates achievable with current treatment regimens and treatment-related toxicity.

ABVD and standard or escalated BEACOPP are highly effective in physically fit patients, however, are less well tolerated in patients >50–60 years old. Patients receiving bleomycin should be regularly assessed for pulmonary toxicity during treatment. Individualised treatment with lower-intensity regimens (e.g., VEPEMB and ChlVPP) that are less effective than ABVD, should be considered for older patients and patients with comorbidities.

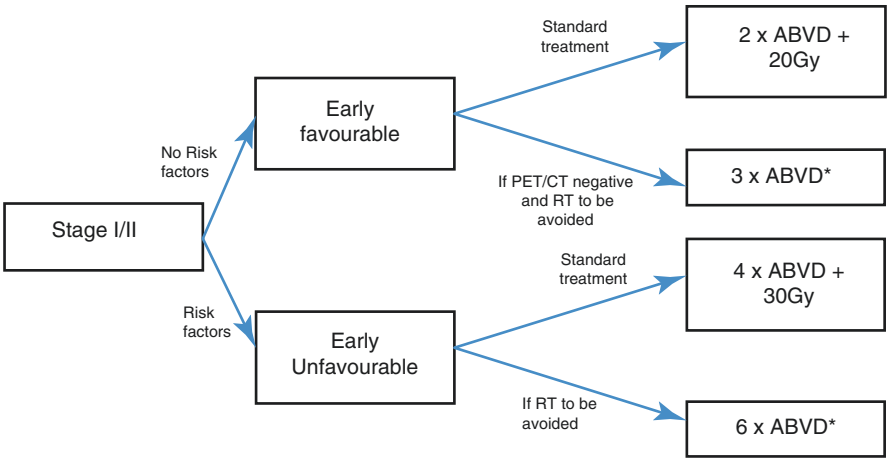
Evidence for the role of radiotherapy in HL is based on involved field radiotherapy (IFRT). Reduced volume approaches, involved node (INRT) or involved site (ISRT) are under evaluation in current protocols. INRT optimises radiotherapy fields by incorporating baseline PET/CT findings into radiotherapy planning—a dedicated pretreatment PET/CT with the patient lying in 'radiotherapy' position is needed.

3.4 Early Stage Favourable cHL

Excellent outcomes have been achieved despite stepwise reductions in treatment intensity in this subgroup. In the landmark German HD10 study, 93% of patients given two cycles of ABVD followed by 20 Gy IFRT remained relapse-free at 5 years, with no significant difference compared to regimens containing four cycles of ABVD and/or 30 Gy IFRT. Two cycles of ABVD followed by 20 Gy IFRT is the current standard of care. The UK RAPID study evaluated the potential for omitting radiotherapy altogether in patients with a negative CT/PET after 3 cycles of ABVD led. There was a small absolute reduction in progression-free survival (PFS) of 3.8% at 3 years in the UK RAPID study. Outcomes are still excellent and this approach may be considered for patient preference or where radiotherapy is contraindicated.

3.5 Early Stage Unfavourable cHL

The GHSG HD11 trial showed that four cycles of ABVD with 30 Gy IFRT produces an OS of 93–96% at a median of 6.8 years of follow-up and is the current standard of care in this subgroup. Many centres omit radiotherapy in favour of two additional cycles of ABVD chemotherapy (i.e. six cycles of ABVD), particularly for younger females with mediastinal/axillary disease, where radiotherapy field would encroach onto breast tissue (Fig. 3.1).



* In selected patients after discussion that omission of RT confers a small adverse impact on PFS

Fig. 3.1 Management of early stage cHL

3.6 Treatment of Advanced-Stage Disease

ABVD (six to eight cycles) or escalated BEACOPP (six cycles) is recommended for advanced disease. ABVD is associated with PFS of about 70% and overall survival of 82–90%. Escalated BEACOPP gives better PFS, but no improvement in long-term overall survival. In the UK, the balance of efficacy to toxicity has favoured the use of ABVD.

A negative interim PET/CT after two cycles of ABVD or BEACOPP is predictive of favourable PFS. The UK RATHL study has recently shown that a risk-adapted approach, with two cycles of ABVD followed by an interim PET/CT to inform decisions about treatment escalation (to escalated BEACOPP) or de-escalation (omission of bleomycin in ABVD), is a feasible strategy. Early results are promising, however, further follow-up is warranted.

Radiotherapy was traditionally offered to patients with bulky disease; however, in PET/CT era, the need for radiotherapy in patients with an end-treatment PET/CT showing complete metabolic remission is controversial. Consolidation radiotherapy is not indicated for patients in CR by CT following ABVD or those with residual masses >2.5 cm if in metabolic CR after escalated BEACOPP. It is uncertain whether RT can be omitted if metabolic CR is achieved after ABVD with PET negative residual soft tissue (>1.5 cm).

High-dose chemotherapy and autologous stem cell transplantation in first remission do not confer a survival benefit over observation alone and are not therefore recommended.

3.7 Follow-Up Evaluation

Patients are usually followed up using clinical and laboratory parameters 3–6 monthly for up to 3–5 years. Follow-up PET/CT should not be used routinely. Management decisions should not be based on PET scan alone-clinical and/or pathologic correlation is always needed.

Assessment for late effects of combined modality treatment, including fertility problems, cardiac and pulmonary toxicity, secondary solid cancers, myelodysplasia and hypothyroidism is required. The incidence of infertility in adults <30 years with ABVD is low and significantly higher with escalated BEACOPP. An eight-fold increase in breast cancer risk is reported after axillary/mediastinal irradiation in females aged 10–30 years-these women should be offered early breast screening.

3.8 Management of Refractory and Relapsed Disease

Overall about 10% of early stage and 20–30% of advanced stage cHL patient will have primary refractory disease or experience relapse after ABVD. Refractory disease and short remission durations of <12 months have poorer outcomes. The current approach in the majority of fit patients of <60–65 years, is to use a second-line (salvage) chemotherapy regimen (e.g., ESHAP, IGEV, ICE) to obtain a second remission, as assessed by PET/CT, prior to high-dose therapy and autologous stem cell transplantation (ASCT). A negative scan pre-ASCT is highly predictive of a favourable outcome (>70% 5-year PFS). PET-positive patients have a poor outcomes (25–30% 3–5-year PFS) and should generally not proceed to ASCT. Overall, after ABVD failure, over 60% of relapsing patients and about 30% of primary patients can be cured with this approach, with a procedure-related mortality of about 3%.

For those who remain PET-positive following salvage chemotherapy, second-line non-cross reactive salvage chemotherapy can be used. In younger patients with a suitable donor and chemo-sensitive disease, allogeneic stem cell transplantation is an option.

Radiotherapy has a role in selected relapsed/refractory cases with limited localised disease, in patients ineligible for transplantation and in late relapses (>5 years), where retreatment with chemotherapy and radiotherapy may be sufficient.

3.9 Novel Agents

New immunotherapy options in cHL have been the most important advance in the feld for decades. The role of an anti-HL immune effect was demonstrated by a potent graft-versus-lymphoma effect in HL patients treated with donor lymphocyte ifusions after allogeneic SCT. Brentuximab vedotin, an anti-CD30 monoclonal

antibody-toxin conjugate shows significant single-agent activity in relapse/refractory cHL. Similarly, a new class of drugs known as immune checkpoint inhibitors, which work by inhibiting pathways that overcome immune escape mechanisms used by the tumour cells, appears promising in cHL. These drugs may be used alone and/or in combination with chemotherapy in relapse/refractory cases. There is also much interest in analysing their role in upfront therapy.

3.10 Management of NLPHL

Given the relative rarity of NLPHL, limited prospective and randomised studies inform management.

Stage 1A disease is generally treated with radiotherapy alone, with surgical excision alone used by some clinicians, albeit with a higher rate of relapse.

For stage II and beyond, B-cell lymphoma and cHL-type chemotherapy regimens are effective, including the anti-CD20 monoclonal antibody rituximab, as these cells strongly express CD20. Rituximab-CVP (cyclophosphamide, vincristine, prednisone) seems effective in stage II disease. More advanced disease (stage III/IV) responds well to rituximab-ABVD. R-CHOP (CVP with doxorubicin) also appears to be effective, particularly in cases of high-grade transformation.

Key Points

- Hodgkin's lymphoma (HL) was the first solid malignancy in adults to be cured by chemotherapy.
- cHL is sensitive both to radiotherapy and chemotherapy.
- The aim of combined modality treatment is to obtain an optimum balance between the high remission rates achievable with current treatment regimens and treatment-related toxicity.
- Regimens such as ABVD and standard or escalated BEACOPP are highly effective and suitable for physically fit patients.
- Individualised treatment with lower-intensity regimens is necessary for older patients and patients with comorbidities.
- Evidence for the role of radiotherapy in HL is based on involved field radiotherapy (IFRT) and has an important role in early stage cHL.
- The role of RT in advanced cHL with bulk in complete metabolic remission by PET/CT after ABVD is less clear.
- Patients are usually followed up using clinical and laboratory parameters 3–6 monthly for up to 5 years. Follow-up PET/CT should not be used routinely.

- High-dose chemotherapy and ASCT offers a potential for cure for patients with relapsed/refractory disease, after second remission induction with salvage chemotherapy.
- PET/CT is recommended for response assessment. A negative scan post-salvage is highly predictive of outcome after ASCT.
- The role of allogeneic stem cell transplantation in patients who fail first line salvage chemotherapy is still being fully defined.
- Brentuximab vedotin and immune checkpoint inhibitors are likely to become an important treatment option in relapsed/refractory cHL and upfront, with several clinical trials under way to assess the best ways to use them.

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Radiological Imaging in Lymphoma

4

Harbir Sidhu

Contents

4.1 Introduction

Advances in staging and response assessment of lymphomas with use of evolving imaging techniques have occurred in concert with introduction of prognostic indices and molecular profiling offering the potential to improve disease characterisation and treatment selection.

4.2 Primary Diagnosis/Staging

The latest World Health Organization classification (2008) lists 70 different forms of lymphoma [1] with rapid expansion through use of immunological and molecular techniques. Where diagnosis is uncertain/unexpected, image-guided (e.g. ultrasound) fine needle aspiration (FNA) may be carried out for isolated lymphadenopathy or in deep-seated/inaccessible lymphadenopathy where tissue is derived via

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endoscopic ultrasonography (both offering real-time high spatial and temporal resolution in appropriately skilled hands). However, the role of FNA remains controversial and certain subtypes cannot be reliably diagnosed. Therefore, if a node is >1 cm diameter or has been present for >6 weeks, it is preferable to omit FNA and proceed straight to (excision) biopsy to avoid a delay in diagnosis. For multiple enlarged nodes where lymphoma is most likely, excision biopsy should be carried out as the primary investigation.

The 1988 Cotswolds modification of the Ann Arbor classification is used internationally for anatomical staging of both HL and NHL [1]. All patients with lymphoma, except those with subtypes of primary cutaneous lymphoma normally limited to skin (e.g. mycosis fungoides), should be imaged for staging at diagnosis to [2]:

- Stage nodal disease.
- Stage extranodal disease.
- Stage primary cerebral, orbital and head/neck lymphoma.
- Investigate suspected spinal cord compression.
- Assess marrow involvement.
- Evaluate musculoskeletal involvement.

Computed tomography (CT) is widely available with comparatively low cost and has traditionally been the mainstay staging modality though increasing evidence indicates superiority of combined PET/CT in initial staging [3]. Routine CT staging includes the chest, abdomen and pelvis, and head/neck CT may also be indicated. Multidetector (MD) CT scanners with faster gantry rotation combined with rapid bolus administration of intravenous contrast medium enable lymph nodes of ≤5 mm diameter and focal extranodal lesions on the order of a few millimetres to be identified. Disadvantages include ionising radiation (though dose should be below the relevant national reference dose for the region of scan/patient group), lack of functional information and low sensitivity for visceral (e.g. splenic) involvement.

RCR guidelines [2] recommend 100–150 ml of intravenous iodinated contrast medium injected at 3–4 ml/s acquiring post-contrast scans through the chest, abdomen and pelvis (portal venous phase). Post-contrast images of the neck can be acquired in either early arterial or late venous phase. Using MDCT, slice thickness will depend on scanner capability—sections are acquired at 1.25–2.5 mm and reformatted at ≤5 mm for viewing [4]. Oral contrast medium may improve visualisation of mesenteric and retroperitoneal lymphadenopathy and detection of bowel involvement in NHL (e.g. mantle cell lymphoma).

Determination of nodal involvement is based on size criteria. In general lymph nodes greater than 1 cm in short axis are considered abnormal on CT. In lymphoma, however, node >1.5 cm in longest transverse dimension regardless of short-axis dimension is considered enlarged [5]. Nodes with longest dimension between 1.1

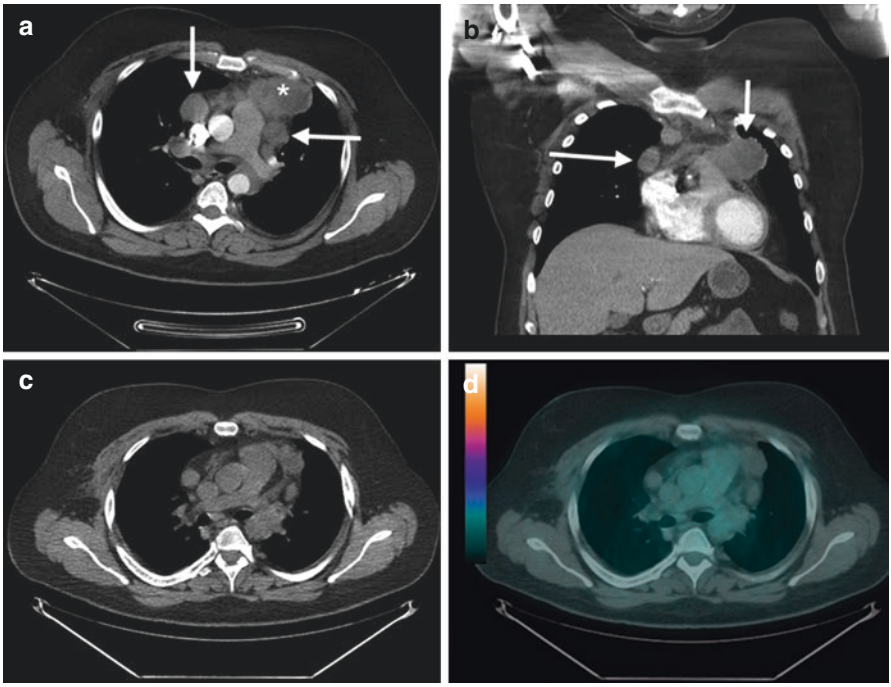

Fig. 4.1 Staging intravenous contrast-enhanced CT in a 26-year-old female presenting with cervical lymphadenopathy with biopsy demonstrating Hodgkin lymphoma; (**a**) axial section and (**b**) coronal reformat demonstrate multiple pathologically enlarged mediastinal nodes (*arrows*) and largest at the anterior mediastinum with low-density necrotic centre (*asterisk*). Subsequent FDG PET/CT post two cycles of systemic therapy (2-month interval); (**c**) unenhanced CT component and (**d**) fused FDG PET/CT images show some decrease in size and virtually no FDG activity (SUVmax 1.4) in keeping with complete metabolic response

and 1.5 cm are considered enlarged if short axis is greater than 1 cm [5]. Furthermore, clustering of normal-sized but prominent lymph nodes in the anterior mediastinum and mesentery is suspicious for disease. General criteria for extranodal involvement are organomegaly, abnormal mass or structural changes in a normal-sized organ and abnormal contrast enhancement.

MRI has comparable accuracy to CT in detection of involved lymph nodes but is considered overall to be a complementary staging technique to contrast-enhanced CT. MRI is the investigation of choice for suspected central nervous system involvement (with intravenous gadolinium) and head/neck local staging due to superior anatomical delineation. The excellent soft tissue contrast of MRI also achieves superior results to CT in imaging extranodal soft tissue and intraosseous lesions. Due to lack of ionising radiation, MR is the investigation of choice in pregnant women and in children. Drawbacks centre on variations in availability and local expertise as well as longer scan times.

4.3 Response Assessment

The original International Workshop Criteria (IWC) were developed to standardise response assessment in NHL and were based on biochemical markers, bone marrow aspiration, clinical assessment and radiologic evaluation of disease extent on CT [6]. Revised IWC integrates FDG PET, immunohistochemistry and flow cytometry into IWC [5, 7], adding sensitivity to both staging and treatment response evaluation. Target and nontarget lesions should be evaluated at baseline and follow-up. Evaluation of target lesions is performed quantitatively by calculation of the sum of perpendicular diameters (SPD) of up to six measurable lesions. Greatest transverse diameter >15 mm or short-axis diameter >10 mm is considered a measurable nodal lesion, and greatest transverse diameter ≥10 mm is considered a measurable extranodal lesion. More than six measurable lesions, hepatosplenomegaly, bone lesions, small lesions, pleural/pericardial effusion, ascites and irradiated lesions, are considered nontarget lesions and should be followed qualitatively. For Hodgkin's and other typically avid lymphomas, a negative PET scan constitutes complete response regardless of morphological response. A partial response on CT is defined by ≥50% reduction of the SPD of index lesions.

Post-treatment assessment is typically performed with the same imaging modality as employed for staging (Fig. 4.1). For HL and aggressive NHL, this is normally PET/CT [8], whereas for low-grade NHL, this may be CT or possibly MRI (e.g. head/neck lymphoma combined with CT for disease elsewhere). Mid-treatment CT is not routinely indicated, though may be required to investigate clinical suspicion of poor response.

No clear evidence base exists on the optimal modality, interval or duration of routine follow-up in lymphoma, either following treatment or in watchful waiting (e.g. early-stage low-grade NHL); however, benefits must be perceived to outweigh costs and the risks of increased radiation exposure. Imaging is normally used for the evaluation of clinically suspected relapse in symptomatic patients only.

CT has been the mainstay of radiotherapy treatment planning for lymphoma though given superiority of PET/CT in the staging of HL and aggressive NHL, it may be more accurate in defining disease extent pre-radiotherapy.

4.4 The Future

Whole-body MRI is an emerging imaging modality which holds considerable promise for staging and treatment response assessment in lymphoma [9, 10] with whole-body diffusion-weighted imaging offering functional information (by inferring cellularity) and may offer a viable alternative to (PET) CT (Fig. 4.2). Current studies of role in lymphoma imaging are mainly limited to small or pilot series, with much larger studies needed for validation.

Integrated PET/MRI systems are becoming available for integration into routine clinical practice and offer true multifunctional imaging complemented by the molecular information of PET.

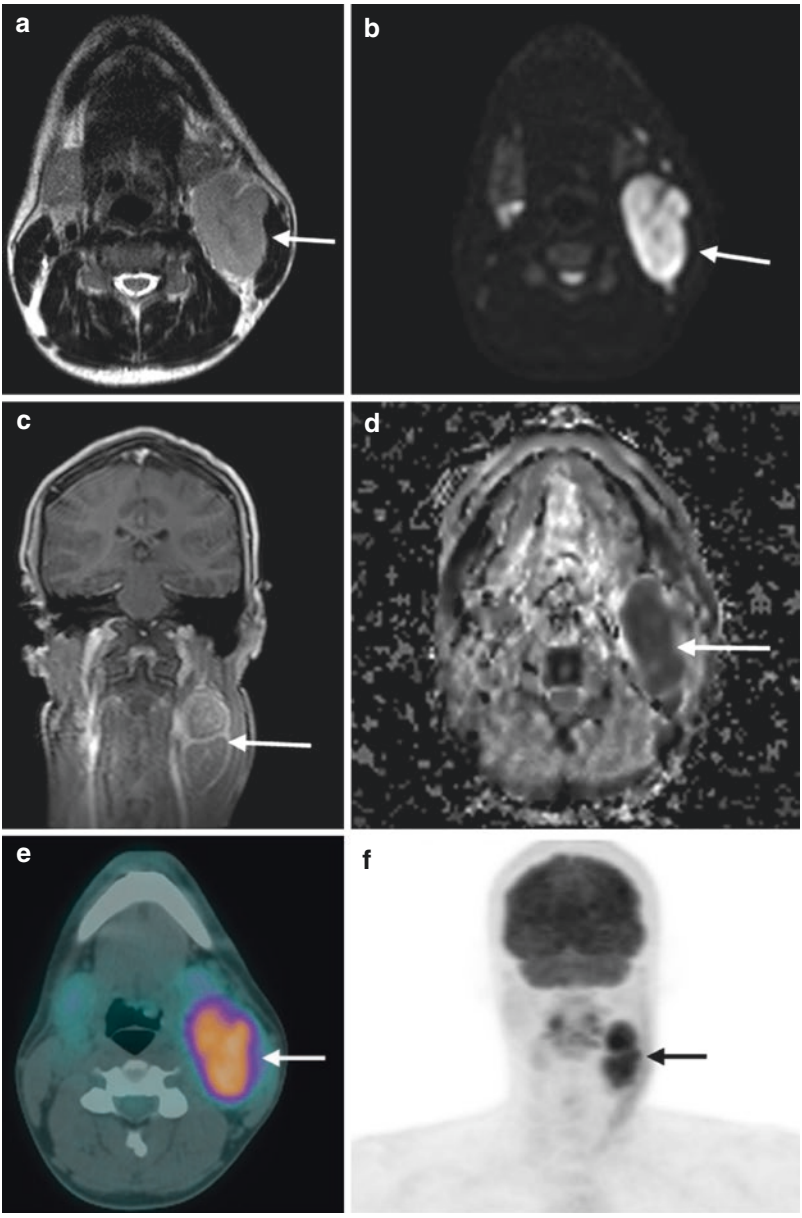

Fig. 4.2 Whole-body MRI study in a 26-year-old male patient presenting with cervical lymphadenopathy confirmed to represent Hodgkin lymphoma by biopsy; (**a**) axial T2 demonstrating left deep cervical level 2/3 confluent nodal mass; (**b**) diffusion-weighted axial (b1000) shows high signal; (**c**) mDixon T1 (in phase) coronal post intravenous contrast shows moderate lesional enhancement; (**d**) ADC map demonstrates low signal which together with DWI imaging defines restricted diffusion suggesting hypercellularity. Correlative contemporaneous FDG PET/CT, (**e**) fused PET/CT images, and (**f**) anterior coronal maximum intensity projection (MIP) show the same lesion that demonstrates intense FDG uptake (SUVmax 10)

Key Points

- Computed tomography (CT) has traditionally been the mainstay staging modality though increasing evidence indicates superiority of combined PET/CT in initial staging.
- Routine CT staging includes the chest, abdomen and pelvis, and head/neck CT may also be indicated.
- Disadvantages of CT include ionising radiation, lack of functional information and low sensitivity for visceral (e.g. splenic) involvement.
- Oral contrast medium may improve visualisation of mesenteric and retroperitoneal lymphadenopathy and detection of bowel involvement in NHL.
- Determination of nodal involvement is based on size criteria.
- General criteria for extranodal involvement are organomegaly, abnormal mass or structural changes in a normal-sized organ and abnormal contrast enhancement.
- MRI has comparable accuracy to CT in detection of involved lymph nodes but is considered overall to be a complementary staging technique to contrast-enhanced CT.
- MRI is the investigation of choice for suspected central nervous system involvement and head/neck local staging due to superior anatomical delineation.
- Drawbacks of MRI centre on variations in availability and local expertise as well as longer scan times.
- For Hodgkin's and other typically avid lymphomas, a negative PET scan constitutes complete response regardless of morphological response. A partial response on CT is defined by ≥50% reduction of the SPD of index lesions.
- Post-treatment assessment is typically performed with the same imaging modality as employed for staging. For HL and aggressive NHL, this is normally PET/CT, whereas for low-grade NHL, this may be CT or possibly MRI (e.g. head/neck lymphoma combined with CT for disease elsewhere).
- Mid-treatment CT is not routinely indicated, though may be required to investigate clinical suspicion of poor response.
- CT has been the mainstay of radiotherapy treatment planning for lymphoma though given superiority of PET/CT in the staging of HL and aggressive NHL, it may be more accurate in defining disease extent pre-radiotherapy.
- Whole-body MRI is an emerging imaging modality which holds considerable promise for staging and treatment response assessment in lymphoma.

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^{18}F-FDG PET/CT in Hodgkin's Lymphoma

5

Irfan Kayani and Asim Afaq

Contents

5.1 Pretreatment Assessment

5.1.1 Staging

PET has a very high sensitivity for detection of nodal disease which is FDG avid in 97–100% of cases, and when used as PET/CT, it also has a high specificity. There is a large volume of data indicating staging accuracy with PET/CT is greater than

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CECT (contrast-enhanced CT). PET/CT can often upstage and rarely downstage compared to CECT. Upstaging is reported in 10–15% of patients, whereas about 5% of patients are downstaged with PET/CT [1]. Baseline PET/CT scans aid interpretation of subsequent PET/CT.

In cases where histopathologic diagnosis has not been performed, PET may be used to select the most appropriate/ accessible site for biopsy.

Sites of extranodal disease are usually FDG avid, but in some cases, additional imaging may be useful for delineation or characterization of disease sites, e.g. CT and MRI for pulmonary and CNS involvement, respectively. CECT can be performed on the same visit as staging PET if clinically indicated.

PET/CT has a superior ability to detect marrow involvement compared to biopsy [1]. This is done by detecting focal FDG avid lesions (often without a morphological abnormality on the CT), in contrast to diffuse bone marrow FDG uptake which is a non-specific finding and thought to relate to reactive hyperplasia.

A recent meta-analysis of nine eligible studies [2] comprising 955 patients with newly diagnosed HL found that the pooled estimated sensitivity and specificity of FDG PET/CT for the detection of bone marrow involvement was 96.9% and 99.7%, respectively. The chance of having a negative PET scan with a positive bone marrow biopsy was very low at 1.1%. The largest study of 454 patients found not only that routine bone marrow biopsy had an inferior sensitivity to PET/CT but also that biopsy had no impact on management over staging PET/CT [3].

As a result of these published findings, the International Conference on Malignant Lymphoma (ICML) imaging group has recommended that staging BM biopsy is no longer routinely indicated for HL [4, 5].

5.1.2 Prognostication

Identifying prognostic markers at baseline imaging is an area of particular importance in HL, given the typically young age at onset and potential acute and late treatment toxicities. Adverse outcomes related to treatments may include reduced quality of life, arterial disease and second cancers [6].

Bulky disease is considered an adverse factor in early stage (stage I or II) but not in advanced (stage III or IV) HL [6]. Bulky disease along with contiguous extranodal involvement from a nodal site and involvement of three or more nodal sites are imaging features which confer a status of unfavourable disease in early-stage HL [6].

Bulky disease can be assessed using CECT or the CT component of the PET/CT and is defined by long-axis measurement of a nodal mass greater than 10 cm. For mediastinal disease there are several slightly varying definitions of bulk but all equate approximately to a nodal mass of greater than one third of the thoracic diameter [6].

Volumetric methods including combining information on metabolic activity and volume are now being explored as potential prognosticators. Recently neither metabolic tumour volume (MTV) nor SUVmax correlated with outcome, but the change in these parameters between baseline and interim studies was predictive of progression-free survival (PFS) [7]. In another study baseline MTV predicted PFS more accurately than tumour bulk [8].

5.2 Interim Scanning

5.2.1 Prognostication

A large number of studies have assessed the potential use of interim PET (iPET) scanning, mostly after two cycles of chemotherapy. Many of the most convincing studies have involved advanced-stage disease, and the majority of evidence for use of PET is following two cycles of chemotherapy [9]. IPET has been shown to be a stronger predictive factor than the International Prognostic Score. A negative iPET has a very high negative predictive value. A positive iPET is predictive of poor outcome although the positive predictive value of iPET is not as high. In a recent multicentre centre of 260 patients with HL, the sensitivity, specificity and negative and positive predictive values of interim positron emission tomography scans for predicting treatment outcome were 0.73, 0.94, 0.94 and 0.73, respectively [10].

IPET may have reduced positive predictive value in patients with early-stage disease and in patients treated with more intense BEACOPP chemotherapy regime as these patients have inherently better early remission rates.

5.3 Response-Adapted Therapy

Given the overwhelming evidence of iPET as a potential prognostic indicator, particularly in advanced HL, the next question was to consider if outcomes could be improved by altering management based on iPET results (response-adapted therapy). Several major clinical trials were launched, only a few of which have so far released interim results or have been completed.

Response-adapted therapy involves two basic approaches. Firstly, a positive interim PET scan can be taken as a marker of inadequate response and used to escalate treatment. Alternatively, a negative interim PET scan could be used to safely de-escalate treatment.

Both of these approaches were utilized in a recent major multicentre international prospective trial with encouraging results demonstrating the efficacy of this approach [11]. De-escalation of treatment by omission of bleomycin and radiotherapy following negative interim PET scans resulted in significantly less pulmonary toxicity but not significantly lower treatment efficacy. Also, escalation of chemotherapy in patients with positive interim PET scans led to improvement in outcome, with 3-year PFS of 65%. Similar results have also been found in two other studies, demonstrating improved outcome if a more intensive chemotherapy regime is given following standard chemotherapy and a positive interim PET scan [12, 13].

Recent trials have been performed to assess the ability of iPET to guide response-adapted treatment to avoid RT. The RAPID and EORTC/LYSA/FIL/H10 trials both found that omitting radiotherapy on basis of a negative interim PET scan (post two cycles) led to a small increase in early relapse [14, 15]. The reported 3-year progression-free survival in RAPID trial was 94.6% for radiotherapy arm and 90.8% when radiotherapy was not given. Balanced against the small increase of early

relapse, however, is the expectation that omitting radiotherapy means patients will have reduced incidence of long-term adverse effects linked to radiotherapy treatment such as second cancers and cardiovascular disease.

5.4 End of Treatment Scanning

End of treatment (EOT) PET will confirm disease status and response to treatment, with a goal of this being the final routine imaging episode. EOT PET provides strong prognostic information, with greater accuracy than CT due to its ability to distinguish viable tumour (FDG avid) from fibronecrotic scarring in patients with a residual mass [16]. The German Hodgkin Study Group in their HD15 trial showed 5-year progression-free survival was 92% in 540 patients with a negative PET/CT scan after a full course of chemotherapy [17].

If there is FDG activity suspicious for disease, consideration should be given to biopsy as false-positive uptake can occur, and care should be given to compare with original sites of FDG avid disease, particularly in often reactive nodal areas such as within the neck. As an alternative to biopsy, a short interval follow-up scan can be performed if clinical suspicion for disease is lower or biopsy is not possible.

The German HD15 trial showed that in advanced Hodgkin's lymphoma FDG PET/CT following treatment with BEACOPP chemotherapy was able to guide the need for subsequent radiotherapy. Omitting radiotherapy in patients with a negative PET scan did not adversely affect outcome relative to those who received radiotherapy following positive end of treatment PET scans [17].

5.5 PET Before High-Dose Chemotherapy or Transplant

Patients who are refractory to primary treatment and those who relapse are offered second-line chemotherapy. Patients who respond to this are offered high-dose chemotherapy followed by autologous stem cell transplantation. PET may be able to risk stratify those most likely to be poor responders who may benefit from alternative or consolidative therapies.

A negative PET/CT scan following second-line and prior to high-dose chemotherapy is associated with a greater chance of curative treatment. PET positive status at this point is associated with 3-year PFS or EFS of 31%, compared with 75% in patients with PET negative scans [18].

5.6 Surveillance

There is no role for PET in routine surveillance following complete metabolic remission. Dann et al. found no benefit in PFS or OS in HL using PET when compared with clinical follow-up but a tenfold higher cost [19]. The most common utility for PET in post successful treatment is in the case of clinical suspicion for relapse.

5.7 Radiotherapy Planning

Technological advances, including those in PET, have led to greater contribution of functional imaging in radiotherapy planning, with the goal of minimizing radiation dose to non-tumour tissue.

Radiotherapy is a standard treatment for early-stage classical Hodgkin's lymphoma following chemotherapy. Radiotherapy may also be given to patients with advanced lymphoma following chemotherapy. Involved-site radiotherapy (ISRT) and involved-node radiotherapy (INRT) have replaced older involved-field and extended-field radiotherapy techniques [20, 21]. These newer techniques reduce exposure to normal tissues while ensuring treatment of all involved sites. INRT reduces treated volume to a minimum but requires optimum pre- and post-chemotherapy imaging with FDG PET/CT to guide planning of the radiotherapy treatment volumes. The FDG PET/CT should be performed with the patient on a flat couch in the radiotherapy position with the same breathing instructions that will be used later for radiotherapy. In order to provide optimal delineation of lymph nodes, the CT should be acquired with IV contrast as well as oral contrast if there is abdominal and/or pelvic nodal disease. Pre-chemotherapy FDG PET/CT images are used to derive the gross tumour volume (GTV) based on the CT and FDG PET images. The FDG PET/CT with the GTV CT and GTV PET volumes are subsequently fused with the post-chemotherapy radiotherapy planning CT and used to define the clinical target volume and planned treatment volume.

5.8 Combined Scanning of PET/CT with Contrast-Enhanced Diagnostic Quality CT

Performing diagnostic CT including IV contrast may lead to detection of additional lesions, particularly within the abdomen and pelvis, but does not appear to significantly impact tumour staging or management. Diagnostic CT may also have a complementary role to PET/CT for characterization of lung lesions and detection of small lung lesions for which PET will have low sensitivity. A separate low-dose CT without IV contrast should be used for attenuation correction of PET data [4]. Using IV contrast CT for attenuation correction is not recommended as this leads to errors in quantification of FDG uptake. Although these errors are small (10–15%) and are unlikely to be clinically significant, they may be important for comparison of uptake between scans [4].

5.9 Scan Interpretation

Current guidelines recommend a visual qualitative assessment for interpretation of PET scans in lymphoma with a fixed scale and colour table, scaled to the standardized uptake (SUV) value to reduce impact of patient size and improve consistency of reporting, especially for comparison between serial scans [4].

Criteria for defining FDG activity at disease sites following completion of therapy as positive or negative were provided by International Harmonization Project in

2007 [22]. Significant uptake was defined for lesions greater than or equal to 2 cm as uptake greater than mediastinal blood pool, while for smaller lesions, uptake above surrounding background was significant.

Subsequently the recognition that FDG uptake is better represented as a spectrum, rather than a dichotomous negative or positive, led to the development of a five-point scoring system, also commonly referred to as the 'Deauville' scoring system [23]. The Deauville scoring system provides a simple, reproducible and useful method for assessing FDG uptake in lymphoma lesions following treatment [24]. The uptake at the most avid site of initially involved disease site is scored relative to FDG activity in the mediastinum and liver (Table 5.1). Although the IHP criteria for a positive scan corresponds to a Deauville score of 3 or more, updated guidelines consider those with a score of 3 at EOT to have probable complete metabolic remission as these often have a good prognosis [4, 5]. Scores at disease sites of 4 or 5 at end of treatment have metabolically active residual disease representing treatment failure [5]. An exception is made for sites with high physiological activity, e.g. Waldeyer's ring or bone marrow following chemotherapy. Remission at these sites is assumed if uptake is no greater than surrounding normal tissue. Those patients with reduced uptake and a score of 4 or 5 on interim PET have a partial metabolic response. Nonresponsive or progressive disease on both interim and EOT scans is defined as those with score of 4 or 5 with no decrease in uptake, an increase in score from 4 to 5 or new FDG avid disease sites [5].

For interim scans a substantial but incomplete reduction in metabolic activity may be sufficient to indicate an adequate response to treatment. The optimum threshold for interpreting interim PET scans depends on expected patient prognosis and proposed escalation or de-escalation of treatment. In particular, where standard treatment is omitted on the basis of a negative interim PET (e.g. fewer cycles of chemotherapy and or no radiotherapy), a lower threshold of positivity, using a score of 3, is recommended to prevent possibility of under treatment.Both positive and negative results at end of treatment need to be considered in the light of the inherent limitations of FDG PET imaging. Infection and inflammatory uptake can lead to more intense false-positive scans of 4 or more. Positive scans should therefore, wherever possible, be confirmed with histology prior to subjecting patients to treatment escalation. If it is not possible or practical to obtain histology, follow-up imaging following adequate treatment for any reversible benign causes of uptake, e.g. infection, may be helpful in supporting detection of residual disease. Finally, a negative PET scan cannot exclude the presence of residual microscopic disease which is especially relevant in considering whether patients should undergo radiotherapy following chemotherapy.

Table 5.1 The Deauville scoring system for assessing FDG uptake at original disease sites in lymphoma

Uptake	Score
No uptake	1
Uptake less than or equal to the mediastinum	2
Uptake greater than the mediastinum but less than or equal to the liver	3
Uptake moderately greater than the liver	4
Uptake markedly greater than the liver and/or new lesions	5
Areas of uptake which are likely secondary to incidental, inflammatory or infectious pathology	X

Key Points

- PET/CT should be performed as part of staging, is more accurate than CECT and precludes the need for routine bone marrow biopsy.
- Interim PET is an accurate predictor of end of treatment status and progression-free survival.
- Multiple prospective trials are assessing response-adapted therapy based on interim PET. The results of several completed studies have shown encouraging results indicating that escalating or de-escalating treatment based on interim PET can improve outcome or reduce toxicity.
- The 5-point Deauville score has been well established in clinical trials and now forms the basis of response assessment description in HL in all clinical reports.
- Deauville 1 and 2 represent CMR, and Deauville 3 also most likely represents CMR in the context of standard treatment.
- EOT PET is the determinant of curative treatment and provides useful prognostic information.
- For interim PET the optimum cut-off for a positive PET scan depends on the intended management. A lower threshold of Deauville 3 is more appropriate if standard treatment, e.g. radiotherapy or further chemotherapy cycles, will be omitted on the basis of a negative scan.

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^{18}F-FDG PET/CT: Normal Variants, Artefacts and Pitfalls in Lymphoma

6

Sai Han

Contents

6.1 Introduction

FDG PET/CT has become a standard imaging in the staging and response assessment of FDG-avid lymphoma. Accurate interpretation of scan findings is crucial in guiding most effective treatment. It is important to recognise normal variants and potential artefacts and pitfalls in lymphoma FDG PET/CT to achieve optimal results. These potential limitations include the issues applicable to FDG PET/CT in general as well as situations more relevant to lymphoma and its locations.

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6.2 General PET/CT Issues

Lymphoma imaging is affected by general PET/CT issues including various technical artefacts caused by movement and misregistration; these can cause significant reductions or alterations of tracer activity but are usually readily apparent from review of images. Areas most susceptible to physiological movement artefact are the lungs, liver margins and bowel. Patient factors such as inadequate fasting or raised blood glucose levels may significantly reduce sensitivity of scan. In order to avoid this fasting and/or discontinuation of intravenous fluids containing glucose is required for at least 4 hours prior to tracer injection. The blood glucose concentration for clinical scans should be less than 11 mmol/l.

6.2.1 False Positive

FDG PET is not malignancy-specific and can light up physiological as well as benign and malignant processes (Figs. 6.1 and 6.2). Assessment of lesions in high physiological uptake areas such as GI and GU tracts, brain and heart can be difficult. High ureteric uptake may be differentiated from adjacent nodes by thorough review of PET and CT including multiplanar reformat.

A common physiological process which can affect the lymphoma FDG PET/CT quality is brown fat uptake. It is common in colder environment and in children but can also occur in adults. Neck/supraclavicular, mediastinal, axillary and paraspinal regions are common sites masking the view. The symmetrical uptake in typical locations together with reassuring CT findings will exclude pathology. Brown fat uptake may be decreased by keeping a warm environment at FDG uptake phase. Beta-blocker and diazepam can also be used in advance.

Physiological uptake in muscles can sometimes be confused with nodal uptake if focal and close to nodal sites, e.g. scalene.

Some of the false-positive benign FDG-avid conditions include reactive nodes; inflammation related to injection, immunisation, trauma, biopsy, surgery, chemotherapy or radiotherapy; granulomatous inflammation; and acute and chronic infection such as TB, fungal infection, toxoplasmosis, etc. The recommended time between treatments and FDG PET/CT is at least 10 days for chemotherapy (6–8 weeks post chemotherapy if end of treatment scans), 2 weeks for growth factors (G-CSF and GM-CSF), 6 weeks for surgery and 3 months for radiotherapy (Figs. 6.3 and 6.4).

Lymphoma PET/CT assessment now widely utilises Deauville criteria. Persistent or new lesions (Deauville score 4 or 5) represent positive scans, but false-positive results could lead to incorrect treatment decisions. The new FDG-avid areas which are unlikely to be lymphoma are marked as “X” in

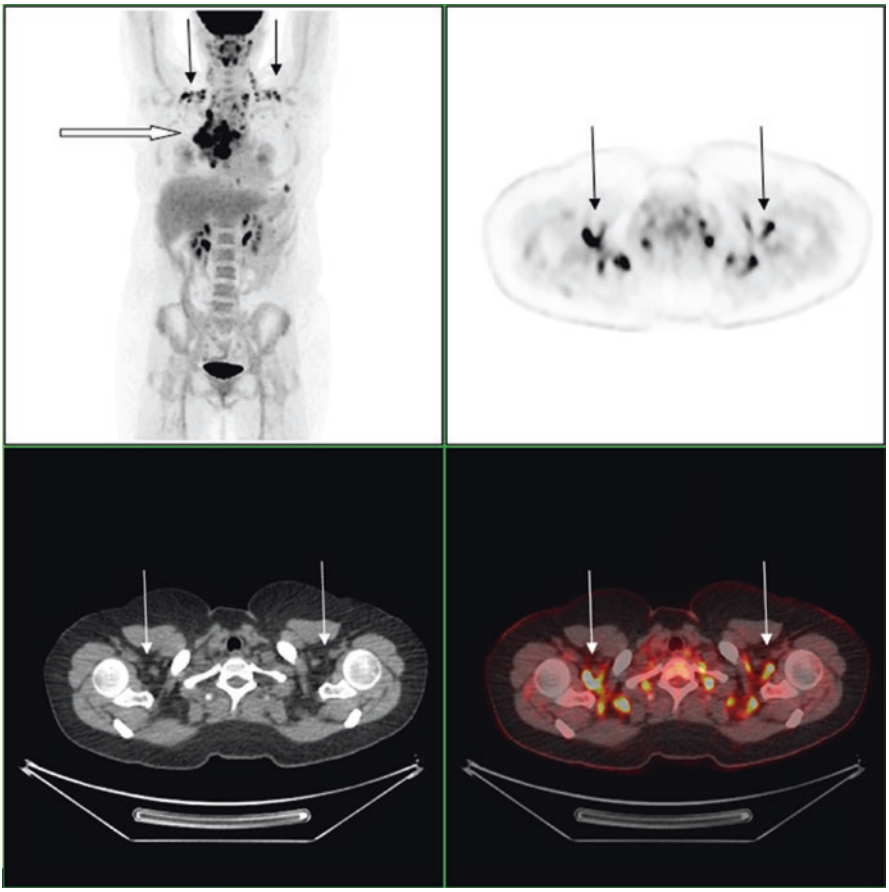

Fig. 6.1 FDG PET/CT of a 34-year-old patient with suspected relapse in previously treated Hodgkin disease showed intensely FDG-avid mediastinal disease (*big arrow*). Intense physiological brown fat uptake in bilateral neck/supraclavicular fossae (*small arrows*) can hamper the assessment of FDG uptake in the small nodes in these sites

Deauville criteria. New or residual uptake while other known disease locations respond may indicate a separate pathology such as inflammation/infection or another tumour. It is important to correlate clinical, laboratory and imaging results in multidisciplinary settings when unexpected results or mixed response arise. Residual PET positve lesions may need pathology confirmation (e.g. when salvage treatment is considered) or follow up imaging (e.g. when clinical probability of active disease is low).

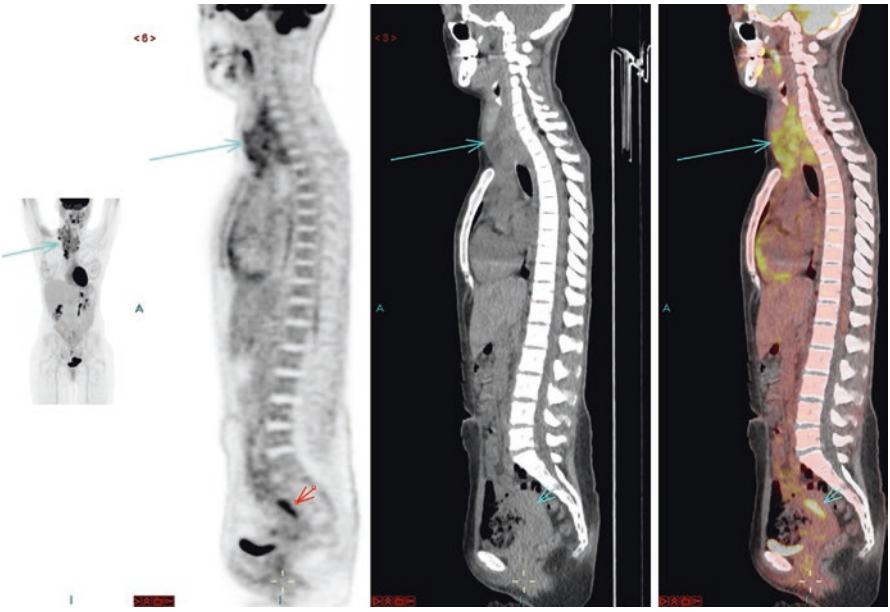

Fig. 6.2 Pretreatment FDG PET/CT of a 40-year-old patient with Hodgkin disease showed intensely FDG-avid bulky cervical lymphadenopathy (*long arrow*) extending into superior mediastinum (stage II). Linear intense endometrial uptake (*short arrow*) was confidently reported as physiological uptake because of patient's menstrual history in the scan preparation checklist

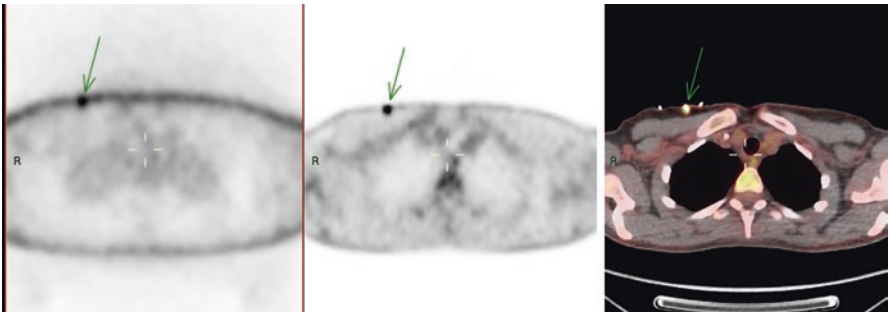

Fig. 6.3 Baseline FDG PET/CT of a lymphoma patient showing a reactive FDG-avid focus at the recently inserted Hickman line site (images from left to right – Non attenuation corrected PET, Attenuation corrected PET, Fused PET/CT)

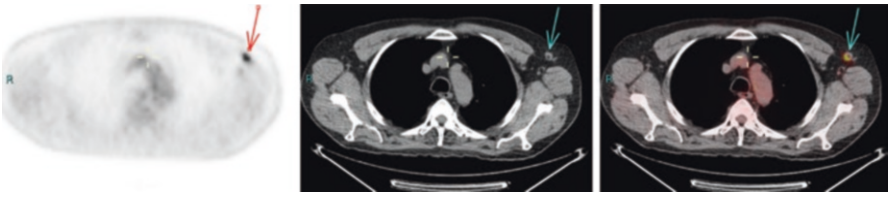

Fig. 6.4 FDG PET/CT of a lymphoma patient showing an FDG-avid small reactive left axillary node. Patient gave a history of flu vaccination in the left arm a week before coming to PET/CT

6.2.2 False Negative

FDG PET/CT can be false negative in small lesions, in lesions masked by adjacent high physiological uptake structures, and in some indolent lymphoma. The PET/CT response relies on treatment-induced changes in FDG uptake which are difficult to detect if the disease is not FDG avid or too small. Common types of lymphoma, e.g. HD and NHL such as DLCBL, are usually highly FDG avid. Some lymphoma such as MALT lymphoma and small lymphocytic lymphoma have low FDG avidity. Lymphoma involving the skin and mucosa may be less FDG avid or difficult to detect. In non-FDG-avid lymphoma, response assessment should be by standard CT instead of FDG PET.

6.3 Anatomy Based

6.3.1 Lymphatic Sites

6.3.1.1 Waldeyer's ring

Waldeyer's ring is often involved in NHL, but these lymphoid tissues frequently have high physiological/reactive FDG uptake. Their interpretation can be difficult when FDG uptake is asymmetrical. Clinical correlation (infection, tonsillectomy, etc.) and review of CT or MRI are crucial to check any mass lesion which would require direct examination and histology confirmation (Fig. 6.5).

6.3.1.2 Lymph Nodes

Although lymphoma can affect any nodal sites, FDG PET false-positive reactive/inflammatory nodes are relatively common in neck, axillary and inguinal regions. Reactive nodes may have benign CT morphology (small, bean shaped, with fatty hilum, without necrosis or extracapsular spread, etc.). Assessment of drainage areas may also point to a possible aetiology, e.g. FDG extravasation, immunisation, surgical procedures, inflammation/infection, etc.

Granulomatous inflammation such as sarcoid reactions can appear following chemotherapy and can be misinterpreted as lymphoma. Typical pattern of sarcoid is FDG-avid bilateral hilar and mediastinal lymphadenopathy but can also be

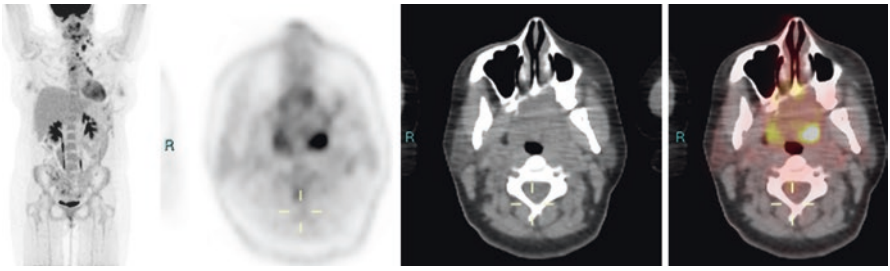

Fig. 6.5 Baseline FDG PET/CT of a patient with nodal lymphoma showed intensely FDG-avid mediastinal and left neck nodal disease. There was asymmetrical increased left tonsillar uptake without CT abnormality. Physiological/reactive uptake is usually symmetrical but can also be asymmetrical

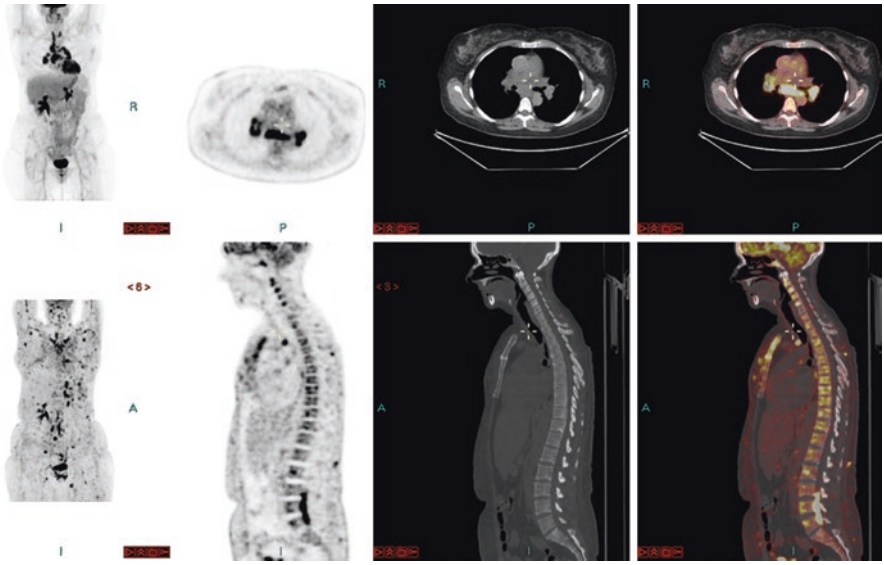

Fig. 6.6 A 49-year-old man with intravascular large B cell NHL of pelvic and mediastinal disease. (*Upper row*) End-of-treatment FDG PET/CT showing intensely FDG-avid bilateral hilar and mediastinal lymphadenopathy. Clinical and imaging results were inconclusive for residual disease or sarcoid reaction. Mediastinal nodal biopsy confirmed sarcoidosis (false-positive inflammatory FDG uptake). (*Lower row*) FDG PET/CT 2-year post-treatment showed widespread focal FDG-avid bone marrow and soft tissue relapses including cutaneous and intramuscular deposits but no active disease in the mediastinum (lymphoma can relapse following complete metabolic response)

generalised lymphadenopathy. Acute as well as chronic infection such as TB, toxoplasma and fungal infection can also result in FDG-avid lymphadenopathy (Figs. 6.6 and 6.7).

Other potential false-positive inflammatory conditions include sclerosing mesenteritis (panniculitis) which can appear as FDG-avid diffuse 'hazy mesentery' or focal nodularity/masses and can mimic active mesenteric nodal lymphoma. Development of new mesenteric/peritoneal lesions while other sites show FDG response may indicate panniculitis rather than new lymphoma (Fig. 6.8). Similarly inflammatory conditions such as fibrosing mediastinitis can mimick mediastnal lymphoma.

6.3.1.3 Thymus

Thymus can have some physiological uptake in children and young adult. During and after treatment of lymphoma, thymus can become variably FDG avid because of rebound thymic hyperplasia. Physiological/hyperplasic thymus is usually triangle-shaped, smooth and symmetrical, and interpretation may be straightforward. However, in certain cases with baseline mediastinal lymphadenopathy, ongoing anterior mediastinal activity can be difficult to differentiate between residual/recurrent disease and thymic hyperplasia. Correlating with response pattern in

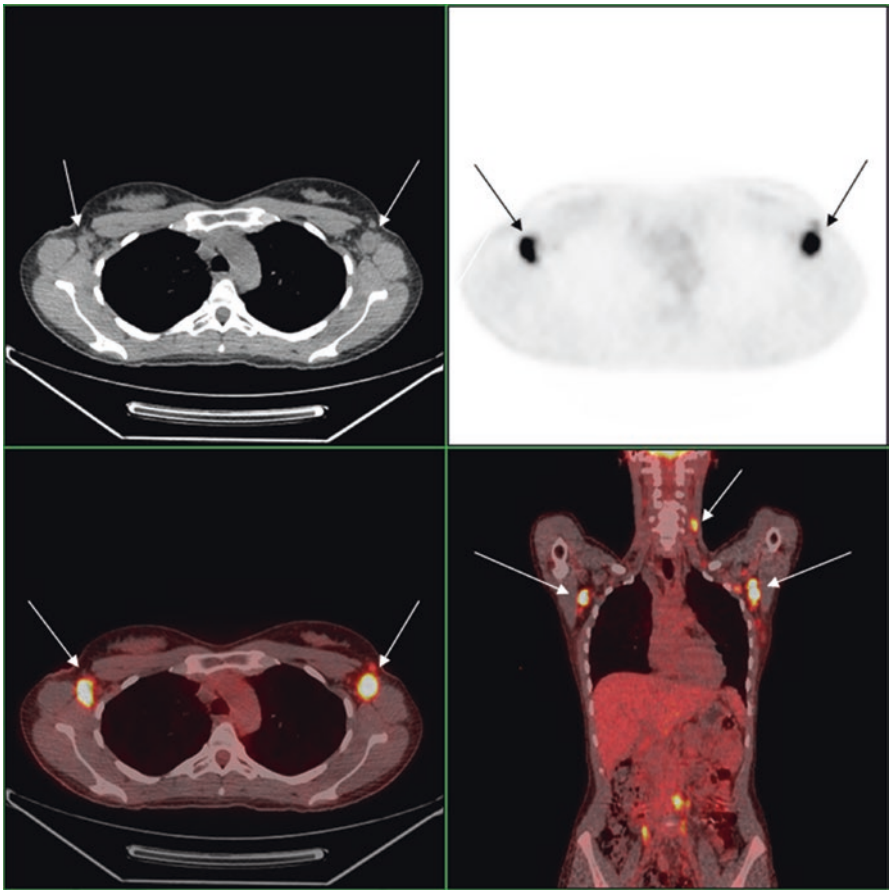

Fig. 6.7 FDG PET/CT of a 28 year old lady with suspected relapse Hodgkin Disease showed intensely FDG avid left neck and bilateral axillary lymphadenopathy. Excisional biopsy of the left axillary node showed no evidence of lymphoma but showed toxoplasma infection. (False positive infection FDG uptake)

other sites, morphological and clinical status and multidisciplinary discussions would be helpful, but if still inconclusive then tissue diagnosis may be required (Fig. 6.9).

6.3.1.4 Spleen

Increased splenic FDG uptake can be due to reactive hyperplasia or pathology. Diffuse increased splenic uptake favours reactive uptake, while focal lesion(s) usually represent pathology although spleen can be involved diffusely too. Other pathologies such as sarcoidosis, abscess and toxoplasma infection can have FDG-avid splenic mass.

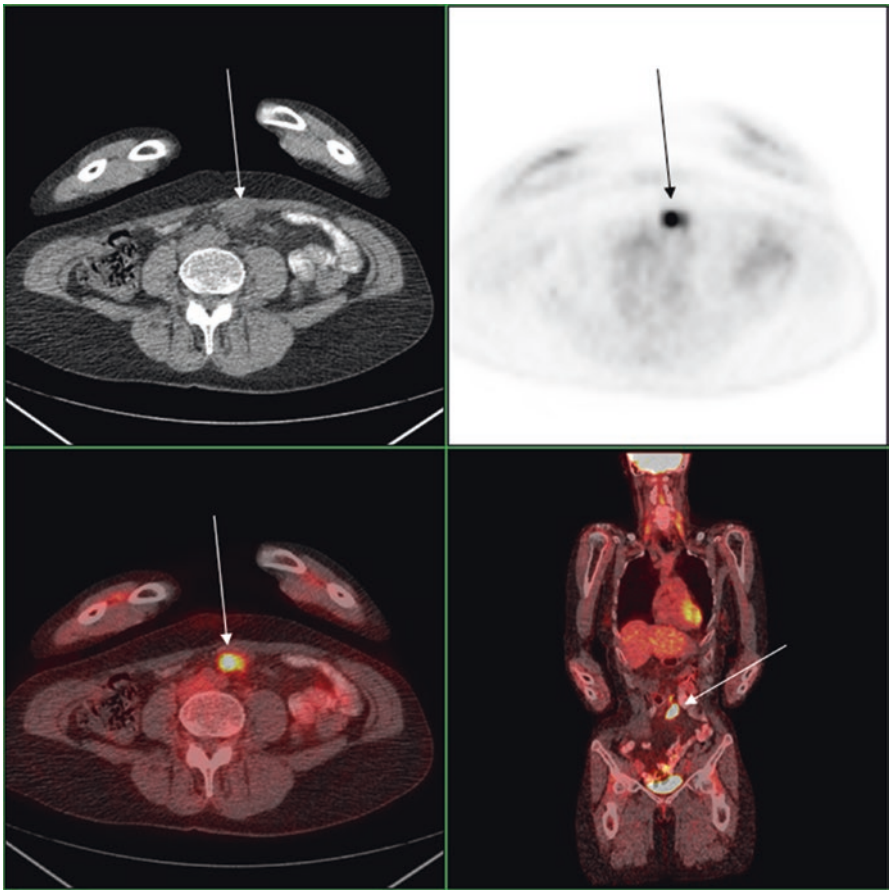

Fig. 6.8 FDG PET/CT of a 54-year-old man status 2-month post R-CHOP chemotherapy for DLBCL of pelvic mass showed no significant pelvic activity but an intensely FDG-avid new ill-defined mesenteric nodule. The subsequent mesenteric nodule biopsy revealed no evidence of malignancy but showed fat necrosis and inflammation consistent with panniculitis (false-positive inflammatory FDG uptake)

6.3.2 Extralymphatic Sites

6.3.2.1 CNS

High physiological brain FDG uptake makes assessment of pathological lesions difficult—can result in false-positive uptake as well as can miss small low-grade disease. Moreover, steroid therapy for CNS lymphoma can suppress tumour FDG uptake. Some literatures have reported that FDG PET/CT is sensitive for CNS lymphoma but not the ocular involvement because of small size and proximity to high physiological uptake. The recent European guidelines on CNS lymphoma stated that FDG PET can be useful for differential diagnosis, but it has insufficient specificity.

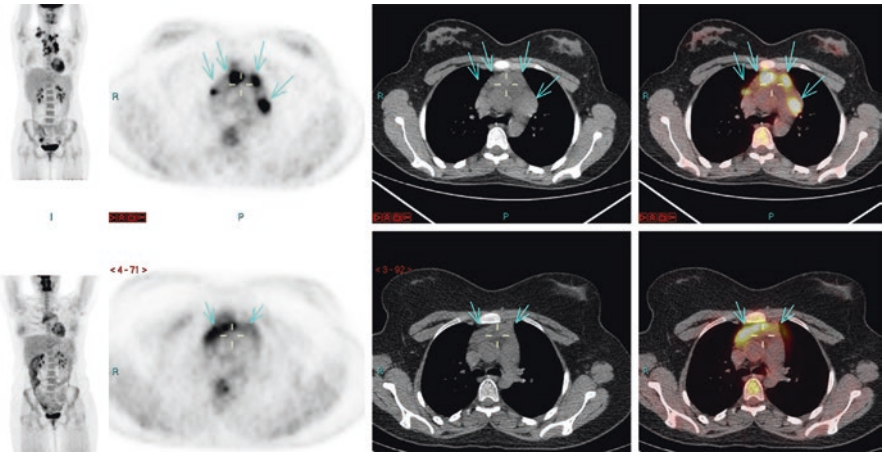

Fig. 6.9 (*Upper row*) Pretreatment FDG PET/CT of an 18-year-old lady with mediastinal and neck nodal Hodgkin disease showing intensely FDG-avid lesions including anterior mediastinal nodal mass. (*Lower row*) End-of-treatment FDG PET/CT showed smooth but asymmetrical FDG-avid anterior mediastinal mass, while other disease sites have responded. Biopsy of the anterior mediastinal mass confirmed reactive thymic hyperplasia

6.3.2.2 Thyroid

Increased thyroid FDG uptake is a common incidental finding in FDG PET/CT scans. Diffuse increased uptake represents thyroiditis or autoimmune thyroid, but a third of focal FDG-avid lesions can be thyroid malignancy, and USS +/− FNA is recommended. Primary thyroid lymphoma is a very rare type of thyroid malignancy.

6.3.2.3 Lungs

Focal or diffuse FDG-avid lung lesions can be due to infection/inflammation or neoplasm including lymphoma. This can confuse interpretation on staging as well as treatment responses. Correlation with clinical features and CT morphology would be useful. In post-treatment settings, patients are more susceptible for chest infection because of immunosuppression. They can also have treatment-related changes such as bleomycin pneumonitis and radiation pneumonitis (Fig. 6.10). The FDG-avid lung inflammation/infection can also lead to active hilar and mediastinal nodes. Lung mass refractory to lymphoma chemotherapy could be a separate pathology including lung cancer.

6.3.2.4 Liver

Liver has moderate homogeneous physiological FDG uptake, and diffusely increased uptake or focal uptake may indicate liver involvement. However, it can have patchy uptake from noises/artefacts or other pathologies which could lead to false-positive PET. On the other hand, small and low-grade lymphoma can be missed.

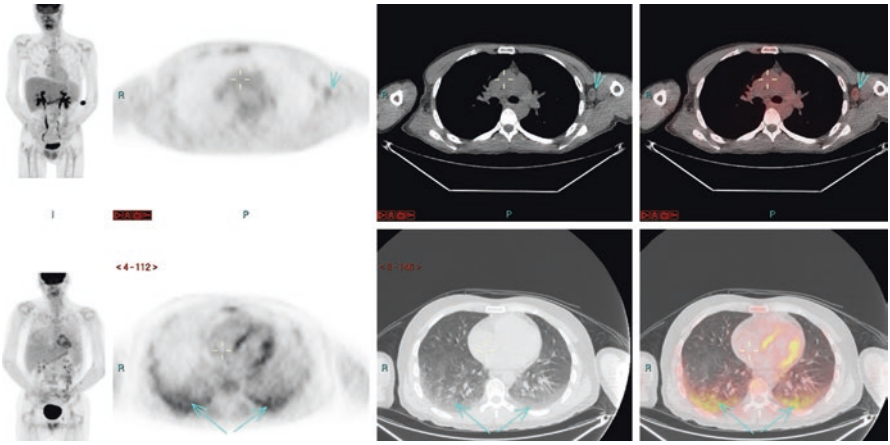

Fig. 6.10 (*Upper row*) Baseline FDG PET/CT of a 33-year-old man with a history of HIV and biopsy-confirmed **HD** in left axillary node showed only **low-grade** nodal FDG uptake. (*Lower row*) End-of-treatment FDG PET/CT showed no residual FDG uptake in axillae. There were new bilateral moderately FDG-avid diffuse ground glass opacification suggesting chemotherapy-induced pneumonitis or infection

6.3.2.5 GI

High physiological FDG uptake in stomach and intestines makes assessment of pathological lesions difficult if there is no associated mass/mural thickening on CT. Unprepared stomach may appear as having FDG-avid thick wall, which can be mistaken as residual/recurrent disease. Diffuse or segmental increased intestinal FDG uptake usually represents physiological or inflammatory processes, but focal uptake can be due to focal inflammation, polyp or neoplasm. Histology type can also affect the PET/CT results, e.g. MALT lymphoma has low FDG avidity.

6.3.2.6 Renal Lymphoma

Kidney can be a blind spot in FDG PET/CT because of high physiological urine FDG excretion. Small lesions close to collecting system are particularly susceptible to be masked, and correlation with contrast-enhanced CT is required. Renal lymphoma is usually part of widespread NHL and involved by direct invasion or haematogenous spread. They are often intensely FDG avid.

6.3.2.7 Bone Marrow

Similar to the spleen, the diffuse bone marrow uptake usually represents reactive hyperplasia, and focal lesion(s) indicate disease involvement. FDG PET/CT is more sensitive than bone marrow biopsy in HL. In DLBCL FDG PET/CT is still more sensitive than bone marrow biopsy but can miss low-volume involvement (up to 10–20% of bone marrow). Sensitivity of PET/CT in bone marrow involvement in follicular and indolent lymphomas is limited (Fig. 6.11).

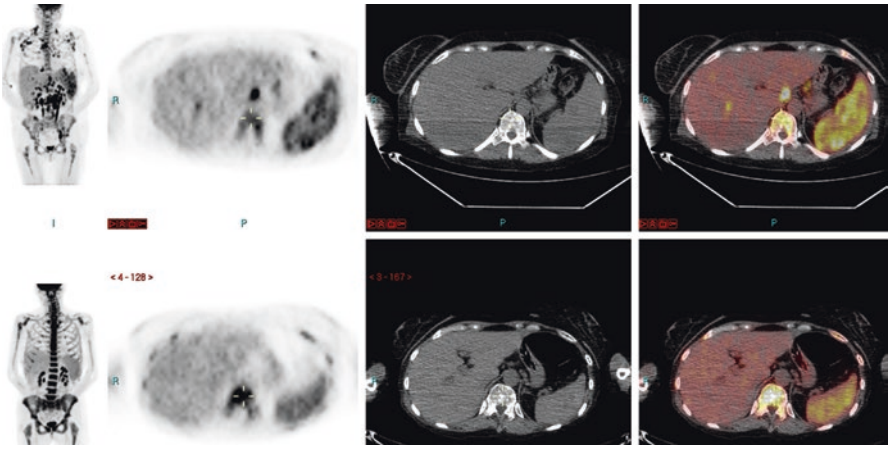

Fig. 6.11 (*Upper row*) Baseline FDG PET/CT showing intensely FDG-avid stage IV lymphoma including nodal and multifocal splenic and bone marrow disease. (*Lower row*) Interim FDG PET/CT showing resolution of nodal uptake. Spleen and bone marrow uptake changed from multifocal disease pattern to diffuse reactive hyperplasia pattern

6.3.2.8 Skin

FDG PET/CT results in cutaneous lymphoma are variable—may be useful in aggressive types but have poor results in early-stage IA peripheral T cell lymphoma due to small-volume disease.

Conclusions

The lymphoma FDG PET/CT results can be affected by general PET/CT issues as well as some particular physiological, reactive and pathological changes relevant to lymphoma and its FDG avidity and locations. Appreciating these potential pitfalls and correlating with clinical, laboratory and multimodality imaging results would help provide accurate pre- and post-therapy assessment of lymphoma.

Key Points

- Accurate interpretation of FDG PET/CT scan findings including normal variants, and potential artefacts and pitfalls is crucial in guiding the most effective treatment.
- False-positive benign FDG-avid conditions include physiological brown fat; reactive nodes; inflammation related to injection, immunisation, trauma, biopsy, surgery, chemotherapy or radiotherapy etc; granulomatous inflammation; and acute and chronic infections.

- Physiological uptake in muscles can sometimes be confused with nodal uptake if focal and close to lymph nodes.
- The recommended time between treatments and FDG PET/CT is at least 10 days for chemotherapy (6–8 weeks post chemotherapy if end of treatment scans), 2 weeks for growth factors (G-CSF and GM-CSF), 6 weeks for surgery and 3 months for radiotherapy.
- Residual PET positve lesions may need pathology confirmation (e.g. when salvage treatment is considered) or follow up imaging (e.g. when clinical probability of active disease is low). Correlating with response pattern in other sites, morphological and clinical status and multidisciplinary discussions helps.
- FDG PET/CT can be false negative in small lesions, in lesions masked by adjacent high physiological uptake structures, and in some indolent lymphoma.
- In non-FDG-avid lymphoma, response assessment should be by standard CT instead of FDG PET. Some lymphoma such as MALT lymphoma and small lymphocytic lymphoma have low FDG avidity. Lymphoma involving the skin and mucosa may be less FDG avid or difficult to detect.
- Increased splenic FDG uptake can be due to reactive hyperplasia or pathology. Diffuse increased splenic uptake favours reactive uptake, while focal lesion(s) usually represent pathology although spleen can be involved diffusely too.
- High physiological brain FDG uptake makes assessment of pathological lesions difficult—can result in false-positive uptake as well as can miss small low-grade disease.
- Increased thyroid FDG uptake is a common incidental finding. Diffuse increased uptake represents thyroiditis or autoimmune thyroid, but a third of focal FDG-avid lesions can be thyroid malignancy, and USS +/− FNA is recommended.
- Focal or diffuse FDG-avid lung lesions can be due to infection/inflammation or neoplasm including lymphoma.
- Liver has moderate homogeneous physiological FDG uptake, and diffuse increased or focal uptake may indicate liver involvement.
- High physiological FDG uptake in the stomach and intestines makes assessment of pathological lesions difficult if there is no associated mass/mural thickening on CT.
- Unprepared stomach may appear as having FDG-avid thick wall, which can be mistaken as residual/recurrent disease.

- Diffuse or segmental increased intestinal FDG uptake usually represents physiological or inflammatory processes, but focal uptake can be due to focal inflammation, polyp or neoplasm.
- Kidney can be a blind spot in FDG PET/CT because of high physiological urine FDG excretion. Renal lymphoma is usually part of widespread NHL and involved by direct invasion or haematogenous spread. They are often intensely FDG avid.
- Diffuse bone marrow uptake usually represents reactive hyperplasia, and focal lesion(s) indicate disease involvement.

Further Reading

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PET/CT in Hodgkin's Lymphoma: Teaching Cases

7

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Contents

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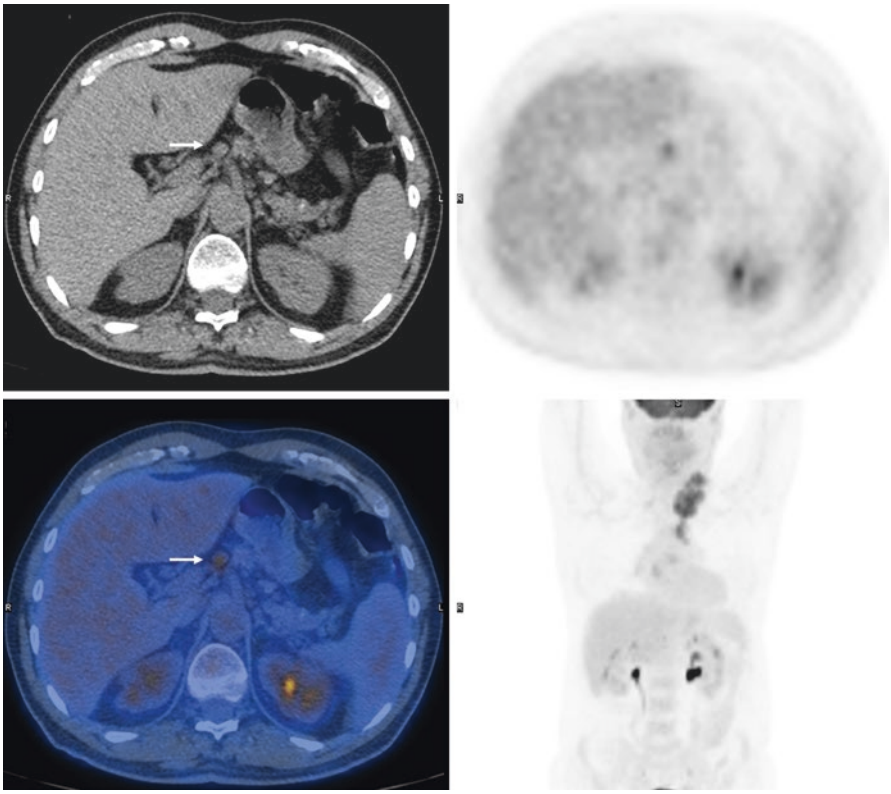
7.1 Case 1: Upstaging of Disease with PET/CT

Baseline staging scan in 66-year-old male with Hodgkin's lymphoma. There is multiple FDG-avid lymphadenopathy above the diaphragm. PET/CT also, however, shows a small FDG-avid node in upper abdomen (arrows), upstaging patient to stage III disease.

7.1.1 Teaching Points

PET/CT is the most sensitive imaging modality for staging Hodgkin's lymphoma.

Relative to CT, PET/CT upstages approx. 10–15% and downstages 5% of patients.

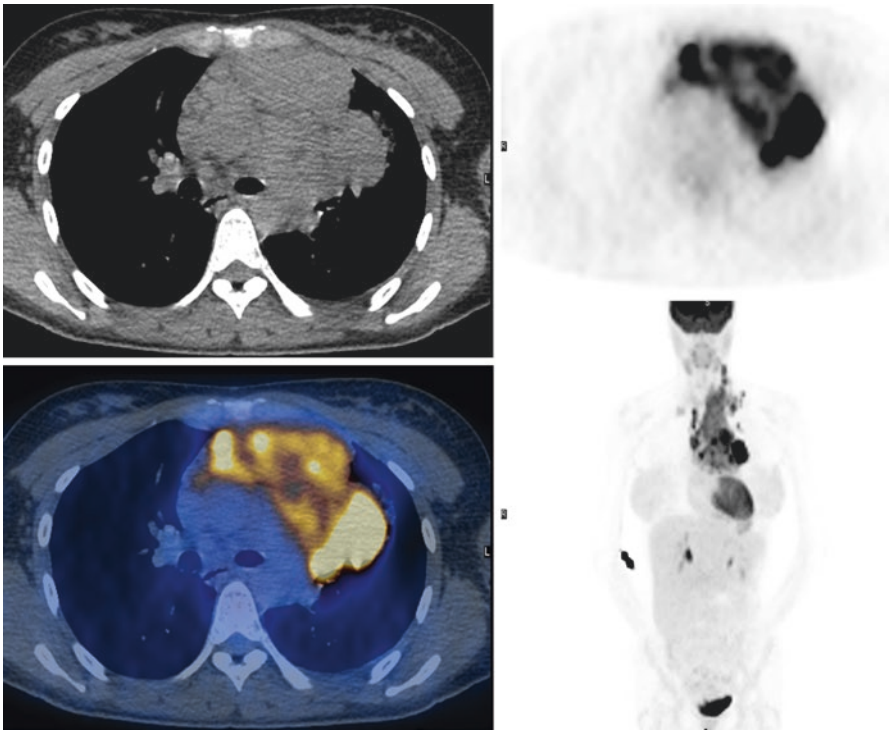


7.2 Case 2: Early Stage Unfavourable Disease

Baseline staging scan in 32-year-old female patient with Hodgkin's lymphoma. PET/CT scan shows early stage (stage II) unfavourable disease. There is bulky disease within the mediastinum, involvement of three nodal sites (right cervical, left cervical, mediastinum) and suspicion of contiguous involvement of left lung from a nodal site.

7.2.1 Teaching Points

Hodgkin's lymphoma is divided into early (stage I or II) and advanced (stage III or IV) disease. Early disease is further subdivided into favourable and unfavourable disease based on combination of imaging, laboratory and clinical markers and has different treatments. Three imaging markers of unfavourable disease include disease bulk, involvement of three or more nodal sites and extranodal (E) involvement.



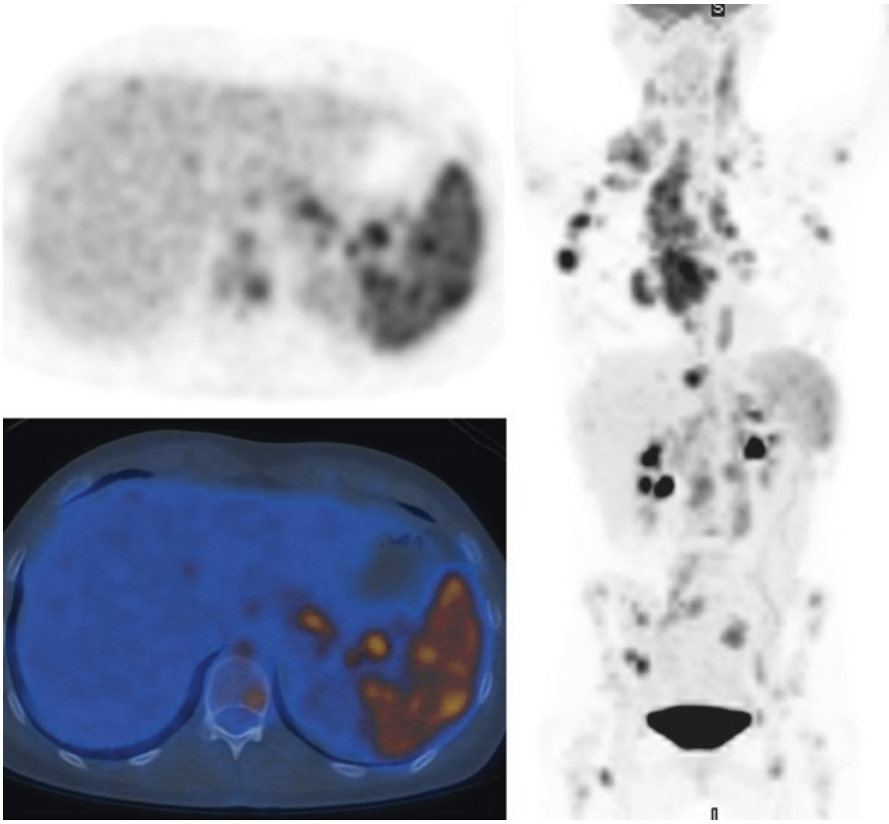
7.3 Case 3: Splenic Involvement on PET/CT

Baseline Staging PET/CT in 22-year-old female with Hodgkin's lymphoma. PET/CT shows stage IV disease. There is also abnormal increased heterogeneous FDG uptake within the spleen with reversal of normal hepato-splenic ratio.

7.3.1 Teaching Points

Normally in untreated patients, FDG activity within the spleen is less than the liver.

Splenic involvement on PET can be seen as diffuse increased uptake with reversal of normal hepato-splenic ratio, heterogeneous increased splenic activity or focal/multifocal avid splenic lesions.

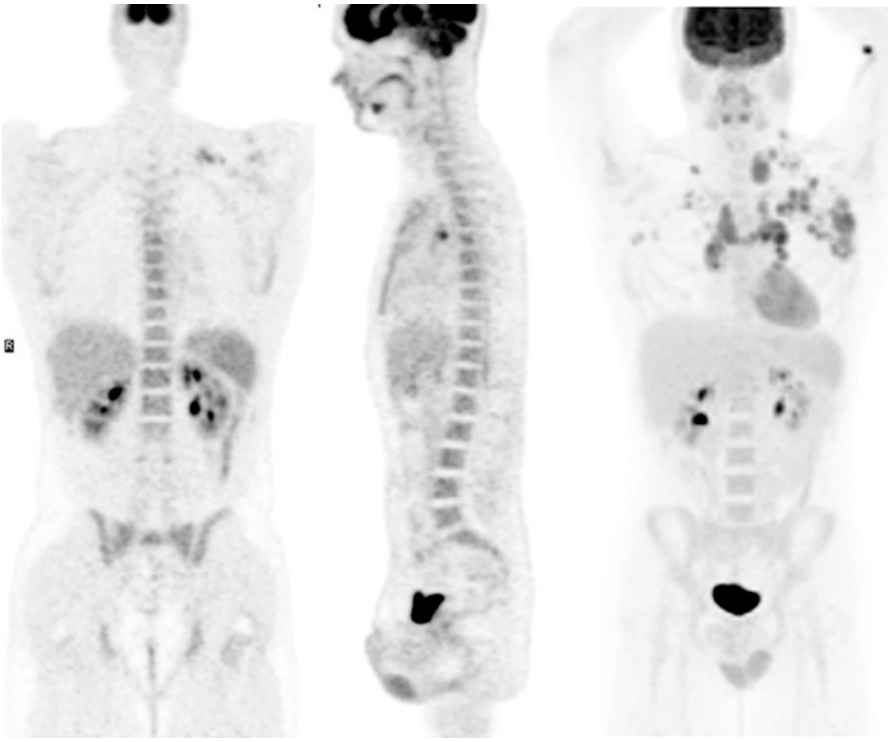


7.4 Case 4: Reactive Marrow Activity Pre-Treatment

Staging PET scan in 21-year-old male with newly diagnosed Hodgkin's lymphoma. Note the prominent diffuse FDG activity within bone marrow.

7.4.1 Teaching Points

Diffuse marrow activity in newly diagnosed HL is a relatively common finding and does not indicate bone marrow involvement being felt to represent reactive bone marrow activity.

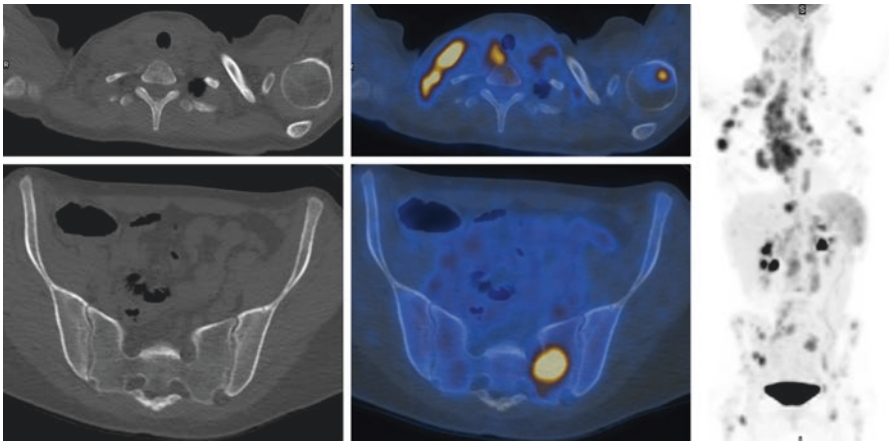


7.5 Case 5: Bone Marrow Involvement

Baseline staging PET/CT in 22-year-old female with Hodgkin's lymphoma. PET/CT shows stage IV disease with multifocal uptake within bone marrow. Two sites are shown on axial CT and fused PET/CT images in left humerus and sacrum.

7.5.1 Teaching Points

- Multifocal FDG-avid lesions are typical patterns of bone marrow involvement in HL.
- Often, as in this case, CT images show no morphological abnormality.
- PET/CT is the most sensitive staging modality for assessment of bone marrow involvement and is superior to CT and routine bone marrow biopsy.



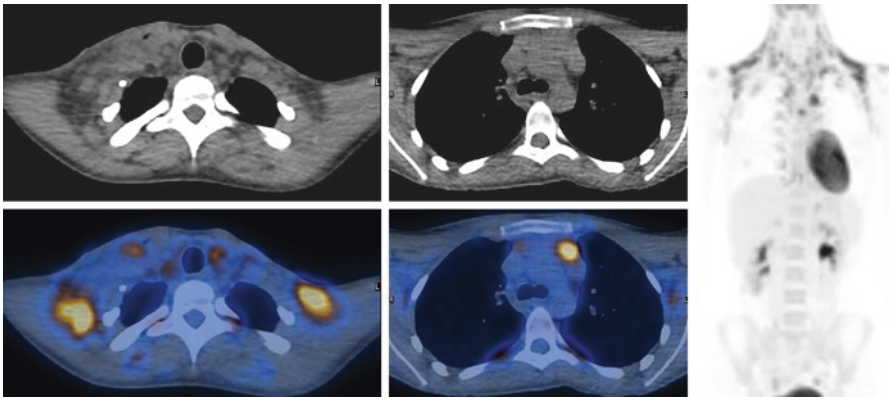
7.6 Case 6: Brown Fat Activity

Baseline staging scan in 20-year-old female with Hodgkin's lymphoma. There is FDG-avid nodal disease within the mediastinum but also florid FDG activity within fat planes of the neck and shoulder girdle.

7.6.1 Teaching Points

FDG activity in brown fat is a common physiological variant. This can usually be distinguished from nodal activity with PET/CT but in florid cases can adversely impact the assessment of scans.

Techniques to minimise brown fat activity include keeping patient warm and giving diazepam or propranolol.

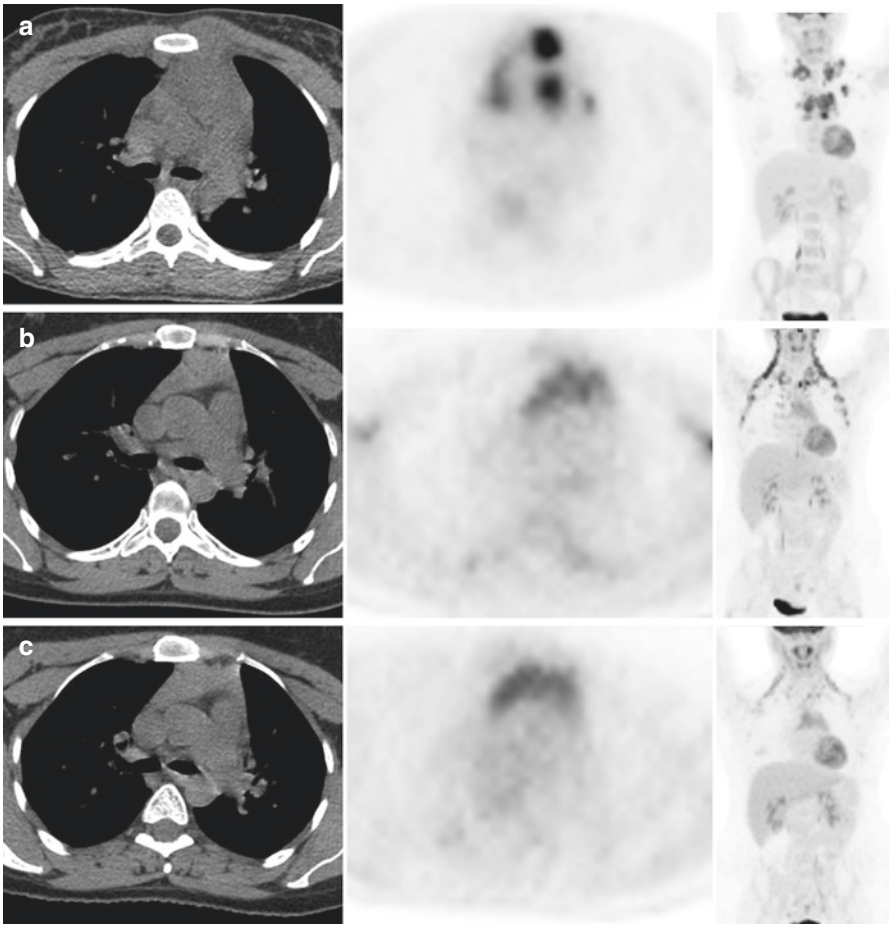


7.7 Case 7: Thymic Hyperplasia

PET/CT scans at baseline (A), end of treatment (B) and 7 months post end of treatment (C) in a 21-year-old female patient. End of treatment scan shows diffuse FDG activity in anterior mediastinum in soft tissue which has a thymic configuration. This was taken as representing thymic hyperplasia rather than disease despite the anterior mediastinum clearly being an involved disease site on the baseline scan. The patient was monitored clinically with a follow-up scan (C) showing persistent thymic activity. She remained well with no further treatment.

7.7.1 Teaching Points

Thymic hyperplasia is a common finding post chemotherapy.

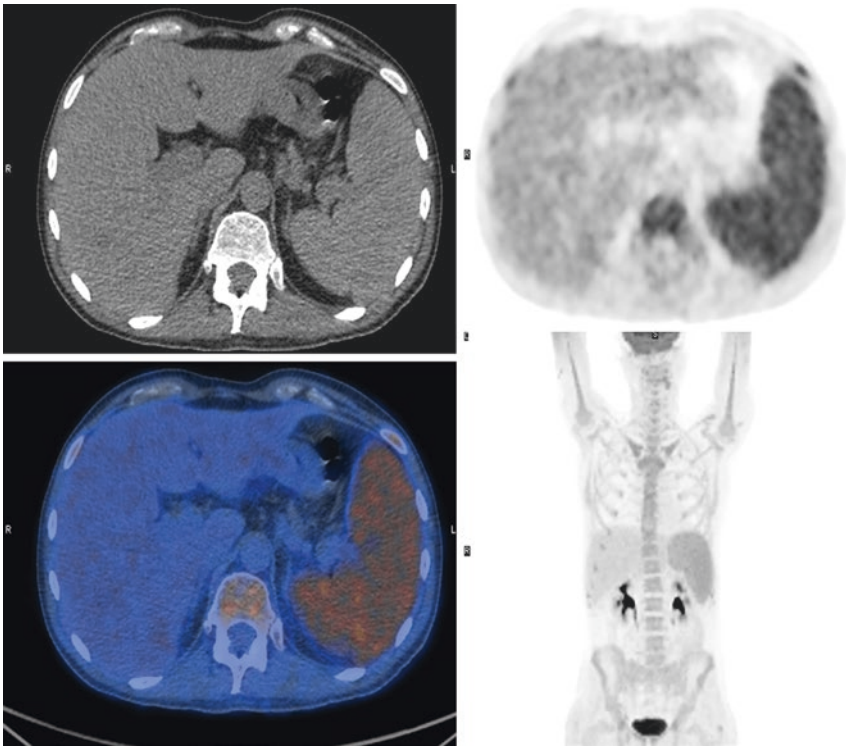


7.8 Case 8: Reactive Bone Marrow and Spleen Activation

PET/CT scan post chemotherapy in 42-year-old male patient with lymphoma. There is diffuse increased FDG activity within the spleen and bone marrow. Neither site was involved at baseline. The findings are typical for post chemotherapy bone marrow and splenic activation.

7.8.1 Teaching Points

Reactive bone marrow and splenic activation occurs commonly post chemotherapy and GCF administration and should not be called active disease.



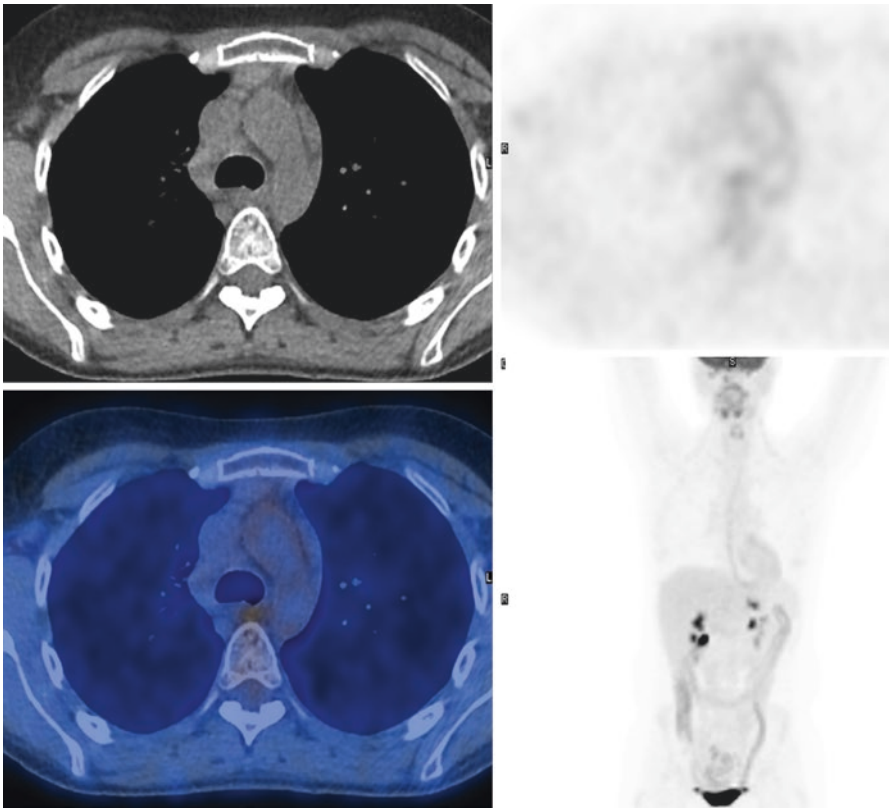
7.9 Case 9: Metabolic Remission

Interim (post two cycles of chemotherapy) PET/CT in a 22-year-old female patient with Hodgkin's lymphoma. There are mildly enlarged residual nodes in the mediastinum which show very low-grade FDG activity. The uptake score is 2 (not greater than mediastinum background).

7.9.1 Teaching Points

An uptake score of 2 is considered to represent a negative scan on both interim and end of treatment scans.

Mediastinal activity should be assessed in large vessels, taking care to avoid uptake along walls of vessel.



7.10 Case 10: Interim PET Scan with Uptake Score of 3

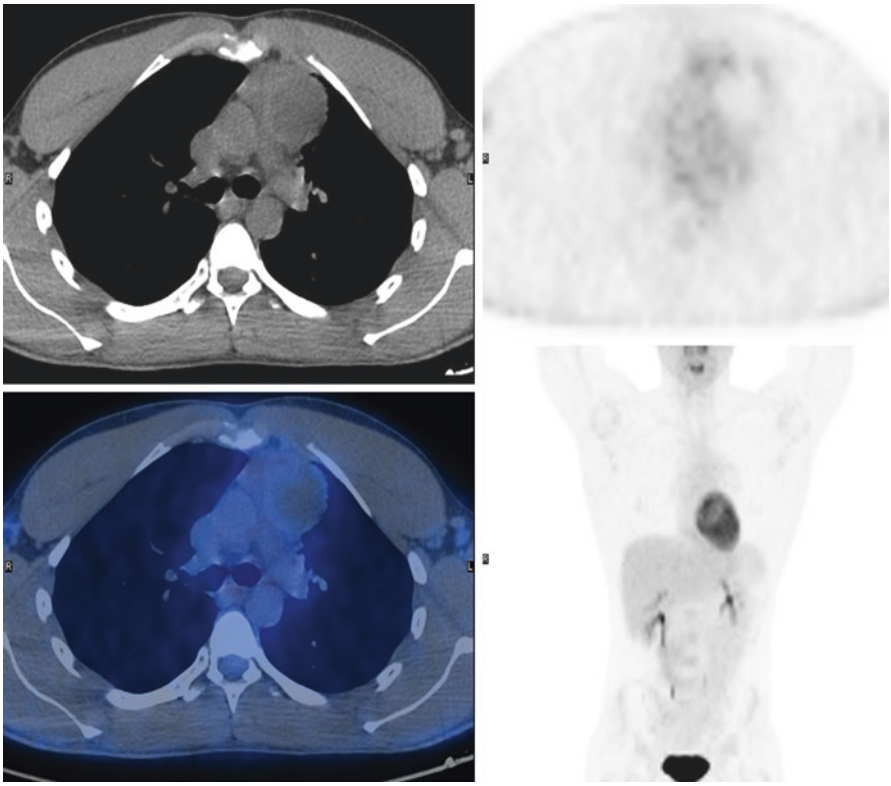
Interim PET/CT post two cycles of ABVD chemotherapy in 21-year-old male patient with Hodgkin's lymphoma. There is low-grade FDG activity within soft tissue in the anterior mediastinum. The uptake score is 3 (greater than the mediastinum but not greater than the liver).

7.10.1 Teaching Points

Interim PET is predictive of outcome in Hodgkin's lymphoma.

A score of 3 is considered adequate response to chemotherapy if patient is to receive standard treatment.

If treatment is intended to be de-escalated as a result of a negative PET scan, then a lower threshold of 2 for a negative PET scan may be appropriate.

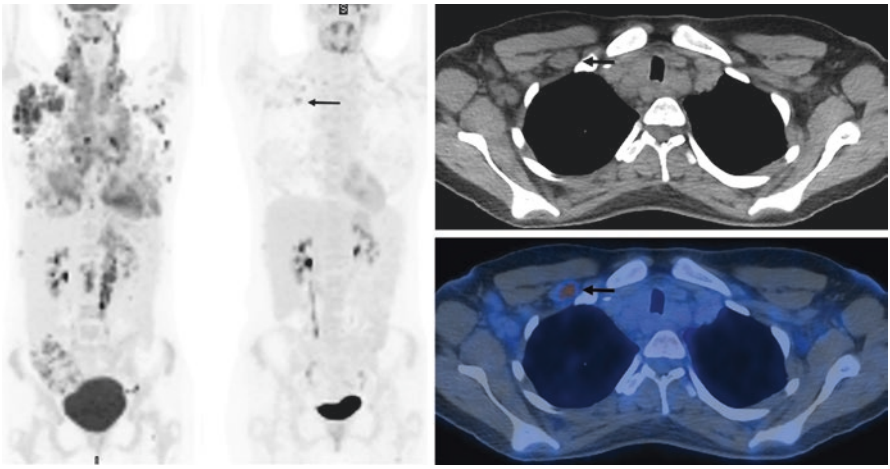


7.11 Case 11: Interim PET Scan with Uptake Score of 4

Baseline and interim (post cycles ABVD chemotherapy) scans in a 24-year-old female with advanced Hodgkin's lymphoma. The highest uptake at disease site on interim scan is in an infraclavicular node (arrows) with an uptake score of 4 (moderately greater than liver).

7.11.1 Teaching Points

A score of 4 on an interim PET scan is considered positive for active disease.

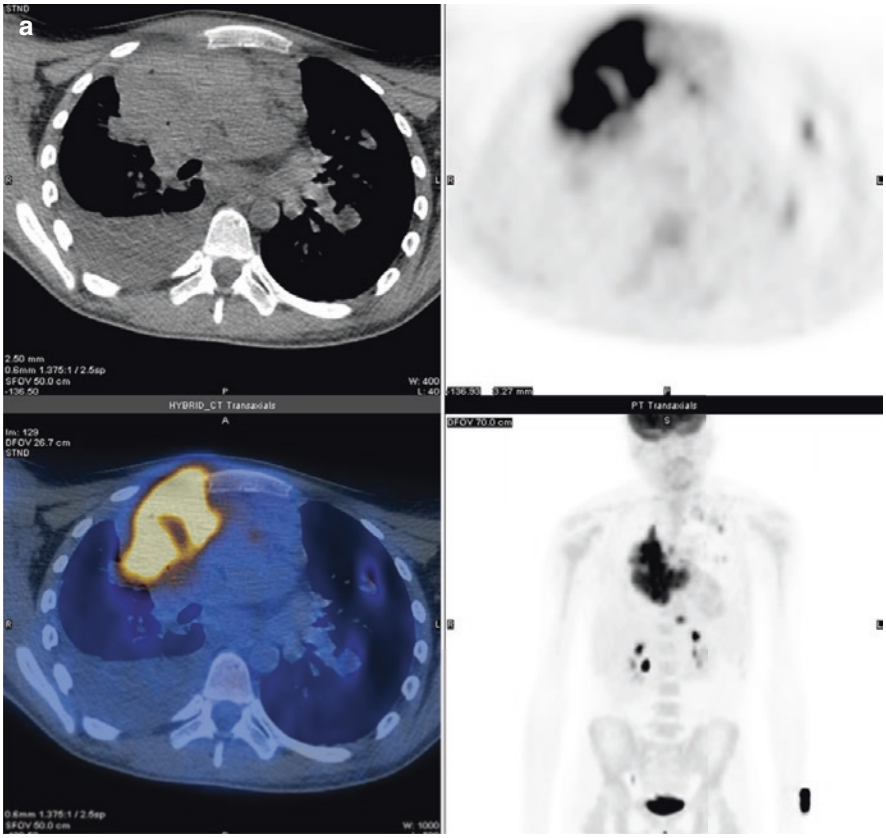


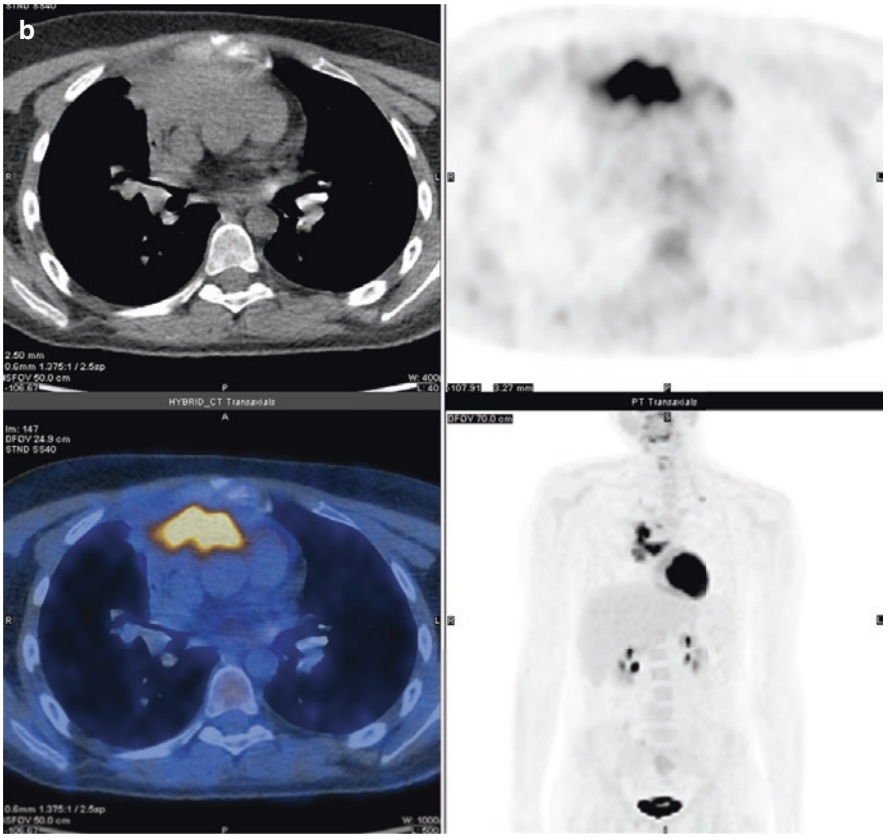
7.12 Case 12: Interim PET Scan with Uptake Score of 5

Baseline (A) and interim (B, post two cycles ABVD chemotherapy) PET/CT scans in 20-year-old female. There is intense residual FDG uptake on interim PET scan with an uptake score of 5 (uptake markedly above liver).

7.12.1 Teaching Points

A score of 5 on an interim PET scan represents inadequate treatment response and is predictive of a poor prognosis. These patients should be considered for escalation of therapy.

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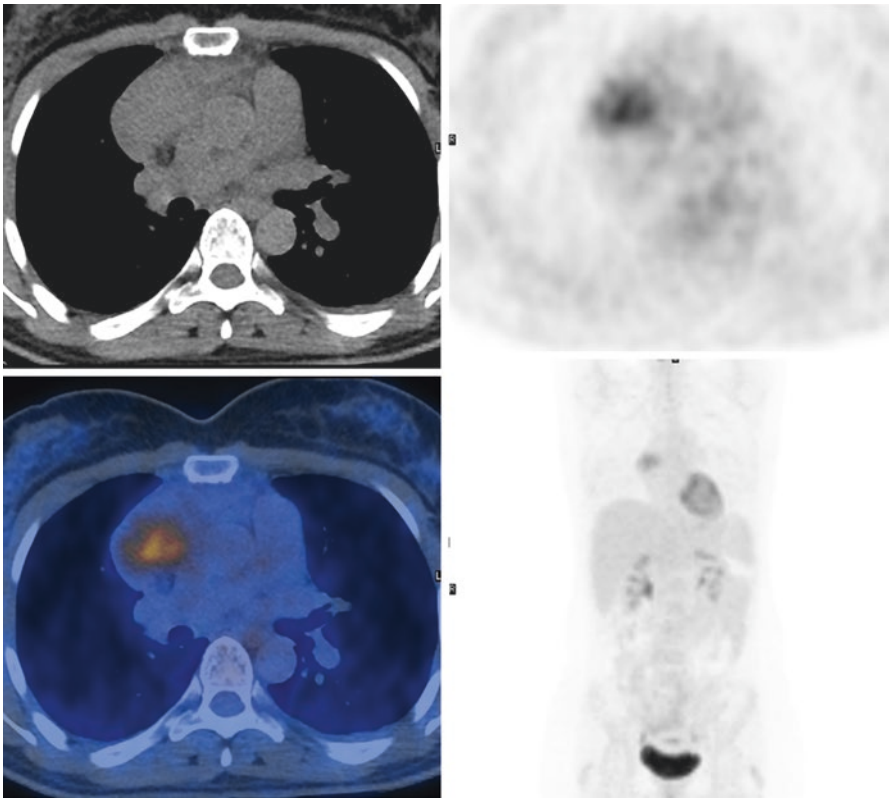
7.13 Case 13: False-Positive FDG Uptake at End of Treatment Scan

End of treatment PET/CT scan in a 42-year-old female patient with Hodgkin's lymphoma. There is clear focal positive uptake within a residual mediastinal mass, and the uptake score is 4. The mass was biopsied, with care taken to target the metabolically active portion of the mass. Histology showed no evidence for active lymphoma but a prominent foamy macrophage infiltrate which may have explained the FDG positivity. The mass remained stable and patient well with no evidence for relapse over follow-up of 8 months.

7.13.1 Teaching Points

False-positive FDG uptake can occur in inflammatory conditions as FDG is taken up by activated macrophages. Hodgkin's lymphoma is associated with a prominent inflammatory cell infiltrate.

If patient is to be subjected to further more intensive therapy on basis of a positive PET scan, active disease should be confirmed with histology. Where biopsy is not possible or practical close clinical and imaging follow-up may be helpful.



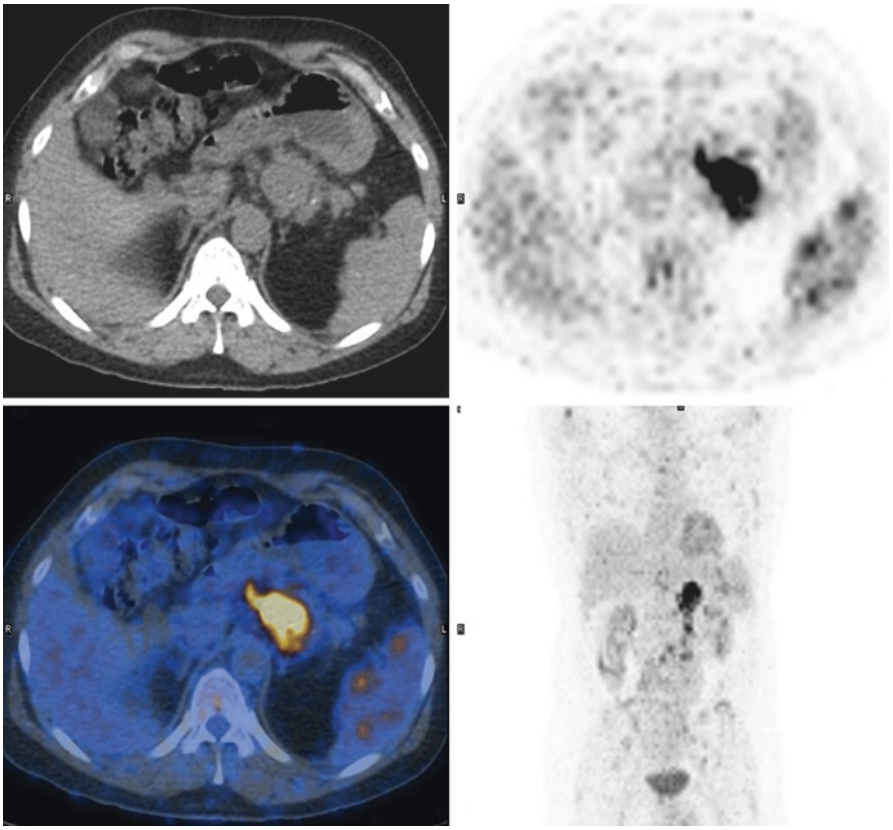
7.14 Case 14: Relapsed Disease

A 29-year-old male with treated Hodgkin's lymphoma had a PET/CT for suspected relapse due to constitutional malaise. PET/CT shows metabolically active splenic and nodal disease in keeping with relapsed Hodgkin's lymphoma which was confirmed with histology.

7.14.1 Teaching Points

Following treatment for Hodgkin's lymphoma, there is no role for routine surveillance with PET/CT if patient has achieved metabolic remission.

PET/CT is however indicated for patients with clinical suspicion of relapse post-treatment and can be used to restage disease and assess response to salvage chemotherapy.



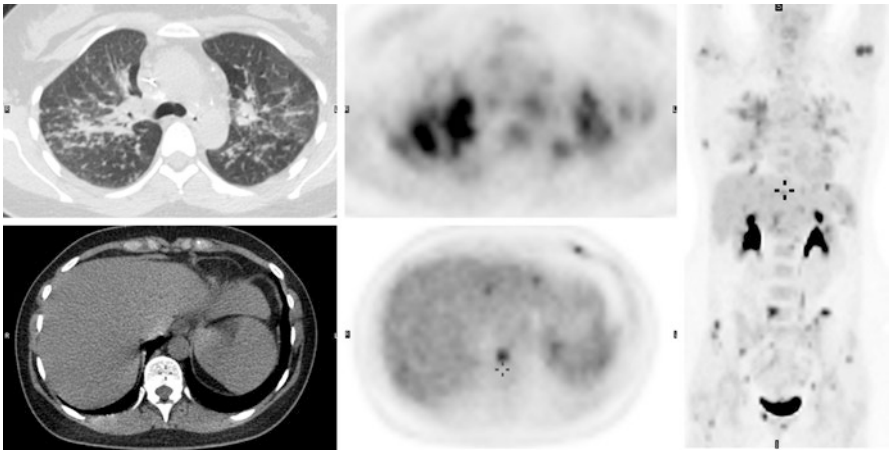
7.15 Case 15: Co-existing Sarcoidosis and Hodgkin's Lymphoma

Forty-five-year-old female patient with Hodgkin's lymphoma (right lower cervical node). There is FDG-avid pulmonary, hepatic, splenic and skeletal disease. Pulmonary appearances are suggestive of sarcoidosis. Biopsies of liver and avid bone lesions showed non-necrotising granulomas in keeping with sarcoidosis. The extranodal disease persisted on post-treatment scans, but patient remained clinically well and remains free of relapse on clinical and imaging follow-up.

7.15.1 Teaching Points

Sarcoidosis can mimic active lymphoma. Sarcoidosis on a PET scan most often involves thoracic nodes but can show multi-organ involvement.

Sarcoidosis can co-exist with active lymphoma; a sarcoid-like reaction can also be seen post-treatment highlighting need for awareness, histopathological correlation and close clinical and imaging follow-up.



7.16 Case 16: Spinal Cord Compression in Hodgkin's Lymphoma

Nineteen-year-old female with 3-month history of increasing back pain and 2-week history of difficulty walking due to weakness of the legs. An MRI scan followed by a PET/CT scan was performed.

The MRI shows a retroperitoneal nodal mass with extension of soft tissue into spinal canal filling the epidural space and causing effacement of the thecal sac with intramedullary signal abnormality in the spinal cord.

PET/CT shows nodal disease above and below the diaphragm with splenic and multifocal bone marrow involvement.

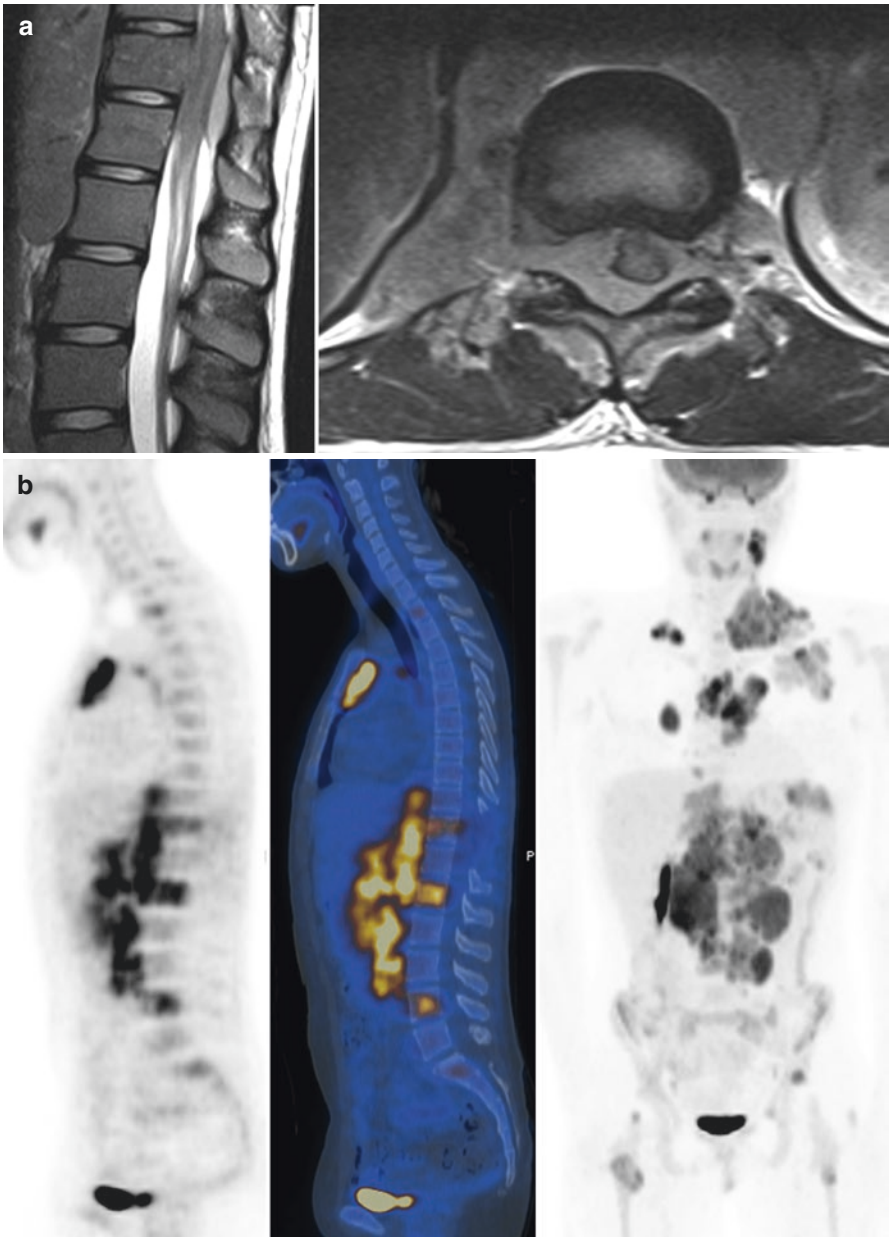
The patient underwent an urgent surgical decompression of the spinal canal. Biopsy from epidural soft tissue revealed Hodgkin's lymphoma.

7.16.1 Teaching Points

The incidence of spinal cord compression in Hodgkin's lymphoma is 5% usually in patients with widespread advanced disease. Hodgkin's lymphoma presenting as cord compression is very uncommon, quoted as occurring in 0.2% of cases.

Tumour is thought to reach the epidural space by contiguous extension from a paravertebral mass through the neural foramen or from the vertebral body.

The thoracic spine is the most common site of involvement followed by the lumbar spine.



Reference

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7.17 Case 17: Incidental Focal Thyroid Activity on a Lymphoma Staging Scan

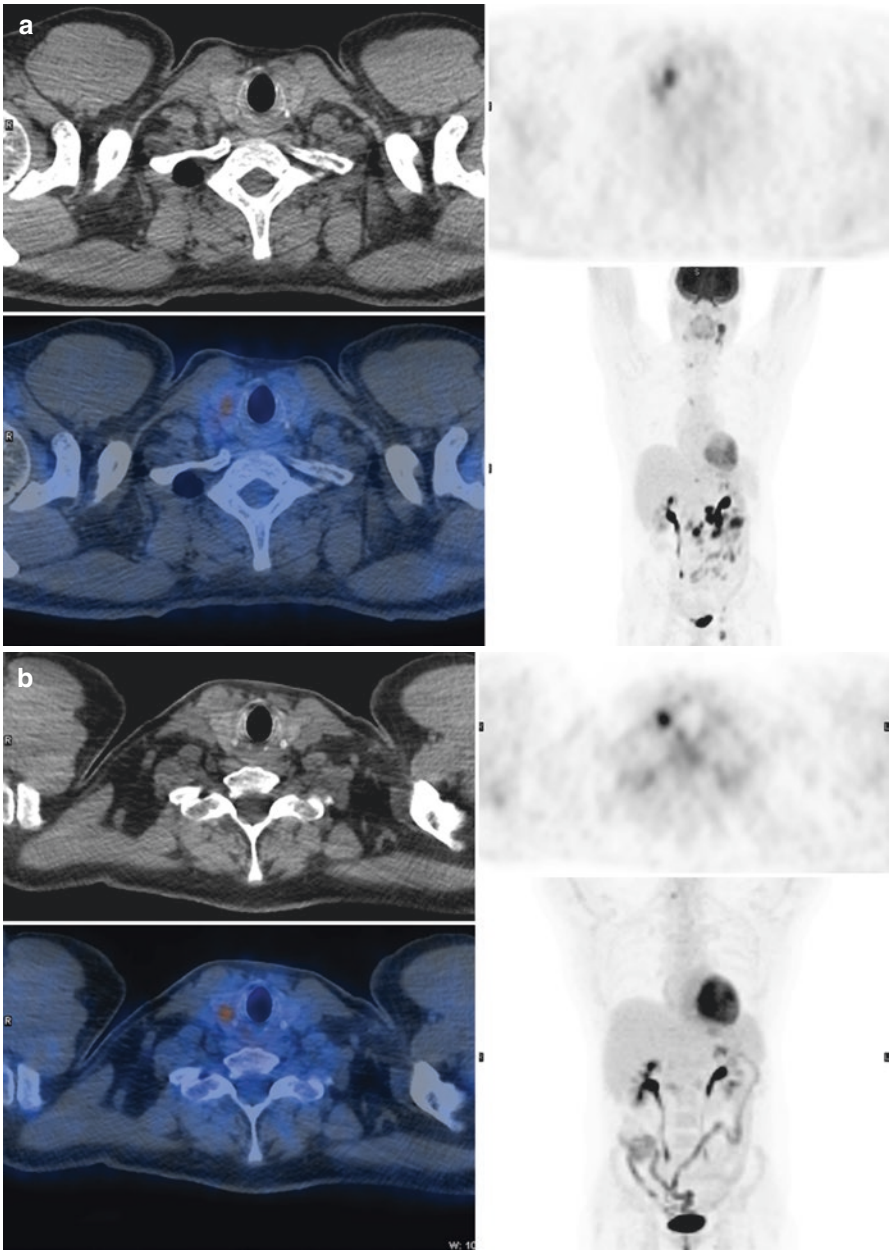
Forty-six-year-old male with Hodgkin's lymphoma had a staging PET/CT scan.

PET/CT (Figure A) reveals nodal disease above and below the diaphragm in keeping with stage III disease. There is also focal uptake in thyroid. This was reported as indeterminate but suspicious for an incidental lesion. A decision was made to monitor and biopsy if still present at end of first-line lymphoma treatment. End of treatment PET/CT scan (Figure B) revealed persistent focal thyroid activity with resolution of uptake at other lesion sites.

Following this an USS revealed a small hypoechoic nodule which was biopsied and shown to be a papillary thyroid carcinoma (pT1a N0 M0).

7.17.1 Teaching Points

Focal thyroid activity in a lymphoma patient is more commonly due to synchronous thyroid pathology rather than involvement by lymphoma. It is a non-specific finding which is seen in benign and malignant primary thyroid tumours. Many thyroid carcinomas detected by PET are indolent and slowly progressing.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7.18 Case 18: Management of Early Stage Hodgkin's Lymphoma

Twenty-one-year-old female with Hodgkin's lymphoma underwent a staging PET/CT scan.

PET/CT scan (Figure A) demonstrates stage II disease in keeping with early stage favourable (no mediastinal bulk, less than three nodal sites involved, no E involvement) Hodgkin's lymphoma.

PET/CT scan (Figure B) following treatment with two cycles of ABVD chemotherapy and 20 grays of radiotherapy reveals metabolic remission.

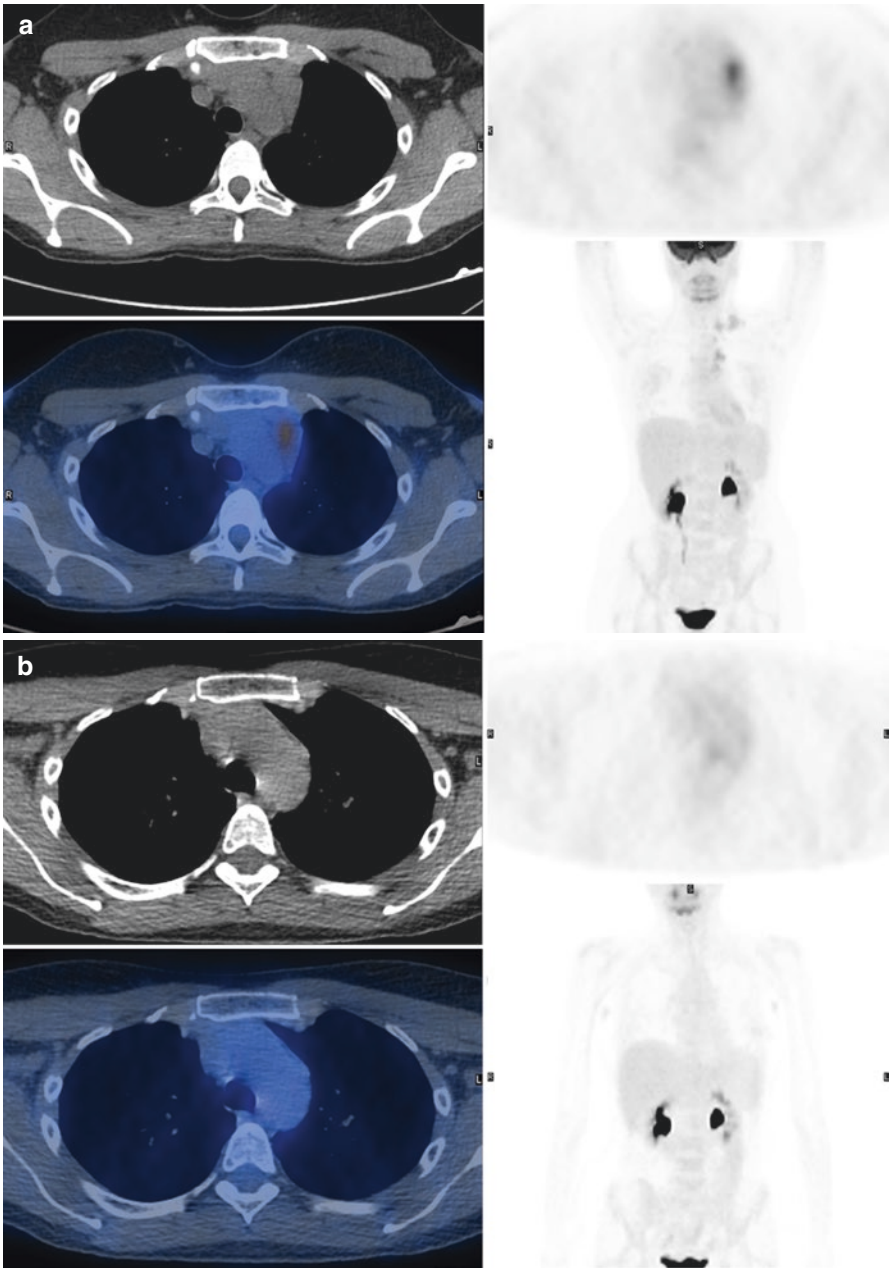
7.18.1 Teaching Points

Early stage Hodgkin's lymphoma (stages I–II) is divided into favourable and unfavourable disease based on a combination of clinical, laboratory and imaging markers. Imaging markers for unfavourable disease include involvement of three or more nodal sites, bulky disease and extranodal (E) involvement.

Combination therapy with ABVD chemotherapy followed by radiotherapy is a standard treatment for early stage Hodgkin's lymphoma. An alternative is to increase the number of chemotherapy cycles and omit radiotherapy. The potential benefits and risks of both options should be discussed with patients, including late adverse effects such as radiation-induced breast cancer and cardiomyopathy and the slightly increased risk of infertility with a higher number of chemotherapy cycles.

The treatment options in this case with early stage HL include two cycles of ABVD chemotherapy followed by 20 grays of involved field radiotherapy or an increased number of ABVD chemotherapy cycles alone.

The patient was treated with two cycles of ABVD chemotherapy followed by 20 grays of involved field radiotherapy to metabolic remission (Figure B).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7.19 Case 19: Management of Early Stage Hodgkin's Lymphoma

Twenty-year-old female with Hodgkin's lymphoma underwent staging PET/CT scan.

PET/CT scan (Figure A) demonstrates stage II disease in keeping with early stage unfavourable (mediastinal bulk, number of nodal sites) Hodgkin's lymphoma.

PET/CT scan (Figure B) following treatment with six cycles of ABVD chemotherapy reveals metabolic remission.

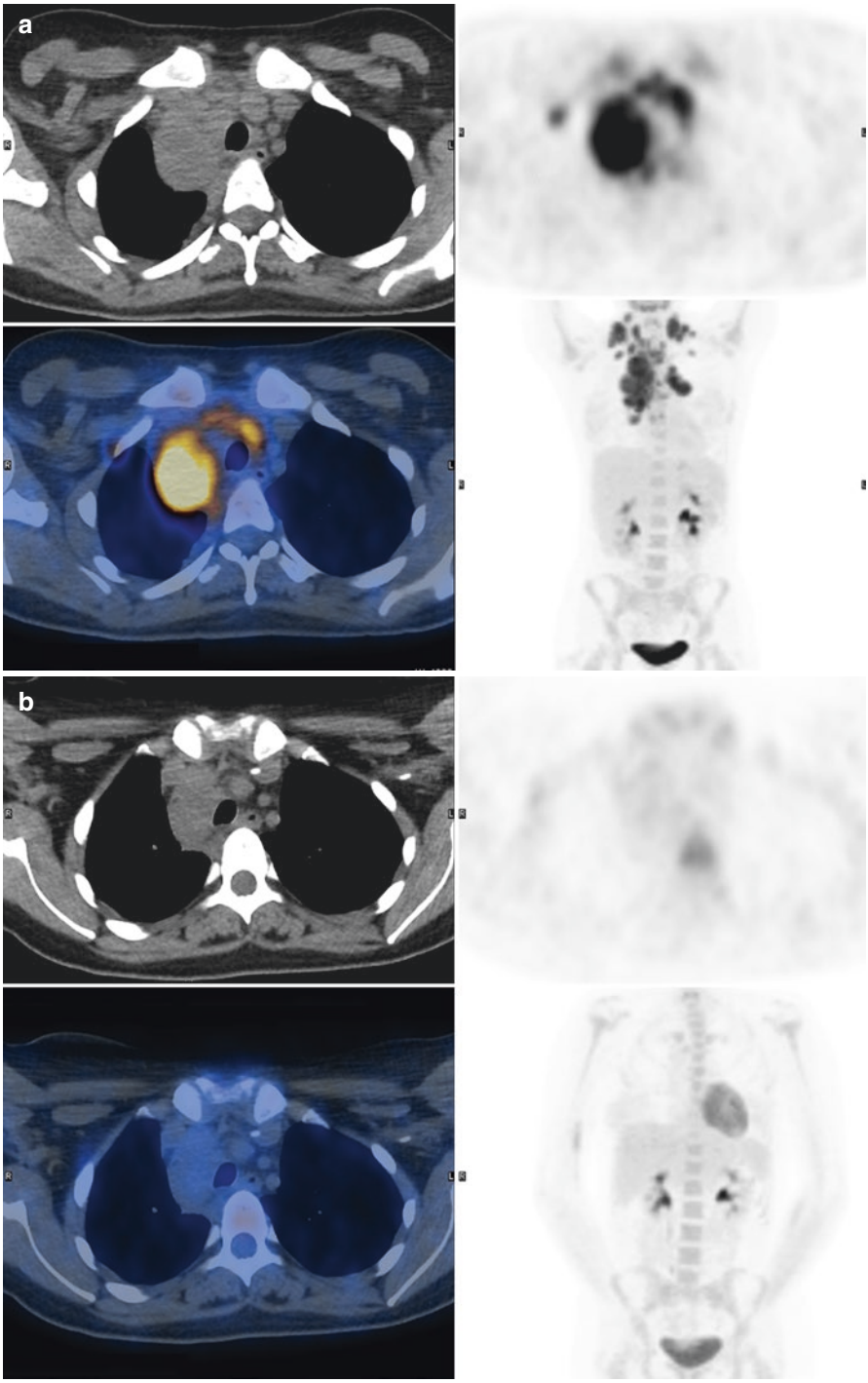
7.19.1 Teaching Points

Early stage Hodgkin's lymphoma (stages I–II) is divided into favourable and unfavourable disease based on a combination of clinical, laboratory and imaging markers. Imaging markers for unfavourable disease include involvement of three or more nodal sites, bulky disease and extranodal (E) involvement.

Combination therapy with ABVD chemotherapy followed by radiotherapy is a standard treatment for early stage Hodgkin's lymphoma. An alternative is to increase the number of chemotherapy cycles and omit radiotherapy. The potential benefits and risks of both options should be discussed with patients, including late adverse effects such as radiation-induced breast cancer and cardiomyopathy and the slightly increased risk of infertility with a higher number of chemotherapy cycles.

The treatment options in this case with early stage unfavourable disease include four cycles of ABVD chemotherapy followed by 30 grays of involved field radiotherapy or six cycles of ABVD chemotherapy. In young female patients where the breasts may receive a large dose, a decision is often made to increase the number of chemotherapy cycles and omit radiotherapy.

The patient was treated with six cycles of ABVD chemotherapy to metabolic remission (Figure B).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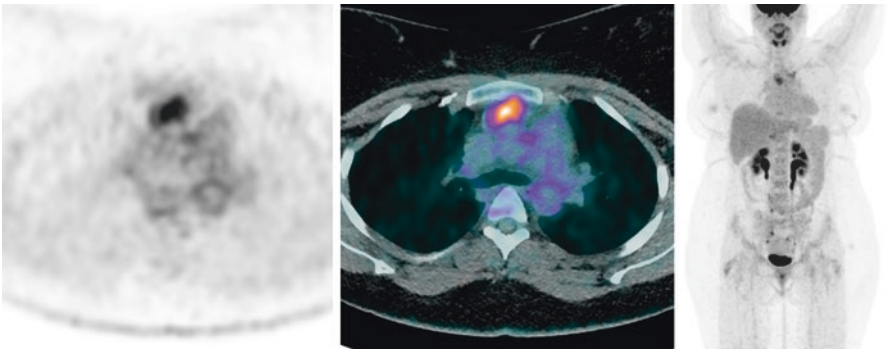
7.20 Case 20: Suspected Relapse Following Treatment for Hodgkin's Lymphoma-1

Thirty-eight-year-old female patient treated 5 years earlier to complete remission with six cycles of ABVD for early stage favourable Hodgkin's lymphoma (stage IIA). An MRI performed for investigation of palpitations revealed anterior mediastinal nodules; these were shown to be metabolically active on PET scan and considered suspicious for relapsed lymphoma. The mass was felt to be not amenable to percutaneous biopsy or accessible via mediastinoscopy. The patient was therefore referred for thoracotomy and excision biopsy.

Histology of the mediastinal nodule revealed a benign thymoma.

7.20.1 Teaching Point

This case illustrates the importance of biopsy in confirming positive PET findings even if this may necessitate invasive surgical biopsy procedures.



7.21 Case 21: Suspected Relapse Following Treatment for Hodgkin's Lymphoma-2

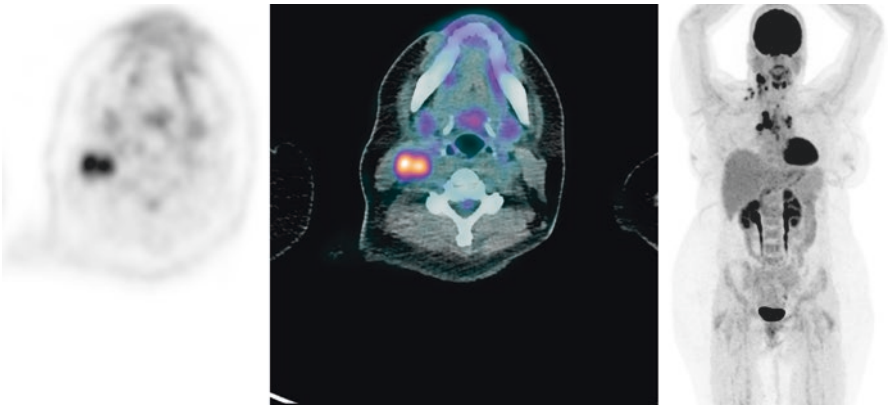
Thirty-eight-year-old female with treated early stage favourable Hodgkin's lymphoma. Same patient as in last case. The patient presented 5 months following excision of thymoma in mediastinum with enlarging cervical nodes and was referred for a PET/CT scan.

The PET/CT scan shows multiple metabolically active cervical and mediastinal nodes.

Biopsy of a cervical node revealed classical Hodgkin's lymphoma.

7.21.1 Teaching Point

This case, in conjunction with last case on the same patient, illustrates the importance of confirming PET positive findings with histology.



7.22 Case 22: Interim PET/CT Scan Assessment

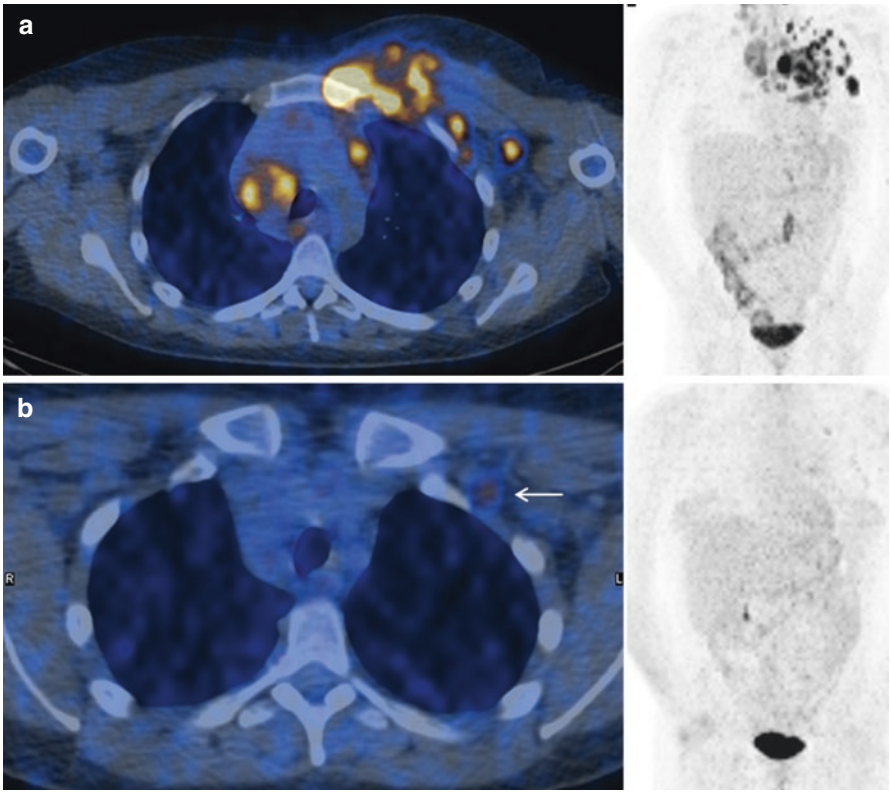
Thirty-six-year-old female with advanced (stage III) Hodgkin's lymphoma. Baseline PET/CT scan is shown in Figure A. The patient was assessed at local hospital as having a good response on interim PET/CT (Figure B) after two cycles of ABVD chemotherapy. A PET/CT scan (Figure C) following two further cycles of ABVD showed an increase in nodal activity. A biopsy of a left axillary node was performed which revealed Hodgkin's lymphoma. The patient was subsequently referred for further management.

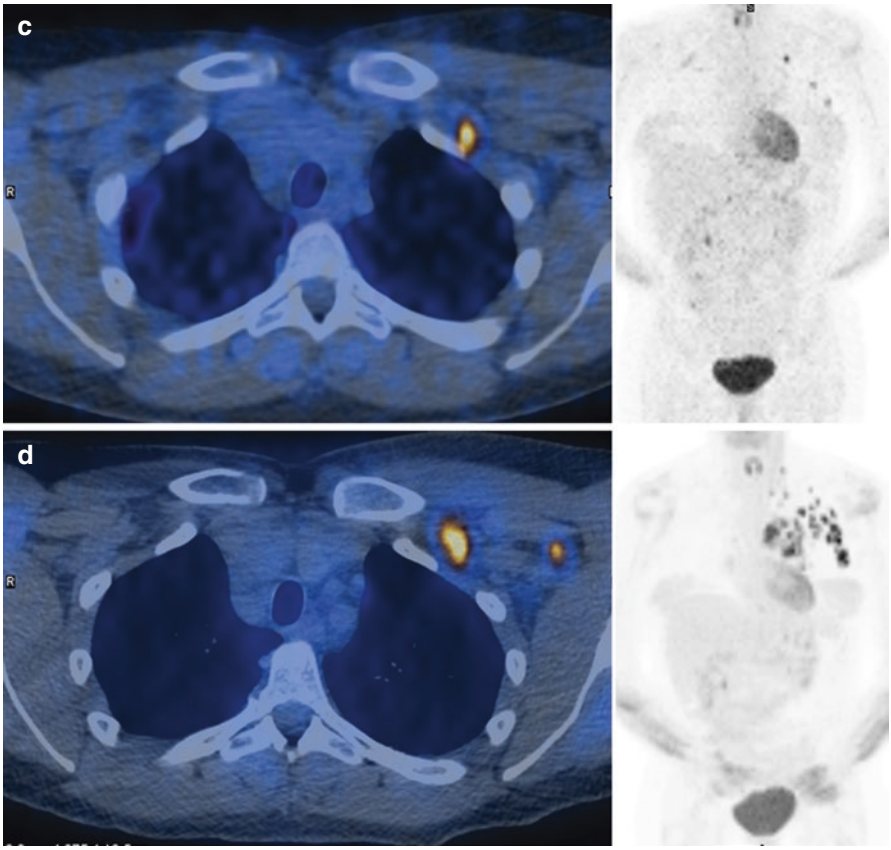
The interim PET scan (Figure B) reveals significant nodal activity (arrow, Deauville score 4; SUVmax 4.3) which increases on post four cycle scan (Figure C) (Deauville score 5, SUVmax 10.5).

A decision was made to treat the patient with salvage chemotherapy. A repeat baseline PET/CT scan (Figure D) pre-salvage chemotherapy showed progressive nodal disease in left chest wall and axilla.

7.22.1 Teaching Points

In patients treated with first-line ABVD chemotherapy, a Deauville score of 4 or higher on an interim PET scan is considered a marker of active disease. Earlier escalation of therapy following positive interim PET scans may potentially improve outcome in these patients.

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7.23 Case 23: Immunotherapy for Refractory and Relapsed Hodgkin's Lymphoma

Twenty-year-old male with stage III Hodgkin's lymphoma. PET scans showed persisting nodal disease in right axilla at end of treatment (Figure A) followed by progressive disease after further first-line salvage chemotherapy (Figure B), on both occasions confirmed by biopsy.

Subsequently the patient was treated with three cycles of brentuximab vedotin to complete metabolic remission (Figure C) and underwent autologous stem cell transplantation.

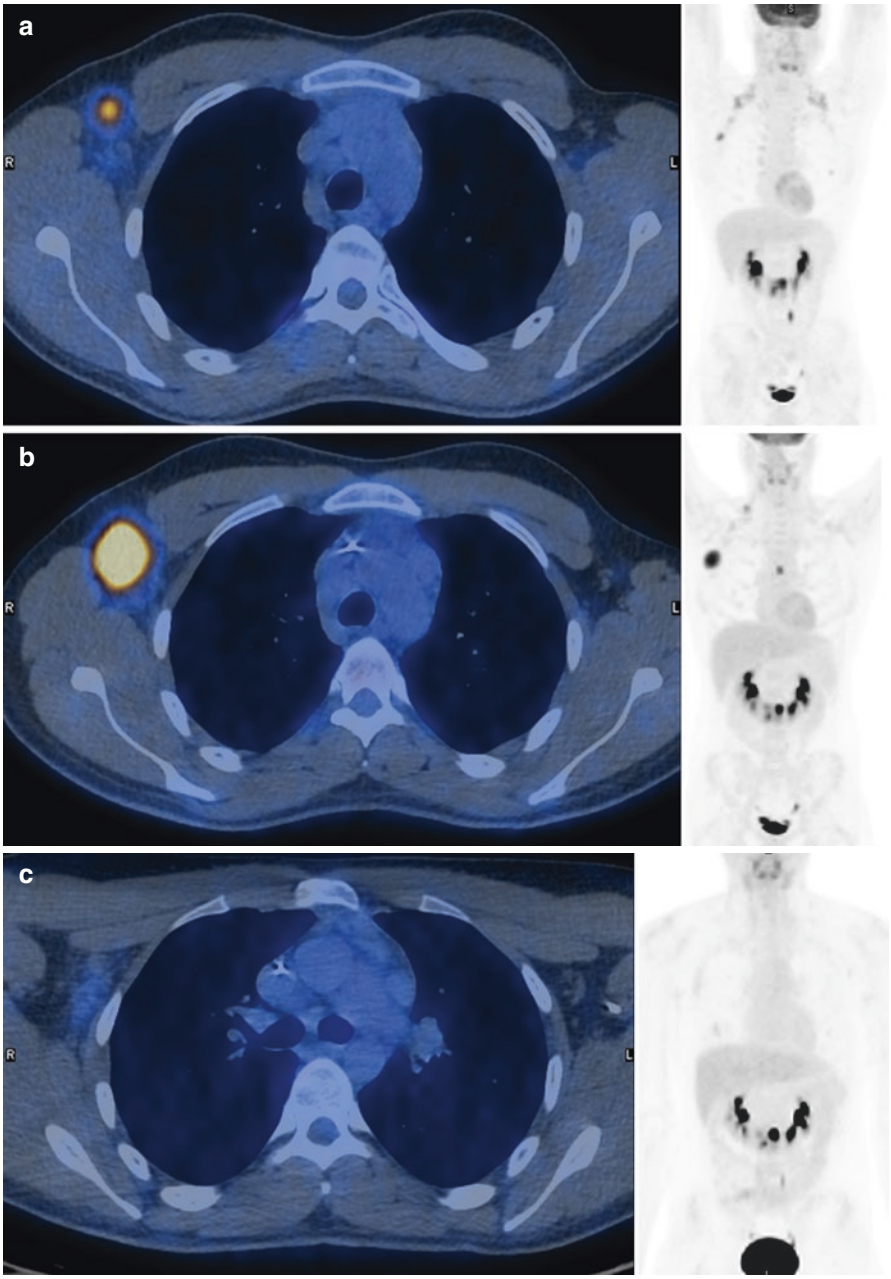
Patient also has a horseshoe kidney.

7.23.1 Teaching Points

Brentuximab vedotin is an immunotherapy made of an antibody-drug conjugate. Brentuximab vedotin targets CD30, a protein on the surface of some Hodgkin's lymphoma cells and a key driver of tumour pathogenesis.

Management of patients with relapsed or refractory disease is based on high-dose chemotherapy followed by autologous stem cell transplantation.

Brentuximab vedotin is approved by the FDA for treatment of relapsed and refractory Hodgkin's lymphoma and may be used prior to transplantation. Patients who achieve a negative PET scan following treatment and prior to transplant have an excellent prognosis.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7.24 Case 24: Immunotherapy for Refractory and Relapsed Hodgkin's Lymphoma

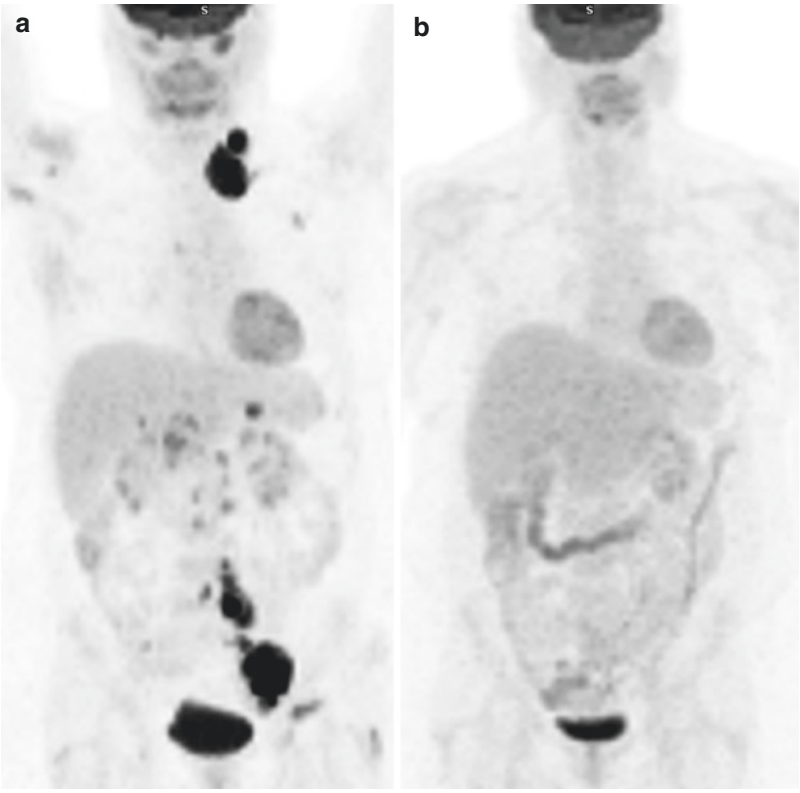
Fifty-year-old female presented with relapsed Hodgkin's lymphoma post-transplant. PET/CT (A) demonstrated widespread nodal disease above and below the diaphragm. The patient was treated with brentuximab vedotin therapy. Following treatment a restaging PET/CT (B) showed metabolic remission.

7.24.1 Teaching Points

Brentuximab vedotin is an immunotherapy made of an antibody-drug conjugate. Brentuximab vedotin targets CD30, a protein on the surface of some Hodgkin's lymphoma cells and a key driver of tumour pathogenesis.

Brentuximab vedotin is approved by the FDA for treatment of relapsed and refractory Hodgkin's lymphoma.

Management of patients with relapsed or refractory disease is based on high-dose chemotherapy followed by autologous stem cell transplantation. Those who relapse following transplant have a poor prognosis. Brentuximab vedotin is a potential curative treatment for these patients and has been shown to induce long-lasting (>5 years) remissions in 38% of patients who respond to treatment with an overall survival rate of 64% at 5 years.



Reference

Chen R, Gopal AK, Smith SE, Ansell SM, Rosenblatt JD, Savage KJ, Connors JM, Engert A, Larsen EK, Huebner D, Fong A, Younes A. Five-year survival and durability results of brentuximab vedotin in patients with relapsed or refractory. Hodgkin's lymphoma. Blood. 2016;128(12):1562–6.

7.25 Case 25: Post-transplant Lymphoproliferative Disorder

Twenty-one-year-old female with Hodgkin's lymphoma presented with widespread nodal relapse (Figure A). She was treated with high-dose chemotherapy followed by allogeneic transplantation but subsequently presented less than 1 year following transplant with epigastric pain, vomiting and cervical nodal enlargement. A PET/CT scan (Figure B) revealed metabolically active nodes above and below the diaphragm, multiple active pulmonary and hepatic lesions and diffuse thickening and FDG-avid uptake in gastric wall.

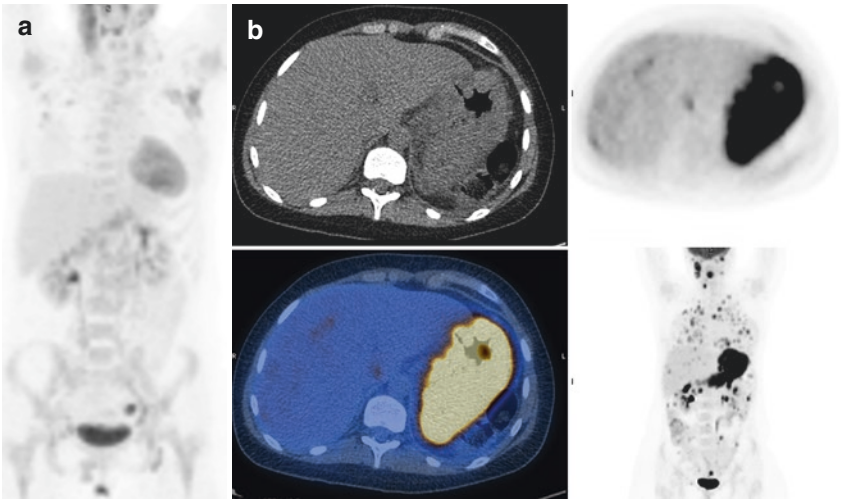
Epstein-Barr virus (EBV) titres were raised. Histology from nodal biopsy and gastric biopsy revealed a diffuse high-grade B-cell lymphoma, positive for EBV in keeping with post-transplant lymphoproliferative disorder (PTLD).

7.25.1 Teaching Points

The standard treatment for relapsed Hodgkin's lymphoma is salvage chemotherapy followed by autologous stem cell transplantation (ASCT).

Allogeneic transplantation is usually reserved for those patients who relapse following ASCT or who are refractory to chemotherapy.

PTLD is a complication of allogeneic haematopoietic stem cell (HSCT) and solid organ transplants. PTLD occurring post HSCT is related to reactivation of Epstein-Barr virus. Diagnosis is based on demonstration of two of the following histological features: histological evidence for a lymphoproliferative process, a monoclonal or oligoclonal cell proliferation and positive EBV in biopsy material. Management is based on rituximab therapy and reducing immune suppression, with donor lymphocyte infusion, EBV targeting cytotoxic T cells, donor lymphocyte infusions and chemotherapy as second-line options.



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I. Kayani (ed.), *PET/CT in Hodgkin's Lymphoma*, Clinicians' Guides to Radionuclide Hybrid Imaging – PET/CT, DOI 10.1007/978-3-319-57225-3