Positron Emission Tomography (PET) in hematologic and lymphatic mailgnacy

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Hematologic malignancies

- **Acute lymphoblastic leukemia (ALL):**
- **Acute myeloid leukemia (AML):**
- **Chronic lymphocytic leukemia (CLL):** overlaps in diagnosis with other lymphomas like MCL, MZL, and lymphoplasmacytic lymphoma.
- **Chronic myeloid leukemia (CML):**
- **Multiple myeloma (MM):** can present from asymptomatic MGUS to serious organ damage.
- **Lymphomas**

Lymphomas are a diverse group of cancers primarily affecting lymphoid organs:

- **Non-Hodgkin lymphomas (NHL)** make up about 90% of lymphomas.
- **Hodgkin lymphoma (HL)** accounts for the remaining 10%.

NHL is categorized by cell type:

- **B-cell lymphomas** (85–90% of cases),
- **T-cell lymphomas**, and
- **Natural Killer (NK) cell lymphomas**.

HL is divided into:

- **Classical HL** and
- **Nodular lymphocyte-predominant HL**.

Summary of REAL classification for non Hodgkin's lymphomas

B cell	T cell
• precursor B lymphoblastic	• precursor T lymphoblastic
• small lymphocytic (CLL)	• T cell chronic lymphocytic leukaemia
• lymphoplasmacytic	• large granular lymphocyte leukaemia
• mantle cell	• mycosis fungoides
• follicle centre lymphoma, follicular	• peripheral T cell, unspecified
• follicle centre lymphoma, diffuse	• angioimmunoblastic
• marginal zone B cell, MALT	• angiocentric, nasal
• marginal zone B cell, nodal	• intestinal
• marginal zone B cell, splenic	• adult T cell lymphoma/leukaemia
• hairy cell leukaemia	• anaplastic large cell
• plasmacytoma	• anaplastic large cell, Hodgkin's like
• diffuse large B cell	• unclassifiable, low grade
• mediastinal large B cell	• unclassifiable, high grade
• Burkitt's	
• high grade B cell, Burkitt-like	
• unclassified low grade	
• unclassified high grade	

CLASSIFICATION

- **Aggressive types** include HL, Diffuse Large B-Cell Lymphoma (DLBCL), and Burkitt Lymphoma (BL).

- **Indolent forms** like Follicular Lymphoma (FL) can transform into aggressive forms (commonly DLBCL).

- **Richter's transformation** refers to the progression of CLL into an aggressive lymphoma.

Table 3 Overview of NHL subtypes

Indolent NHL	Aggressive NHL	Highly aggressive NHL	Immunodeficiency-associated NHL
B-cell			
Follicular lymphoma	Diffuse large-cell lymphoma	Burkitt's lymphoma	Lymphoproliferative disorders associated with immune disease
Small lymphocytic lymphoma	Mantle cell lymphoma	Lymphoblastic lymphoma	HIV-related lymphoma
Extranodal marginal zone lymphoma (MALT lymphoma)	Mediastinal large B-cell lymphoma		Post-transplant lymphoproliferative disorders
Nodal marginal zone lymphoma	Intravascular large B-cell lymphoma		Methotrexate-associated lymphoproliferative disorders
Lymphoplasmacytic lymphoma (Waldenstrom's macroglobulinaemia)	Primary effusion lymphoma		
Splenic marginal zone lymphoma	Lymphomatoid granulomatosis		
T cell and NK cell			
	Angioimmuno-blastic T-cell lymphoma	Lymphoblastic lymphoma	
	Peripheral T-cell lymphoma		
	Extranodal NK/T-cell lymphoma		
	Hepatosplenic T-cell lymphoma		
	Anaplastic large-cell lymphoma		

INDICATIONS

	Staging	Interim Evaluation	End of Treatment Evaluation	Routine Follow-Up	Suspected recurrence
Lymphoma type					
Hodgkin lymhoma (HL)					
Classical HL	X	X	X		X
Nodular HL	X	X	X		X
Non-Hodgkin lymphoma (NHL)					
DLBCL	X	X	X		X
Follicular lymphoma	X (st I and II)		X		
T-cell lymhomas	X	X	X		X
Mantle cell lymphomas	X		X		X
Multiple myeloma	X		X	X	X
Transformation	X				
Biopsy localization	X				
Leukemias					
ALL extramedullair disease	X		X		X
AML extramedullary disease	X		X		X

Indications of PET-CT in Lymphoma

- Staging
- Restaging
- Monitoring of Therapy (Interim Assessment)
- End of treatment evaluation
- Radiation therapy planning

STAGING of LYMPHOMA

Due to the wide variety of lymphoma subtypes, clinical presentation and prognosis can vary significantly. Staging has evolved from the traditional Ann Arbor system to the modern Lugano classification, integrating advanced imaging techniques for both HL and NHL.

STAGING

Stage I

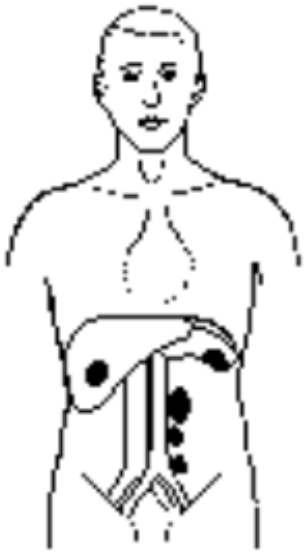
single lymph node region or single extralymphatic site (Ie)

Stage II

two or more sites, same side of diaphragm or c̄ contiguous extralymphatic site (IIe)

Stage IIIs

both sides of diaphram or c̄ spleen (IIIs) or contiguous extralymphatic site (IIIe)



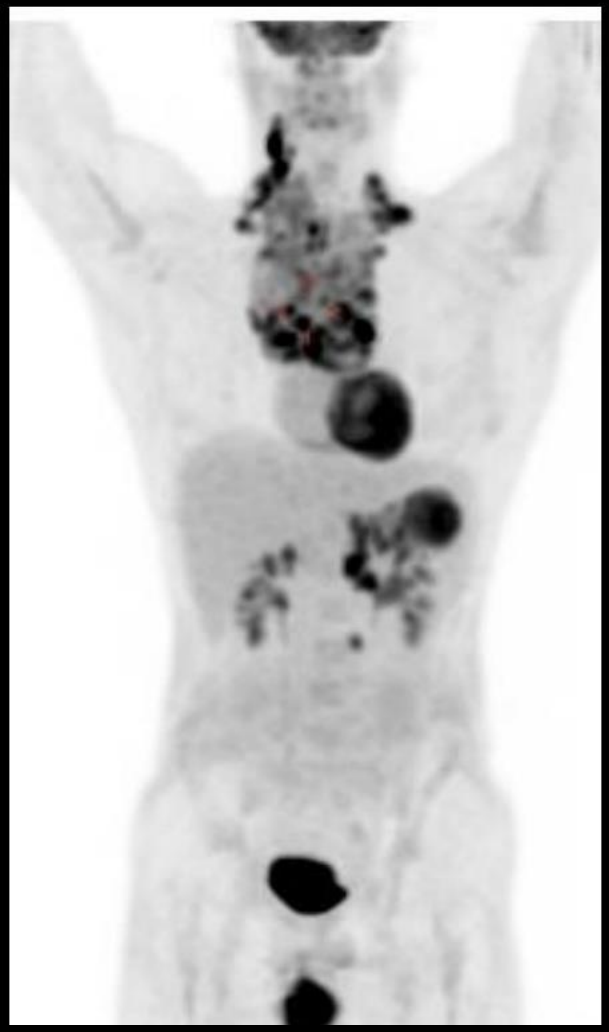
Stage IV

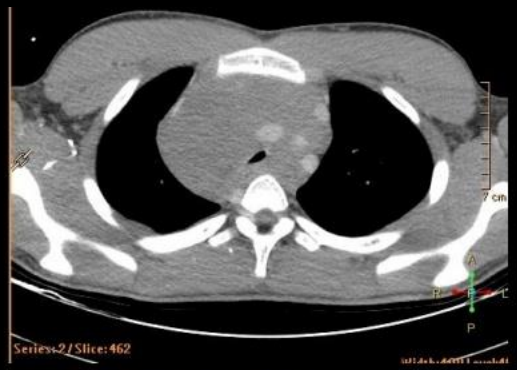
diffuse involvement of extralymphatic sites ± nodal disease

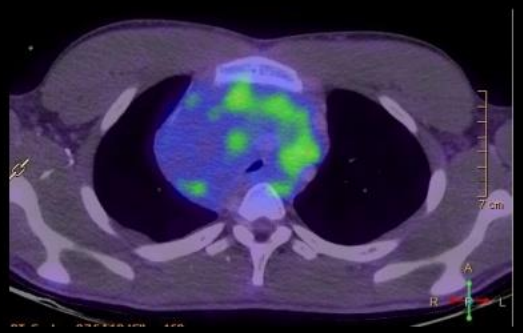
Stage subdivision: A-asymptomatic B-unexplained weight loss>10% in 6m and/or fever and/or night sweats

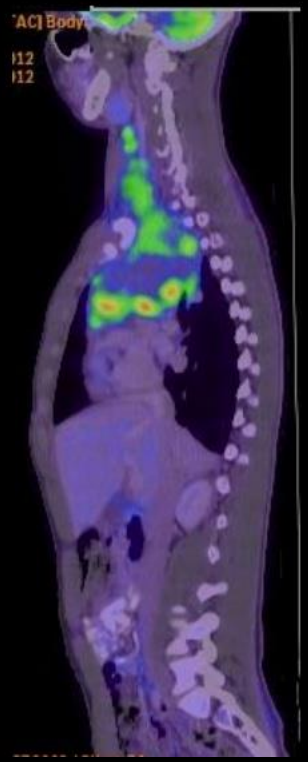
Extralymphatic = tissue other than lymph nodes, thymus, spleen, Waldeyer's ring, appendix & Peyer's patches

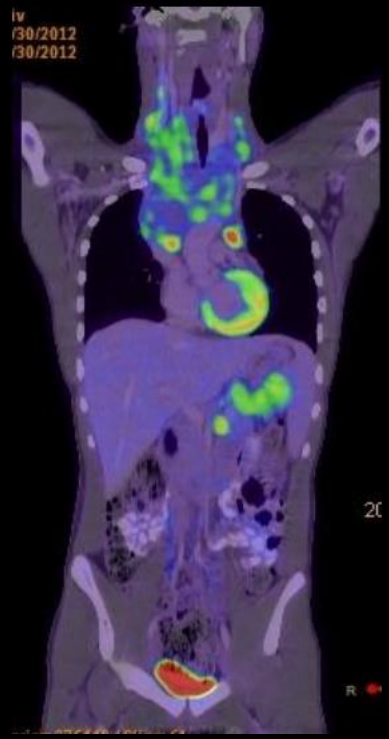
Staging: IIIS











Hodgkin Lymphoma
Staging

- PET scans useful in **upstaging** in stage I-II disease.
  - 10-40% alter in stage.
  - 40-60% change management

- Accurate in assessing nodal, extra-nodal disease, soft tissue lesions, BM and spleen.

-PET accuracy 96% compared to 56% with CT.

- PET sensitivity 91% " " 80% " ".

Lymphoma

Restaging
Interim Assessment
End of treatment Evaluation

Restaging

- A process used to find out the amount or spread of cancer in the body if it regress or progress after treatment.

- Restaging may also be done to find out how the cancer responded to treatment.

Hodgkin Lymphoma
Restaging:

- FDG-PET is the primary restaging tool in:
  - Unfavorable or Bulky Stage I / II
  - Stage III / IV

- FDG-PET is the **restaging tool** after therapy in **favorable stage I / II**

Unfavorable Factors

Bulky mediastinal or > 10 cm disease

B symptoms

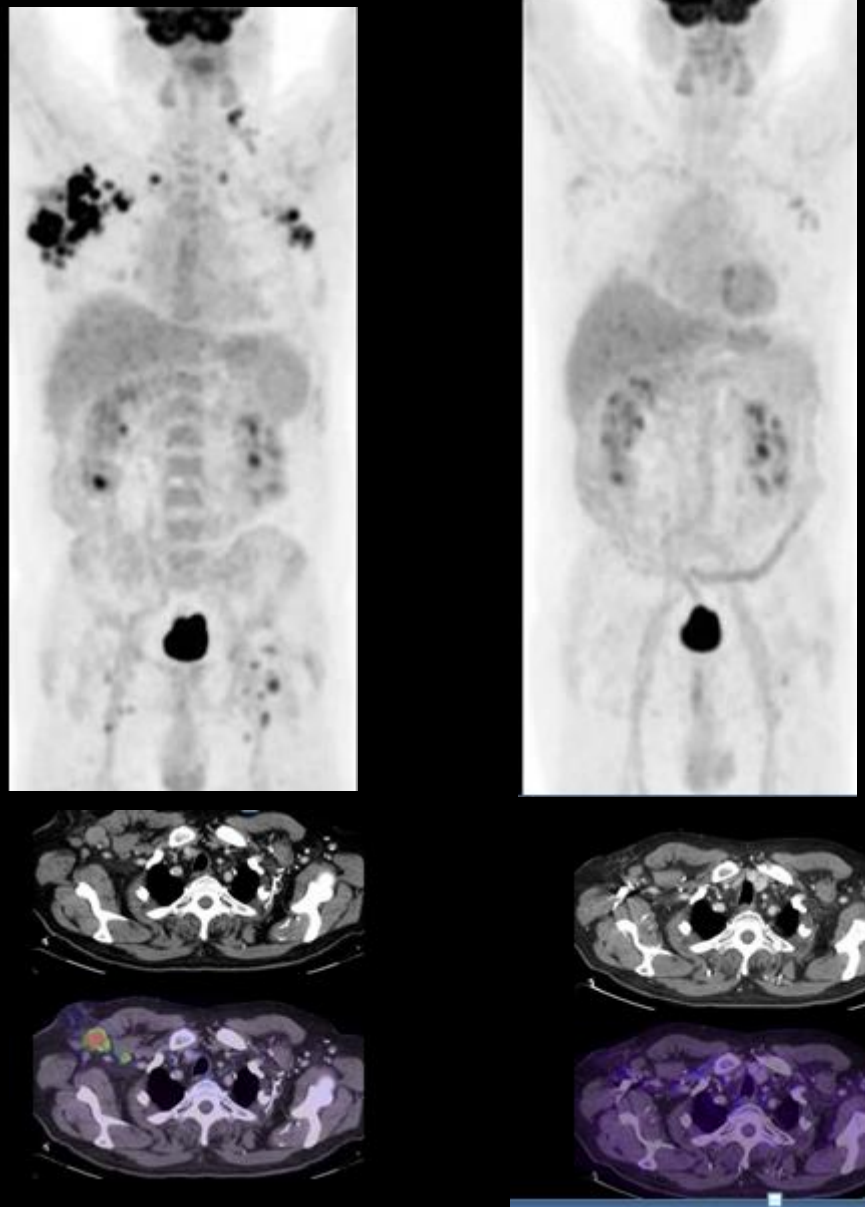
ESR ≥50

> 3 sites

Restaging after Treatment

Before Treatment

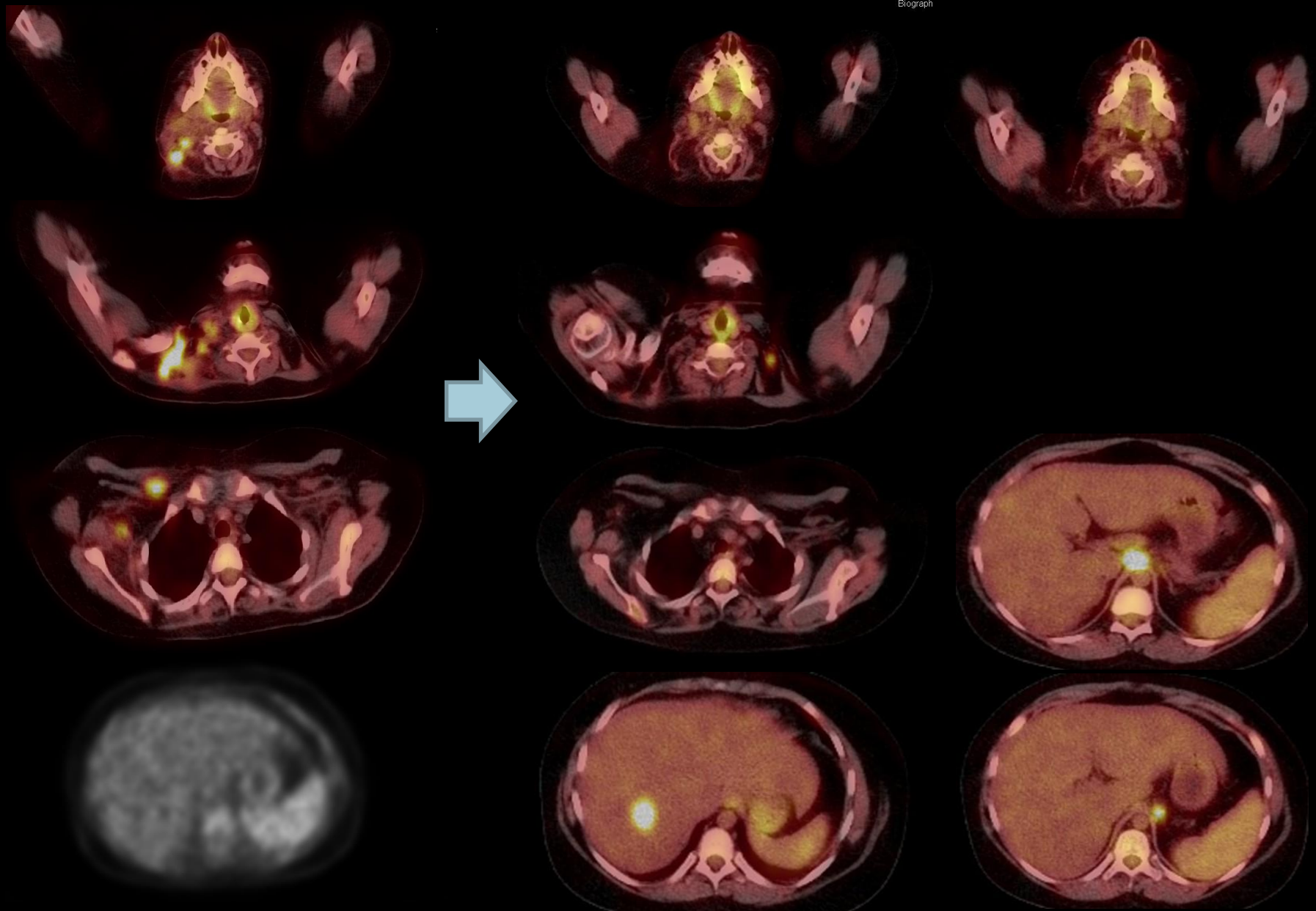
After Treatment



Restaging: upstage

Before therapy

After therapy



Deauville Criteria

- Based on **Visual Assessment** of FDG uptake in the involved sites

Deauville five-point scale (Deauville 5ps)

An internationally recommended scale for clinical routine and clinical trials using FDG-PET/CT in the **initial staging** and **assessment of treatment response** in HL and certain types of NHL.

Deauville Criteria

- Visual analysis using a five point-scale (5-PS)

- FDG uptake in the involved sites relative to Mediastinum and Liver

NCCN Guidelines Version 1.2017
Hodgkin Lymphoma (Age ≥18 years)

PET 5-POINT SCALE (DEAUVILLE CRITERIA)

Score	PET/CT scan result
1	No uptake
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but ≤ liver
4	Uptake moderately higher than liver
5	Uptake markedly higher than liver and/or new lesions
X	New areas of uptake unlikely to be related to lymphoma

Deauville Scores:

Score 1 (no uptake) **& 2** (≤mediastinum): Negative

Score 3: might be considered Positive or Negative (depending on institution and/or treatment plan)

Score 4 (moderately>liver) **& 5** (markedly>liver or new lesions): Positive

- **Score 3** might be either considered as FDG-PET **positive** when a therapy decrease is planned or **negative** when treatment intensification is planned.

- In some literatures Score 3 is also concluded as complete metabolic response.

Evaluating treatment response at the end of treatment by PET scan:

Complete Response: PET negative in a mass which was FDG avid before therapy.

Mass of any size is permitted.

Partial Response: One or more PET positive sites remain positive (FDG avid in baseline scan).

Stable Disease: PET still positive in prior sites of disease - No new site.

Progressive or Relapsed Disease: Any new FDG avid site

Metabolic Response: European Organization for Research and Treatment of Cancer (EORTC) criteria

- Progressive disease: Increased FDG uptake (SUV max) by 25 % or new sites with FDG uptake

- Stable metabolic disease: Increased FDG uptake (SUV max) in previous lesions no more than 25 %, or **decreased** FDG uptake **no more than 15 %** of baseline activities.

- Partial metabolic response: Decreased FDG uptake in previous lesions more than 15 % after 1st cycle of chemotherapy and more than 25 % after next cycles compared to baseline.

- Complete metabolic response: No FDG uptake above background level in the previous lesions

Rsponece according to D5PS

Score 1 and 2 reveals complete metabolic response to treatment

Score 3: ?

Response according to 5-PS

Score 4, 5 with reduced uptake from baseline is partial metabolic response (PMR)

-At interim this suggests responding disease

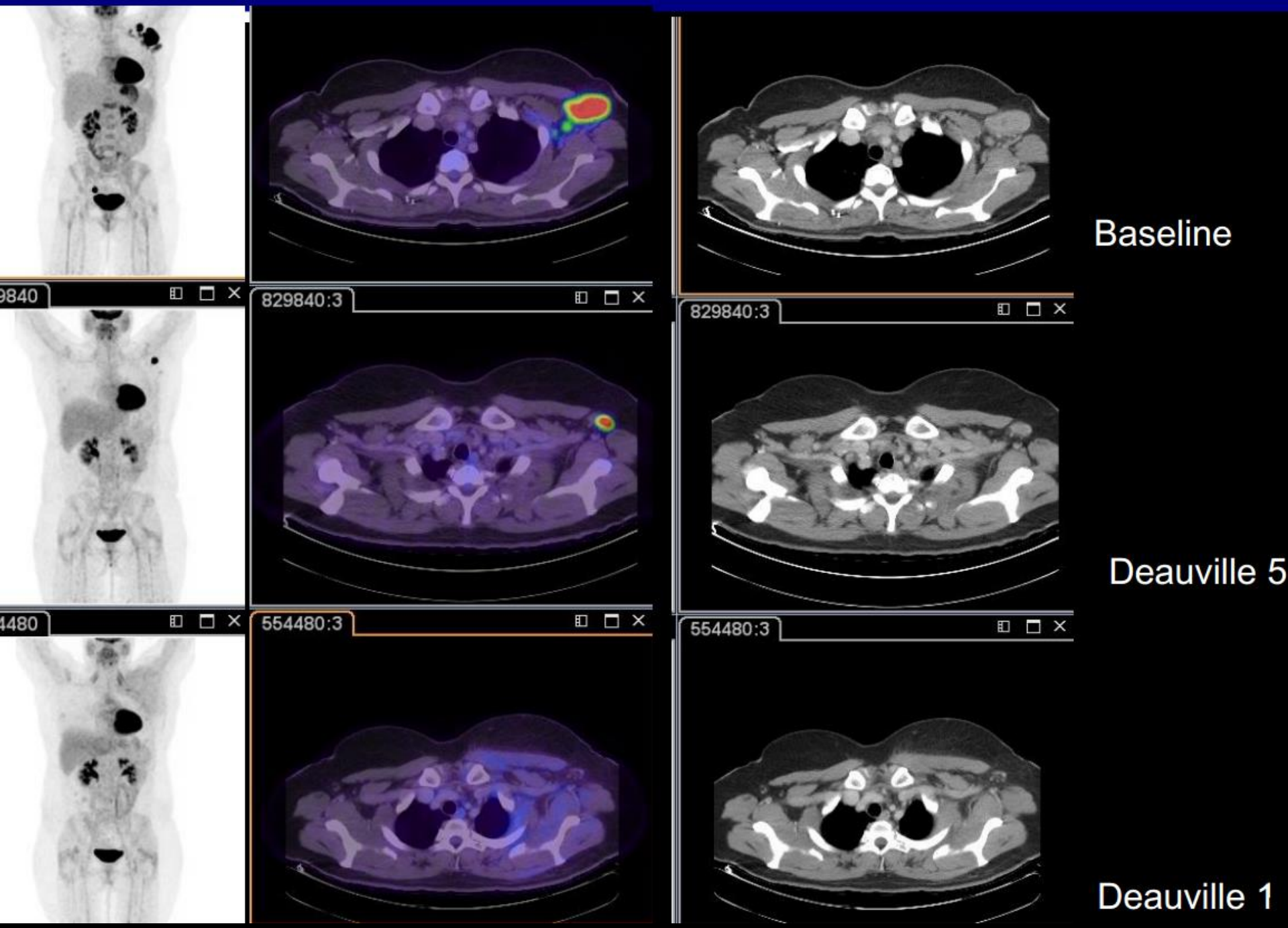
-At end of treatment this suggests residual metabolic disease

Response according to 5-PS

Score 4, 5 with no change in uptake from baseline means no metabolic response (NMR)

Score 4, 5 with an increase in uptake from baseline &/or new lesions is progressive metabolic disease (PMD)

-At interim and end of treatment NMR and PMD indicates treatment failure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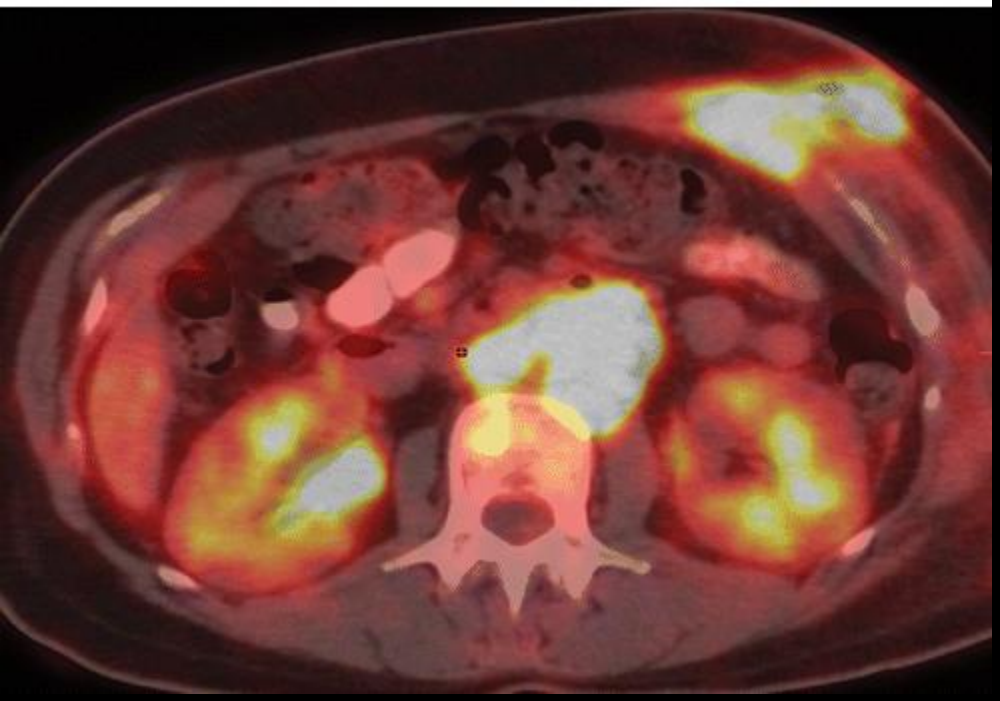
554480:3
554480:3
Baseline
Deauville 5
Deauville 1

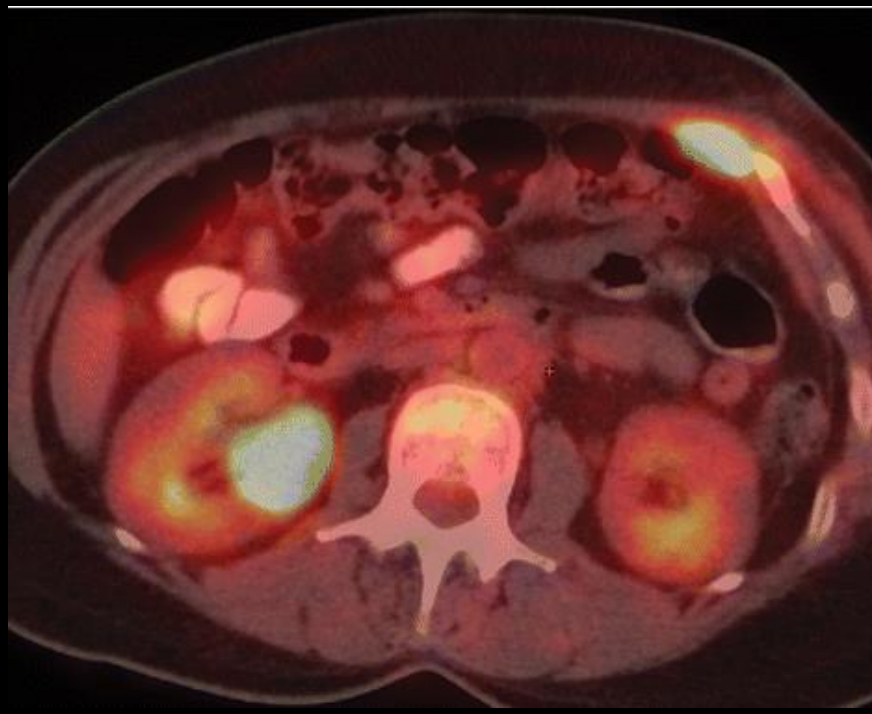
Retroperitoneal Mass

Post-surgical abdominal wall inflammation

Deauville score 5

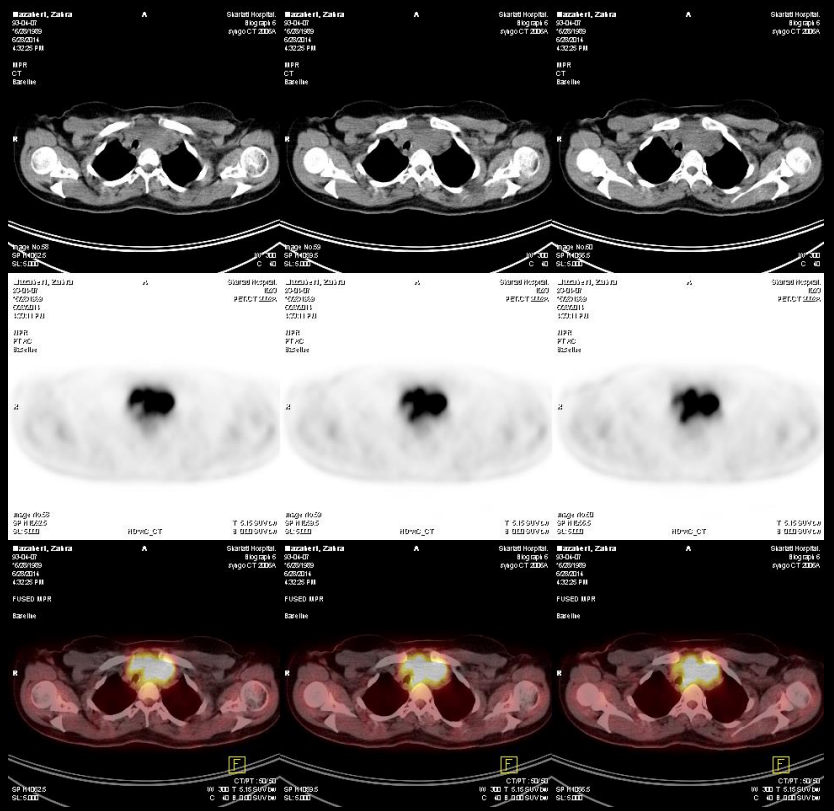


Deauville score 1

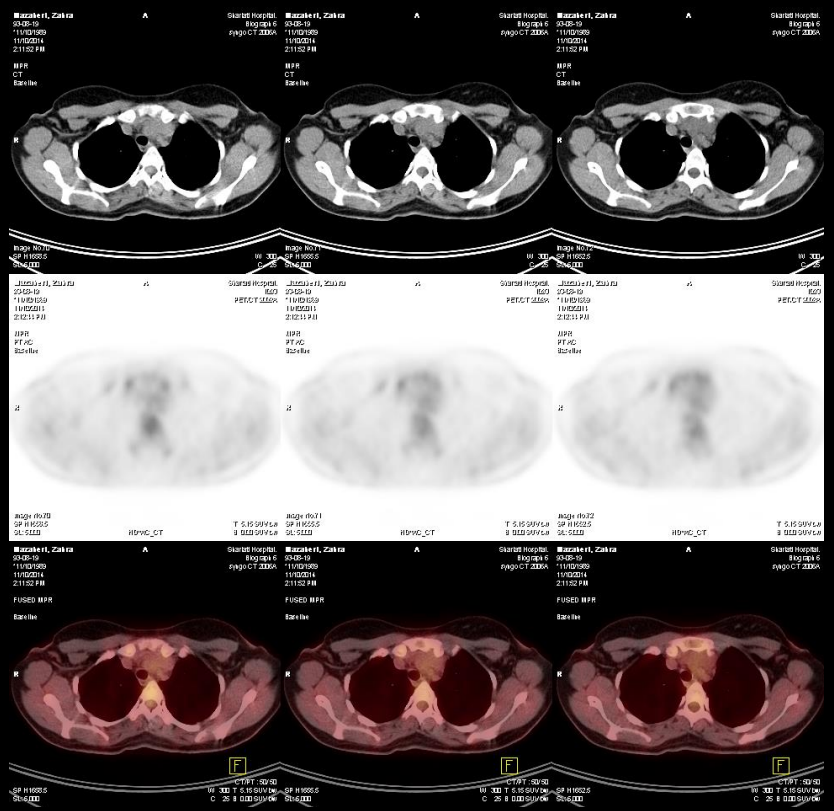


Complete Metabolic Response

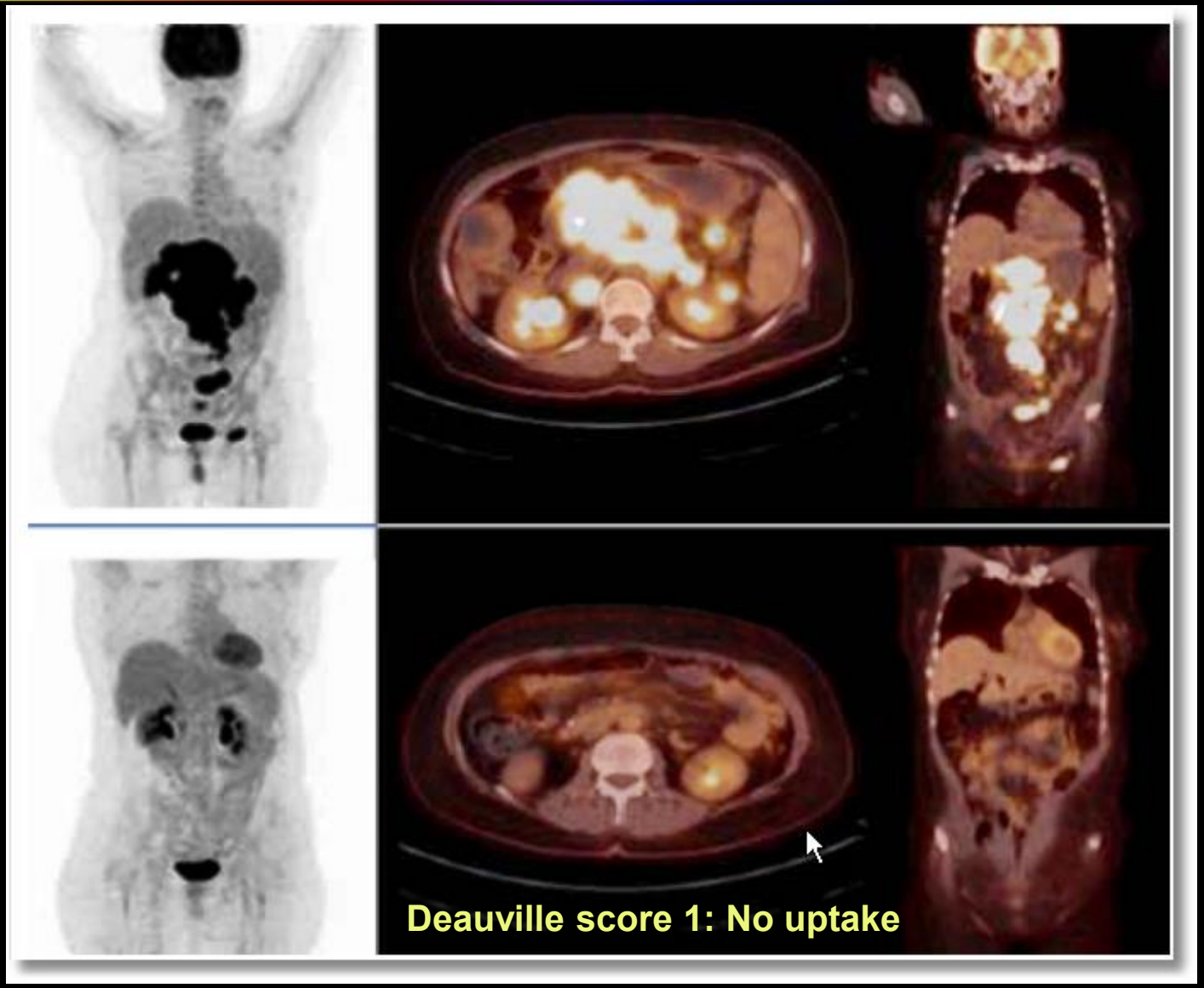
- Before Treatment



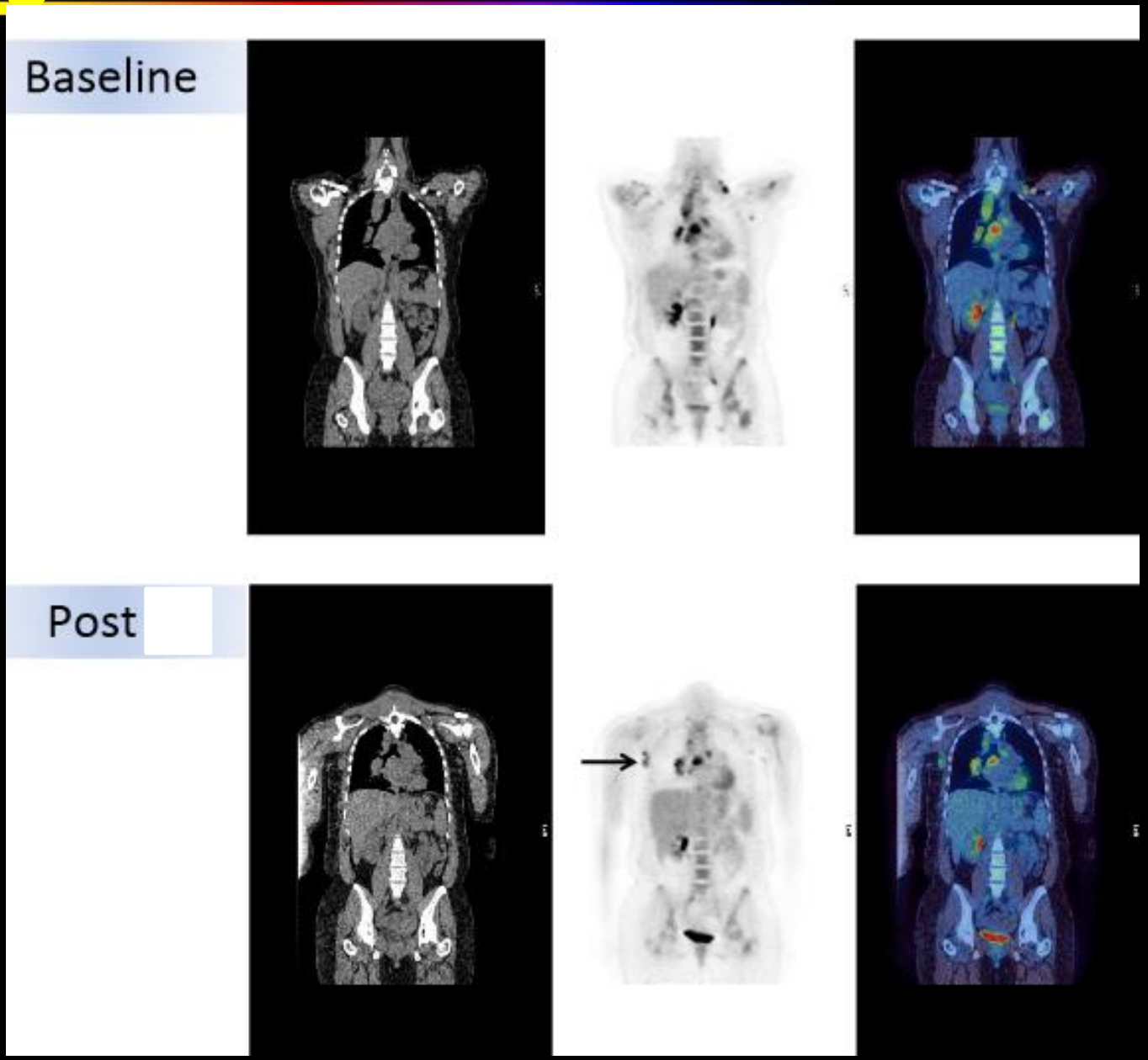
- After Treatment



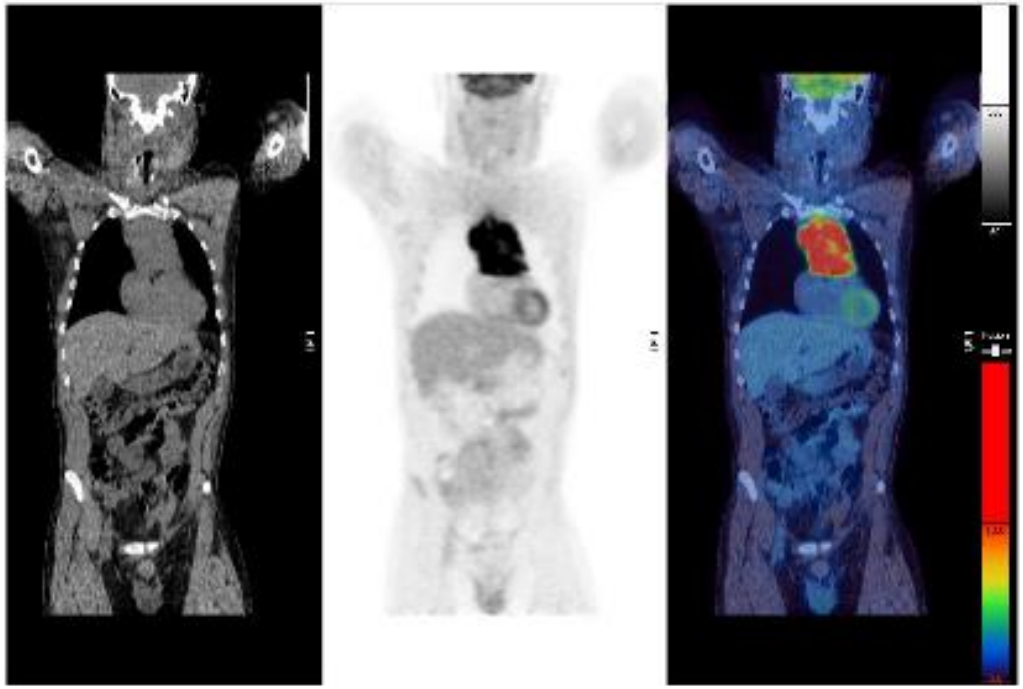
Complete metabolic response



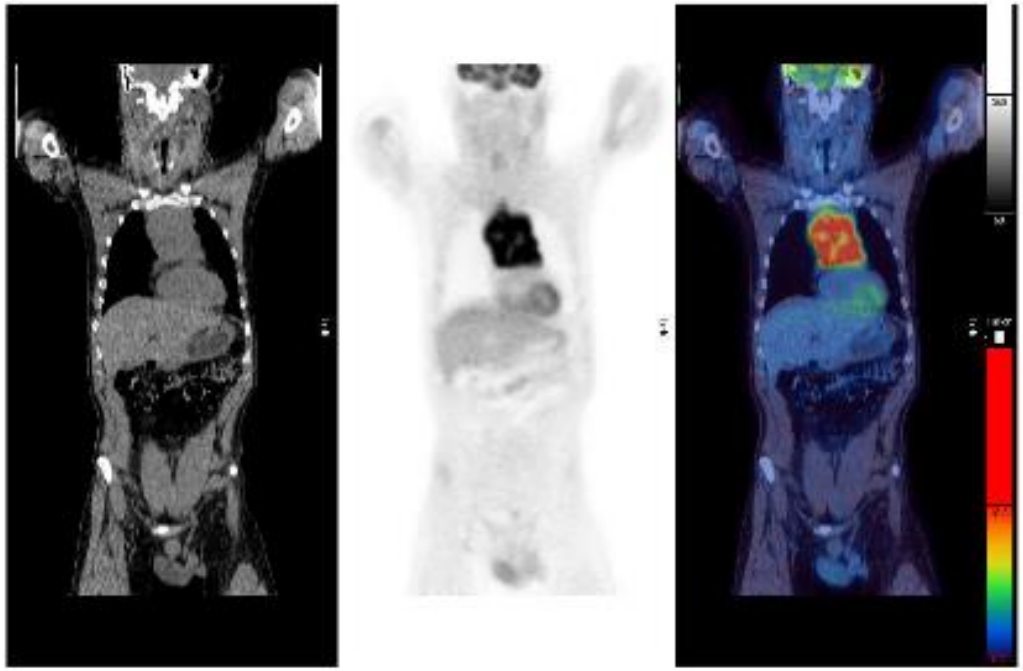
Progressive Metabolic Disease



Baseline



Response

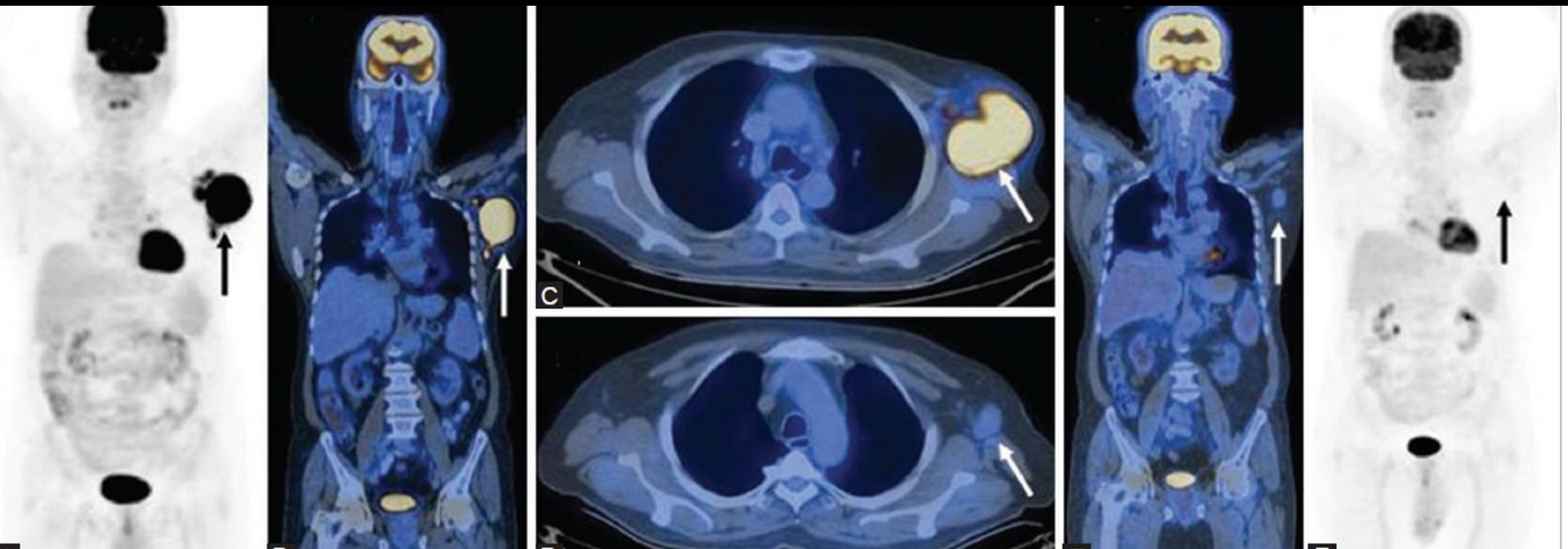


Score 5

NMR

Response to Treatment

- Evaluating residual mass at the end of treatment



Residual masses

- After completion of therapy CT will often reveal residual masses.
- Very difficult to assess whether this represents viable lymphoma, fibrotic scar tissue or necrosis in patients with otherwise clinical complete response.
- Biopsy on all these lesions would be impractical, and even if it were done it would be too inaccurate.

Interpretation of Treatment Response in NON-Hodgkine Lymphoma

- In some cases, a baseline FDG-PET/CT should be performed prior to therapy initiation.

Minimal Residual Disease

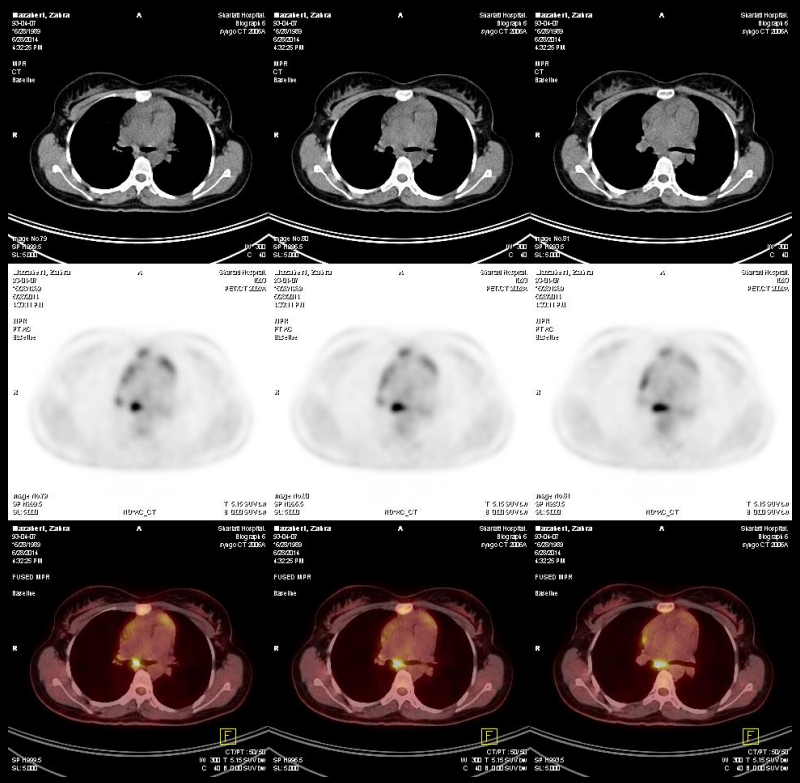
- A persisting faint residual FDG, most often in a site with previous bulky disease.

- Grey-zone in interpretation

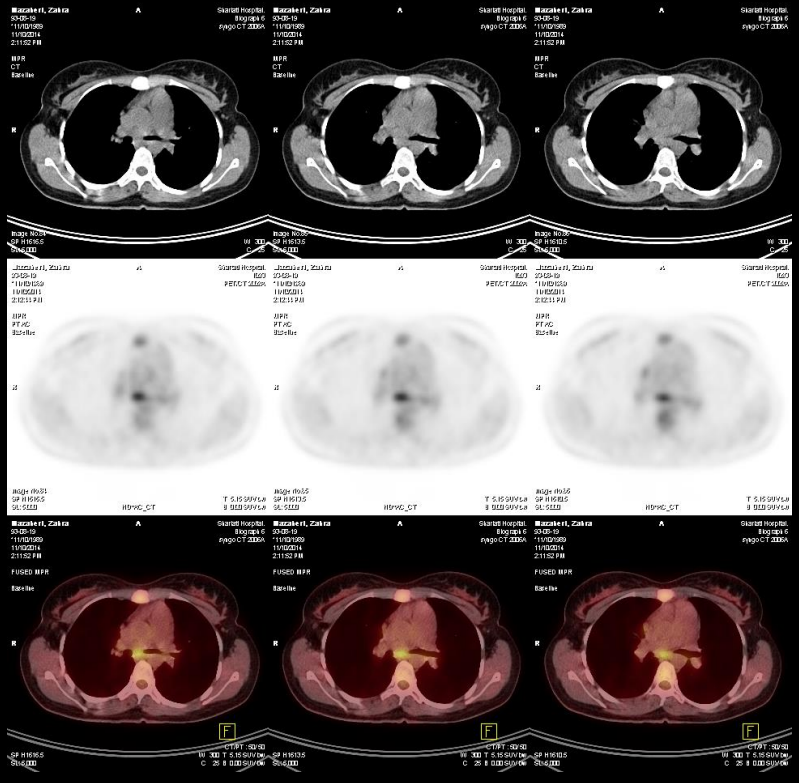
- In a study, these patients behaved similarly to PET negative patients

- However, the decision making could be challenging for the oncologist

- Before Treatment

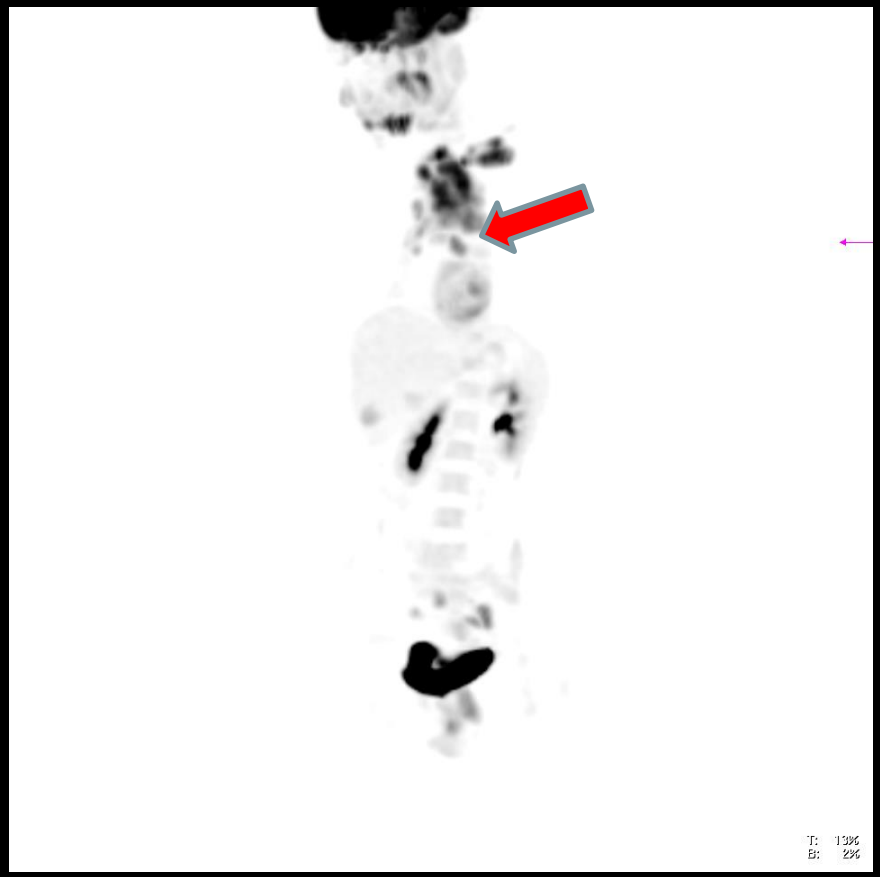


- After Treatment

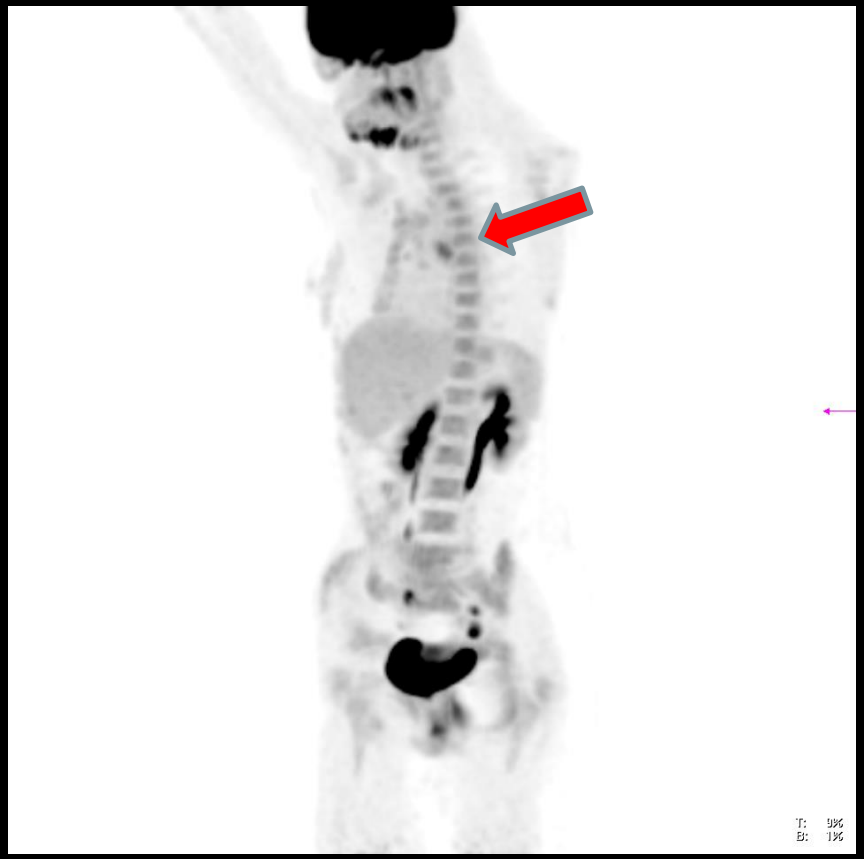


Response to Treatment
Minimal Residual Disease

- Before Treatment

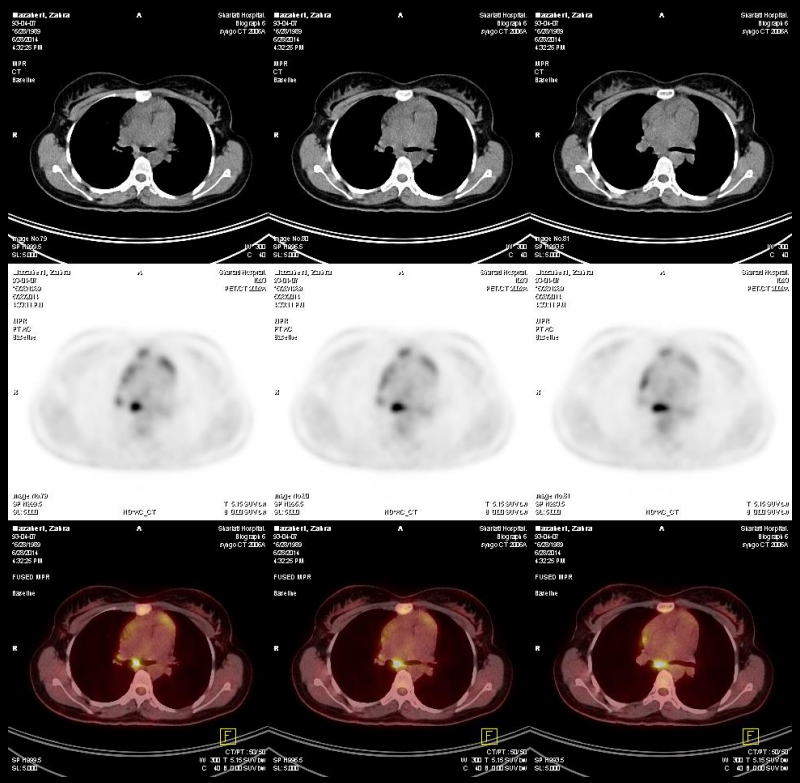


- After Treatment

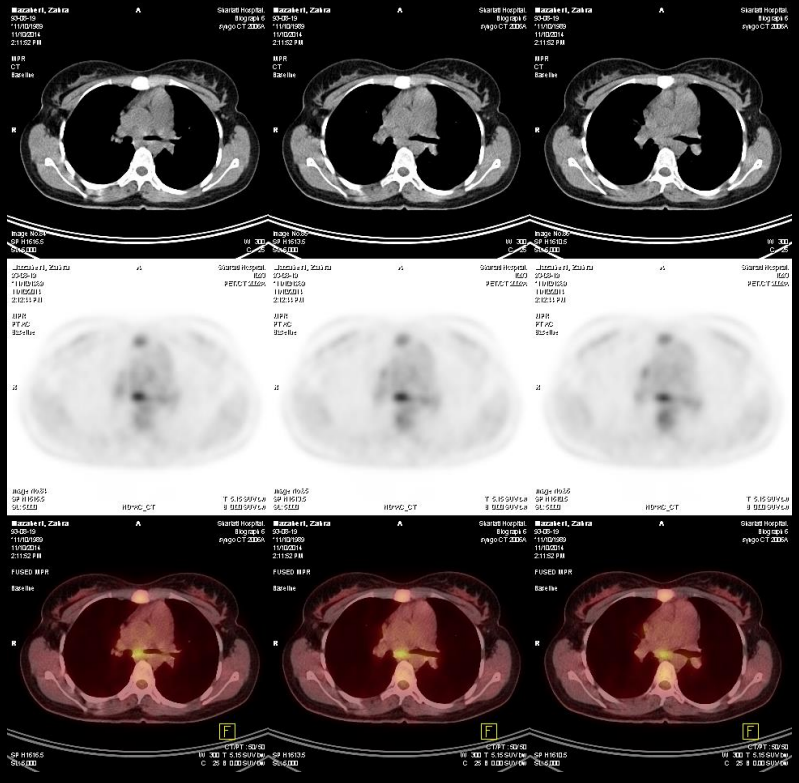


Stable disese

- Before Treatment



- After Treatment



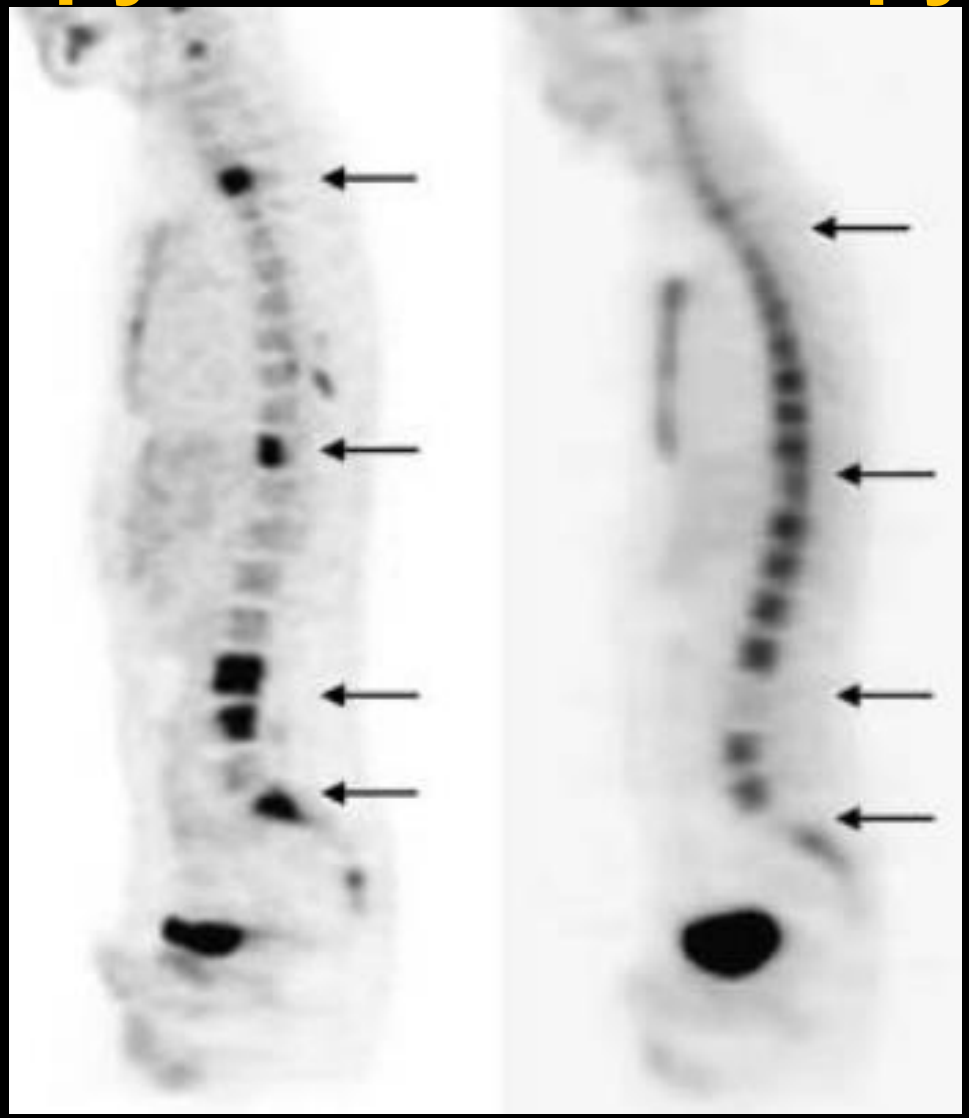
Minimal Residual Disease

5-y progression-free survival

PET-negative group	Minimal residual uptake	PET-positive group
90%	**60 %**	**16%**

Management of Hodgkin's disease on the basis of NCCN, in relation to PET imaging

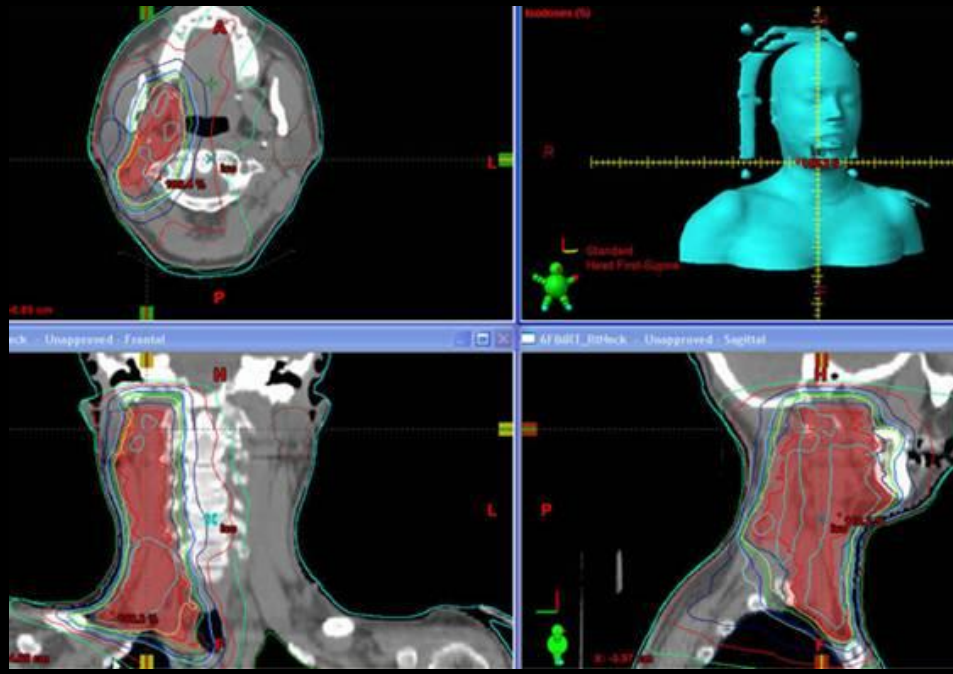
BM involvement (stage IV) , Pretherapy and Post-therapy scans



Radiation treatment planning

•Incorporation of PET can enhance treatment planning.

•The gross tumor volume **(GTV)** defined by PET/CT prior to chemotherapy or surgery provides the basis for determining the clinical target volume **(CTV),** and hence planning target volume **(PTV)** which is an enhancement of CTV to account for possible variations and internal organ motions.



Role of PET in diagnosis of Hodgkin Lymphoma?

Diagnosis is based on **HISTOPATHOLOGY**

- PET has limited role, as FDG is nonspecific
- However, it can help **guide biopsy**

Surveillance for Hodgkin by PET

- Should not be done routinely due to risk for false positives.

- Management decisions should not be based on PET scan alone; clinical or pathologic correlation is needed.

Technical Considerations in [18F]FDG-PET/CT for Hematologic Malignancies

Pitfalls and Limitations

Normal Findings

Common pattern of visceral involvement


Thank you

Pitfalls and Limitations

1.Limited spatial resolution of PET scanners may reduce sensitivity for detecting small lesions. Advanced reconstruction methods (e.g., point spread function) can improve image clarity but may lead to overinterpretation, increasing the risk of **overtreatment** and long-term **toxicities or secondary cancers**.

2.Misalignment between PET and CT data can occur, especially due to respiratory motion when CT is performed in deep inspiration. This can result in **localization errors** and inaccurate attenuation correction, necessitating compromises in CT image quality.

3.CT contrast agents may introduce artifacts that artificially increase PET signal (SUVs), particularly in non-tumor areas like the liver or mediastinal blood pool, potentially misleading interpretation.

- **Tumor SUV changes**
  - **Residual disease assessment** (e.g., Deauville score),
  - **Tumor-to-background SUV ratios**, and
  - **Changes in SUV over time** (e.g., ΔSUVmax).

Normal Findings

Head and Neck Normal [18F]FDG Distribution and Considerations

•**Brain:**
•**Waldeyer's Ring: symmetric uptake**. Slight asymmetry can be non-pathological, but in **lymphoma patients**, significant asymmetry should be evaluated carefully with both **PET** and **CT scans**, and **biopsy** may be needed if it changes patient management.

•**Cervical Lymph Nodes:** Bilateral cervical lymph nodes, especially in **level II**, can also be seen, raising diagnostic challenges in lymphoma patients. Comparison with other involved nodes or biopsy may be necessary for accurate diagnosis.

•**Salivary Glands and Thyroid:**
- **Salivary glands** may show mild, homogeneous, and symmetric uptake.
- **Thyroid** typically shows **absent or mild uptake**, with a diffuse, homogeneous distribution.

Normal Findings

•**Thymus:** The thymus is commonly seen in children and young adults, appearing as an **anterior mediastinal soft tissue** with an inverted "V" shape and **mild [18F]FDG uptake**. In patients with hematological malignancies, care is needed as the thymus can **hypertrophy and increase FDG uptake** after chemotherapy (thymic rebound), which may lead to **false-positive findings**.

•**Breast Tissue:** Generally shows **low FDG uptake**, but this can increase:

- In the **postovulatory phase** of the menstrual cycle or with more **active glandular tissue**.
- **Lactating breasts** can show **bilateral high, heterogeneous uptake**.
- Uptake **decreases with age** and reduced breast density.

•**Mediastinum and Myocardium:**

- Mediastinal activity is influenced by **blood pool FDG activity**.
- **Myocardial activity** is variable and depends on fasting:
  - Under normal conditions, the heart uses glucose, showing increased uptake.
  - During fasting, the heart shifts to **fatty acid metabolism**, decreasing uptake.
  - **Homogeneous left ventricular myocardial uptake** is the most common finding.

•**Lipomatous Hypertrophy:** The **lipomatous hypertrophy** of the atrial septum and **crista terminalis** can cause **false-positive FDG findings** due to increased uptake.

•**Lung and Pleura:** Typically, the **lungs and pleura** show **very low FDG uptake** unless associated with pathology.

Normal Thymus

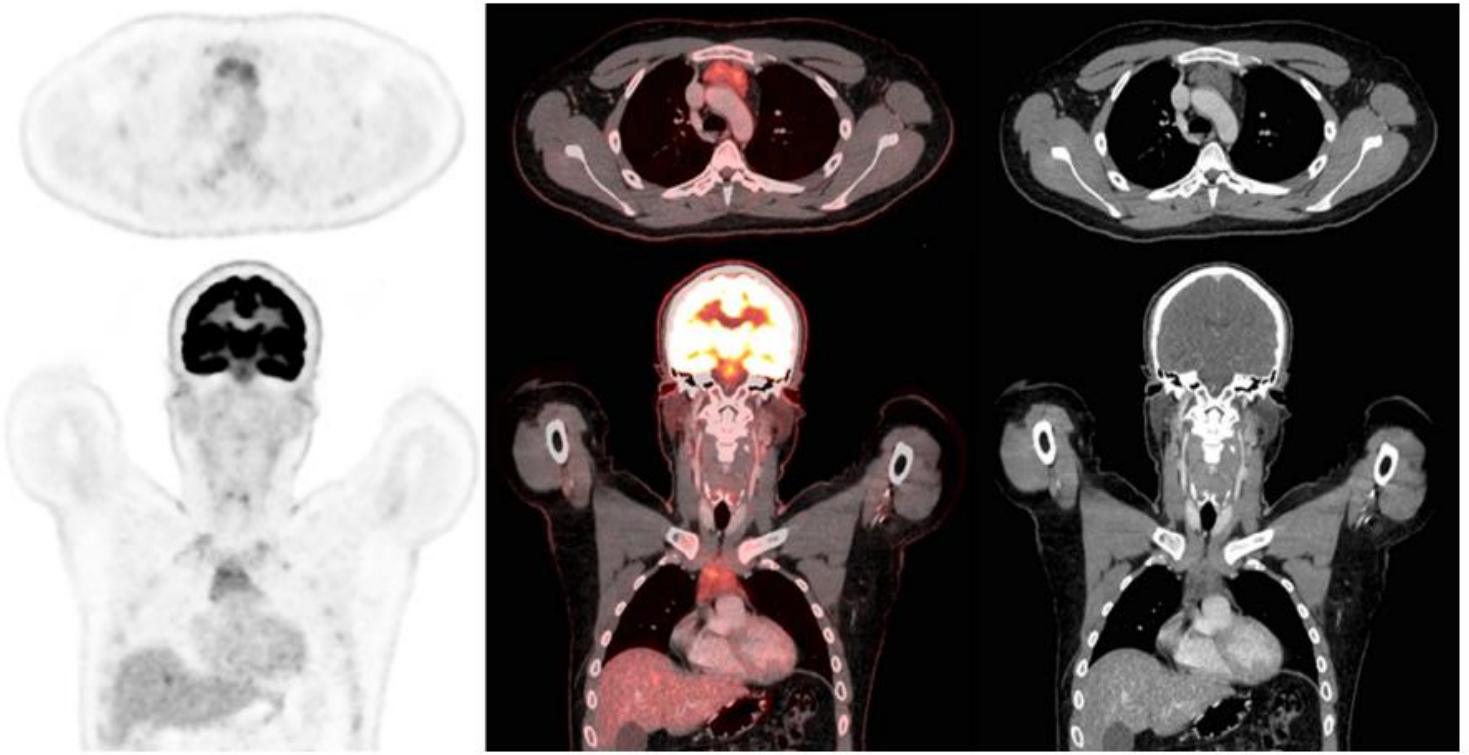


Figure 2 Transverse and coronal slices of FDG-PET/CT, fusion and CT in a 22- year-old male patient with common variable immune deficiency and weight loss in whom malignant disease needed to be excluded. FDG-PET/CT showed moderately to strongly increased FDG-uptake in the anterior mediastinum, representing thymus hyperplasia. This physiological entity is a pitfall of FDG-PET imaging and should not be interpreted as a malignant finding. No malignant lesions were detected in this patient.

- **[18F]FDG activity** in the GI tract is common and usually benign. Its mechanism is not fully understood but likely involves **mucosal and smooth muscle uptake**, **microbial overgrowth**, and **FDG excretion**.

- **Normal FDG uptake** is typically **mild to moderate** and **diffuse**.

- **Focal activity** (e.g., in polyps, inflamed diverticula, focal colitis) is a normal variant but should be evaluated to rule out malignancy by:
  - **Correlating with CT findings**,
  - **Using dual-time-point imaging**, or
  - **Recommending colonoscopy**.
- **Intense colonic activity** with **diffuse distribution** can occur in conditions like **colitis**, **inflammatory bowel disease**, or with the use of **oral antidiabetic drugs** like **metformin**.

•**Solid Abdominal Organs (Liver, Spleen, Pancreas, Adrenals):**
- **[18F]FDG uptake** in these organs is usually **mild**, **diffuse**, and **homogeneous**.
- The **liver** generally shows the **highest FDG uptake** among the solid abdominal organs.

•**Kidneys and Urinary Tract:**
- **[18F]FDG** is excreted by the kidneys, leading to **uptake in the calyces, ureters, and bladder**.
- **Ureteral activity** can appear **heterogeneous** due to **peristalsis**.

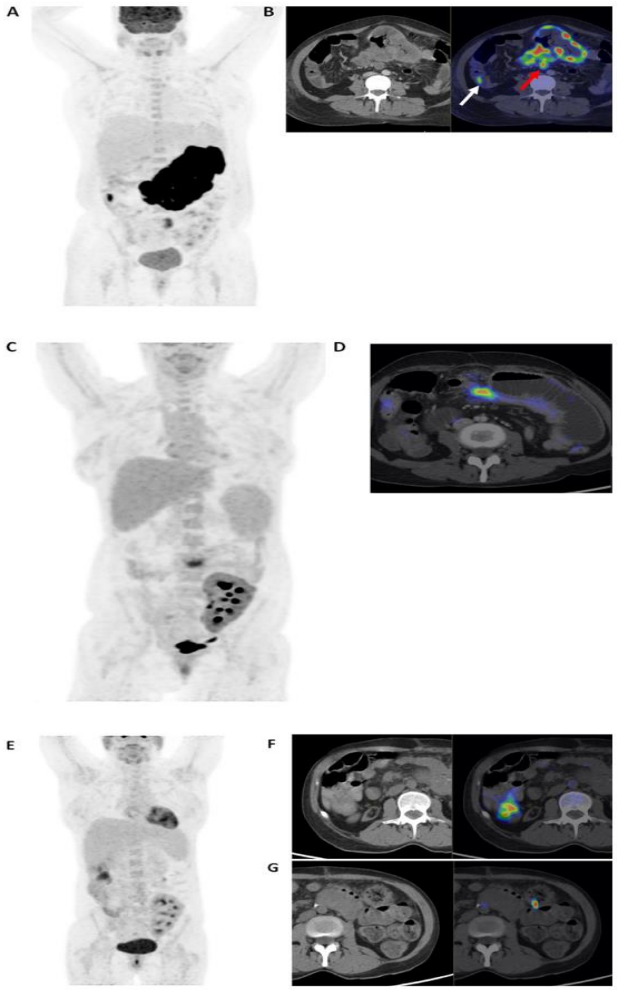


Figure 3 Forty-two- year-old patient with renal transplant and the diagnosis of intestinal non-Hodgkin's lymphoma, diffuse large beta cell subtype. (A and B) Staging PET-CT shows extensive involvement of the small intestine with wall thickening that shows increased metabolic activity. At least two necrotic mesenteric lymph nodes are noted (red arrow). Also, another two sites of focally increased uptake are noted near the hepatic angle of the colon (white arrow) and in the terminal ileum, which are also considered as lymphoma involvement. (C) PET-CT after four cycles of R-CHOP shows a very good response, nevertheless, there is persistent uptake in the lesion at the terminal ileum (D) which causes intestinal obstruction. (E) PET-CT after completing 6 cycles of the treatment, shows response of all previously visualized lesions, but 2 new sites of increase metabolic uptake are seen in the (F) hepatic angle of the colon and (G) in the proximal transverse colon. Due to the paradoxical findings, colonoscopy was performed and biopsies were taken from both lesions, with a final histopathological result of: (F) tubular adenoma with low grade epithelial dysplasia and (G) hyperplasic polyp.

- **Pre-menopausal Women:**
  - **Endometrial Uptake:** Increased FDG uptake may be seen during the **flow phase** (first 4 days of the menstrual cycle) and during **ovulation** (day 14).
  - **Ovarian Uptake:** Can be seen during **ovulation** and in association with a **corpus luteal cyst**.
- **Post-menopausal Women:**
  - No FDG uptake should be seen in the **endometrium** or **ovaries**. Any uptake in these areas is **suspicious** and should prompt further investigation.
  - **Documenting the date of the last menstrual period** is crucial for interpreting FDG uptake in post-menopausal women.
- **Men:**
  - **Prostate Uptake:** Generally **mild and homogeneous**, even in cases of **benign prostate hyperplasia**. Any **focal uptake** should be further investigated.

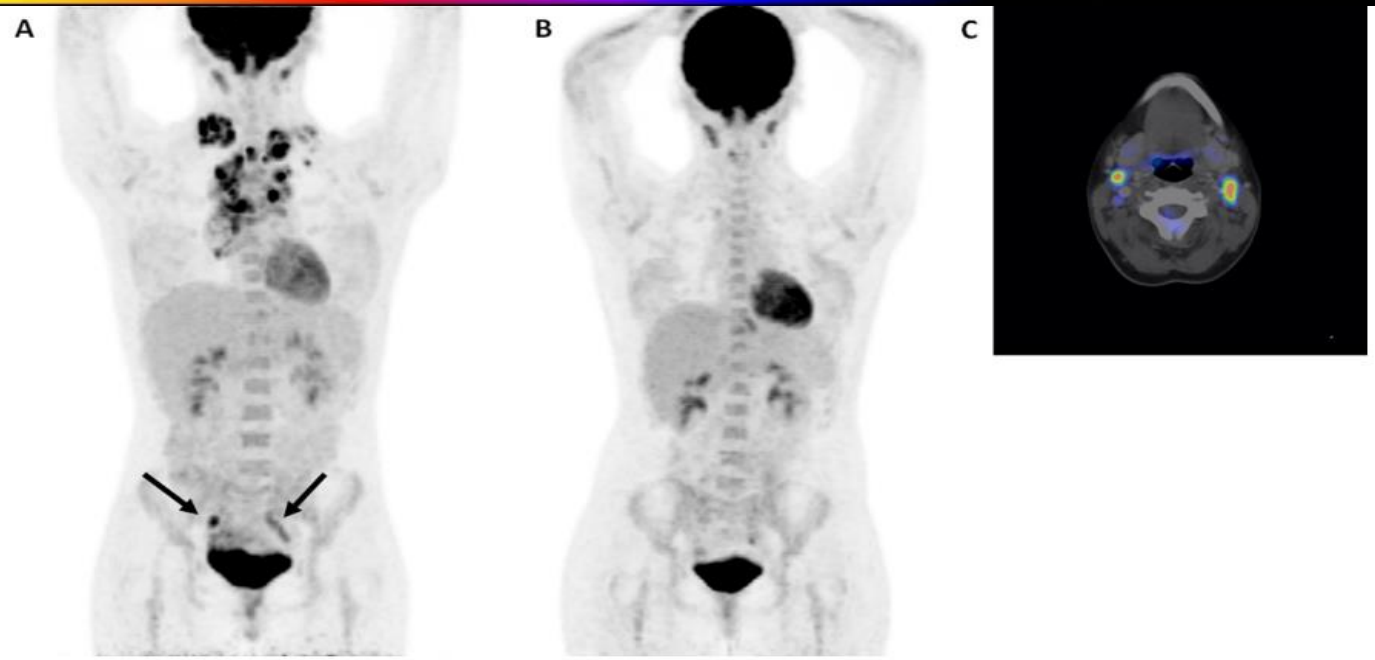


Figure 1 This is the case of a 22-year-old patient with Hodgkin's Lymphoma, Nodular Sclerosis subtype. (A) Staging PET-CT show cervical and mediastinal lymph node involvement (Stage II). Arrows show bilaterally increase uptake in ovaries due to menstrual cycle. (B) PET-CT after 4 cycles of ABVD treatment shows a complete metabolic response of most of the mediastinal and cervical lymph nodes, (C) while the superior cervical lymph nodes (bilateral level II) show persistent increased metabolic activity. Due to the discordant findings, ultrasound guided core needle biopsy of both cervical lymph nodes is performed. Histopathological examination of both cervical lymph nodes shows reactive follicular lymphoid hyperplasia with no signs of infiltration by lymphoma, therefore no change in management was needed.

Skeletal and Muscular System:

•Muscles:

- **[18F]FDG uptake** is commonly observed in muscles such as those in the **ocular region**, **tongue**, **mastication**, and **phonation** due to activation before or during the imaging period.

- Recent **insulin injections** or **food intake** can also lead to increased FDG uptake in muscles.

- Uptake is typically **symmetric**, but can be **asymmetric** in cases of **surgery**, **irradiation**, **muscle contraction**, or **unilateral palsy**.

- **Focal uptake** at the **genioglossus insertion** in the oral cavity is common and relates to muscle activity that helps maintain the upper airway when lying down.

•Bone and Bone Marrow:

- **Cortical bone** generally shows **mild and homogeneous** uptake if no underlying abnormalities are present.

- **Bone marrow activity** is typically lower than that of bone, except in certain cases, which are detailed in a subsequent section.

Brown Fat Normal [18F]FDG Distribution and Variants

Brown Fat:

- **Incidence and Characteristics:**
  - **Brown fat uptake** is commonly observed in **young female patients**).
- **Common Locations of Uptake:**
  - **Head and Neck Region** (mostly posterior aspect)
  - **Suprasternal notch/ Upper axilla/ Mediastinum/ Paraspinal regions/ Cardiac apex/ Pararenal space**

Brown Fat

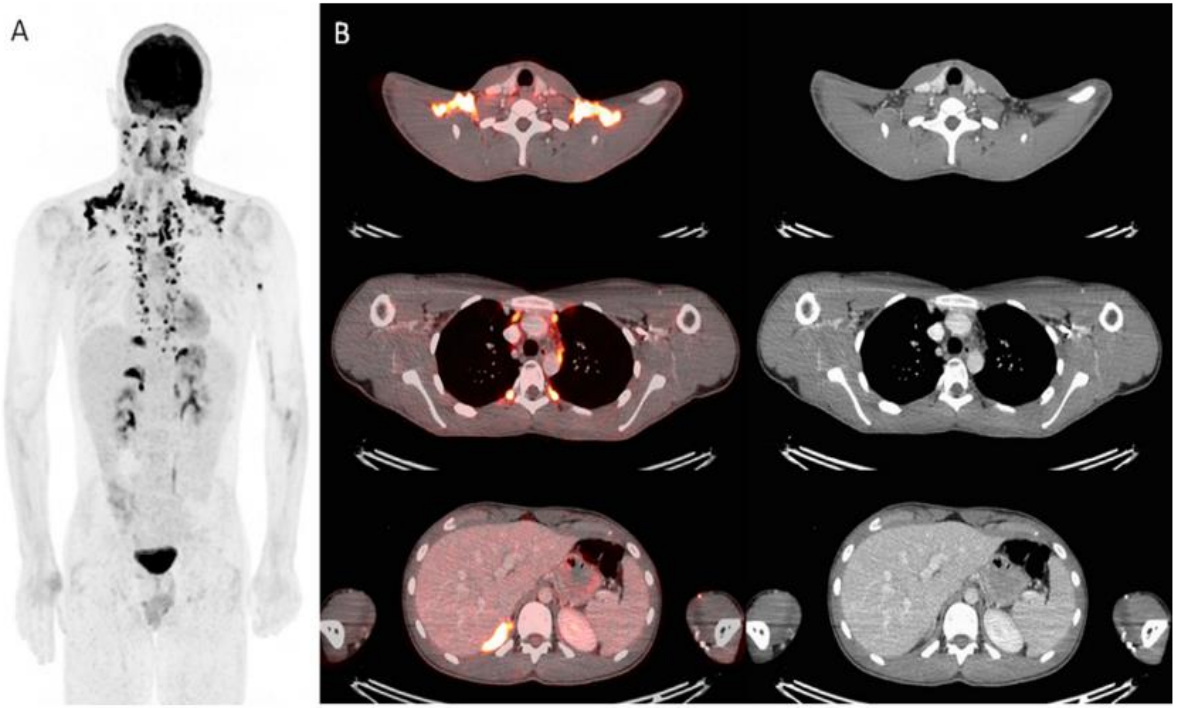


Figure 4 Maximum-intensity projection (MIP) (A) and transverse slices of fusion of FDG-PET/CT and CT (B) demonstrating physiological high FDG-uptake in brown fat in cervical, paraclavicular, paravertebral, mediastinal, parasternal, retrocrural and pararenal regions in a 17-year old male patient with suspicion of lymphoma due to eosinophylic fasciitis. No lesions suspicious of lymphoma were diagnosed on FDG-PET/CT.

Common patterns of visceral involvement

Common patterns of lung involvement include:

•**Bronchovascular/lymphangitic spread**: often from direct invasion by lymph nodes or lymphatics.

•**Nodular lesions**: may be single or multiple; in AML, MDS, or MPN, consider **myeloid sarcoma**.

•**Pneumonic/alveolar pattern**: may mimic bacterial pneumonia.

•**Miliary pattern**

•**Other findings: endobronchial disease**, **pleural effusion**, and **vascular complications** (e.g., SVC syndrome, thromboembolic events).

Interpretation challenges include:
•**Infectious lung diseases**, especially from opportunistic pathogens in immunosuppressed patients. Typically present as **mild and diffuse increased uptake** with **typical CT findings**. If **lung involvement** was not present before treatment, such findings should not be interpreted as disease progression.
Noninfectious causes like **drug-induced lung injury** (e.g., from immunotherapy or transfusions), which account for up to half of lung-related findings.
•**Primary lung cancer** must also be considered in the differential diagnosis.

Pulmonary Infection

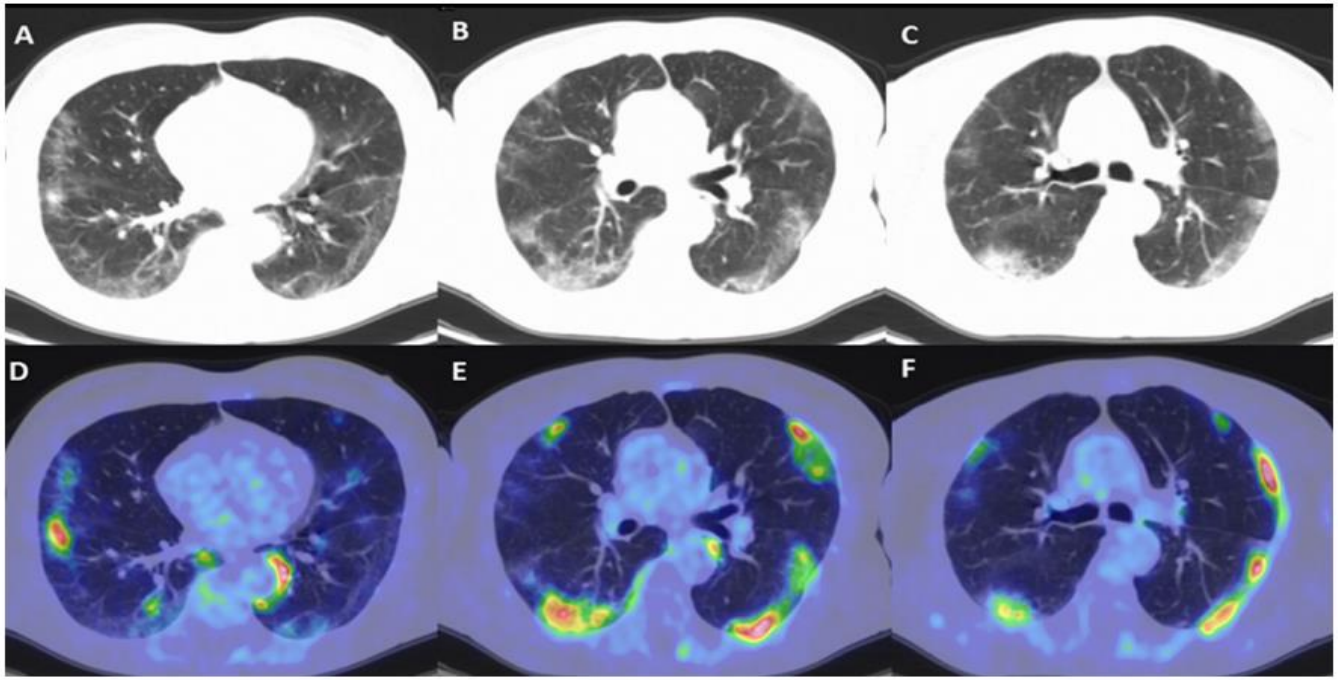


Figure 5 Herein we report on a 62 year-old male referred for restaging ^{18}F-FDG PET/CT during Non-Hodgkin lymphoma treatment. The patient had no history of pulmonary disease and was overall asymptomatic, that is, no fever or cough prior to the scan. An unexpected diffuse lung parenchyma involvement with inflammatory infiltrate was seen (A-C). Fused ^{18}F-FDG PET/CT images (D-F) documented an associated intense hypermetabolism in all subpleural and periaortic lung opacities; in addition, the presence of some residual lymphoma was seen in the abdominal region. Given the pandemic situation, the imaging findings required a differential diagnosis with COVID-19. The patient was therefore immediately tested by reverse transcriptase- polymerase chain reaction (RT-PCR), which confirmed positive for COVID-19. In the subsequent weeks, the patient was hospitalized and treated. After a period of quarantine and two consecutive negative nasal swabs, the patient was considered recovered. Subsequent lymphoma restaging, two months after initial diagnosis, documented some minor residual subpleural ocapities on CT. with no evidence of residual metabolism in the lungs on restaging ^{18}F-FDG PET/CT, confirming the complete recovery of pulmonary inflammation.

Common pattern of GI Tract involvement in [18F]FDG PET-CT

Key points :

- **Primary GI lymphomas** are rare (1–8% of all GI cancers), but the GI tract is one of the most common extranodal sites for NHL (30–40%). In contrast, it's **extremely rare in Hodgkin lymphoma (HL)**.
- **Stomach** is the most commonly affected site (47–75%), followed by the **ileum** and **colon**.
- **Imaging patterns** include:
  - Diffuse wall thickening/ Focal lesions/ Multifocal lesions ("lymphomatous polyps")
  - All typically show moderate to high FDG uptake, depending on the histologic subtype.

Hepatic involvement is a frequent **extranodal manifestation** in hematological malignancies, but PET-CT findings are often **nonspecific** and can overlap with other conditions.

Key points:

- In **non-Hodgkin lymphoma (NHL)**:
  - **Primary hepatic lymphoma** is rare (<1%).
  - **Secondary involvement** is much more common (seen in ≥50% of autopsies).
  - Liver infiltration can appear as **focal masses**, **diffuse**, **multifocal**, or **miliary** patterns on imaging, with varying FDG uptake.
- In **multiple myeloma**:
  - The liver is one of the most frequent sites of **extramedullary disease** (~30% incidence at autopsy).
  - Lesions present similarly to lymphoma: **unifocal**, **multifocal**, or **diffuse**, often with **moderate to high FDG uptake**.
- In **leukemia**:
  - **ALL and CML** typically show **diffuse uptake**.
  - **AML** tends to present with a **multifocal pattern**.

The **spleen** is a common site of involvement in hematological malignancies, especially **lymphoma**, but interpretation of FDG uptake can be tricky due to overlapping benign conditions.

Key points:

•In **lymphoma**, splenic involvement is seen in **30–40% of patients** and can appear as:

- **Focal**, **miliary**, or **diffuse** FDG uptake.
- **Homogeneous splenomegaly** on CT without focal lesions may still suggest infiltration, though splenomegaly can also occur **without tumor involvement**.

•In **leukemia**, spleen involvement usually presents as:

- **Diffuse FDG uptake** and **splenomegaly**, though **focal/miliary** patterns are also possible.

•In **multiple myeloma**, presenting similarly to lymphoma (with or without focal lesions and increased uptake).

Common false positives (pitfalls):

•**Focal lesions**: Can be caused by **infection**, **infarction**, or **extramedullary hematopoiesis**.

•**Miliary uptake**: Often related to **fungal microabscesses**, especially in immunosuppressed leukemia patients.

•**Diffuse uptake**: May result from **infection response**, **post-therapy effects**, or **hematopoietic proliferation** (often accompanied by increased FDG uptake in the bone marrow).

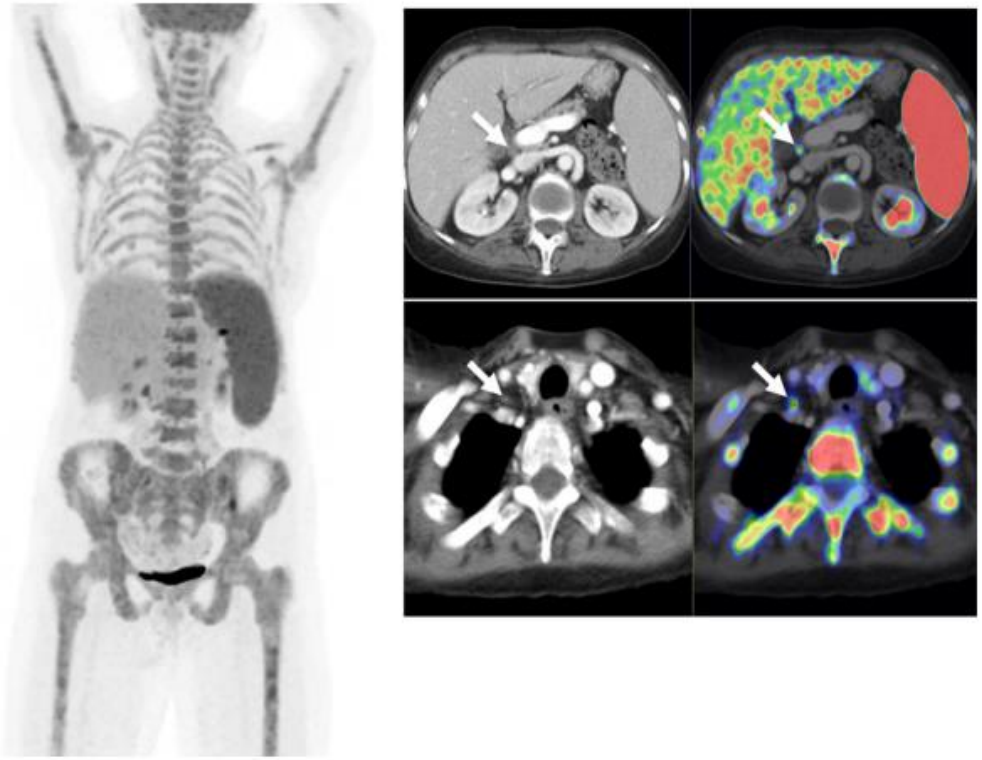


Figure 6 Diffuse bone marrow and spleen uptake (with splenomegaly) in a patient with diffuse large beta cell lymphoma after receiving granulocyte colony-stimulating factor. Persistent lymph nodes (white arrows) present an uptake that is lower than the hepatic pool uptake (Deauville score: 3).

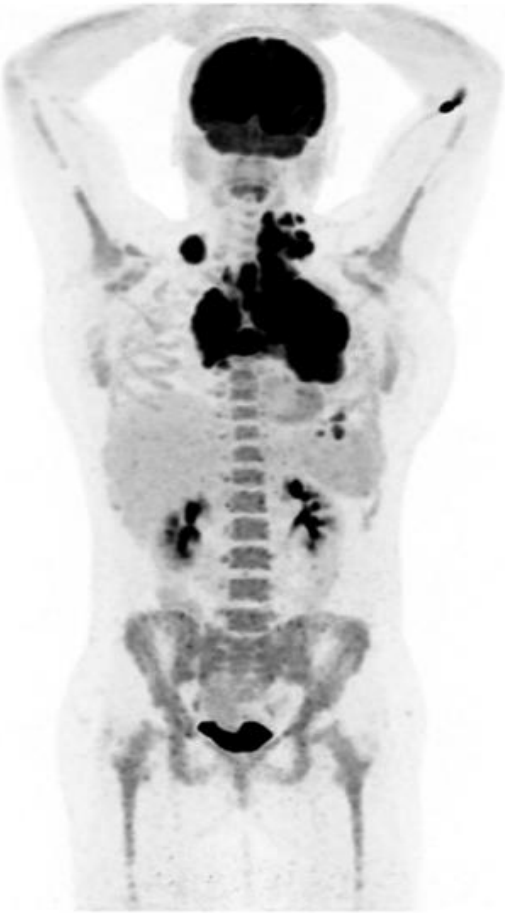


Figure 7 Staging PET-CT in a 25 year-old patient with Hodgkin Lymphoma, nodular sclerosis subtype extensive supra diaphragmatic lymph node involvement. Diffusely increased metabolic uptake is seen in the bone marrow with negative bone marrow biopsy. Care should be taken when interpreting bone marrow uptake in HL patients, as a diffusely increased bone marrow activity should not be regarded as lymphoma involvement.

Reactive bone marrow hypermetabolism

Granulomatous Inflammtion

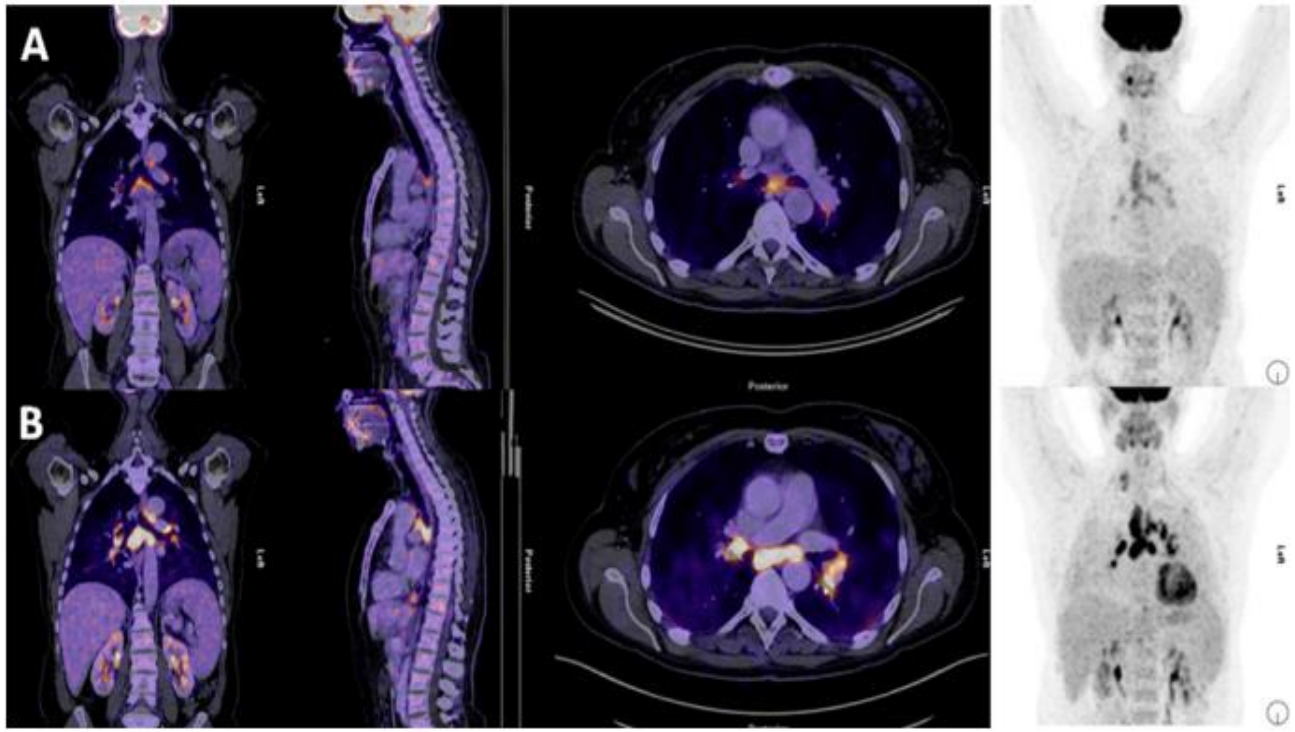


Figure 8 Fifty-five year-old female with Mantel cell lymphoma of the milt in the history, presenting with B symptoms (fever and weight loss) and high suspicion of transformed NHL. [A] [^{18}F]FDG-PET/CT shows multiple enlarged and highly [^{18}F]FDG-avide lymph nodes in the mediastinum and right supraclavicular. Due to the symmetrical uptake sarcoid like reaction was part of the differential diagnosis but recurrent lymphoma could not be ruled out. Pathology results of lymph nodes 4R and 11R (via EBUS) showed granulomatous inflammation. [B] Follow-up scan 10 weeks later show decreased [^{18}F]FDG-uptake in all nodes, confirming self-limiting sarcoid like reaction.

2. Treatment-Induced Pitfalls

Several treatment-related factors can lead to **false positive findings**:

•**Granulocyte-colony stimulating factor (G-CSF)**: G-CSF is commonly used to stimulate **bone marrow production** and can cause increased **[18F]FDG uptake** in the **bone marrow** and **spleen**. This should be considered when interpreting **PET-CT images**.

•**Chemotherapy effects**: Chemotherapy can lead to **bone marrow activity** changes and **spleen enlargement**, which may mimic disease progression.

•**Interstitial lung disease**: Treatment with drugs like **rituximab** or **bleomycin** can cause **lung toxicity** and **interstitial lung disease**, detectable on **CT scans**, and should be recognized as a treatment-induced side effect.

•**Thymic hyperplasia or rebound**: **Thymic hyperplasia** can occur as the thymus "rebound" after chemotherapy, especially in the **first 6 months post-treatment**, although it may persist for up to 2 years. It can be difficult to distinguish from **residual disease** in patients with **mediastinal involvement**. In **doubtful cases**, a **biopsy** or **diffusion-weighted MRI** can be helpful.

•**Radiotherapy effects**: Radiotherapy can induce inflammation in tissues or organs within the **radiation field**, causing conditions like **pneumonitis**, **esophagitis**, or **pharyngitis**, which can lead to false positive **[18F]FDG uptake**.

3.Post-Surgical Pitfalls

Post-surgical **false positive findings** are commonly related to **inflammation**, **infection**, **abscesses**, **fistulas**, **fat necrosis** (which can also be induced by chemotherapy), and **reactive lymphadenitis**. These conditions can occur **near** or at the **surgical site** and should not be mistaken for tumor recurrence or progression.

Immunotherapy and Its Impact on Imaging with [18F]FDG PET-CT

Immunotherapy, especially with immune checkpoint inhibitors like **PD-1/PD-L1 blockers** or **CAR-T cell therapies**, has revolutionized the treatment of certain hematological and solid tumors. However, while these treatments have demonstrated significant anti-tumoral effects, they also present unique challenges when assessing treatment response, particularly with **[18F]FDG PET-CT**. These challenges stem from **atypical response patterns** and the potential development of **immune-related adverse events (irAEs)**.

1. Atypical Response Patterns in Immunotherapy

One of the challenges with immunotherapy is the occurrence of **pseudo-progression**. This is a phenomenon where there is an initial **increase in tumor size** after starting immunotherapy, which may later stabilize or shrink in subsequent imaging scans. This could be misinterpreted as tumor progression.

To address this, **new response criteria** for **immunotherapy** were proposed in 2016, specifically for **lymphoma**: **LYRIC (Lymphoma Response to Immunomodulatory Therapy Criteria)**. These criteria aim to categorize **indeterminate responses (IR)**, especially in cases of **pseudo-progression**, to help distinguish this from actual progression.

2. Immune-Related Adverse Events (irAEs)

irAEs are another challenge associated with immunotherapy. These adverse effects are caused by the immune system attacking normal tissues, and they can manifest as a variety of clinical conditions. **irAEs** are most commonly seen after the **first months** of immunotherapy treatment and affect about **10% to 11% of patients**.
Some common **irAEs** include:

- **Pneumonitis**
- **Colitis**
- **Pancreatitis**
- **Hypophysitis**
- **Hepatitis**

The benefit of **[18F]FDG PET-CT** is its ability to detect these **irAEs early**, which is crucial for patient safety, as these conditions can have a significant impact on the patient's health.

However, **sarcoidosis-like reactions** to immunotherapy can be challenging to differentiate from **lymphoma progression**. These reactions typically affect the **mediastinum** and **lung hila**, and they can cause **increased FDG uptake**. The key difference in these cases is the **pattern of distribution**, particularly if **new sites of FDG uptake** do not correlate with previous areas of lymphoma involvement.

Summary of Key Points

- **[18F]FDG PET-CT** remains the imaging modality of choice for **FDG-avid lymphomas** and provides valuable information in **other hematological malignancies**.
- However, **[18F]FDG uptake** is not specific to malignancy; it also reflects glucose metabolism in **inflammatory lesions**, **infections**, **benign tumors**, and in tissues affected by **chemotherapy**, **radiotherapy**, or **surgical procedures**.
- It's crucial to understand the **clinical history**, **symptoms**, **laboratory findings**, and **previous imaging** when interpreting **[18F]FDG PET-CT** results, as this can help narrow down the differential diagnosis.
- Familiarity with **common differential diagnoses** for lesions in each organ system is essential for correct interpretation.
- In case of uncertainty, or if a lesion is suspected to change **clinical management**, further diagnostic workups, such as **biopsy** or **alternative imaging modalities**, should be considered.