

Oncologic imaging

PICTORIAL ESSAY

Lymphoma- PET-CT - initial staging and response assessment

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ABSTRACT

The most common primary hematopoietic malignancy is lymphoma. Proper initial staging and therapy response is important. Staging defines disease location and extent and is important because it provides a baseline evaluation and allows comparison among studies. PET-CT is preferred for the staging of FDG-avid lymphomas, and a CT scan is preferred in non-avid types. Response assessment is also important in lymphoma patients. PET-CT should be used for response assess-

ment in FDG-avid types, both for early assessment during therapy, known as interim, and at end of treatment. A scale was suggested as the standard reporting tool, and these so-called Deauville criteria have been widely used using the 5-point scale. In this pictorial essay, we present several cases of lymphoma patients to understand how to evaluate initial examination-staging and interim or end therapy response assessment according to Deauville criteria.



KEY WORDS

PET CT, lymphoma, response assessment, Deauville criteria.

Introduction

The most common primary hematopoietic malignancy is lymphoma. Non-Hodgkin lymphoma accounts for around 5% of all cancer occurrences, and it has a higher tendency for spreading to extra-nodal locations [1]. Positron emission tomography-computed tomography

(PET-CT) is becoming more widely utilized in lymphoma staging and response assessment, both for early assessment during therapy, known as interim PET-CT (iPET) [2] and for remission assessment at the end of treatment. Almost all lymphomas are fluorodeoxyglucose (FDG) avid, however, the majority of published



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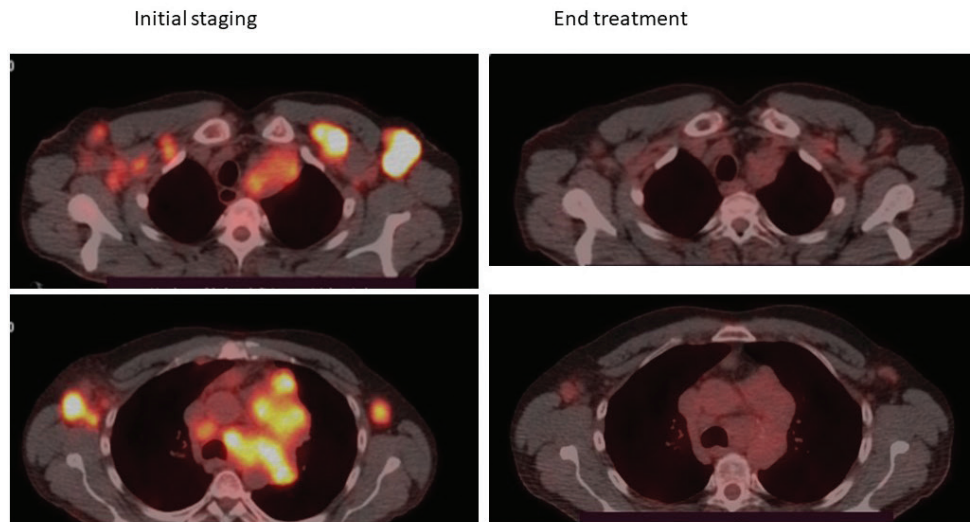


Fig.1: Initial evaluation-Lymph node blocks and pathologic enlarged lymph nodes were detected lateral to aortic arch (size 8X6cm) (SUVmax=11), left pulmonary hilum, pretracheal, aortopulmonary window (diameter 5,6cm) (SUVmax=16,6), supraclavicular bilateral (diameter 3,4cm) (SUVmax=11,2), subclavicular bilateral (diameter 5cm), upper left paratracheal (SUVmax=14,7), axillary bilateral (diameter 4,3cm)(SUVmax=17,4). End treatment evaluation- Lymph node blocks and pathologic enlarged lymph nodes were detected with decreased size and uptake.

data is focused on the utility of PET in Hodgkin lymphoma, Diffuse large B cell lymphoma, and follicular lymphoma [3,4,5].

Discussion

Initial evaluation of a patient with lymphoma involves history taking, clinical examination like measurement of accessible nodal groups, the dimensions of the spleen and liver, laboratory examinations, and excisional or core needle biopsy [6]. The Ann Arbor classification remains the standard staging system for noncutaneous lymphomas. PET-CT is preferred for the staging of FDG-avid lymphomas, primary extranodal diffuse large B-cell lymphoma (DLBCL), nodal lymphomas except chronic lymphocytic leukemia/small lymphocytic lymphoma, lymphoplasmacytic lymphoma/Waldenstrom's macroglobulinemia, mycosis fungoides, and marginal zone NHLs, unless there's a suspicion of aggressive transformation. Contrast-enhanced CT scan is preferred in FDG non-avid histologies and is additionally recommended if measuring nodes is important and preferred for radiation planning.

Staging defines disease location and extent and is important because it provides a baseline evaluation and allows comparison among studies. For Hodgkin lymphoma and FDG-avid Non-Hodgkin lymphoma sub-

types, PET-CT is the preferred modality for staging, especially for identifying extranodal sites, since focal uptake in such sites is considered involvement. For this reason, bone marrow biopsy is not essential in most patients of diffuse large B-cell lymphoma and HL. Upstaging and downstaging can be observed by PET-CT. For patients with peripheral T-cell lymphoma, PET-CT identifies more disease sites and usually upstages diagnosis compared to CT. Downstaging by FDG-PET-CT can occur mainly because of splenomegaly with normal FDG-uptake or enlarged lymph nodes without FDG-uptake. In studies [7], they mentioned that It upstaged HL or Follicular lymphoma in a range of 8-41% whereas it downstaged in a range of 1-10%. Improving staging accuracy ensures that fewer patients are undertreated or overtreated.

When CT is used for staging up to six of the largest target nodes, nodal masses, or other lymphomatous lesions are recognized and measured in two directions [6]. On the other hand, when PET-CT is the modality of choice, we consider involvement, if focal uptake is noticed in nodal and extranodal sites, including spleen, liver, and bone, in addition to CT characteristics. Also, diffusely increased or focal uptake, with or without focal or disseminated nodules, supports liver or spleen involvement. Low-volume involvement, typically 20% of

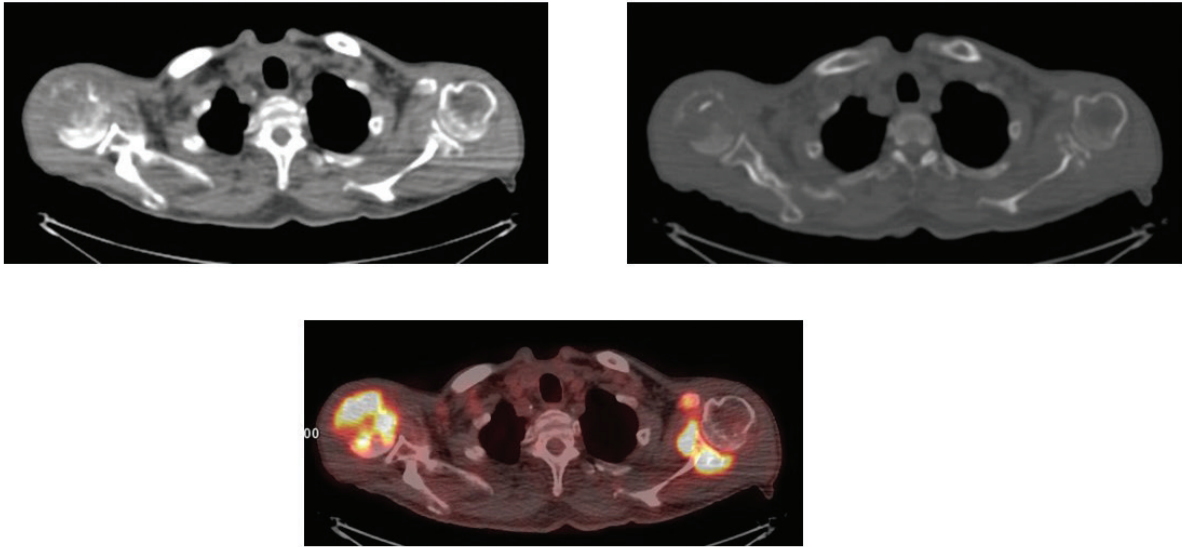


Fig. 2: Right femoral bone head osteolysis with soft tissue mass and high-grade uptake (SUVmax=16,8). Left scapula acromion, glenoid fossa osteolysis with soft tissue mass and high-grade uptake (SUVmax=18,5). Pathologic enlarged axillary lymph nodes (diameter 1,3cm) with uptake (SUVmax=6,5).

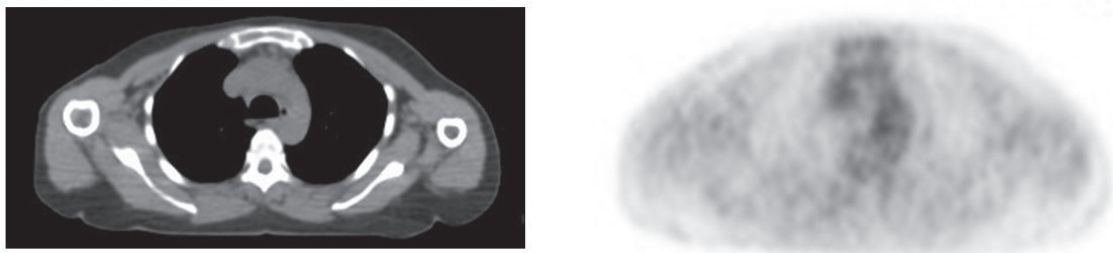


Fig. 3: Anterior mediastinal lymph nodes were detected with no 18-FDG intake.

the marrow, and coexisting low-grade lymphoma in Diffuse large B-cell lymphoma can be missed by PET-CT, albeit this seldom affects care [8]. In Follicular lymphoma, mantle-cell lymphoma, and most indolent lymphomas, where biopsy is important for staging, the sensitivity of PET-CT for diffuse marrow involvement is restricted [9-11]. Since the brain has a high physiologic FDG uptake, MRI is the modality of choice for suspected CNS lymphoma and, leptomeningeal involvement [12].

Evaluation of therapy response is one of the most difficult elements of lymphoma imaging. The major method of assessing therapy response was to use CT to detect changes in lymph node size. It is, however, difficult to differentiate the appearances between post-treatment fibrosis and residual viable tissue. PET-CT, with its better potential in discriminating benign fibrosis and re-

sidual active lymphoma, has been discovered [13].

PET-CT scans are conducted 4-6 weeks following surgery or chemotherapy, and 8-12 weeks after external beam radiation therapy or radioimmunotherapy. These intervals help to reduce the likelihood of false-negative and false-positive results.

The first universally accepted response criteria for non-Hodgkin lymphoma used also for Hodgkin lymphoma were published in 1999 by the National Cancer Institute Working Group [12]. Later, in 2007, the International Harmonisation Project (IHP) published guidelines about the application of positron emission tomography (PET) using FDG in lymphoma, and PET was integrated into revised response criteria. The IHP criteria specified that uptake should be \leq the mediastinal blood pool for lesions ≥ 2 cm or the adjacent background for smaller

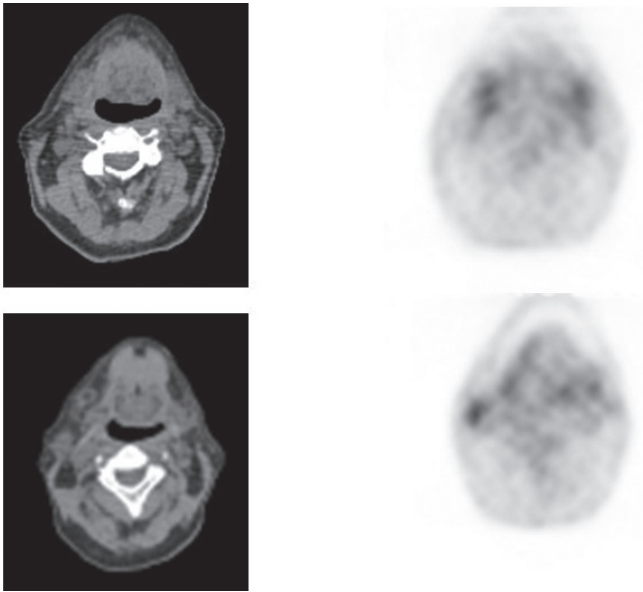


Fig.4: Small submandibular lymph nodes (diam. \leq 1cm) were detected with no uptake.

Right internal jugular lymph node (diameter 1,2cm) (SUV_{max}=2,6). Right parotid focal uptake (SUV_{max}=4).

lesions to define metabolic response at the end of treatment [14,15].

Later, at the First International Workshop on PET in Lymphoma in Deauville, France, in 2009, the α scale was suggested as the standard reporting tool, and these so-called Deauville criteria [16]. Images are scored using a five-point scale (5-PS), which was designed to assess varying degrees of response at the mid-and end of therapy.

Using the 5-PS scores, the most intense uptake in a site of initial disease is described as follows: 1. No uptake, 2. Uptake \leq mediastinum, 3. Uptake \geq mediastinum but \leq liver, 4. Uptake moderately higher than liver, 5. Uptake markedly higher than liver and/or new lesions. It is suggested according to published data [17,18,19] that score 4 be applied to uptake $>$ the maximum SUV in a large region of normal liver and score 5 uptakes should be $>$ 2-3 times of SUV max of the liver.

In 2011, a workshop was convened at the International Conference on Malignant Lymphoma (ICML), attended by representatives from major cooperative groups, in response to changing requirements for PET-CT, to accommodate assessments at staging, during, and after treatment, especially for response-adapted trials. Later on, the Fourth International Workshop on PET in Lym-



Fig.5: Left side large retrobulbar mass causing proptosis.

phoma in Menton, France, in 2012 and the 12th ICML in Lugano, Switzerland, in 2013 followed [7]. Some of their recommendations are concerning the interpretation of PET-CT scans such as using a five-point scale and no need for biopsy in case of focal bone marrow involvement in patients with HL and NHL. Additionally, some of their suggestions concern the role of PET-CT for staging such as that it should be used for staging in clinical practice but not in lymphomas with low FDG avidity and may be used to select the best site to biopsy and other recommendations suggest its role for interim and end treatment evaluation [7].

Also, according to some recommendations above [7], the results should be examined in light of the expected prognosis, clinical findings, and other response indicators. The complete metabolic response is represented by scores 1 and 2; score 3 is also likely to indicate complete metabolic response in individuals undergoing conventional treatment. In response-adapted trials exploring de-escalation, a score of 3 may be deemed an inadequate response to avoid under-treatment. Interpretation of score 3 depends on the timing of assessment, clinical context, and treatment. Scores 4 and 5 with reduced uptake from baseline most likely indicate a partial metabolic response, but they also represent residual metabolic disease at the end of treatment. Treatment failure and/or progression are indicated by an increase in FDG uptake to a score of 5, with no decrease in uptake, and new FDG-avid foci consistent with lymphoma [7].

CT is preferred for response assessment in low or variable- FDG avidity. A partial response requires a decrease by more than 50% in the sum of the product of the perpendicular diameters of up to six representative

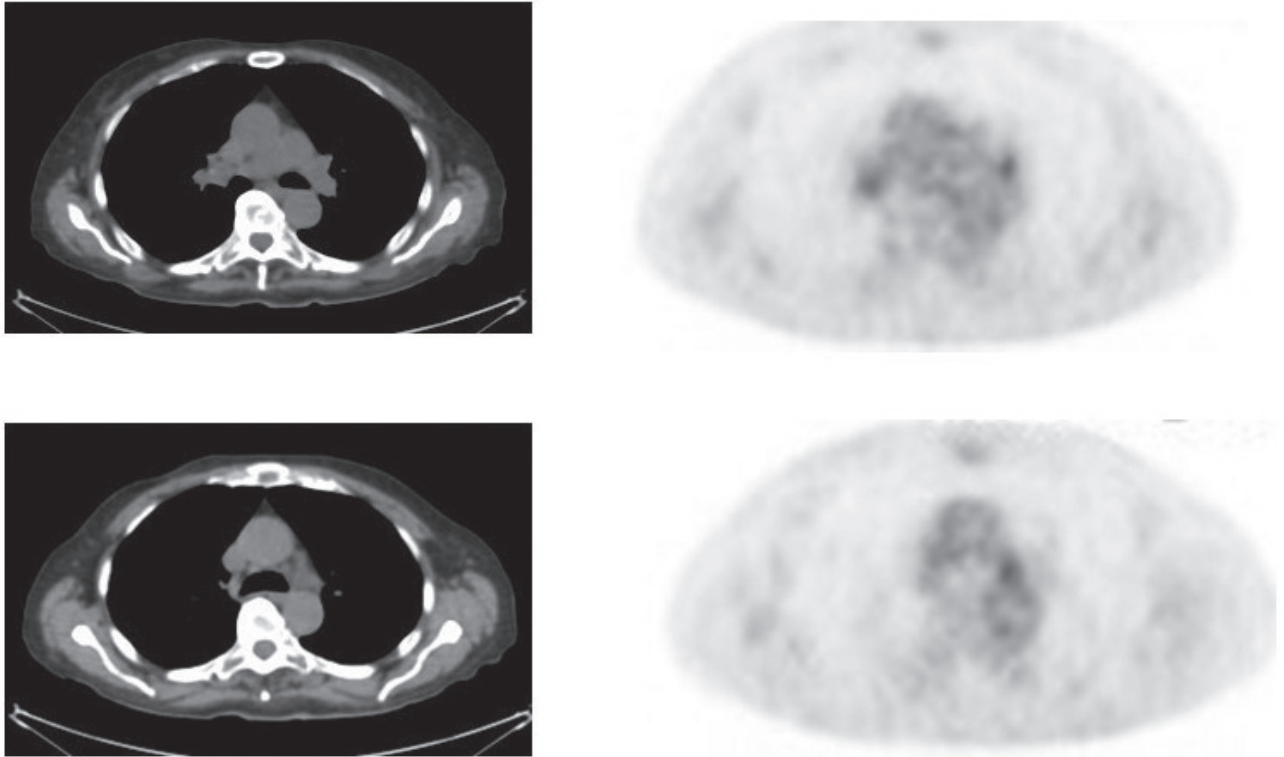


Fig.6: Low-grade uptake (SUV max=3,6) of small lymph nodes in left hilum and aortopulmonary space.

nodes or extranodal lesions. Progressive disease by CT criteria only requires an increase in the product of perpendicular diameters of a single node by 50%.

End-of-treatment residual or new metabolic disease requires biopsy confirmation before salvage therapy where feasible or an interval scan if the clinical index of residual disease is low [6]. Caution should be taken not to mistake flare reaction with progressive disease. It is described as an increase in tumor size and the appearance of new lesions, suggestive of progressive disease seen in patients taking immunomodulatory agents. It is caused by an immune reaction between natural killer cells and malignant lymphoid cells [21]. If it is suspected, it is recommended that either a biopsy be performed or lesion reassessment in at least 2 weeks. At follow up it is resolving or remaining stable [22]. Also, a significant proportion (10.4%) of patients with lymphoma treated with immune checkpoint inhibitors showed pseudoprogression. The Lymphoma Response to Immunomodulatory therapy Criteria (LYRIC) was proposed in 2016 [21], an updated version of the Lugano Classification Lymphoma Response Criteria. They suggest using 'indeterminate response (IR)' to describe the initially increased tumor burden, which distinguished

pseudoprogression from true progression on subsequent imaging or biopsy. The LYRIC mandated a subsequent imaging assessment for patients with IR within 12 weeks to confirm or refute progressive disease [21].

In the following part of this pictorial essay, we present several cases of lymphoma initial staging and response assessment using Deauville criteria.

Case 1.

A male patient, age 53 years old with Hodgkin lymphoma- initial staging. (Fig.1)

Lymph node blocks and pathologic enlarged lymph nodes were detected:

- mediastinal (SUVmax=16,6)
 - left pulmonary hilum (SUVmax=16,6)
 - supraclavicular bilateral (diameter 3,4cm) (SUVmax=11,2)
 - axillary bilateral (diameter 4,3cm)(SUVmax=17,4)
- Same patient- End treatment evaluation (Fig.1).

Lymph node blocks and pathologic enlarged lymph nodes were detected with decreased size and uptake. In detail:

- mediastinal (SUVmax=7,4)

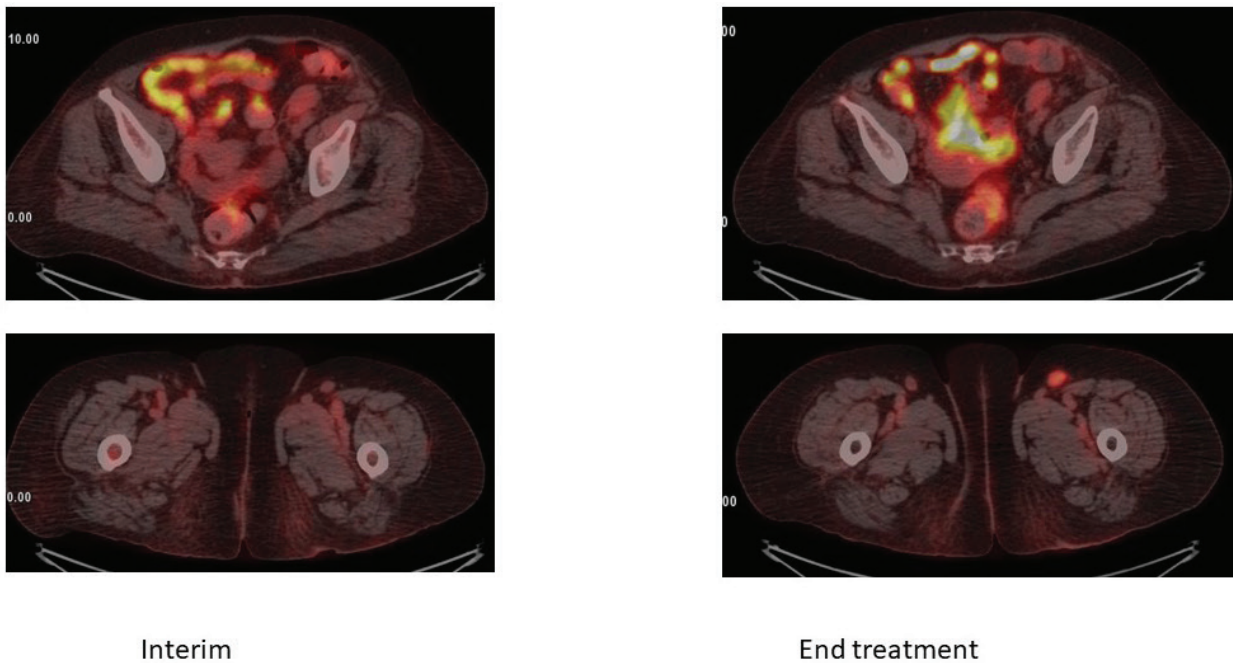


Fig.7: Interim evaluation -Low-grade uptake of left external iliac lymph node block of size 4,5X2,8cm (SUVmax=3,1). End treatment evaluation-Low-grade uptake of left external iliac lymph node block of reduced size 3,5X1,8cm (SUVmax=2,95). Left inguinal lymph node increased size (diameter 2,3cm instead of 1,3) with high-grade uptake (SUVmax=6,3).

- left pulmonary hilum (size 5X3cm) (SUVmax=2,1)
- supraclavicular bilateral (diameter 2,6cm) (SUVmax=2,2)

- axillary (diameter 2,2cm) (SUVmax=1,9)

The SUVmax of the blood pool was 2,4 and SUVmax of the liver was 3,6. According to Deauville criteria was graded as 2.

Case 2.

A male patient, age 82 years old with osteolysis of femoral head and scapula- Bone lymphoma- initial staging (Fig.2):

- Right femoral bone head osteolysis with soft tissue mass (SUVmax=16,8)

- Left scapula acromion, glenoid fossa osteolysis with soft tissue mass (SUVmax=18,5)

- Pathologic enlarged axillary lymph nodes (diameter 1,3cm) (SUVmax=6,5)

Case 3.

A female patient, age 55 years old with a history of Hodgkin lymphoma with anterior mediastinal lymph nodes. End treatment evaluation.

Anterior mediastinal lymph nodes were detected with

no 18-FDG intake. According to Deauville criteria, it is graded as 1 (Fig.3).

Case 4.

A male patient, age 50 years old with Non-Hodgkin lymphoma. End treatment evaluation after 6cycle of RCHOP (Fig.4):

- Few small submandibular and paratracheal lymph nodes (diam.≤1cm) were detected with no uptake.

Also, we detected:

- Right internal jugular lymph node (diameter 1,2cm) (SUVmax=2,6)

- Right parotid focal uptake (SUVmax=4) due to incidental lesion, not related to lymphoma.

The SUVmax of the blood pool was 2,8 and the SUVmax of the liver was 3,8. According to Deauville criteria was graded as 1.

Case 5.

A male patient, age 88years old, with nodular lymphoma - End treatment evaluation.

In a previous CT evaluation, he had a left orbital fossa mass (Fig. 5) and lymph nodes (diameter ≤1cm) in the subcarinal place, aortopulmonary space, left hilum, and

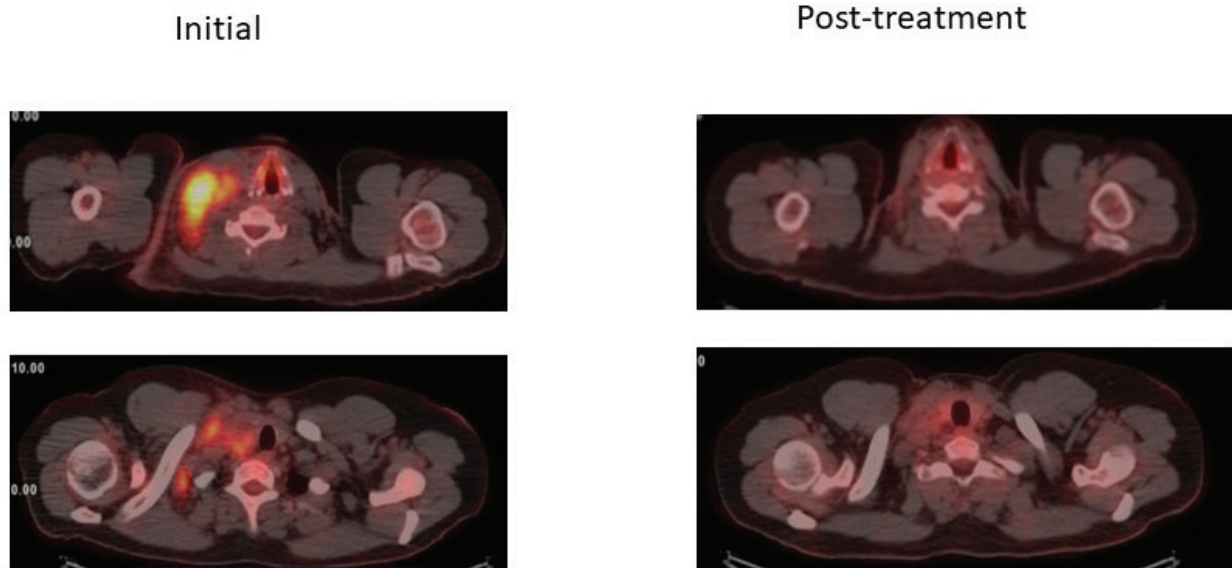


Fig.8: Initial evaluation-Right supraclavicular lymph node blocks (size 8X6cm) with high-grade uptake (SUVmax=12,8). Multiple enlarged lymph nodes (diam. >1cm) in right subclavicular, axillary area, and right upper paratracheal with high-grade uptake (SUVmax=8,1). End treatment evaluation- All lymph node blocks are decreased in size. Right supraclavicular lymph nodes with low-grade uptake (SUVmax=2,6). Enlarged lymph nodes (diameter 1,3cm) right subclavicular and axillary area, right upper paratracheal with no uptake (SUVmax=1,8).

right axillary space.

End treatment evaluation with PET-CT:

- No uptake in the initial mass of the left orbital fossa.
- Low-grade uptake (SUV max=3,6) of small lymph nodes in the left hilum, and aortopulmonary space (Fig.6).

-He also had right breast low-grade uptake (SUV max=2,2) which was further investigated and was due to inflammation.

The SUVmax of the blood pool was 2,8 and the SUVmax of the liver was 3,8. According to Deauville criteria was graded as 3.

Case 6.

A female patient, age 60 years old, with Hodgkin Lymphoma. Interim and end treatment evaluation after therapy (Fig.7). In the initial study, she had a left external lymph node block with low-grade uptake and a pathologic enlarged left inguinal lymph node with low-grade uptake.

Interim evaluation:

Low-grade uptake of the left external iliac lymph node block of size 4,5X2,8cm (SUVmax=3,1). No uptake is seen in the postsurgical left inguinal area.

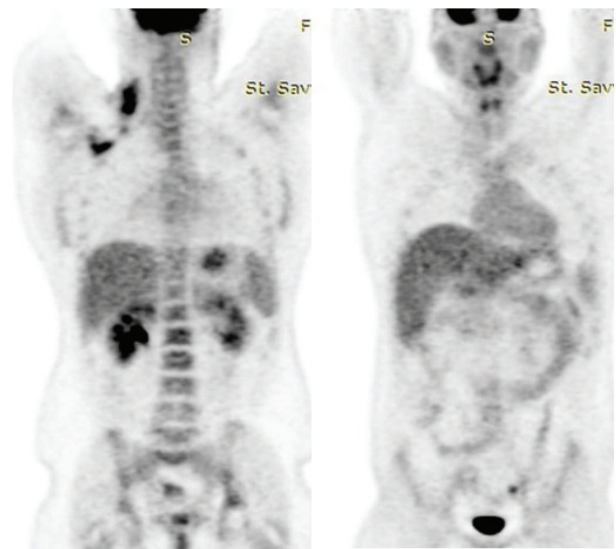


Fig.9: FDG PET- MIP images -of the PET CT case mentioned in Fig.8

The SUVmax of the blood pool was 2,8 and SUVmax of the liver was 4. According to Deauville criteria was graded as 3.

End treatment evaluation (Fig.7):

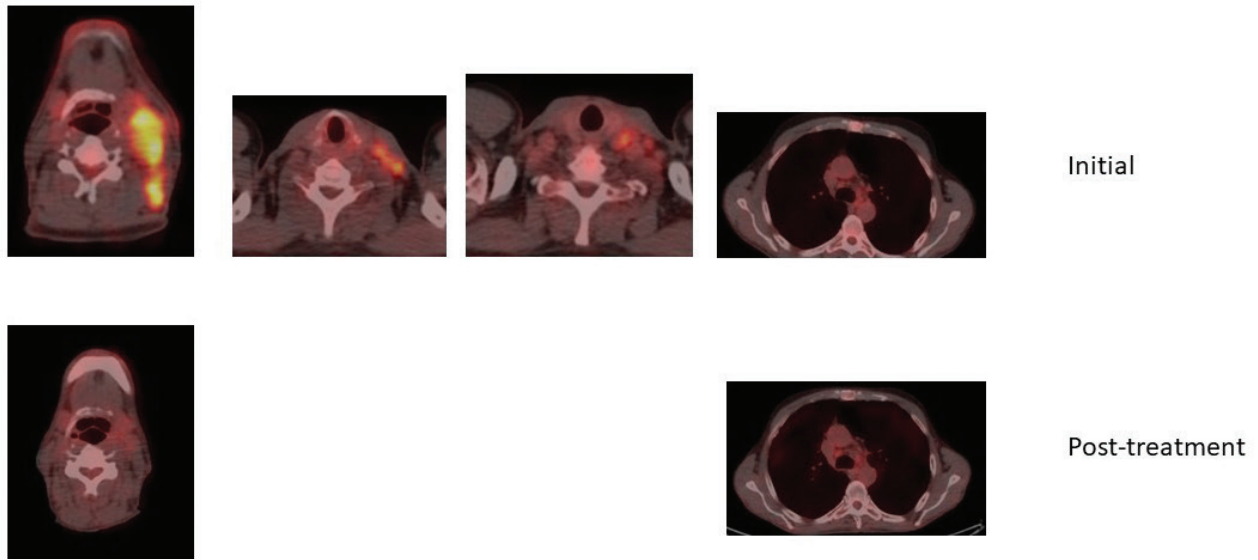


Fig.10: Initial evaluation-Lymph node block (size 8X3cm) and multiple enlarged lymph nodes on the left side of neck region from submandibular up to supraclavicular region with high-grade uptake (SUV max=10,6). Lymph nodes in the pretracheal region and aortopulmonary window with low-grade uptake (SUVmax=3,2). Post-treatment evaluation- Disappearance of lymph node block in the left neck region.

Lymph nodes in the pretracheal region and aortopulmonary window with smaller size and low-grade uptake (SUVmax=2,8).



Fig. 11: FDG PET- MIP images of initial, interim, and post-treatment evaluation of case 8 as described in the text.

Low-grade uptake of left external iliac lymph node block of reduced size 3,5X1,8cm (SUVmax=2,95). Left inguinal lymph node increased size (diameter 2,3cm instead of 1,3) with high-grade uptake (SUVmax=6,3).

Bilateral small inguinal lymph nodes with low-grade uptake (SUVmax=3). Low-grade uptake of the small lymph node in the left hilum (SUVmax=3). Left axillary lymph nodes (diam.1,2cm) with high-grade uptake

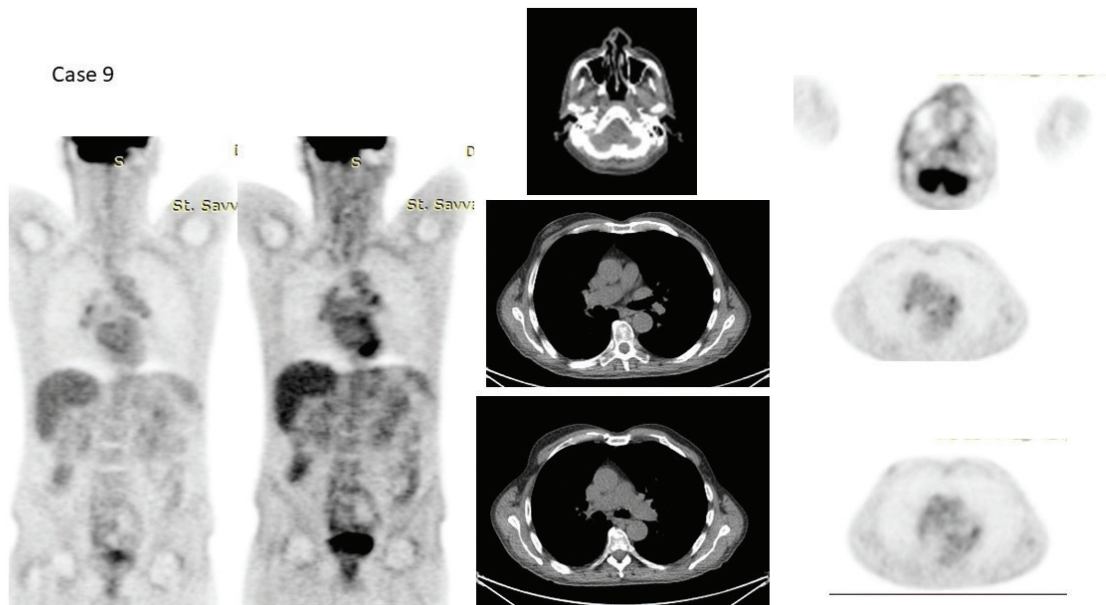


Fig. 12: End treatment evaluation- Enlarged lymph node of right pulmonary hilum with high-grade uptake (SUVmax=4,3). Left pulmonary hilum lymph node with high-grade uptake (SUVmax=3,7). High-grade uptake at the posterior wall of the nasopharynx (SUV max=6,3).

(SUVmax=4,4) and right axillary lymph nodes with low-grade uptake (SUVmax=2,5).

The SUVmax of the blood pool was 2,6 and the SUVmax of the liver was 4. According to Deauville criteria was graded as 4.

Case 7.

Male patient aged 24 years old with Hodgkin Lymphoma-initial staging:

- Right supraclavicular lymph node blocks (size 8X6cm) with high-grade uptake (SUVmax=12,8) (Fig.8,9).
- Multiple enlarged lymph nodes (diam. >1cm) in right subclavicular, axillary area, and right upper paratracheal with high-grade uptake (SUVmax=8,1) (Fig.8,9).
- Enlarged lymph node (diameter 1,8cm) anterior to superior vena cava with high-grade uptake (SUVmax=6).
- Enlarged lymph node (diameter >1cm) in left substernal with low grade uptake (SUVmax=2,9).
- Diffuse low-grade uptake of bone marrow.

Same patient- end treatment evaluation:

- All lymph node blocks are decreased in size.
- Right supraclavicular lymph nodes with low-grade uptake (SUVmax=2,6).
- Enlarged lymph nodes (diameter 1,3cm) right subclavicular and axillary area, right upper paratracheal with no uptake (SUVmax=1,8) (Fig. 8,9).

- Enlarged lymph node (diameter 1,5cm) anterior to superior vena cava with no uptake (SUVmax=1,8).

- Enlarged lymph node left substernal with no uptake.
- Diffuse low-grade uptake of bone marrow remained.

The SUVmax of the blood pool was 2,6 and the SUVmax of the liver was 4,2. According to Deauville criteria are graded as 2.

Case 8.

A male patient, age 58 years old, with Hodgkin Lymphoma. Initial staging (Fig. 10,11):

- Lymph node block (size 8X3cm) and multiple enlarged lymph nodes on the left side of neck region from submandibular up to supraclavicular region with high-grade uptake (SUV max=10,6).
- Lymph nodes in the pretracheal region and aortopulmonary window with low-grade uptake (SUVmax=3,2).

Interim evaluation after chemotherapy (Fig. 11):

- Lymph node block of left neck region showed low-grade uptake (SUVmax=2,9).
- Lymph nodes pretracheal region, and an aortopulmonary window showed low-grade uptake (SUVmax=3,2).

The SUVmax of the blood pool was 2,5 and the SUVmax of the liver was 3,7. According to Deauville criteria was graded as 3.

End treatment evaluation after chemotherapy (Fig. 10):

- Disappearance of lymph node block in the left neck region.

- Lymph nodes in the pretracheal region and aortopulmonary window with smaller size and low-grade uptake (SUVmax=2,8).

The SUVmax of the blood pool was 2,2 and the SUVmax of the liver was 3,2. According to Deauville criteria was graded as 3.

Case 9.

A male patient, age 65 years old, with Hodgkin Lymphoma. End treatment evaluation (Fig. 12):

- Enlarged lymph node of right pulmonary hilum with high-grade uptake (SUVmax= 4,3). In a previous study, the uptake was SUV max=3,7. Left pulmonary hilum

lymph node with high-grade uptake (SUVmax=3,7).

- High-grade uptake at the posterior wall of the nasopharynx (SUV max=6,3).

The SUVmax of the blood pool was 2,65 and the SUVmax of the liver was 3,7. According to Deauville criteria was graded as 4.

Finally, care should be taken not to consider inflammatory lesions such as axillary lymph nodes after vaccination, diffuse uptake in the bone marrow without focal activity which often represents reactive hyperplasia, and granulomatous inflammation which results in false-positive interpretations. When the clinical presentation seems unusual, or there are significant differences in staging additional targeted biopsies should be considered. **R**

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