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Current State of the PET/CT Hybrid Technique and Clinical Indications

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1. Introduction

In the year 2000, Townsend developed a prototype that integrates FDG-PET and CT, thus creating the possibility of performing both tests sequentially, in order to obtain an image that is the result of the fusion of hardware of anatomical (CT) and metabolic information (PET) of the section under study (Townsend & Beyer, 2002). Since then, PET/CT imaging has been a revolution in the diagnosis of tumours, staging, restaging and detection of local and distant recurrence and assessment of therapy response.

Applications have been developed in very different areas such as oncology, cardiology (cardiac viability), neurology (Alzheimer disease and epilepsy before surgery), etc.

2. Techniques

2.1 Hybrid technique

Therefore, the CT, which was the anatomical imaging technique of choice in the staging and monitoring of the treatment of oncological patients as well as in the planning of radiotherapy, joined the FDG-PET, which is a more functional technique that allows for an early detection of the disease and with which the residual lesions after treatment can be characterized as scar tissue or neoplastic lesions. PET/CT might improve the precision of the initial staging and the detection of residual diseases and recurrences in these patients. This would then optimize the treatment schemes for each patient and prevent the complications of other, more aggressive diagnostic techniques, as well as the toxicity of unnecessary chemotherapy and/or radiotherapy (Beyer, 2011).

2.2 PET/CT imaging protocol

The patients must not eat anything for 4-6 hours prior to the test. Immediately after the administration of a 370 MBq dose of intravenous 18FDG, the patient rests for 45-60 minutes. During this time, each patient receives 1500 ml of oral contrast (Gastrographin 3%), except for the studies on lung cancer, in which water is administered as an oral contrast. Nowadays the data are obtained with a hybrid system PET/CT which combines 4-64 slice multi-detector CT with a PET scanner of 18 bismuth germinate (BGO), lutetium oxyorthosilicate (LSO), or gadolinium silicate(GSO) crystal detector rings. At first, a CT scan is performed at low doses and without intravenous iodated contrast.

The images are taken 45-60 minutes after an injection at rest, starting at the base of the skull, down to the upper area of the thigh. Initially, in Spain, in 2003 (Gómez-León et al., 2007), low dose CT images were obtained at 140 mV, 80 mA, gantry rotation time of 0.5 seconds, 2x5 cm collimation, section thickness of 5 mm and reconstruction interval of 3 mm. Immediately after that, the PET scan acquired 4-6 contiguous volumes. Finally, the diagnostic CT could be studied after an injection of intravenous contrast (Iobitridol 300 mg iodine/ml), with a 50-70 seconds delay for the acquisition of the images (depending on the pathology under study). The parameters used were the same that those for low dose CT, except for the intensity of the current, which varied according to an automatic intensity modulation system that depends on the weight of the patient, with a maximum of 300 mA. A few minutes after the end of the test, PET images went through attenuation correction with the CT data and then reconstructed, like the CT images and the combined PET/CT images (Gómez-León et al., 2007).

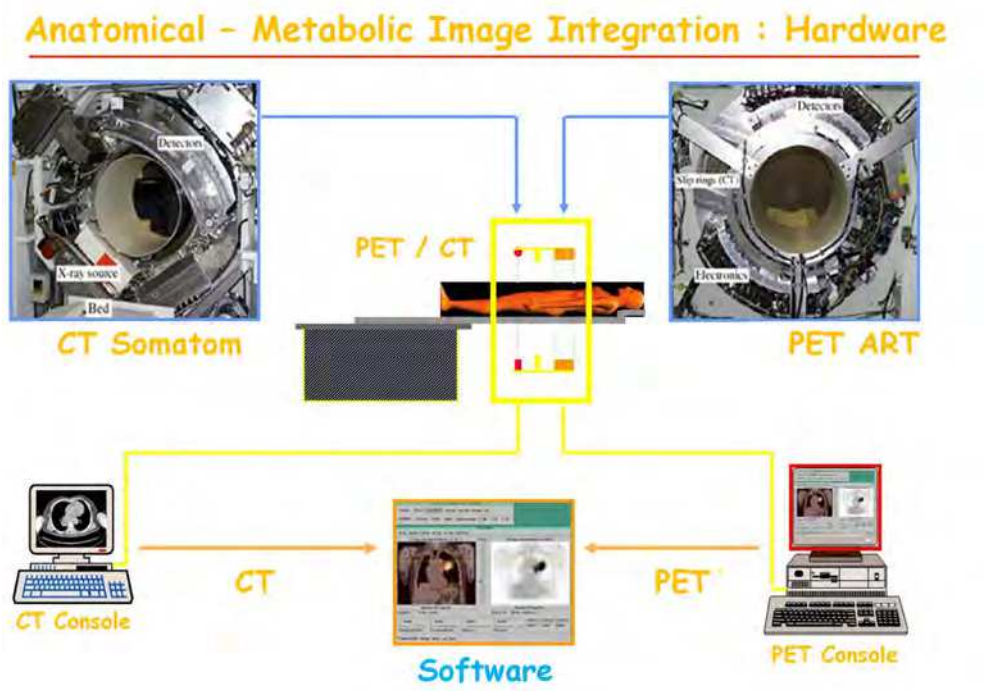

Fig. 1. PET/CT (modified from Townsend, 2002)

Nowadays, PET/CT images can be studied without a prior low-dose CT, using the data obtained in the diagnostic CT with intravenous contrast. There are no differences between PET attenuation with low-dose CT and diagnostic CT with intravenous contrast (Pinilla et al., 2010).

2.3 Assessment of the PET image or CT image

The main limitations of these techniques separately are the inability to distinguish, in many cases, benign lesions from malignant lesions, especially in the lymph nodes, the inability to establish the response to the treatment and the impossibility to distinguish, in some cases, between the changes in recurrences after therapy (chemotherapy, radiotherapy, surgery).

2.4 Advantages of combined PET/CT over PET and CT

- Improvement in locating the lesions thanks to a quasi-perfect anatomical and functional co-register.
- Different physiological and pathological uptake in PET.
- Functional changes precede anatomical alterations.
- Planning of RT.
- CT data can be used for the correction of data attenuation in PET (shorter times).
- PET/CT shows a higher sensitivity and specificity than each of its components individually, and probably higher than the combined retrospective reading of both separated components.
- The most relevant effect is the fact that CT provides more specificity to PET, which allows for a precise anatomical location of PET uptakes and a higher degree of certainty in the interpretation of the tests (Czernin et al., 2010).
- PET, on the other hand, provides some valuable functional information.
- Tumour cells present an increased glucose transport rate and an increased rate of glucose metabolism.

2.5 Implications of CT-based attenuation correction

- Artifacts due to respiratory and deglutition movements.
- Artifacts due to beam hardening (upper limbs) and obesity.
- Artifacts due to the use of contrasts and high-density objects.
- Other artifacts due to the patient's weight, the patient's BMI, the patient's lean weight, the administered dose of FDG, the level of basal glycemia, crystal PET detectors (BGO vs. LSO), etc.
- Asymmetrical uptake of FDG in the muscles, previous record of traumatisms or inflammation.

2.6 PET/CT: Physiological uptake

- 18FDG uptake is more intense in the brain, in which metabolism depends on glycolysis, and in the myocardium, which uses glycol tic metabolism in basal situations.

- 18FDG is excreted through urine, and intense activity can be found in the urinary system, the ureters and the bladder.
- It is present in the liver, the spleen, the bone marrow and the renal cortex.

2.6.1 Physiological uptakes

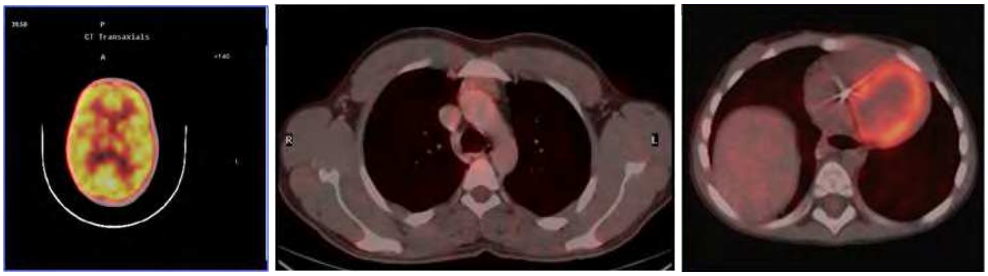

Fig. 2, 3 & 4. Physiological uptake of the brain, thymus and myocardium.

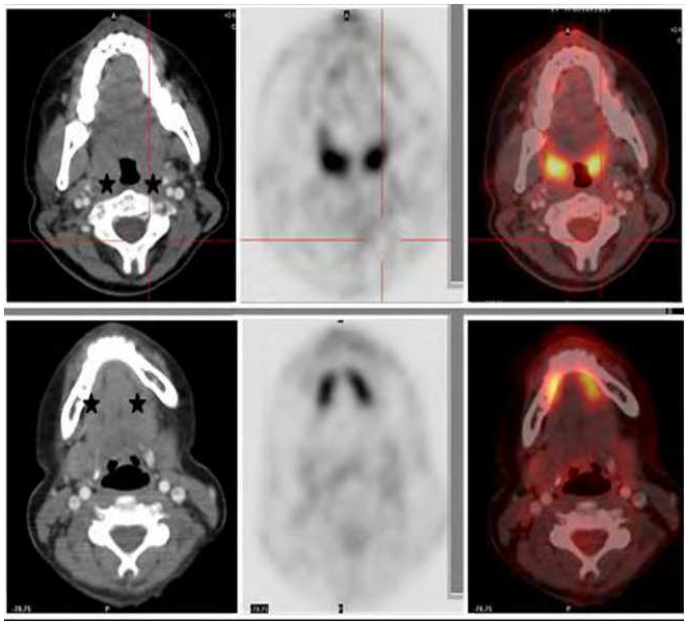

Fig. 5a & b. Physiological uptake of lymph tissue (asterisks) and tongue (asterisks).

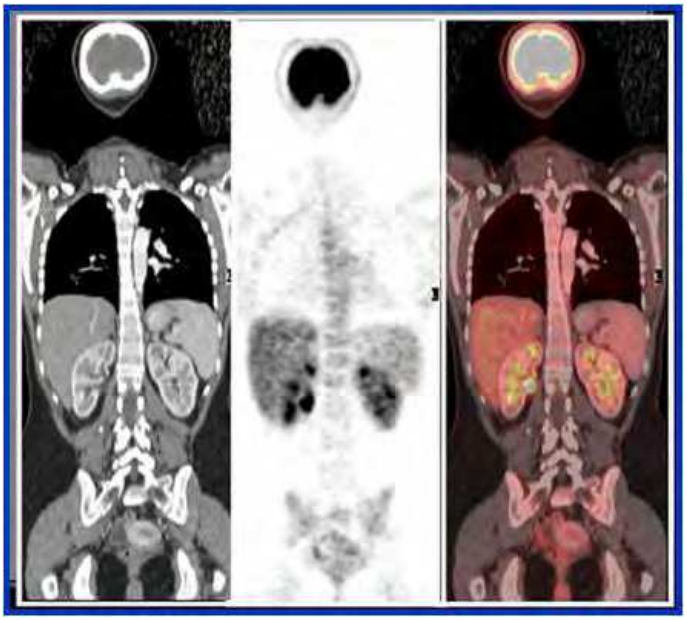

Fig. 6. Physiological uptake of the kidneys and bladder.

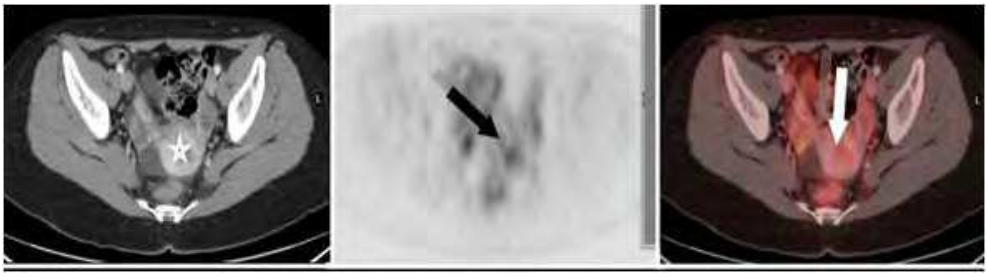

Fig. 7. Uptake of the endometrium (arrow) and bowel loops filled with oral contrast.

Fig. 8. Uptake of the endometrium and bowel loops filled with oral contrast.

2.6.2 Physiological uptakes after treatment

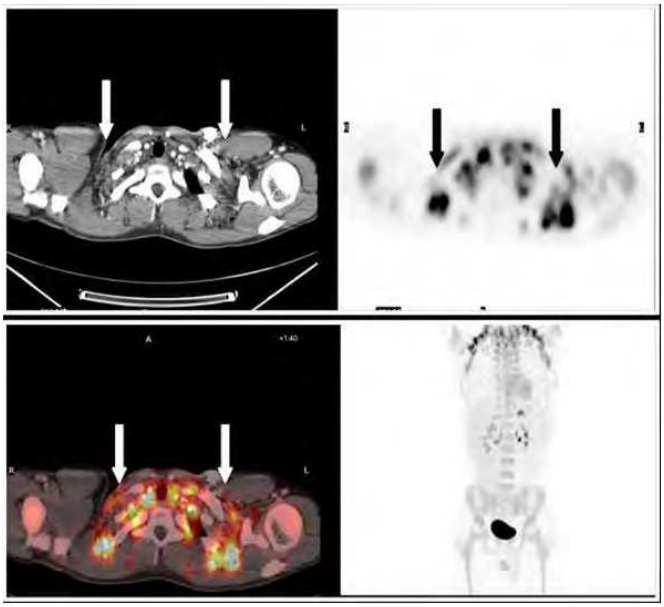

Fig. 9. Axial CT section with intravenous contrast, axial section of the PET component, combination of both techniques and coronal section of the entire PET study. Brown fat (arrows on the different sections).

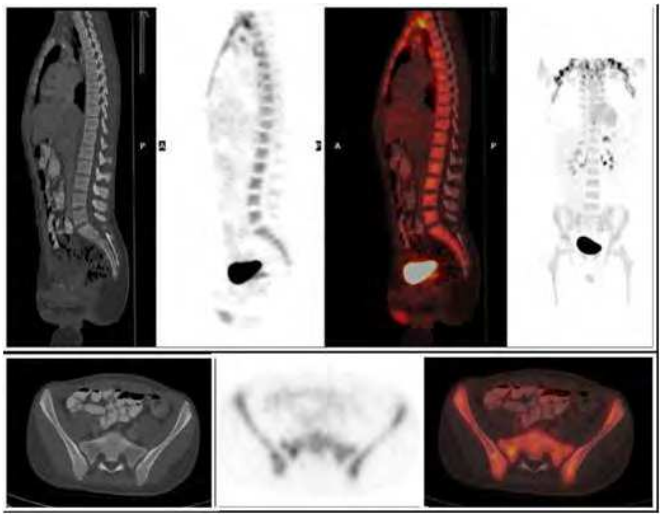

Fig. 10. Sagittal sections of CT component, PET component and combined image. Coronal PET section. Axial sections of the pelvis of the CT component, PET component and combined image. The patient received a bone marrow transplant, with uptake in the entire axial and peripheral skeleton due to granulocyte colony-stimulating factor.

2.7 FDG PET/CT: Limitations

This is a list of tumours with low uptake of FDG: Well-differentiated tumours, hypocellular tumours, mucine-producing tumours, HCC (hepatocell carcinoma), BAC and intraductal mucinous papillary tumours.

On the other hand, there are some difficulties in the detection of the pathological collection:

- High physiological uptake: brain, tonsils
- Physiological elimination: Urothelial carcinoma of the renal pelvis, bladder cancer

2.8 Applications of PET/CT in oncology

PET/CT is used in the staging and re-assessment of specific neoplasias, and it is especially useful in non-small cell lung cancer, lymphomas, colorectal cancer, sarcomas and melanomas.

PET/CT is particularly useful in patients under suspicion of clinical recurrence with conventional imaging techniques, as well as in the characterization of residual masses after chemotherapy and radiotherapy.

We want to highlight an article that was published in Euroradiology in 2011, which analyzed the increase in the use of PET/CT in Europe (Høilund-Carlsen et al., 2011). The most notable results dealt with the fact that the diagnosis, staging and treatment may change in up to 36% of the cases, according to some studies published in the USA: Initial results of The National Oncologic PET registry.

Danish experience: A 3-year clinical experience in a large new Danish PET/CT centre in relation to national and European developments. The use of PET/CT in cancer was registered from early 2006 to 2009, in order to judge the impact on patient management and to compare it with national and European trends.

- Referrals came primarily from the departments of oncology (23.0%), hematology (21.6%), surgery (12.6%), internal medicine (12.7%) and gynecology (5.5%).
- Referral indications were diagnosis (31.3%), staging (22.3%), recurrence detection (21.2%), response evaluation (17.0%) and other causes (8.2%). Response from nearly 60% of users showed that PET/CT caused a change in diagnosis and/or staging and/or treatment plan in 36.0% of cases.
- The working diagnosis was confirmed in 53.7% of the cases, the staging in 42.7% of the cases and the treatment plan in 49.9% of the cases, and changes took place in diagnosis (14.3% of the cases), in staging (22.1%), and in treatment plan (28.3%).
- According to the EANM, during the study period, there was a steep increase in the national use of FDG and in the European use of PET/CT from 166 cases (in 27 countries) to 463 cases (in 46 countries), which represents an increase of 179%, and an increase of the number of studies of 69%.

3. Indications for the monitored use of FDG: High-level research NLCAHR contextualized health research synthesis: PET/CT programs

1. Solitary pulmonary nodule
2. Non-small cell lung cancer
3. Recurrent colorectal cancer
4. Staging and re-staging of lymphoma

5. Recurrent malignant melanoma.
6. Identification of cancer of unknown primary origin
7. Malignant tumours in head and neck
8. Breast cancer.
9. PET-CT and it´s applications in radiation therapy.
10. The future: Neuroradiology and cardiovascular diseases (Demeter et al., 2009).

3.1 Solitary pulmonary nodule

- The role of PET-CT in clinical assessment in indeterminate pulmonary nodules shows two options: biopsy or resection and monitoring over 2 to 5 years. The use of PET-CT in the management of pulmonary nodules helps to stratify patients better according to the risk of malignancy.
- Accuracy depends on: Nodule size ≥ 1cm and FDG-Avidity SUV 2.5: overlapping
- Improvements in the increase of the uptake compared with background activity
- S: 83-100% E: 63-90%, NPV: 95% and change the management in 26% of patients.

3.1.1 Limitations of PET/CT

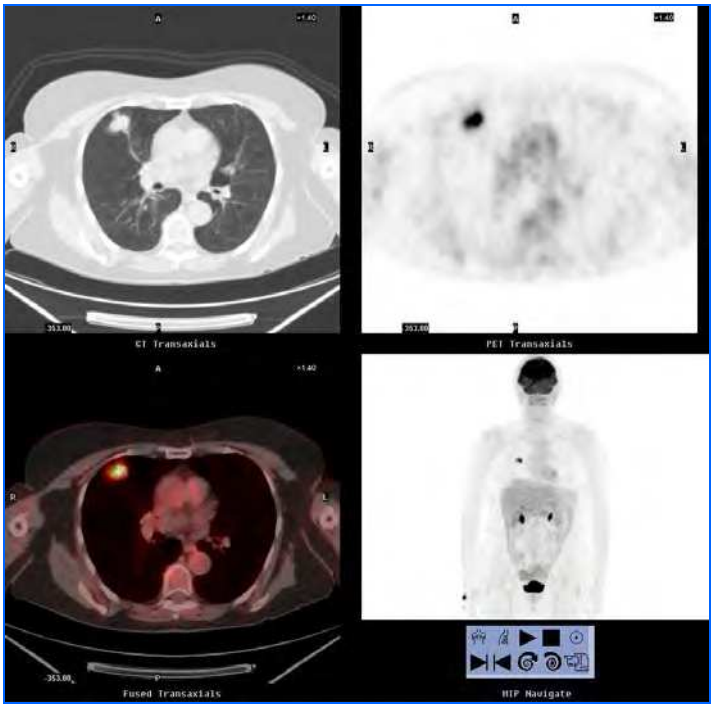

Fig. 11. False positive: Axial section of CT, PET and combined images and coronal section of the PET study. The pulmonary nodule of the right upper lobe shows an intense uptake of 18FDG in the PET and combined image. The anatomopathological analysis revealed a tuberculoma in a patient with colon carcinoma.

Benign uptakes:

- Physiological uptakes. Brown fat
- Inflammation: sarcoidosis, vasculitis, etc.
- Inflammation after surgery (1-2 months) or after radiation therapy (2-3 months)
- Active infections
- Benign tumours

False positive: Tuberculosis, granuloma, sarcoidosis, abscess and fungal infection (aspergillosis, coccidioidomycosis), necrotizing pneumonia, benign tumours: sclerosing hemangioma, myofibroblastic tumour and leiomyoma.

False negative: Well-differentiated adenocarcinoma, BAC (bronchioalveolar carcinoma), carcinoid and nodules of less than 1 cm.

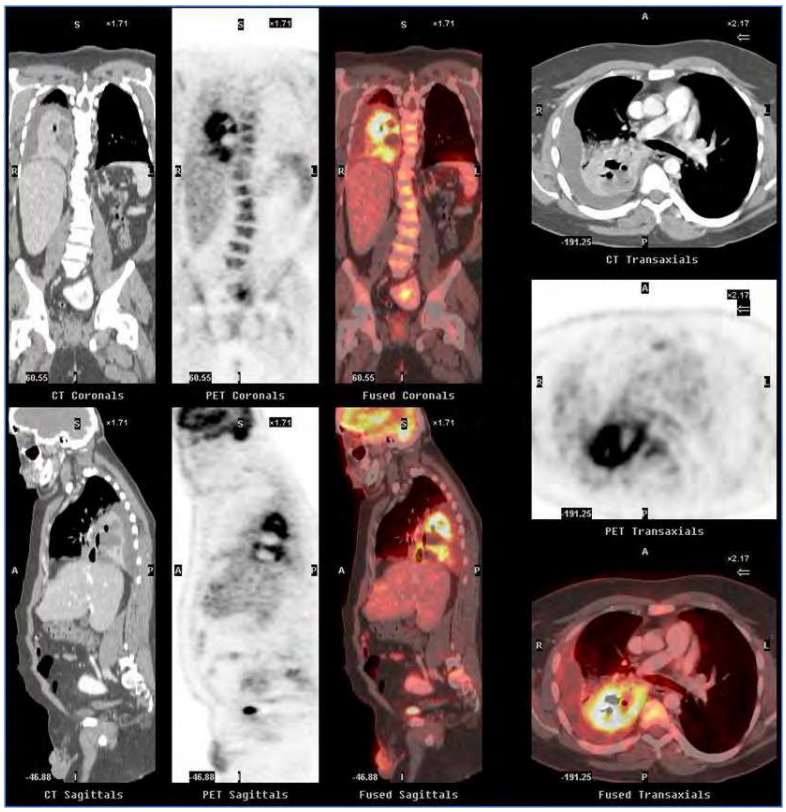

Fig. 12. Coronal and sagittal sections of the entire body with CT, PET and combined images. Axial sections. False positive: Necrotizing pneumonia of middle lobe and lower right lobe with effusion.

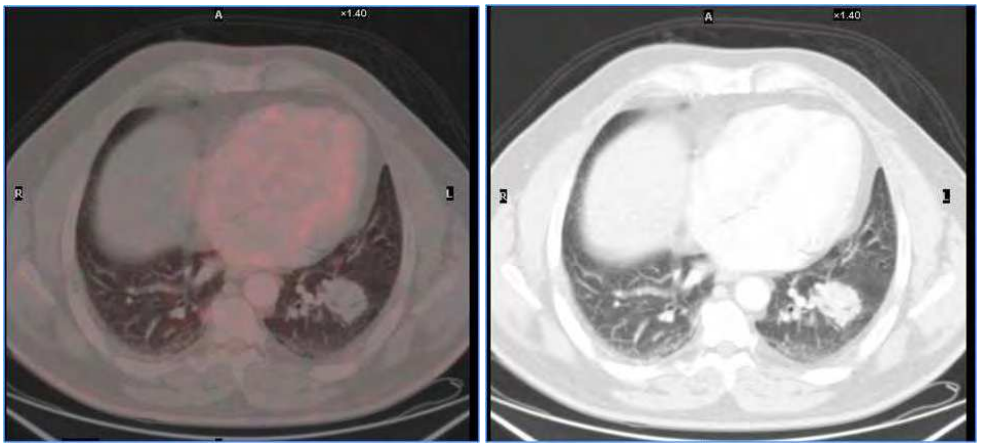

Fig. 13a & b. Axial sections of CT and PET/CT combined image. Lesion on the lower right lobe with air bronchogram, without 18FDG uptake. False negative: Bronchioalveolar carcinoma.

3.2 Non-small-cell lung carcinoma

PET/CT improves the identification and location of the lesions as well as the detection of the involvement of small nodes and neoplastic lesions with low FDG avidity. Diagnostic accuracy of PET/CT: T 70-97%; N: 78-93%; TNM: 83-96%. Global staging is significantly better. It leads to a change of stage in approximately 26% of the patients, and it changes the management approach in 9-19% of the cases.

Advantages of PET/CT:

- Techniques: Better quality than PET study. The PET element is shorter (examination time decreases by 40%), and it provides a more effective use of PET radiotracers.
- For the patient: A single preparation session and study session, and a better clinical management of complementary examinations
- At diagnosis: More sensitivity and specificity than isolated CT and PET.
  - CT adds specificity: Better location, safer reading.
  - PET adds sensitivity: it detects infiltrations without morphological alterations.

3.2.1 Limitations of PET/CT

- Tumours with a decrease in the 18F-FDG uptake: Well-differentiated tumours, hypocellular tumours or mucin-producing tumours.
- Difficult detection of pathological deposits:
  - High physiological uptake: brain, tonsils.
  - Physiological elimination: Urothelial carcinoma of the renal pelvis, bladder cancer

3.2.2 T staging

PET/CT is a better choice because it provides an accurate correlation between the extension of the FDG deposit and the anatomy of the area.

- Improvement of the CT component: Focal chest wall infiltration, invasion of the mediastinum and vascular invasion.
- PET Component: It distinguishes between tumours and atelectasis; malignant pleural effusion (T4) with an accuracy of 92%; metabolic activity with prognostic value.

3.2.3 N staging

PET increases sensitivity and NPV. PET/CT adds specificity and improves accuracy: Improvement of the exact location of the uptake in patients with atelectasis, mediastinal deviation and anatomical variants and proper identification of the node stage.

The problems derived from false positives in granulomatous disease and inflammatory changes caused by a coexistent lung disease leads to a lower PPV. For this reason, a mediastinoscopy is advised if the tumour can be operated, as well as an histological confirmation.

PET/CT is a good guide for an invasive biopsy, if the glands show positive results for the aortopulmonary window, the anterior mediastinum or the posterior subcarinal region. It is useful for a mediastinotomy, a transbronchial biopsy, ultrasound-guided fine-needle aspiration or transbronchial ultrasound-guided endoscopy.

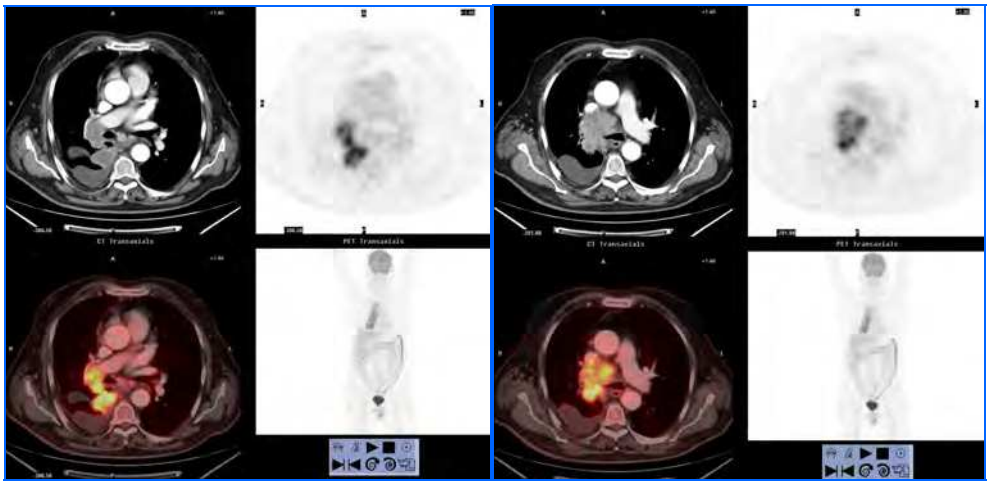

Fig. 14. PET/CT: Staging of NSCLC with mediastinal adenopathies, with an important 18FDG uptake. The invasion of the right main pulmonary artery can be seen thanks to the intravenous contrast. The pleural effusion does not show an 18FDG uptake.

3.2.4 M staging

PET provides an excellent detection of thoracic metastases, detection of unsuspected distant metastases 28% and change of treatment in 53% of the cases. PET/CT allows a more accurate location in adrenal metastases, with diagnostic accuracy in 92 % of the cases. It reduces the number of unnecessary thoracotomies by 25%.

- Hepatic metastases: The specificity and sensitivity of PET/CT is similar to those of other diagnostic techniques. It offers additional information for unspecific lesions.
- Adrenal metastases: Up to 10% of all NSCLC include a metastatic adrenal nodule at diagnosis. The accuracy of PET/CT is 92%, and its specificity ranges between 80 and 100% of all cases. An undetermined nodule in the CT with negative results in the PET scan generally means that it will be benign. False negatives have been described in adrenal metastases for very small lesions or when there is hemorrhage or necrosis.
- Bone metastases: Sensitivity goes up to 90% (similar to scintigraphy with Tc99m), although its specificity is better than scintigraphy with Tc99 (61%). The main limitation can be seen in blastic bone metastases, in which scintigraphy with Tc99m shows higher accuracy, or peripheral bone metastases. However, most bone metastases of NSCLC are central and lithic, which means that PET/CT might replace scintigraphy with Tc99m.
- Limitations of PET/CT in brain metastases are explained by the difficulty of finding small lesions due to cerebral physiological FDG activity. For this reason, brain NMR is recommended in these uncertain cases.

3.2.5 Re-staging

Post-therapy changes are known to make CT assessment more difficult. PET/CT improves the post-therapy accuracy, because 18F-FDG accumulates in the viable tumour cells instead of being captured by post-therapy necrosis and fibrosis.

Recurrence diagnosis in NSCLC with PET/CT improves sensitivity (77-100%) and specificity (62-92%), although this last factor can be reduced due to inflammation after radiation therapy or chemotherapy. For this reason, the diagnosis should be carried out 1-2 months after chemotherapy and 2-3 months after radiation therapy.

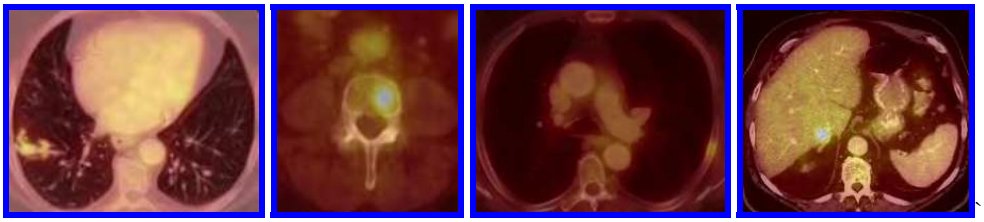

Fig. 15. NSCLC staging on upper left lobe with metastases on the liver, bones (sternum and vertebras) and peripheral pancreas (arrow). The patient is a 61-year-old male with NSCLC (initial stage: N1, according to a recent CT scan), and with several unsuspected metastatic lesions on the spine, liver and ribs.

3.3 Colorectal cancer

At diagnosis, colorectal cancer is found only in 36% of the patients. 39% of them showed lymph node metastases, and 19% of them presented distant metastases. Up to 15-20% of the patients presented liver metastases when their primary tumour was surgically resected. Surgery (of the primary tumour and the liver metastases) is the only known curative treatment.

- Resection of liver metastases is only indicated for patients with 1-4 lesions located on a single lobe (whenever there is no other evidence of more adenopathies or distant metastases)
- Up to 5% of the patients present synchronous colon carcinomas, and 30% of all patients present adenomatous polyps. Moreover, another 5% will develop a metachronic carcinoma of the colon in the future.

PET/CT is very useful in:

- Detection of recurrences in the following cases: high CEA with conventional imaging techniques, non specific or erroneous findings with conventional techniques or presacral masses after treatment.
- Monitoring of treatment with chemotherapy and radiotherapy.

PET/CT is not to be used in: Screening, initial diagnosis and patients with a known disseminated disease

Recurrence of colorectal cancer takes place in 37-44% of the patients within the first two years after the resection of the tumour with curative purposes. An early detection of potentially resectable metastases or local recurrences leads to an increase in survival rates. Serum CEA levels can be used to monitor the presence of recurrences (S: 59%; E: 84%), but they cannot locate the place of the recurrence. PET showed more than 90% sensitivity and more than 95% specificity, compared with CT levels, which were 60-85% sensitivity and 60-90% specificity. PET modifies the therapeutic management in up to 25-35% of the patients, and it detects up to 33% more metastases, compared with conventional methods.

Diagnostic accuracy of PET ranges between 90 and 100%, compared with 50-65% for CT.

Between 15 and 20% of patients with local recurrences are candidates for curative resection. However, long-term survival in these cases is only 35% (due to the presence of hidden metastases).

Correct differentiation between a viable tumour and a post-therapy fibrosis (due to surgery and/or radiation therapy) on the pelvis is vital for a proper management of the patients with suspicion of local recurrence. PET is very useful for a correct classification of these patients, and it can also find additional unsuspected metastatic sources. FDG accumulation 6 months after radiation therapy or later are a sign of a residual tumour or a recurrence.

Importance in liver metastases: The use of PET in the assessment of patients before a curative liver resection probably leads to the selection of a subgroup of "ideal" patients-candidates who can benefit greatly from this technique. 3-year survival rate improves up to 77% (compared with 40-45% with CT), and 3-year disease-free survival rates also improve up to 40% (compared with 15-28% with CT).

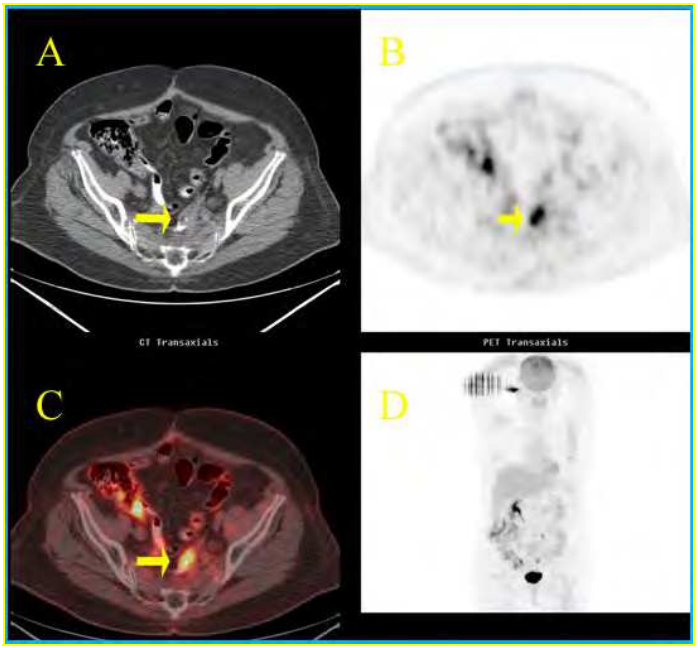

Fig. 16. I. Axial section of CT (A). 64-year-old woman with adenocarcinoma, treated with surgery, chemotherapy and radiation therapy, with clinical suspicion of recurrence. Axial section of PET (B) and combined image (C). PET study in a coronal section (D). A small mass can be seen on the surgical site, showing an intense 18FDG uptake. The recurrence was confirmed with surgery.

3.4 Lymphomas

- In most HL and NHL there is an increase in avidity: HL, DLC-NHL, follicular lymphoma
- Staging and re-staging: higher sensitivity and specificity than CT and PET: sensitivity: 91-94%, specificity: 88-100%.
- PET/CT detects normal-sized node diseases, characterization of residual masses; it detects partial or slow responses and less false positives than PET
- It identifies small lesions and specific locations: Base of lungs, skin and non-distant metastasis
- Residual mass: Early detection of remains/recurrence, more effective treatment.
- Disease exclusion prevents invasive diagnostic procedures and unnecessary treatments and guided biopsy towards uptake regions in the mass.

Non-Hodgkin lymphomas (NHL) can be roughly classified into 3 groups: low grade, intermediate grade and high grade. Low-grade NHL represents 40% of all NHL, and they are usually indolent. Most of the patients are treated with a monochemotherapy regime (or even with a wait-and-see approach). PET can represent an important role in the assessment of patients in which the low-grade NHL is suspected to have turned into a high-grade NHL (this happens in 10-20% of the cases).

Intermediate-grade NHL represents 40% of all NHL, and high-grade NHL represent 5-10% of all cases. Both are treated with chemotherapy and radiation therapy. PET plays several roles in the management of these patients. It determines the extension of the disease (staging) and the response to treatment (therefore, chemotherapy treatments can be modified if they are not being effective).

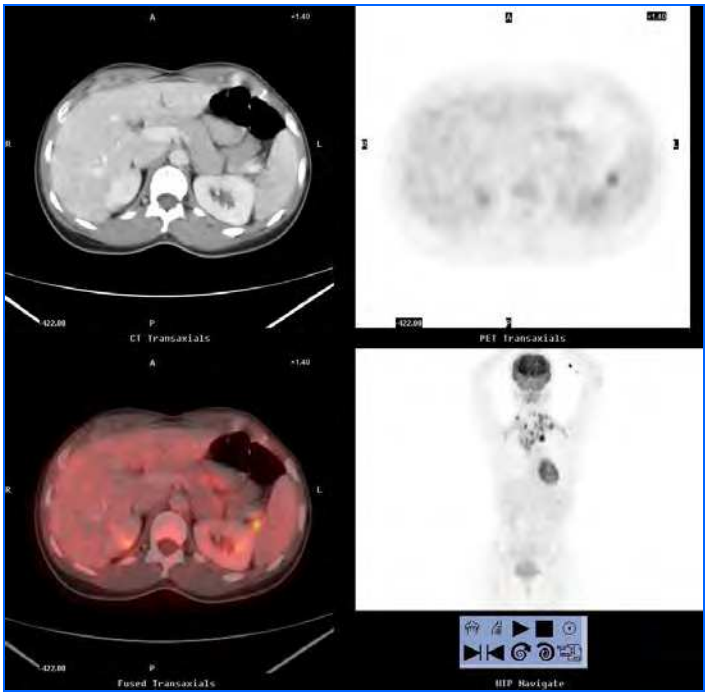

Fig. 17. Axial section of CT with normal intravenous contrast. Axial section of PET. PET/CT detected a pathological FDG uptake in a small adenopathy in the splenic hilium. Therefore, the stage was increased from II to III.

Hodgkin's lymphoma (HL): The extension of the disease is, when taken by itself, the most important prognostic factor for a proper management with regard to global survival and recurrence-free survival in HL patients. Conventional methods are often incapable of revealing the real extension of the tumour (for example, between 20% and 30% of all patients with a HL that is allegedly located over the diaphragm also present infradiaphragmatic involvement when an exploratory laparotomy is performed).

PET provides an excellent contrast for the lesions and a relatively good anatomical location thanks to the tomographic nature of the images, greatly improved with the new PET/CT.

It makes it possible to study, in a single exploration, all the affected organs.

The detection of the lesions depends on their biochemical signal instead of on anatomical criteria. A certain correlation between the FDG uptake degree and the histological degree of the lymphoma has been observed.

However, low-degree lymphomas may not accumulate enough FDG to be detected. PET fulfills two important aspects that are being more and more taken into account in health services: on the one hand, it reduces the number of invasive diagnostic procedures, and on the other hand, it is a technique with a good cost-effectiveness ratio (a study which included PET into the diagnostic algorithm of lymphoma patients showed that expenses were reduced by 50%). Some studies have shown that PET modifies the management of lymphoma patients in up to 62% of the cases (Pinilla et al., 2010).

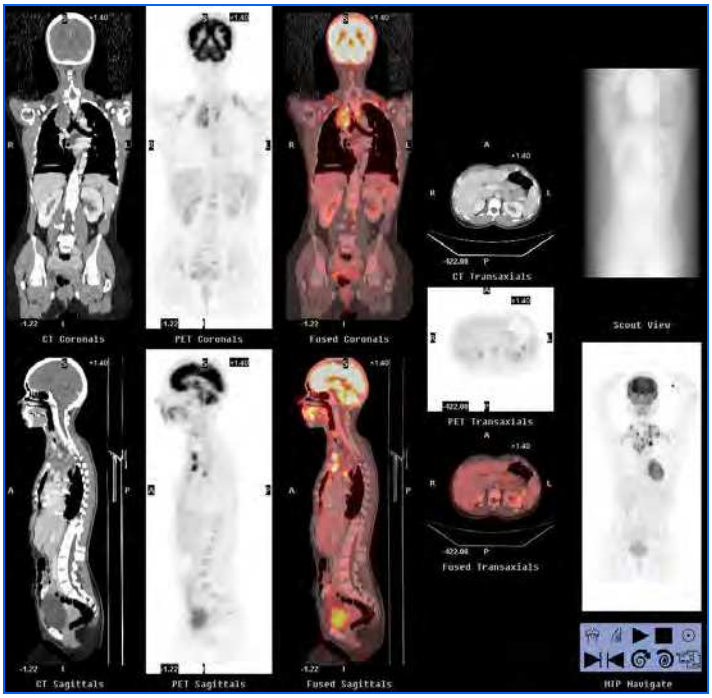

Fig. 18. PET/CT can change the stage of the disease in approximately 10% of all lymphoma patients. Study of PET/CT in initial staging of a patient with nodular sclerosis Hodgkin's lymphoma with laterocervical, supraclavicular and mediastinal involvement.

3.4.1 Lymph node involvement

PET shows high sensitivity for the detection of lymph nodes and staging the patients. Published sensitivities vary between 62% and 100%. In spite of this variability, PET seems to be more sensitive than CT for the staging of lymphoma patients, because it can detect more lesions inside and outside the nodes, than conventional methods. It alters the stage of patients, in any of both directions, in up to 44% of the cases, according to some studies.

3.4.2 Extranodal involvement

Extranodal involvement is associated with a worse prognosis of patients. PET can detect up to 57% more extranodal lesions than CT. Diffuse infiltration in the spleen, bone marrow and

liver cannot be detected with CT. Up to 30% of lymphoma patients with splenomegaly do not present tumour infiltration of the spleen and a significant number of patients presents tumour involvement of the spleen without splenomegaly. FDG uptake by the bone marrow represents a tumour infiltration, although an increased uptake of the bone marrow can also be expected if the patient has undergone chemotherapy or has received colony-stimulating factors recently (post-therapy medullary hyperplasia).

Bone marrow involvement (stage IV) means a worse prognosis in lymphoma patients, and it is more frequent in NHL patients. In order to be detected by CT, the bone involvement must be focused and accompanied by bone destruction. Unfortunately, a diffuse infiltration of the bone marrow does not show bone destruction, and it is usually asymptomatic. PET can detect both the focal involvement and the diffuse infiltration of the bone marrow. According to several studies, it is more sensitive than bone scintigraphy with Tc99m.

3.4.3 Monitoring of response to treatment

Conventional methods (CT, NMR) only show a reduction of the size of the lesions, and they are not very reliable as predictors of the clinical success of the lymphoma treatment. Some studies with CT showed that less than 50% with positive findings in CT developed a recurrence of the disease in the long term. Unlike conventional techniques, PET determines the metabolic activity of a lesion, which reflects the mass of viable cells inside a tumour. After the beginning of chemotherapy or radiation therapy, there is a series of metabolic changes in the tumour before any changes on the size of the mass. Several recent studies suggest that, after successful chemotherapy, the metabolic activity of the tumour rapidly decreases (SUV decrease by 75-90% 7 days after the beginning of treatment). An intense and persistent FDG uptake after the end of chemotherapy cycles shows an absence of therapeutic response.

Patients who show persistently positive PET studies after the first chemotherapy cycle present a much higher risk of recurrence (a recurrence rate of 90%, according to one study) than patients with a positive response (decrease in FDG uptake). Likewise, some studies observed that 85% of all patients with a negative PET study after the first chemotherapy cycle remain in remission (minimum monitoring time of 18 months). A PET study after the first chemotherapy cycle also has been proven to be a better predictor for response to treatment than a PET study at the end of the treatment (diagnostic accuracy of 87% versus 70%).

An early assessment of response to treatment would not only avoid the toxicity of an ineffective treatment, but also reduce the costs of that therapy. In these cases, patients could benefit from second-line therapies. A variation of SUV over 25% must be considered as a real finding.

Differentiation of fibrotic tissue versus viable in a post-therapy residual mass: The presence of a residual mass after the end of lymphoma therapy is a challenge for the clinical diagnosis, because it can represent either a viable tumour or a residual diagnosis. Conventional diagnostic techniques do not offer reliable enough signs that can tell the difference between a viable tumour and a fibrosis, but with PET, FDG accumulates in the viable tumour, whereas fibrosis do not reveal any accumulation. In patients with mediastinal lymphoma, up to 64% of them show some anatomical alteration after the end of the treatment. However, only 18% of them will show a recurrence. FDG uptake in a residual mass is associated to a higher rate of recurrence and worse global survival rates, compared with patients without FDG uptake. The presence of persistent metabolic activity in a residual mass may motivate a change in the

treatment or the addition of new chemotherapeutic agents. In spite of the fact that 25% of all patients with negative PET results and a residual mass will have a recurrence, it will take place in a different location from the residual mass in 80% of the cases (Cronin, 2010).

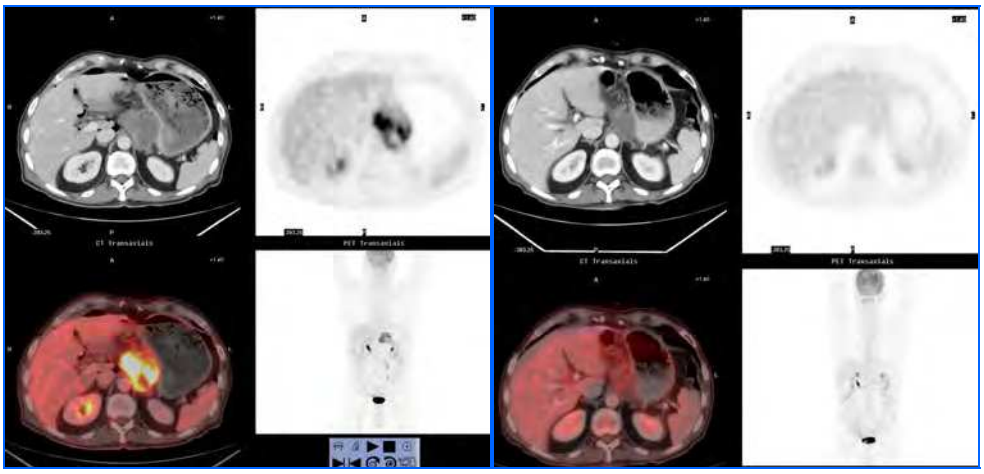

Fig. 19a & b. 45-year old patient with Diffuse large B-cell NHL with a mass that shows an intense FDG avidity at diagnosis (a). The mass persists after the end of the treatment, without FDG uptake. The recurrence was confirmed with monitoring, without additional treatment (b).

3.5 Melanoma

It is one of the tumours with the highest FDG avidity, and it has the potential to metastasize in any part of the body. Therefore, it benefits from a PET/CT assessment, which shows a great sensitivity for the detection of metastases, with the exception of the brain.

PET is useful in the detection of adenopathies and distant metastases (particularly with melanomas thicker than 1.5 mm – Clark level 4). The sensitivity and specificity of PET in the detection of distant metastases is 80% and 87%, respectively (higher than in conventional methods).

PET's sensitivity for the detection of adenopathies in patients with melanoma depends on the size of the metastases (sensitivity is almost 100% for adenopathies >1 cm, and only 23% for adenopathies <5 mm). All data accumulated until now suggest that the diagnostic accuracy of PET is higher for systemic staging than for local staging of regional lymph nodes (especially in Stage I or II patients). Therefore, PET cannot replace sentinel node biopsy in the clinical management of the patients.

3.6 Cancer of unknown primary origin

- Guided biopsy identifies primary tumours in more than 33% of the cases (Wartski et al 2006) and diagnosis of distance metastasis
- Controversial cost-effectiveness analysis in first test for epidermoid carcinoma
- Useful in cervical metastases of adenocarcinoma.

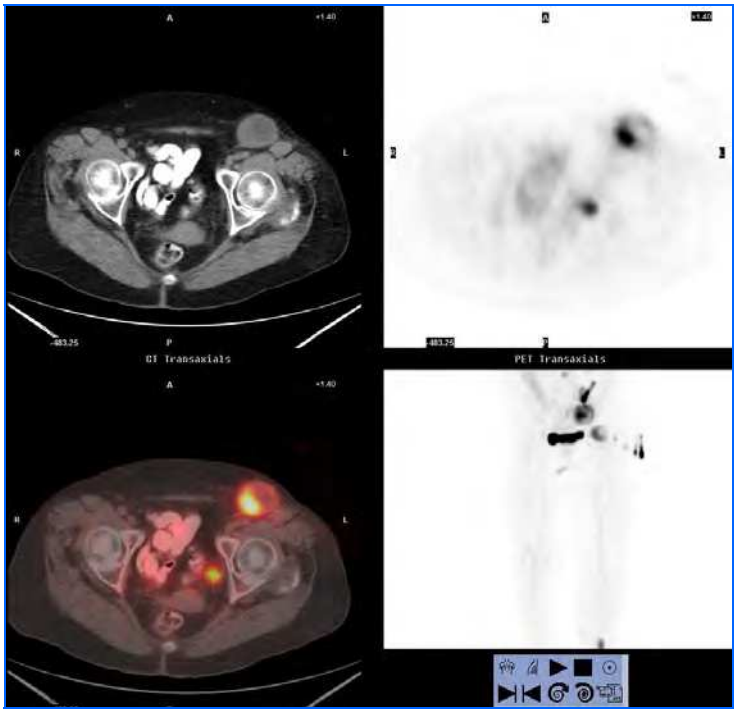

Fig. 20. Patient with melanoma on the leg and inguinal and iliac node involvement.

3.7 Head and neck tumours

They are useful to distinguish, in some cases, between the changes in recurrences after therapy (chemotherapy, radiotherapy, surgery).

3.7.1 Applications of PET/CT in the assessment of head and neck tumours

- Unknown primary tumour: detection of the primary lesion in up to 33% of the cases.
- Staging.
- Re-staging: post-therapy changes versus recurrence.
- Thyroid cancer: especially when the I-131 scintigraphy is negative.
- Metachronic/synchronic tumours: respiratory and digestive tract (up to 30% of the patients).

3.7.2 Possible interpretation errors

- Asymmetrical uptake of FDG in the muscles.
- Submaxillary glands
- Treatment with surgery and radiation therapy.
- Uptake in supraclavicular area fat.
- Hashimoto's thyroiditis.

3.7.3 Esophageal cancer

- USA's Medicare currently includes two indications for PET in esophageal cancer:
  - Preoperative staging and post-therapy re-staging.
  - Monitoring of the treatment (when there is evidence of a potential recurrence).
- Primary tumour: PET is not useful in the assessment of primary esophageal cancer or in the detection of a local invasion of the tumour. A PET/CT combination improves staging.
- Lymph node metastases: The presence of adenopathies on the neck, the supraclavicular areas or the celiac trunk is a sign of M1 metastasis (which means that its detection represents a great impact on the management of the patient).
- Distant metastases: The main advantage of PET with regard to conventional imaging techniques is its capability to detect distant metastasis (diagnostic accuracy of 84% versus 63% for CT). The presence of distant metastases has a great impact on the management of the patient because they are not resectable. PET detects metastatic diseases that are not identified by conventional studies in up to 20% of the patients.
- Recurrent esophageal cancer: The sensitivity of PET for the detection of distant metastases is 95% (specificity of CT is 79%). Moreover, PET provides additional diagnostic information in 27% of the patients with suspicion of tumour recurrence.

3.7.4 Thyroid cancer

- Diagnosis: PET is not indicated in the diagnosis of thyroid cancer (not all carcinomas attract FDG, and some benign lesions can accumulate FDG).
- Staging: Although there are no data in this regard, PET probably does not play an important role in the initial staging of patients with thyroid cancer.
- Patients with suspicion of recurrent cancer and a negative I-131 scintigraphy: The published sensitivity of PET for the detection of recurrent thyroid cancer in patients with negative I-131 scintigraphies ranges between 60% and 94% (specificity between 42-95%). One advantage of PET is the fact that it can detect tumour sites in nodes smaller than 1 cm. However, PET cannot detect small lung metastases.
- Prognosis: 3-year survival rates are significantly reduced in patients with postive PET results (survival of 60%), with regard to patients with a negative result (survival of 98%), which means that PET has an important prognostic value.

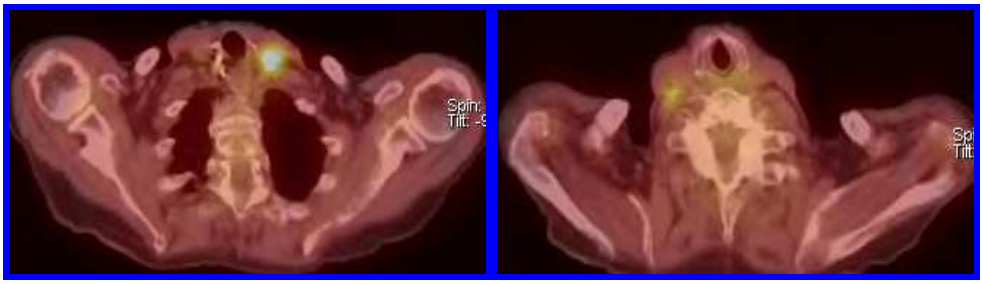

Fig. 21a & b. Recurrent thyroid cancer. The patient is a 73-year-old woman with a record of papillary thyroid cancer. She showed a recent increase of serum thyroglobulin with negative results for I-131 scintigraphy. PET/CT: Tumour remains on the surgical site and right laterocervical adenopathy.

3.7.5 Head and neck tumours

Most head and neck tumours are epidermoid carcinomas. Up to 60% of the patients present an advanced stage of the lesion at diagnosis. The involvement of lymph nodes is the most important prognostic factor with regard to survival. Conventional studies with CT and/or NMR have certain limitations in the assessment of lymph node involvement, because they are mainly based on the size of the nodes (> 1 cm) in order to classify them as pathological nodes. However, up to 40% of all lymph node metastases take place in nodes smaller than 1 cm. PET is particularly useful in the assessment of patients with a clinical stage N0. In this clinical context, between 16% and 60% of all patients reveal hidden lymph node metastases after a PET study.

- Proper preoperative staging (TNM) is essential when planning the type of lymph node dissection and when assessing the need of postoperative radiation therapy or chemotherapy.
- A relatively common presentation of head and neck tumours is the appearance of cervical adenopathies. A careful ENT examination, together with CT/NMR can identify the primary tumour in most cases. However, in up to 32-40% of the patients, the primary lesion will not be identified. PET, particularly combined with CT, is especially useful in these cases.
- Assessment of response to treatment: PET (PET/CT) can be used to monitor the response to treatment in head and neck tumours. Tumours that respond to treatment show a reduced metabolic activity, and those that present a persistent uptake one month after radiation therapy usually contain viable or residual tumour cells. In more than 80% of the cases, PET can establish the difference between a residual tumour and post-radiation therapy fibrosis.

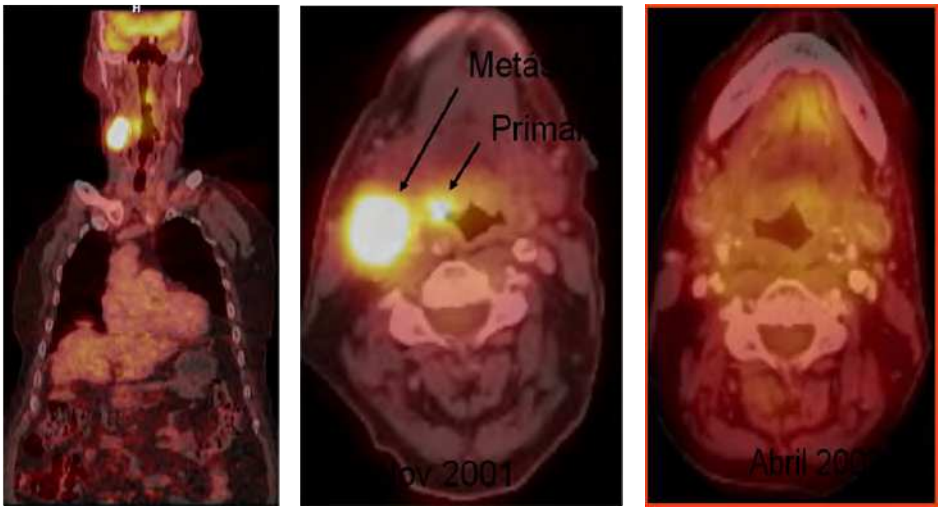

Fig. 22a, b & c. Head and neck tumour: unknown primary tumour. The patient is a 70-year-old male with a recent biopsy of a right cervical mass that was positive for epidermoid carcinoma (unknown primary mucosal lesion). PET/CT shows a favorable response after treatment with surgery and radiation therapy.

- The quantification of FDG uptake by the tumour (through SUV) correlates with the biological behavior of the tumour, and it has been proved that an intense FDG uptake (SUV>5.5) identifies a group of patients who can benefit from a more aggressive treatment.

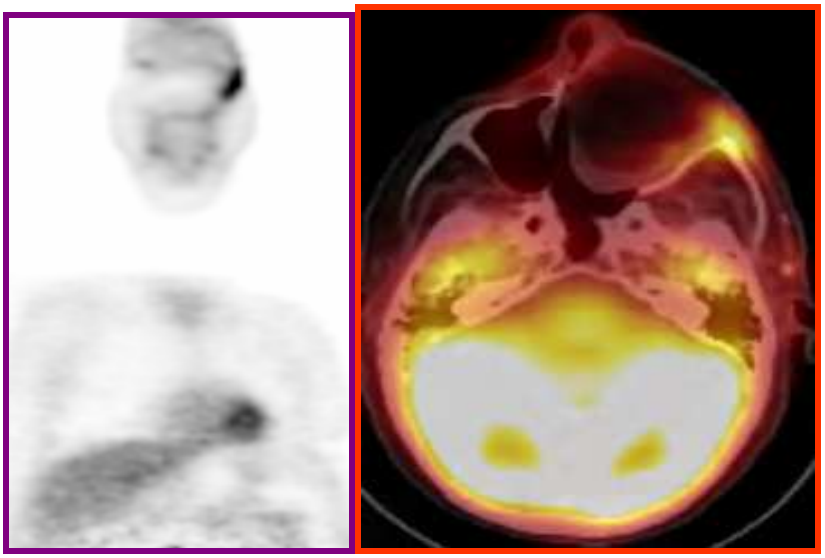

Fig. 23a & b. Re-staging of head and neck tumour. The patient is a 72-year-old male with adenopathy in an adenocarcinoma of the left nasal cavity with extension into the orbitary region that was surgically operated. 6 weeks later, the tests reveal a FDG-uptake area on the anterior region of the left zygomatic arch, compatible with persistence of viable tumour.

3.8 Breast cancer

Assessment of systemic metastases, identification of recurrence locations and possible role in the radiotherapy planning.

- CT Component: extended towards chest wall and skin.
- PET provides a more accurate detection of metastases in the internal mammary gland.

PET studies can have a very significant impact on the management of patients, especially in those with suspicion of advanced disease. PET can modify the clinical stage in up to 36% of the cases (it increases the clinical stage in 28% of the cases and reduces it in 8% of the cases). In 20% of the cases, unsuspected metastases are discovered, and the clinical management of patients is modified in up to 58% of the cases, once that the PET results are taken into account.

3.8.1 Local disease

Breast cancer presents a significantly variable FDG uptake. Generally speaking, a higher proliferation rate of the tumour and a higher degree of undifferentiation mean a higher rate of metabolic activity of the tumour and higher FDG avidity. Invasive ductal carcinoma shows a FDG uptake significantly higher than invasive lobular carcinoma. Focal node

lesions also present high levels of FDG uptake, compared with infiltrative/diffuse lesions. PET/CT has an advantage in the fact that it is not altered by the density of the mammary tissue, and the quality of the image is not altered in case of previous surgery (radiation therapy or mammary prosthesis). Its sensitivity ranges between 64% and 96%, and its specificity is around 75-100%. The main limitation of PET is the fact that it cannot detect lesions smaller than 1 cm, due to the partial volume effect and the physiological accumulation of FDG in the mammary tissue.

3.8.2 Lymph node metastases

The sensitivity that has been published in the literature for PET detection of locoregional adenoapthies ranges between 50% and 100%, and its specificity is around 86-92%. If nodes of less than 1 cm and micrometastases are taken into account, the sensitivity of PET studies significantly decreases. For these reasons, PET cannot replace axillary node dissection. PET is particularly useful in the detection of adenopathies in the mediastinum and the internal mammary chain (PET sensitivity: 85%; CT sensitivity: 54%). The identification of these adenopathies has a very significant impact on the management of the patients (either increasing the radiation field or applying a more aggressive chemotherapy regime) and in their prognosis (Escalona et al., 2010).

3.8.3 Metastatic disease

PET is more accurate in the detection of unsuspected distant metastases, both at initial diagnosis and during the monitoring stage.

3.8.4 Monitoring of response to treatment

The assessment of response to treatment can be established with PET before any other diagnostic method (before there is a noticeable or measurable reduction in the size of the tumour). A PET study after a single chemotherapy cycle can predict the response (or lack of response) of the tumour to the treatment, with a sensitivity of 90-100% and a specificity of 74-85%).

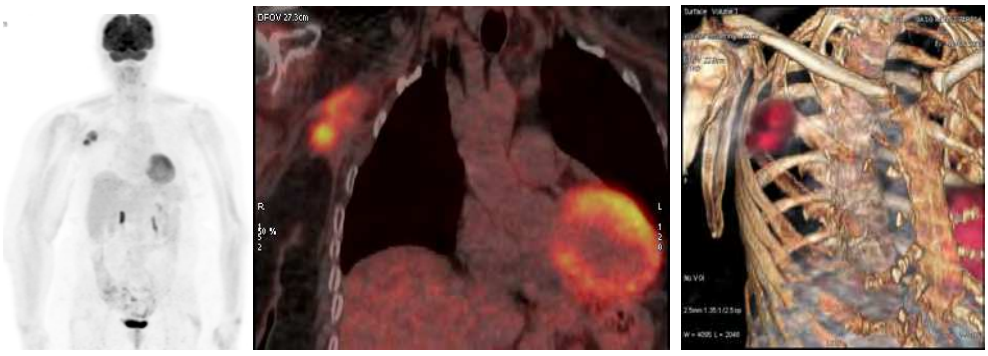

Fig. 24 a, b & c. Patient with breast carcinoma, recurrence on the right axilla.

3.8.5 Assessment of tumour recurrence

Previous surgery and/or radiation therapy can produce fibrosis/scar tissue that will complicate the assessment of potential locoregional recurrences (particularly on the axillary region), although potential distant metastatic areas can be detected.

3.8.6 Other applications of PET in breast cancer patients

The presence or absence of estrogen receptors has a great influence on the choice of a systemic treatment. Between 30% and 40% of the patients with advanced breast cancer and positive result for estrogen receptors (ER) will respond to treatment with antiestrogens (tamoxifen). Another important percentage of patients will have a stable condition for a clinically significant period of time. The presence of ER can be assessed with the use of an estrogen tracer (FES). If a tumour shows SUV>1 in a PET study with FES, it is considered to be a positive result for ER. When the tamoxifen treatment has started, ER are blocked, which means that any tumour that responds to antiestrogen therapy will show a fast decrease of SUV in PET studies with FES.

3.9 PET/CT and its applications in radiation therapy

Ideally speaking, the radiation therapy should administer a dose of ablative radiation to the tumor, leaving the peritumoral healthy tissue intact. With 3D conformational radiation therapy, the doses for the tumor and the other tissues can be calculated more accurately, the therapeutic effect increases, and toxic complications are reduced. In order to apply this therapy, the tumor needs to be accurately located. CT provides anatomical information, as well as the dosimetric bases for the calculation of radiation absorption. However, it also has

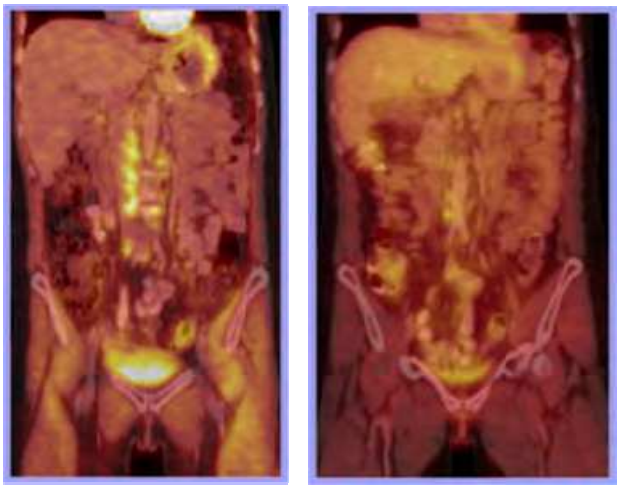

Fig. 25a & b. Intensity-modulated radiation therapy in a patient with cervical cancer (pre- and post-treatment)

important limitations, such as the delimitation of tumor margins, unnecessarily large radiation areas or infiltrated areas that remain untreated. PET/TC integrates structural and molecular information. Therefore, it provides a more accurate estimation of the tumor size and it identifies better areas with tumor viability. The use of this new "anatomobiological outline" in the planning of radiation therapy represents a clinically significant change with regard to the volume of radiation therapy that the patients receive. It can change the treatment approach, avoid unnecessary radical radiation therapy and adjust the volume of treatment, with the possibility of increasing the doses in specific locations.

- PET/CT before treatment: Cervical cancer with inguinal and paraaortic adenopathies. Definition of target volume.
- Planning of radiation therapy. The axial section of the radiation field is extended 14 mm in order to include paraaortic adenopathies, and additional radiation is applied to the pelvic adenopathy.
- Intensity modulated radiation therapy is administered in order to achieve higher effectiveness in the treatment with less side-effects.
- The response to treatment is assessed after the end of the therapy.

3.10 The future: Neuroradiology and cardiac viability

3.10.1 Drug-resistant epilepsy

MRI and PET co-registration in pediatric epilepsy FDG-PET represents a useful tool for presurgical evaluation of epilepsy, particularly when MRI is nonlesional. Previous studies have shown FDG-PET to have 63–100% sensitivity in lateralizing temporal lobe epilepsy (TLE) and to provide complementary information to MRI. For extratemporal lobe epilepsy (ETLE), studies have shown FDG-PET to have slightly lower sensitivity at 36–83%. In addition to increasing detection postsurgical prognostic information independent of information provided by MRI, FDG-PET might thus provide complementary as well as supplementary functional information in regard to the etiology of seizure activity. Given the parallel roles of MRI and FDG-PET in presurgical evaluation for epilepsy patients, co-registration of MRI and FDG-PET might enhance presurgical management of intractable epilepsy. This has not been unequivocally established, but it is already recommended that FDG-PET images be interpreted in light of all structural imaging information. In the recent UCLA cohort, FDG-PET and MRI co-registration demonstrated favorable postsurgical outcomes (Engel class I–II) in 80% of the patients with intractable epilepsy with the application of co-registered imaging to maximally resect the functional abnormal area. This technique uses anatomic imaging to help define the limits of resection, despite previous MRI findings that had been considered to be nonlesional.

3.10.2 PET and brain development in pediatrics

Functional development of the pediatric brain has been evaluated by FDG-PET. Chugani et al. demonstrated that the metabolic pattern of a developing brain follows the order of anatomical, evolutional and behavioral development. Increased glucose metabolism is shown in the visual, sensorimotor cortex and the cerebellum, and this is correlated with early

visuospatial and sensorimotor function and primitive reflexes. Hypermetabolism in the basal ganglia is known to be associated with developing movement and sensorimotor function.

The quantitative analysis of brain FDG-PET has demonstrated that the degree of glucose metabolism of infants is significantly lower than that of adults. The degree of metabolic activity of neonates is about 30% that of adults and it continues to increase with age. It is hypothesized that increased metabolism is associated with increased metabolic demands from neuronal plasticity development. By a child's third year, the metabolic level exceeds that of adults, and it reaches its plateau between ages 4 and 9 with a value 1.3 times higher than that of normal adults. After this period, the value decreases to adult level by the end of the second decade.

Future applications include combined PET-MRI imaging and neuroreceptor imaging.

3.10.3 Dementia

Conventional anatomic imaging (e.g., MRI and CT) play a minimal role in the early detection of dementia, especially for Alzheimer's Dementia AD. There is evolving literature that supports that FDG PET may be more sensitive and specific than conventional nuclear medicine imaging (i.e., ECD and HMPAO imaging) in the diagnosis of dementia, especially in early detection. A more recent multicentre study (Mosconi et al., 2008) enrolled 548 patients (110 normal, 114 with mild cognitive impairment, 199 with AD, and 125 with other forms of dementia). Based on clinical endpoints they found that FDG PET correctly classified 94% of normal variants, 95% of AD, and between 92% and 94% of other types of dementia. There was significant heterogeneity in FDG patterns for patients with mild cognitive impairment. They developed standardized automated methods to analyze FDG brain scans and thought this automated consistent approach resulted in more homogeneous results than previously reported in the literature.

3.10.4 Cardiac viability

A stress PET examination can reliably demonstrate myocardial blood flow using 82Rb or 13Nammonia. PET radiopharmaceuticals can be used to assess both cardiac perfusion (i.e., 13N-ammonia, 15O-water, 82Rb) and heart muscle viability (FDG) (Machac et al., 2006). This section will only address evidence related to FDG viability assessment. Cardiac imaging tests can be roughly stratified into those which assess coronary blood flow/cardiac muscle perfusion, systolic function (i.e., how well the heart is pumping), heart muscle viability (i.e., living, but potentially at risk, heart muscle versus dead/scarred tissue) and other less common studies which assess very specific metabolic processes (e.g., fatty acid metabolism) or neuromuscular function (e.g., MIBG studies). PET can be used to assess all of these areas the CT component, can also assess coronary artery anatomy (e.g., CT angiogram) and coronary calcium scoring. These parameters can also be assessed through conventional CT or with SPECT/CT (Hesse et al., 2005).

4. Conclusion

PET/CT is a multidisciplinary technique which involves nuclear, radiology, radio physics, radio pharmacology and oncology and combines the advantages of the functional information by PET and the special and contrast resolution of CT. This improves the

diagnosis, staging and follow-up of some types of cancer and other pathologies, and new indications could appear in the future.

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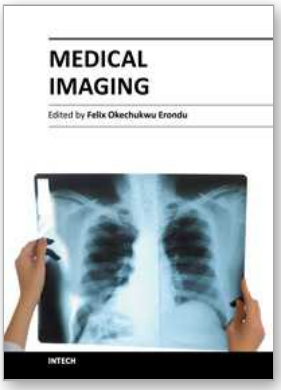

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What we know about and do with medical imaging has changed rapidly during the past decade, beginning with the basics, following with the breakthroughs, and moving on to the abstract. This book demonstrates the wider horizon that has become the mainstay of medical imaging sciences; capturing the concept of medical diagnosis, digital information management and research. It is an invaluable tool for radiologists and imaging specialists, physicists and researchers interested in various aspects of imaging.

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