Place de la TEP dans la prise en charge du myélome multiple en 2017

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Imaging Type (CT, MRI, PET or BS) Per Person-Year stratified by Cancer Type and Year

- Bone Scan Imaging Days per Person Years by Cancer Type
- CT Imaging Days per Person-Year by Cancer Type
- MRI Imaging Days per Person Years by Cancer Type

- PET Imaging Days per Person Years by Cancer Type

- Lung
- Head & Neck
- Colorectal
- Melanoma
- Lymphoma
- Esophagus

Why such an increase?

The fourth dimension....

PET/CT provides a functional characterization of findings detected at tomographic morphological imaging.

✔ Accurate staging
✔ Function evaluation
✔ Therapy assessment

**BETTER STRATIFICATION**
Distribution of bone lesions in MM patients

MOST OF THE BONES ARE INCLUDED
EXTRAMEDULLARY DISEASE CAN BE DETECTED

PET/CT FOV for MM

Field of view

Mandible: 10%
Skull: 35%
Humeri: 33%
Ribs: 33%
Spine: 49%
Pelvis: 34%
Femora: 13%
Function / Early lesions

Morphology

Both

LDCT is accurate enough for the evaluation of bone in MM
In symptomatic MM the bone evaluation is essential: CT contribution

Since X-Ray has a poor sensitivity, in 2014 the IMWG (International Myeloma Working Group) proposed that low dose CT can be employed as an alternative procedure to skeletal radiography: the presence of two clearly defined lytic lesions indicates high tumor burden and stage III disease, which is associated to a poorer prognosis.
Usually **SUV max** is high but not necessarily.

SUV max does depend on:

1. biological characteristics of the disease
2. lesion size

SUV max does not depend on:

1. Stage at diagnosis

Focal uptake may not be related yet to bone damage

Focal uptake may be **extramedullary**

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Massive Extramedullary

Focal Extramedullary
Combination of FDG PET and LDCT in MM: what can ask?

LDCT → Is there bone damage? Accurate morphological evaluation of bone (lytic lesions, osteoporosis, fractures)
How many lytic lesions?
What size?
Low radiation dose delivered to the patient
Total Body
Very short time (5 sec)

FDG PET → SUV

Early detection of bone lesions (no significant lysis yet)
Extramedullary disease
Short time (15 min)

OTHER ADVANTAGES: No collateral effects, standardized procedure, no restrictions in renal failure and bone metallic implants, free decubitus in case of severe pain
Role of FDG PET/CT in MM

• Symptomatic (secretory and non secretory)
• Smouldering
• Plasmacytoma
Staging symptomatic MM


Table 2. Comparative imagings of 18F-FDG PET-CT, MRI and WBXR at baseline.

<table>
<thead>
<tr>
<th>Comparative imagings</th>
<th>Concordant results</th>
<th>Discordant results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N. of pts (%)</td>
<td>N. of pts (%)</td>
</tr>
<tr>
<td></td>
<td>with negative</td>
<td>with positive</td>
</tr>
<tr>
<td></td>
<td>findings</td>
<td>findings</td>
</tr>
<tr>
<td>PET-CT WB vs WBXR</td>
<td>9/46 (19)</td>
<td>12/46 (26)</td>
</tr>
<tr>
<td>PET-CT SP vs MRI SP</td>
<td>4/46 (8)</td>
<td>28/46 (61)</td>
</tr>
<tr>
<td>PET-CT WB vs MRI SP</td>
<td>4/46 (8)</td>
<td>15/46 (34)</td>
</tr>
</tbody>
</table>

WBXR: whole body X Ray; MRI S-P: magnetic resonance imaging of spine-pelvis; PET-CT: positron emission tomography-computed tomography; SP: spine-pelvis; WB: whole body; Pts: patients, vs: versus.

1. AT STAGING DETECTS MORE LESIONS THAN WBXR
2. AT STAGING DETECTS THE SAME NUMBER OF LESIONS AS COMPARED TO CONVENTIONAL MR

FOV: SPINE+PELVIS
STANDARD SEQUENCES

Van Lammeren-Venema D et al., Cancer 2011
18F-Fluoro-deoxyglucose Positron Emission Tomography in Assessment of Myeloma-Related Bone Disease: A Systematic Review

Van Lammeren-Venema D et al., Cancer 2011

COMPARISON OF PET OR PET/CT AND CONVENTIONAL IMAGING AT STAGING

• 18 studies, 798 patients
• 7 studies PET ± CT vs WBXR: 6/7 PET showed more lytic lesions with the exception of the skull
• 5 studies PET ± CT vs MRI spine and/or pelvis: 4/5 MRI was superior in detecting myeloma bone disease, especially in case of diffuse bone infiltration
• 1 study PET/CT vs WBMRI: concordant in 80% cases
• Identification of extra-medullary disease
Comparison of modern and conventional imaging techniques in establishing multiple myeloma-related bone disease: a systematic review

COMPARISON OF PET, PET/CT, MRI OR CT vs WBXR AT STAGING

- 32 directly comparison studies, prospective and retrospective, 1661 patients
- Index test vs reference standard: detection rate
- Quality assessment of diagnostic studies
- All index tests had sensitivity above 0.9 as compared to WBXR (low false negative). Fewer additional lesions detected by PET/CT and MRI as compared to WBLDCT. WBLDCT can replace WBXR
- Modern imaging techniques detected fewer lesions in the skull and ribs. «We therefore recommend additional X-ray of the ribs and the skull if clinically relevant»

Regelink J. et al., BJH 2013
Staging symptomatic MM

N° OF FLs, SUV VALUE

**SUV value**

- SUV ≤ 4.2
- SUV > 4.2

- P = 0.008

**PFS**

- 64% at 4 yrs
- 43% at 4 yrs

**N° FLs**

- N° FLs ≤ 3
- N° FLs > 3

- P = 0.01

- 65% at 4 yrs
- 43% at 4 yrs

Zamagni et al.

**EFS by PET-FL**

- P = 0.001

Baseline PET and MM outcome (4-Y PFS and OS)

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PFS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMD</td>
<td>3.81</td>
<td>1.93-7.50</td>
<td>.000</td>
</tr>
<tr>
<td>Postinduction PET SUV &gt; 4.2</td>
<td>3.44</td>
<td>1.32-8.98</td>
<td>.007</td>
</tr>
<tr>
<td>Post-ASCT PET SUV &gt; 100% reduction</td>
<td>2.69</td>
<td>1.15-6.28</td>
<td>.022</td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse</td>
<td>9.31</td>
<td>2.78-31.16</td>
<td>.000</td>
</tr>
<tr>
<td>Post-ASCT PET SUV &gt; 100% reduction</td>
<td>3.93</td>
<td>1.15-13.42</td>
<td>.029</td>
</tr>
<tr>
<td>EMD</td>
<td>3.91</td>
<td>1.55-9.88</td>
<td>.002</td>
</tr>
<tr>
<td>Postinduction PET SUV &gt; 4.2</td>
<td>3.11</td>
<td>0.77-12.50</td>
<td>.09</td>
</tr>
</tbody>
</table>

PFS according to extramedullary disease at baseline

Logrank P-value = .000
Staging: the bone in symptomatic MM

1 lesion
PFS 73 months

> 4 lesions
PFS 34 months
Staging: the bone in symptomatic MM

SUV max 2.5

PFS 69 months

SUV max 7.9

PFS 39 months
Complete FDG suppression retained independent prognostic value for PFS and OS in Cox regression analysis

Bartel. TB et al, Blood 2009
**PROGNOSTIC VALUE OF PET/CT AFTER ASCT**

**PFS**

- **SUV 100% reduction**
- **SUV < 100% reduction**

<table>
<thead>
<tr>
<th>Time at</th>
<th>Hazard Ratio (95% CI)</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 yrs</td>
<td>0.000</td>
<td>0.02</td>
</tr>
<tr>
<td>8 yrs</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>12 yrs</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>16 yrs</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>20 yrs</td>
<td>0.000</td>
<td>0.000</td>
</tr>
</tbody>
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**OS**

- **SUV 100% reduction**
- **SUV < 100% reduction**

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<td>4 yrs</td>
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<td>12 yrs</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>16 yrs</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>20 yrs</td>
<td>0.000</td>
<td>0.000</td>
</tr>
</tbody>
</table>

**MULTIVARIATE ANALYSIS**

<table>
<thead>
<tr>
<th>VARIABLES</th>
<th>HAZARD RATIO (95% CI)</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extramedullary disease</td>
<td>15.43 (4.11-57.95)</td>
<td>0.000</td>
</tr>
<tr>
<td>del (17p) ± t(4;14)</td>
<td>1.86 (1.12-3.49)</td>
<td>0.05</td>
</tr>
<tr>
<td>Not complete FDG PET suppression</td>
<td>1.82 (1.19-3.77)</td>
<td>0.01</td>
</tr>
<tr>
<td>PFS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extramedullary disease</td>
<td>5.93 (2.27-15.51)</td>
<td>0.000</td>
</tr>
<tr>
<td>del (17p) ± t(4;14)</td>
<td>1.90 (1.09-3.32)</td>
<td>0.023</td>
</tr>
<tr>
<td>Not complete FDG PET suppression</td>
<td>1.89 (1.06-3.35)</td>
<td>0.030</td>
</tr>
<tr>
<td>OS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse</td>
<td>9.35 (2.79-31.31)</td>
<td>0.000</td>
</tr>
<tr>
<td>Not complete FDG PET suppression</td>
<td>3.90 (1.12-13.60)</td>
<td>0.03</td>
</tr>
</tbody>
</table>
PROGNOSTIC VALUE OF PET/CT AFTER ASCT


Score 0: none of the 3 adverse factors, 30% of the patients
Score 1: only 1 of 3, 36%
Score 2: 2 factors, whichever, 25%
Score 3: all three risk factors, 9% of cases
PFS and OS according to PET/CT negativity or positivity in patients achieving conventionally defined CR after up-front therapy.

Interesting in non secretory MM

PROGNOSTIC VALUE OF PET/CT in CR: MRD

PFS 37 months

PFS 3 months
1. Focal uptake without lysis does exist.
2. Identification of patient sub-groups with smoldering multiple myeloma (SMM) at high risk of progression to active disease (MM) is an important goal.

**PROGNOSTIC VALUE OF PET/CT in smouldering MM**

![Graph showing the time to progression of SMM to active MM with Kaplan-Meier curves for PET/CT negative and positive groups.](image)

- **PET/CT negative**
- **PET/CT positive (16%)**

**HR 3.00 (95% CI 1.58-5.69) p=0.001**

Leukemia. 2016 Feb;30(2):417-22
Univariate analysis of baseline variables adversely affecting time to progression of SMM into active MM (TTP)

<table>
<thead>
<tr>
<th>Variables</th>
<th>HR</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMPC &gt; 60%</td>
<td>3.7</td>
<td>1.5</td>
</tr>
<tr>
<td>MC</td>
<td>1.00</td>
<td>1.0</td>
</tr>
<tr>
<td>PET/CT pos</td>
<td>3.0</td>
<td>1.6</td>
</tr>
<tr>
<td>MRI pos</td>
<td>2.3</td>
<td>1.1</td>
</tr>
<tr>
<td>MRI diffuse</td>
<td>2.8</td>
<td>1.2</td>
</tr>
</tbody>
</table>

BMPC bone marrow plasma cells, MC M component, pos positive, HR hazard ratio, CI confidence interval
PET/CT in PLASMACYTOMA
PET/CT in PLASMACYTOMA

Impact of Initial FDG-PET/CT and Serum-Free Light Chain on Transformation of Conventionally Defined Solitary Plasmacytoma to Multiple Myeloma

1. Normal sFLC and PET/CT <2
2. Abnormal sFLC or PET/CT ≥ 2
3. Abnormal sFLC and PET/CT ≥ 2

Time to multiple myeloma transformation

43 patients

serum-free light chain
1. Prognostic factor
2. Therapy choice and pt management
PET/CT: pros and cons

- Whole Body (skeleton and other tissues)
- Safe
- Reasonably fast with last generation scanners (1m z axys is scanned in 14'+CT)
- No absolute contraindications
- Relatively low dose (5-8 mSv + LDCT)
- Sensitivity
- Response to therapy
- Possibility to semi-quantify lesions uptake (objectivation of disease behaviour over time)
- Associated to morphologic imaging (CT)

- Aspecific signal (although in bone false positive results are rare, excluding articular uptake and very recent vertebral collapse)
- Spatial resolution (conventionally 5mm, but depends on lesion uptake)
- Inaccurate semi-quantitation for small lesions (SUV max is underestimated for lesions < 1cm. Problems with positivity criteria usually published in literature)
- Reduced sensitivity for lesions in hot background.
- Reduced sensitivity for lesions with low tracer uptake.
- Corticosteroids may reduce sensitivity
- Interpretation
<table>
<thead>
<tr>
<th>Study</th>
<th>Journal, Year</th>
<th>PET/CT results</th>
<th>Prognostic/Quantitative</th>
<th>SUVmax</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haznedar</td>
<td>Eur J Nuclear Medicine, 2010</td>
<td>Not realized</td>
<td>No</td>
<td>Highest SUV max</td>
</tr>
<tr>
<td>Falcone</td>
<td>Recenti Prog Med, 2012</td>
<td>Not realized</td>
<td>No</td>
<td>Highest SUV max</td>
</tr>
<tr>
<td>Elliott</td>
<td>Eur J Haematol, 2011</td>
<td>Not realized</td>
<td>No</td>
<td>Highest SUV max</td>
</tr>
<tr>
<td>Bartel</td>
<td>Blood, 2009</td>
<td>Visual, Focal uptake higher than background</td>
<td>No</td>
<td>Highest SUV max</td>
</tr>
<tr>
<td>Derlin</td>
<td>Eur Radiol, 2013</td>
<td>Yes, uptake corresponding to CT abnormalities not attributable to benign bone conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fonti</td>
<td>J Nucl Med, 2012</td>
<td>Yes, uptake corresponding to CT abnormalities not attributable to benign bone conditions</td>
<td>MTV</td>
<td></td>
</tr>
<tr>
<td>Zamagni</td>
<td>Blood, 2011</td>
<td>Visual and/or Quantitative, Depending on the size of the lesion</td>
<td>No</td>
<td>Highest SUV max</td>
</tr>
</tbody>
</table>
IN LITERATURE THERE ARE SEVERAL INTERPRETATION CRITERIA APPLIED BY VARIOUS RESEARCH GROUP.

- SEMI-QUANTITATIVE
- VISUAL
- SEMIQUANTITATIVE + VISUAL
- DIFFERENT ARBITRARY CUT OFFs

VERY VARIABLE RESULTS ESPECIALLY IN BORDERLINE CASES
ALL THE CRITERIA ARE IN ACCORDANCE IN CASE OF:

- Focal lesions > 5mm in cold background
- Litic lesions (inequivocal identification of the disease site)
- No increased background (no bone marrow activation)
- No recent vertebral fractures or collapse

DIFFERENT CRITERIA PROVIDE A POS OR NEG RESULT IN BORDERLINE CASES

- Bone marrow infiltration (dd with activation?)
- Low focal SUV max
- Small areas of focal uptake
- Focal lesions in increased background
- Recent fractures or vertebral collapse

STANDARDIZATION
French Criteria

Francoise Kraeber-Bodéré, Caroline Bodet-Milin, Philippe Moreau
Italian Criteria

Cristina Nanni, Elena Zamagni, Annibale Versari, Stephane Chauvie, Andrea Gallamini
WHAT’S THE NEXT STEP?

IMPeTUS

Italian Myeloma criteria for Pet Use

International Myeloma criteria for Pet Use
MULTIPARAMETRIC MR: prognosis, criteria.....

NEW PET/CT TRACERS (Choline, Methionine, 68Ga-DOTANOC, 68Ga-Pentixafor....)

CREATE NOMOGRAMS TO INTERGRATE IMAGING INFORMATION INTO CLINICAL PRACTICE.
Merci!

Elena Zamagni
Michele Cavo
Stephane Chauvie
Annibale Versari
Michel Meignant
Philippe Moreau
Caroline Bodet-Milin
Francoise Kraeber-Bodéré
Caroline Bodet-Milin

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