Modern tools for disease evaluation

Novel imaging techniques

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ROLE OF IMAGING IN MULTIPLE MYELOMA

- Precise identification of bone disease, as sign of organ damage and need to start treatment
- Identification of sites of extra-medullary disease (total body techniques)
- Differential diagnosis between localized disease (BSP) and systemic disease (MM)
- Correct identification of sites of bone disease at risk of complications (fractures, neurological complications)
- Correct follow up of the patients after treatment, in particular in non secretory MM

Zamagni E. et al, BJH 2012
DEFINITION OF MYELOMA BONE DISEASE

- Clear evidence of one or more sites of osteolytic bone destruction (at least 5 mm or more in size) seen on CT, WBLDCT, PET/CT, regardless of weather they can be visualized on skeletal radiography or not
- Osteoporosis per se not attributable to myeloma is not sufficient for CRAB
- Presence of «early» bone marrow infiltration represented by MRI FLs
- If doubt lesions on CT or PET/CT or MRI: close follow-up every 3-6 months and/or biopsy of the lesion

Rajkumar V. et al., Lancet Oncology 2014
SYSTEMATIC REVIEW
NEW IMAGING TECHNIQUES HAD A HIGHER DETECTION RATE AS COMPARED TO WBXR*

* Except for ribs and skull

ROLE OF NEWER IMAGING TECHNIQUES IN MM

• **MORPHOLOGICAL**: assessing bone destruction
  • WB-MDCT-LDCT, CT part of PET/CT

• **FUNCTIONAL**: assessing bone marrow infiltration and disease metabolism
  • ASSIAL/WB-MRI (DCE-MRI, DWI-MRI), PET/CT

• AT DIAGNOSIS/RE-STAGING: staging and prognosis
• AFTER TREATMENT: evaluation of treatment response, MRD definition

Zamagni E. et al, BJH 2012
# Imaging Techniques for Staging

<table>
<thead>
<tr>
<th>WB/LDCT</th>
<th>PET/CT</th>
<th>MRI</th>
</tr>
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<tbody>
<tr>
<td><strong>Pros</strong></td>
<td><strong>Pros</strong></td>
<td><strong>Pros</strong></td>
</tr>
<tr>
<td>Sensitivity and specificity</td>
<td>Sensitivity and specificity</td>
<td>Sensitivity and specificity</td>
</tr>
<tr>
<td>CT-guided biopsy, surgery, RT</td>
<td>Optimal to assess EMD</td>
<td>No radiation</td>
</tr>
<tr>
<td>Can depict EMD, BM involvement, lytic lesions</td>
<td>Can depict lytic lesions (CT part)</td>
<td>Gold standard for detection of diffuse BM involvement</td>
</tr>
<tr>
<td>Rapid acquisition time, low radiation dose (3-7 mSV)</td>
<td>Can assess tumor burden and disease metabolism</td>
<td>Optimal for CNS imaging</td>
</tr>
<tr>
<td>Intermediate cost</td>
<td>Prognostic significance of FLs and SUV</td>
<td>Gold standard for differential diagnosis between osteoporotic and pathological fractures</td>
</tr>
<tr>
<td><strong>Cons</strong></td>
<td><strong>Cons</strong></td>
<td><strong>Cons</strong></td>
</tr>
<tr>
<td>Sub-optimal for diffuse BM involvement</td>
<td>Sub-optimal for diffuse BM involvement</td>
<td>Imaging time (in particular axial)</td>
</tr>
<tr>
<td>Few data/unclear prognostic significance of lesion number and BM abnormalities</td>
<td>High cost, availability</td>
<td>No detection of lytic lesions: no definition of end organ damage (MDE) according to current IMWG criteria</td>
</tr>
<tr>
<td>Detection of lytic lesions</td>
<td>Radiation dose intermediate (10 mSV)</td>
<td>High cost, availability</td>
</tr>
</tbody>
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Choice usually made according to local clinical practice, resources and expertise.
### IMWG Criteria for MRD in Multiple Myeloma

<table>
<thead>
<tr>
<th>IMWGMRD negativity criteria</th>
<th>Response subcategory</th>
<th>Response criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sustained MRD negative</td>
<td>MRD negative in the marrow (Next-generation flow or Next-generation sequencing) and by imaging as defined below, confirmed one year apart. Subsequent evaluations can be used to further specify the duration of negativity (e.g., MRD negative @ 5 years etc)</td>
</tr>
<tr>
<td></td>
<td>Imaging MRD-negative</td>
<td>MRD negative as defined below (Next-generation flow or Next-generation sequencing) PLUS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT³</td>
</tr>
<tr>
<td>Flow MRD-negative</td>
<td>Absence of phenotypically aberrant clonal plasma cells by next-generation flow cytometry⁴ on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in MM (or validated equivalent method) with a minimum sensitivity of 1 in 10⁵ nucleated cells or higher</td>
<td></td>
</tr>
<tr>
<td>Sequencing MRD negative</td>
<td>Absence of clonal plasma cells by next generation sequencing on bone marrow aspirates in which presence of a clone is defined as less than 2 identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the Lymphosight® platform (or validated equivalent method) with a minimum sensitivity of 1 in 10⁵ nucleated cells⁵ or higher</td>
<td></td>
</tr>
</tbody>
</table>

COMPLEMENTARITY BETWEEN IMAGING AND BM MRD

PET/CT and FLOW MONITORING BEFORE MAINTENANCE

- 86/134 evaluated by both PET/CT and flow
- 47.7% both negative
- 86.8% both negative
- 52.9% either positive

Moreau P. et al, JCO 2017
Spatial genomic heterogeneity in multiple myeloma revealed by multi-region sequencing


![Focal lesion at 4th lumbar vertebra:](image1)
- GEP70 high risk
- Non-Hyperdiploid
- Del(1p12)
- Del(1p13)
- Del(13q)
- Biallelic TP53

![Growing heterogeneity with growing size of the lesions](image2)
GEM2012MENOS65 (VRD + ASCT): MRD assessment by NGF
Patients relapsing despite an MRD-ve result

Paiva B et al, ASH 2017
NEWER IMAGING TECHNIQUES IN THE EVALUATION OF RESPONSE TO THERAPY

• MORPHOLOGICAL: assessing bone destruction
  • WB-MDCT-LDCT, CT part of PET/CT

• FUNCTIONAL: assessing bone marrow infiltration and disease metabolism
  • ASSIAL MRI- WBMRI (DCE-MRI, DWI-MRI), PET/CT

• Active MM
  • at diagnosis: staging and prognosis
  • after treatment: evaluation of treatment response
Complete FDG suppression retained independent prognostic value for PFS and OS in Cox regression analysis.

Usmani S.Z. et al, Blood 2013
Zamagni E. et al, Blood 2011

**METABOLIC RESPONSE TO THERAPY**

**PROGNOSTIC VALUE OF PET/CT AFTER ASCT**

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

32% at 4 yrs

47% at 4 yrs

P = 0.02

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

66% at 4 yrs

79% at 4 yrs

P = 0.02

**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>
METABOLIC RESPONSE TO THERAPY

Role of MRI and PET-CT before maintenance (62% normalised)

Table 2. Multivariable Analyses

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression-free survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response ≥ VGPR after three cycles of RVD</td>
<td>0.362</td>
<td>0.230 to 0.569</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>PET-CT normality before maintenance</td>
<td>0.419</td>
<td>0.283 to 0.619</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Extramedullary disease by PET at diagnosis</td>
<td>3.394</td>
<td>2.055 to 5.606</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Overall survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytogenetic abnormalities (17p, t4;14)</td>
<td>3.853</td>
<td>1.531 to 9.692</td>
<td>.004</td>
</tr>
<tr>
<td>Extramedullary disease by PET at diagnosis</td>
<td>3.894</td>
<td>1.540 to 9.851</td>
<td>.004</td>
</tr>
</tbody>
</table>

Abbreviations: PET, positron emission tomography; PET-CT, positron emission tomography-computed tomography; RVD, lenalidomide, bortezomib, dexamethasone; VGPR, very good partial response.

Moreau P. et al JCO 2017
METABOLIC RESPONSE TO THERAPY
PET/CT MRD MONITORING IN CR PATIENTS

ASCT candidates (192 pts)

- 70% PET-CR, 40-50% biochemical CR
- 25-30% of the patients in conventionally-defined CR had PET/CT still positive

Zamagni E. et al, Blood 2011

ASCT eligible and not-eligible (189 pts)

Zamagni E. et al, Clin Canc Res 2015
PROGNOSTIC VALUE OF PET/CT AFTER TREATMENT
3 independent prospective series of patients (US, Italy, France)

• Before ASCT (day 7 CHT, post-induction, at first ASCT)$^1,2,4$
• After ASCT$^3$
• Before maintenance$^4$

**IN CR PATIENTS (25-30% PET/TC pos)**

- PFS and OS difference PET pos vs neg in CR patients$^3,6$
  (retrospective study, 282 pts) and complementary with MFC$^4$
- No stratification of CR patients$^7$ (US study, 45 pts treated with KRd + len maintenance) (sample issue? Different sensitivity with more intense regimens?)

$^1$ Bartel. TB et al, Blood 2009
$^2$ Usmani S.Z. et al, Blood 2013
$^3$ Zamagni E. et al, Blood 2011
$^4$ Moreau P. et al, JCO 2017
$^6$ Zamagni E. et al, Clin Canc Res 2015
$^7$ Korde N, JAMA Oncol 2015
FALSE NEGATIVE PET/CT FOR LOW EXPRESSION OF HEXOKINASE-2
Specific tracers: Daratumumab labelled with Copper-64 and DOTA chelator (Cu-DOTA-Dara) in murine model$^{1,2}$

<table>
<thead>
<tr>
<th>Tracer</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cassou-Mounat et al, 2016$^a$</td>
<td>$^{18}$F-FCH vs $^{18}$F-FDG More sensitive than $^{18}$F-FDG in relapsed or refractory multiple myeloma</td>
</tr>
<tr>
<td>Nanni et al, 2007$^b$</td>
<td>$^{11}$C-choline Allows specific evaluation of cell membrane proliferation; more sensitive than $^{18}$F-FDG, especially in detecting skull lesions</td>
</tr>
<tr>
<td>Luckerath et al, 2015$^c$</td>
<td>$^{11}$C-methionine Highly concentrated in sites of myeloma bone disease; correlates with bone marrow involvement and clinical parameters</td>
</tr>
<tr>
<td>Dankerl et al, 2007$^c$, Lapa et al, 2016$^d$</td>
<td>$^{18}$F-fluorothyridine Uptake correlates with DNA synthesis and high proliferation</td>
</tr>
<tr>
<td>Agool et al, 2006$^5$</td>
<td>$^{18}$F-NaF Uptake is a function of bone blood flow and reflects bone remodelling. $^{18}$F-FDG better than $^{18}$F-NaF for the detection of myeloma focal lesions, but $^{18}$F-NaF better than $^{18}$F-FDG for the assessment of rib fractures or degenerative changes</td>
</tr>
<tr>
<td>Ak et al, 2015$^e$</td>
<td>$^{11}$C-acetate Uptake depends both on the tri-carboxylic acid cycle and cell membrane lipid synthesis. Possible advantages over $^{18}$F-FDG suggested in the staging of patients with newly diagnosed multiple myeloma</td>
</tr>
<tr>
<td>Ho et al, 2014$^7$, Lin et al, 2014$^8$</td>
<td>$^{18}$F-4-thiophenolide More sensitive than $^{18}$F-FDG for the detection of active lesions and more closely related to bone marrow plasma-cell infiltration</td>
</tr>
<tr>
<td>Ogasaki et al, 2015$^9$</td>
<td>$^{18}$F-4-thiophenolide More sensitive than $^{18}$F-FDG for the detection of active lesions and more closely related to bone marrow plasma-cell infiltration</td>
</tr>
<tr>
<td>Herrmann et al, 2016$^{10}$</td>
<td>$^{68}$Ga-pentixafor Excellent PET imaging characteristics and favourable human dosimetry</td>
</tr>
</tbody>
</table>

$^{18}$F-FDG= $^{18}$F-fluorodeoxyglucose, $^{18}$F-FCH= $^{18}$F-fluorochloride, $^{18}$F-NaF= sodium fluoride.

Table 1: Studies investigating tracers other than $^{18}$F-FDG for PET/CT imaging in patients with multiple myeloma

Cavo M. et al, Lancet Oncology 2017

$^{1}$Ghai A et al, JNM 2017

$^{2}$Caserta E et al, Blood 2018 epub
PROGNOSTIC VALUE OF STANDARD MRI AFTER TREATMENT

- Late response after ASCT\(^1\)
- 100 pts after ASCT\(^2\)
- 79 patients prior and after allo-SCT: correlation of $\geq 1$ FLs with PFS/OS (uni and multivariate analysis)\(^3\)

Often false positive results

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\(^1\) Walker R. et al, JCO 2007
\(^2\) Hillengass J. et al, Haematologica, 2012
\(^3\) Mosebach J et al, Haematologica 2017 epub
PROGNOSTIC VALUE OF FUNCTIONAL MRI AFTER TREATMENT: DCE AND DWI

Independent experiences on small series of patients

FUNCTIONAL DCE-WBMRI: evaluating differences in perfusion

- 30 pts after CHT or ASCT: good correlation with clinical response¹
- 27 pts after treatment: correlation of DCE and DWI MRI and with clinical response²,³

FUNCTIONAL DWI- WBMRI: evaluating differences in cellular density

- Detection of early response after induction (12-30pts per group): detectable modifications of apparent diffusion coefficient (ADC) (increase for oedema/necrosis) and correlation with clinical response⁴,⁵,⁶,⁷
- Detection of late response at the end of therapy (15-20 pts per group): significant decrease of ADC after treatment, for return of fat marrow ⁶,⁸,⁹

¹ Lin C et al, Radiology 2010
² Bourillon C et al, Radiology 2015
³ Dutoit JC et al, Eur J Radiol 2016
⁴ Lacognata C. et al, Clinical Radiology 2017
⁵ Horger M et al, AJR 2011
⁶ Messiou C et al, BJR 2012
⁷ Giles SL et al, Radiology 2014
⁸ Hillengass J et al, BJH 2011
⁹ Latifoltojar A et al, Eur Radiol 2017
**IMAGING TECHNIQUES AFTER TREATMENT**

**PET/CT**
- Large prospective studies
- Early post-therapy changes
- Prognostic significance in CR patients (MRD monitoring) and complementarity with MFC
- Good correlation with biochemical response
- Standardization on-going
- Applicability in 75-90% of the patients
- Availability, highest cost

**FUNCTIONAL MRI**
- High sensitivity in detecting diffuse BM infiltration
- Pathological fractures assessment
- Quantification of structural and functional changes of tissues, related to cellular density and perfusion

**PROS**

**CONS**
Table 6: Recommendations for use of 18F-FDG PET/CT in MM

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Grade</th>
</tr>
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<tbody>
<tr>
<td><strong>Active MM:</strong></td>
<td></td>
</tr>
<tr>
<td>18F-FDG PET/CT can be considered as part of the initial workup in patients with newly diagnosed MM since it provides information useful for prognostication and allows to more carefully assess the bulk of the disease, particularly in patients with extramedullary sites of the disease. This latter indication for use of 18F-FDG PET/CT applies also to patients with relapsed/refractory MM</td>
<td>B</td>
</tr>
<tr>
<td>In newly diagnosed MM, EMD and &gt;3 FLs on 18F-FDG PET/CT identify subgroups of patients with unfavorable outcomes, particularly those who are candidates to receive upfront ASCT. Controversies exist about the prognostic role of SUV&lt;sub&gt;max&lt;/sub&gt;</td>
<td>B</td>
</tr>
<tr>
<td><strong>18F-FDG PET/CT is by now the preferred technique for evaluating and monitoring response to therapy. Metabolic changes assessed by 18F-FDG PET/CT provide an earlier evaluation of response compared to MRI</strong></td>
<td>A</td>
</tr>
<tr>
<td>18F-FDG PET/CT should be coupled with sensitive bone marrow-based assays as part of MRD detection inside and outside the bone marrow</td>
<td>B</td>
</tr>
</tbody>
</table>

Cavo M. et al, Lancet Oncology 2017
OPEN ISSUES

• Standardization of imaging definitions and positivity cut-off for PET/CT and DWIBS-MRI (on-going for PET/CT)
• Comparison between PET/CT and DWIBS MRI (prospective trials just started in UK and Germany)
• How to incorporate imaging- MRD with BM-MRD after treatment: design of trials MRD-driven
Treatment to suppression of focal lesions on positron emission tomography-computed tomography is a therapeutic goal in newly diagnosed multiple myeloma

(A) PFS from ASCT-1

(B) OS from ASCT-1

(C) PFS from maintenance

(D) OS from maintenance

Davies F et al, Haematologica 2018
KRD consolidation in myeloma patients with a positive PET-CT after standard first line treatment; a phase II study (NMSG#24/16)

First-line treatment*
FDG PET/CT
FDG PET/MRI
Flow MRD

Screen N ≥ 120

PET positive
KRD x 4
20/36mg m²
PET-CT
PET-MRI
Flow MRD
Lenalidomide

PET negative
SoC / Lenalidomide

N=50

* Induction (VTD/VCD/VRD)
+ ASCT
or MPV/Rd/VRD in TNI
* at least VGPR

Primary outcome: Switch from PET-positivity to PET-negativity after 4 KRD
Secondary outcomes: Number of pats with PET positivity after EOT, MRD negativity, improved response, safety, QOL, PFS, TTNT, OS

Courtesy of Niels Abilgaard
CONCLUSION

• **Newer imaging techniques** have proved reliable tools in the staging and as predictors of outcome in MM patients, both in early stage and active disease and should be used in the work-up of patients

• **PET/CT and DCE/DWI-MRI** are the favorite techniques for assessing and monitoring response to therapy and are becoming complementary investigation tools for detecting minimal residual disease, going beyond the conventionally defined CR level

• **Comparative studies** between PET/CT and functional MRI are warranted

• **Standardization process** is on-going for PET/CT

• **Implementation of prospective clinical trials** with newer imaging techniques will help to address several issues, standardize the interpretation of the results and optimize the use of these promising tools