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Prognostic role of FDG-PET/CT in myeloma

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ROLE OF FDG-PET/CT IN MULTIPLE MYELOMA

- **Symptomatic MM**
  - **at diagnosis: staging and prognosis**
  - after treatment: evaluation of treatment response, follow-up
- Early stage/smouldering MM

ACTIVE MYELOMA: the CRAB CRITERIA

Myeloma-related end organ damage due to the plasma cell proliferative process

- **C:** Calcium levels increased
- **R:** Renal insufficiency
- **A:** Anemia
- **B:** Bone lesions, osteolytic or osteoporosis

Definition of multiple myeloma

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following myeloma defining events:

- Myeloma defining events:
  - Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
    - Hypercalcaemia: serum calcium >0·25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2·75 mmol/L (>11 mg/dL)
    - Renal insufficiency: creatinine clearance <40 mL per min† or serum creatinine >177 μmol/L (>2 mg/dL)
    - Anaemia: haemoglobin value of >20 g/L below the lower limit of normal, or a haemoglobin value <100 g/L
    - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT‡
  - Any one or more of the following biomarkers of malignancy:
    - Clonal bone marrow plasma cell percentage* ≥60%
    - Involved:uninvolved serum free light chain ratio§ ≥100
    - >1 focal lesions on MRI studies¶

Rajkumar V. et al., Lancet Oncology 2014

IMWG, BJH 2003

INTERNATIONAL MYELOMA WORKING GROUP UPDATED CRITERIA FOR THE DIAGNOSIS OF MULTIPLE MYELOMA

- **Definition of myeloma bone disease (CRAB):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**
- If doubt lesions on CT or PET/CT: close follow-up every 3-6 months and/or biopsy of the lesion
- Oseoporosis per se in the absence of lytic lesions is not sufficient for CRAB

Rajkumar V. et al., Lancet Oncology 2014

^{18}F-Fluoro-deoxyglucose Positron Emission Tomography in Assessment of Myeloma-Related Bone Disease: A Systematic Review

Danielle van Lammeren-Venema, MD[1]; Josien C. Regelink, MD[1]; Ingrid I. Riphagen[2]; Sonja Zweegman, MD, PhD[1]; Otto S. Hoekstra, MD, PhD[3]; and Josée M. Zijlstra, MD, PhD[1]

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

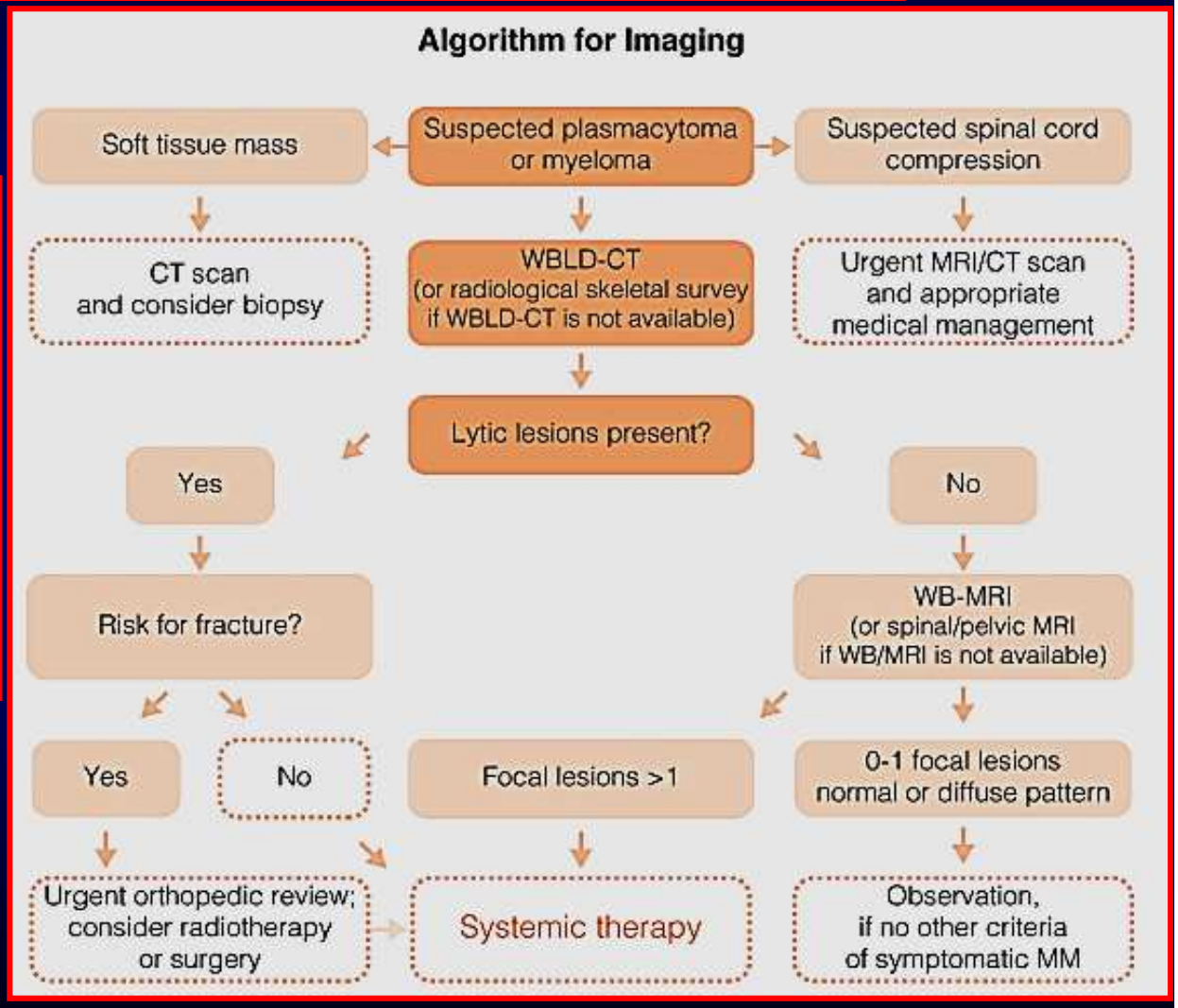
- 18 studies, 798 patients
- 7 studies PET ± CT vs WBXR: 6/7 PET showed more lytic lesions with the exception of the skull
- 5 studies PET ± CT vs MRI spine and/or pelvis: 4/5 MRI was superior in detecting myeloma bone disease, especially in case of diffuse bone infiltration
- 1 study PET/CT vs WBMRI: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

Van Lammeren-Venema D et al., Cancer 2011

European Myeloma Network Guidelines for the Management of Multiple Myeloma-related Complications

Evangelos Terpos,[1*] Martina Kleber,[2,3*] Monika Engelhardt,[2*] Sonja Zweegman,[4] Francesca Gay,[5] Efstathios Kastritis,[1] Niels W.C.J. van de Donk,[6] Benedetto Bruno,[5] Orhan Sezer,[7] Annemiek Broijl,[8] Sara Bringhen,[5] Meral Beksac,[9] Alessandra Larocca,[5] Roman Hajek,[10] Pellegrino Musto,[11] Hans Erik Johnsen,[12] Fortunato Morabito,[13] Heinz Ludwig,[14] Michele Cavo,[15] Hermann Einsele,[16] Pieter Sonneveld,[8] Meletios A. Dimopoulos,[1] and Antonio Palumbo[5] on behalf of the European Myeloma Network

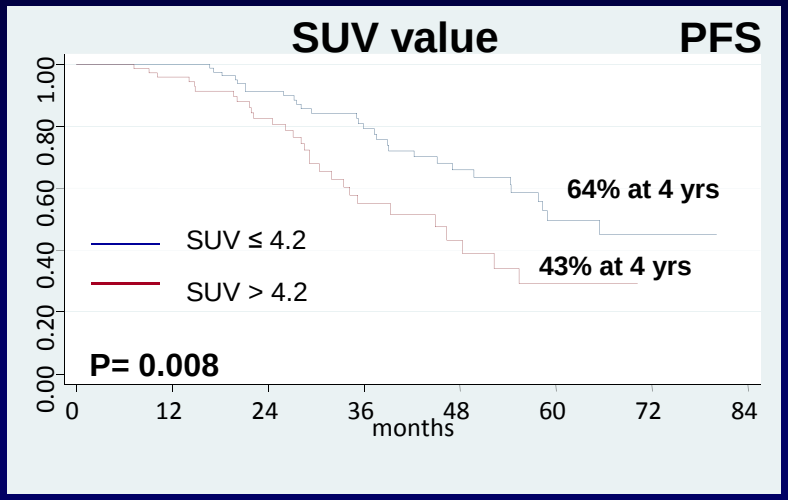
Recommendation: WBLD-CT is the novel standard procedure for the diagnosis of lytic disease in patients with MM (grade 1A). Conventional radiography can also be used if WBLD-CT is not available. In asymptomatic patients with no lytic disease in WBLD-CT, whole body MRI (or spine and pelvic MRI if WB-MRI is not available) has to be performed and in the presence of more than 1 focal lesion the patients are characterized as having symptomatic disease that needs therapy (grade 1A). PET/CT may be useful for the better definition of complete or stringent complete response (CR or sCR) and for the progression of the disease (grade 2B). Figure 1 presents the imaging algorithm which is proposed by the EMN for use in myeloma-related bone disease.

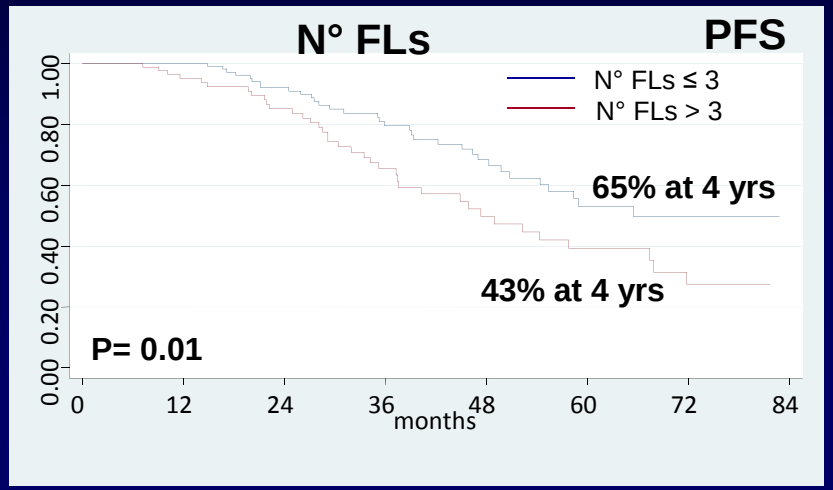


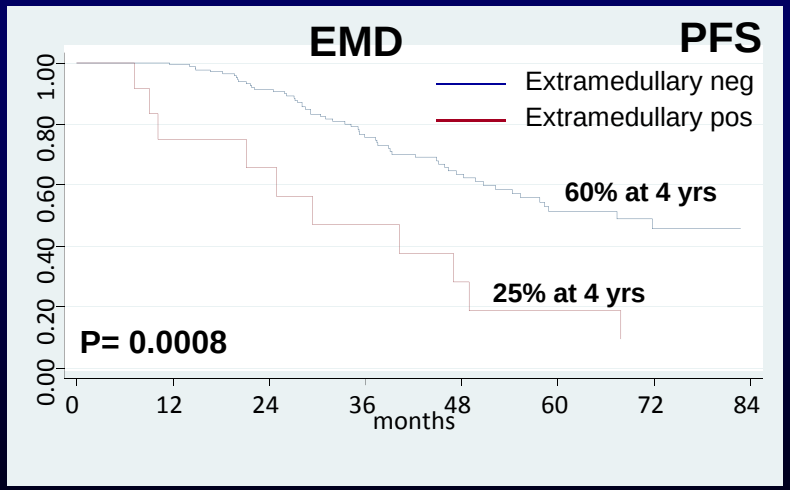
Terpos E. et al., Haematologica 2015

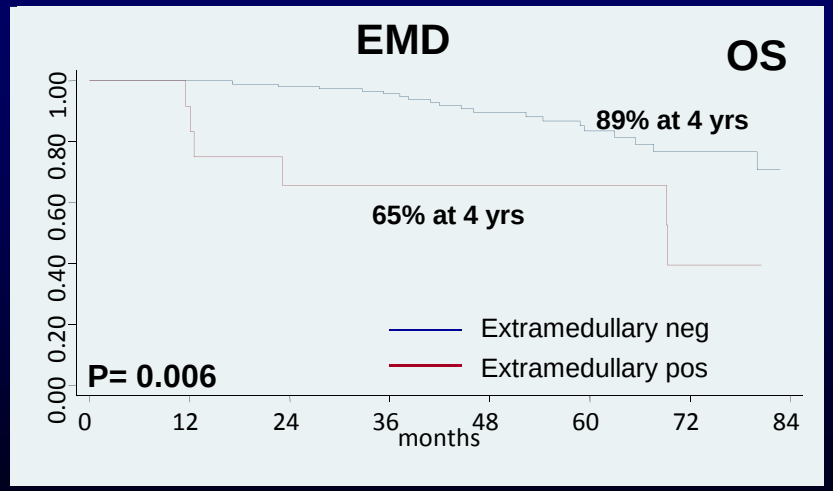
PROGNOSTIC VALUE OF PET/CT AT DIAGNOSIS IN ASCT CANDIDATES

N° OF FLs, SUV VALUE, EMD









Zamagni E. et al, Blood 2011

PROGNOSTIC VALUE OF PET/CT AT STAGING

- Several independent series of patients ASCT candidates, correlating with MRI findings, standard prognostic factors and molecular features of PCs[1,2,3,4]
- Small group of patients non ASCT eligible (retrospective study) [5]
- Series of patients pre- ALLO SCT (retrospective study) [6]
- Re-staging at relapse (retrospective studies) [7,8]

[1] Zamagni E. et al, Blood 2011

[2] Bartel. TB et al, Blood 2009

[3] Waheed S et al, Haematologica 2012

[4] Usmani S.Z. et al, Blood 2013

[5] Zamagni E. et al, Clin Canc Res 2015

[6] Patriarca F. et al, Biol BMT 2015

[7] Lapa C. et al, Oncotarget 2014

[8] Derlin T. et al, EJNM Mol Imag 2011

IMAGING TECHNIQUES AT DIAGNOSIS IN ACTIVE MM: PET/CT

PROS

- Sensitivity and specificity
- Optimal to assess EMD
- Can depict lytic lesions (CT part)
- Can assess tumor burden and disease metabolism
- Prognostic significance of FLs and SUV
- Useful for staging of SPB

CONS

- Sub-optimal for diffuse bone marrow involvement and skull lesions
- Cost > WBLDCT, WBXR and MRI
- Radiation dose > WBXR, WBLDCT
- Availability

ROLE OF FDG PET/CT IN MULTIPLE MYELOMA

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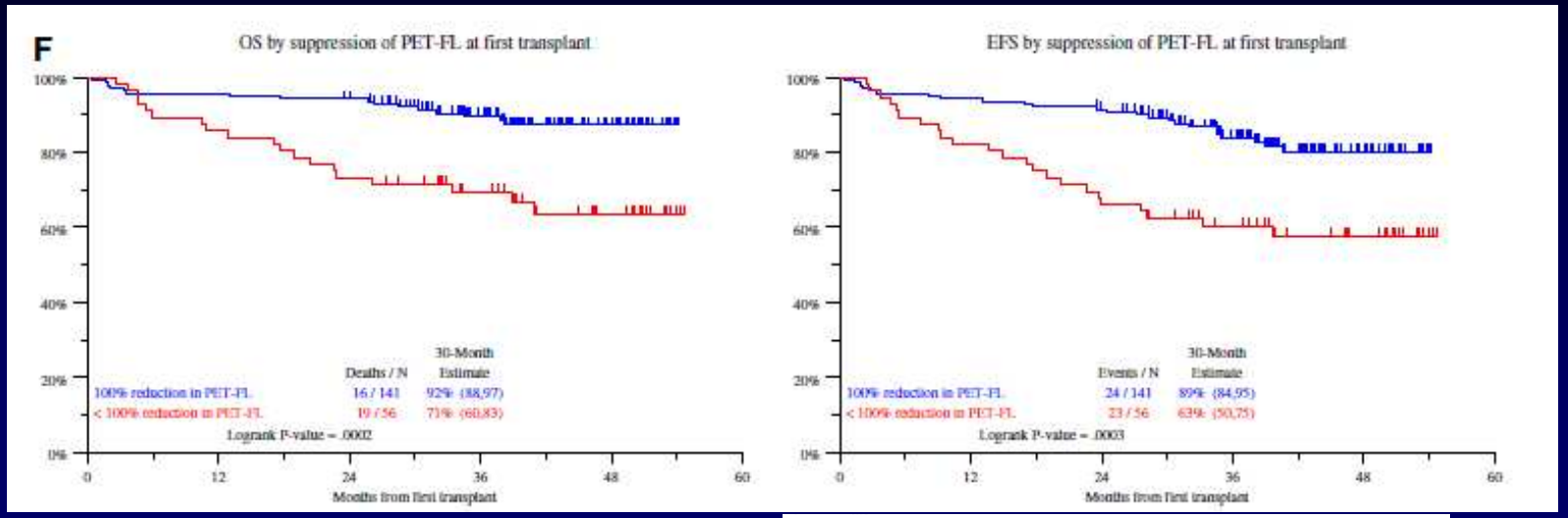
- Early stage/smouldering MM

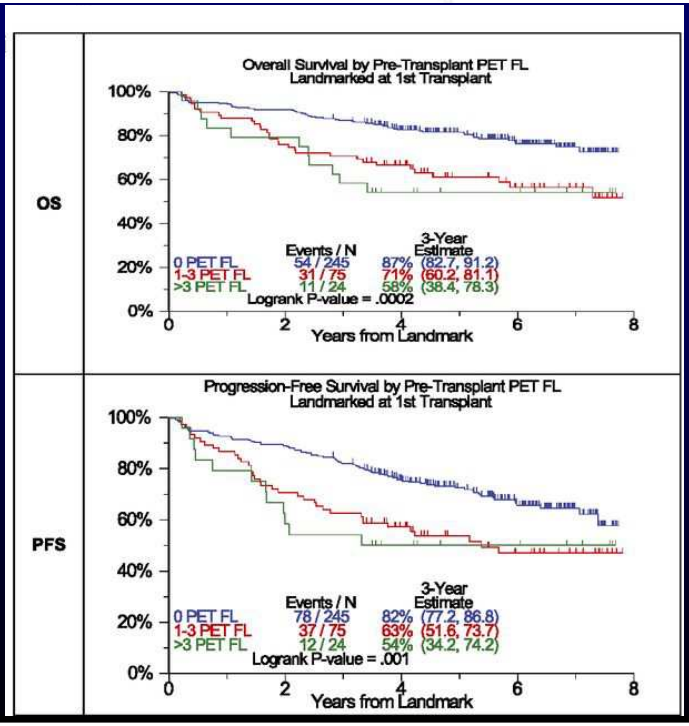
METABOLIC RESPONSE TO THERAPY

PROGNOSTIC VALUE OF PET/CT BEFORE ASCT



Bartel. TB et al, Blood 2009

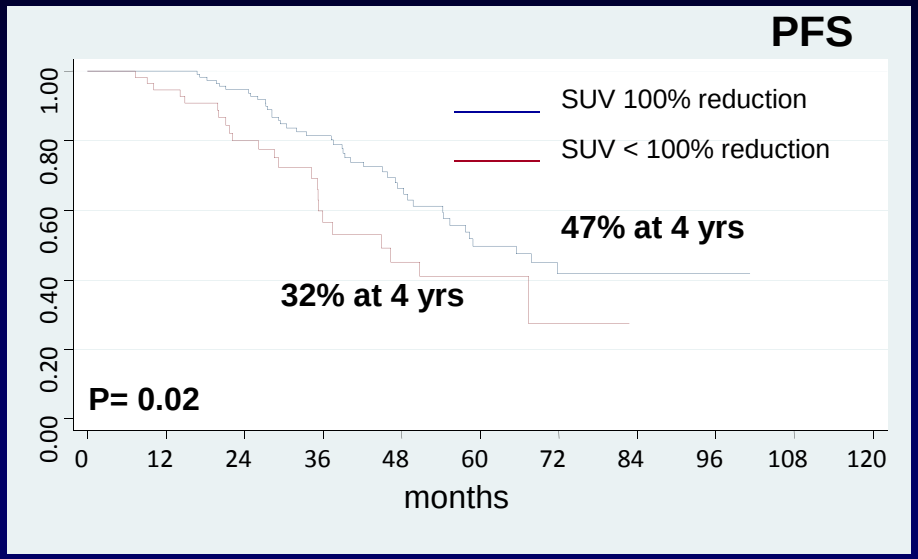
- Complete FDG suppression retained independent prognostic value for PFS and OS in Cox regression analysis

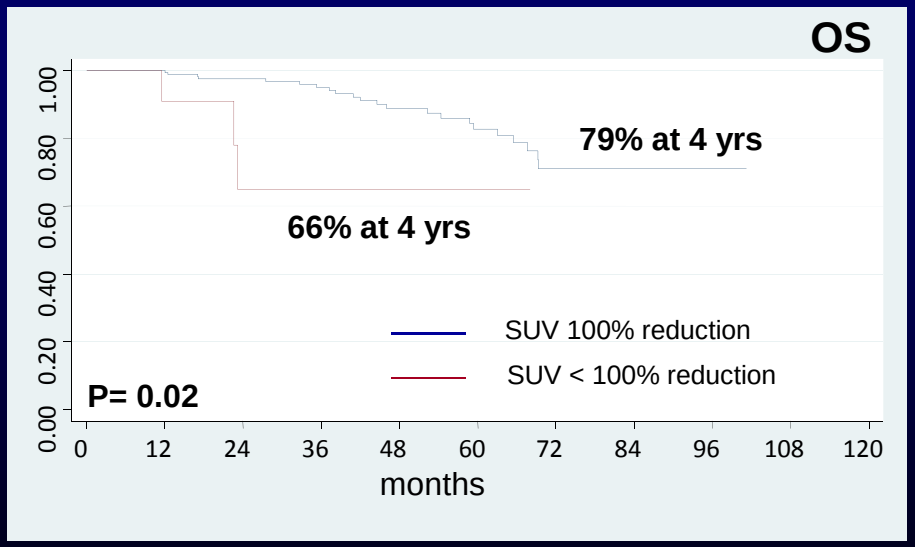


Usmani S.Z. et al, Blood 2013

METABOLIC RESPONSE TO THERAPY

PROGNOSTIC VALUE OF PET/CT AFTER ASCT





MULTIVARIATE ANALYSIS

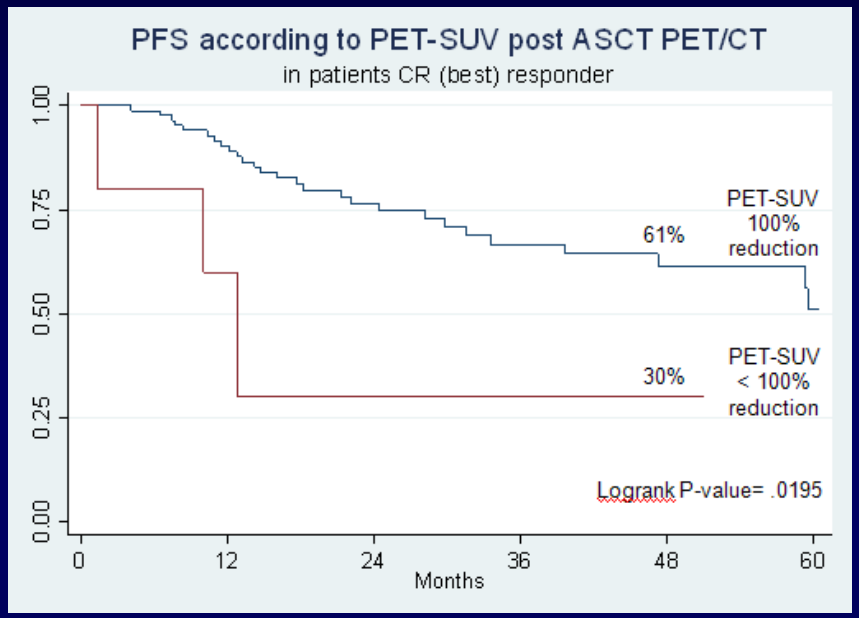
VARIABLES	HAZARD RATIO (95% CI)	P VALUE
TTP		
Extramedullary disease	15. 43 (4.11-57.95)	0.000
del (17p) ± t(4;14)	1.86 (1.12-3.49)	0.05
Not complete FDG PET suppression	1.82(1.19-3.77)	0.01
PFS		
Extramedullary disease	5. 93 (2.27-15.51)	0.000
del (17p) ± t(4;14)	1.90 (1.09-3.32)	0.023
Not complete FDG PET suppression	1.89 (1.06-3.35)	0.030
OS		
Relapse	9.35 (2.79-31.31)	0.000
Not complete FDG PET suppression	3.90 (1.12-13.60)	0.03

Zamagni E. et al, Blood 2011

METABOLIC RESPONSE TO THERAPY

PET/CT MRD MONITORING IN CR PATIENTS

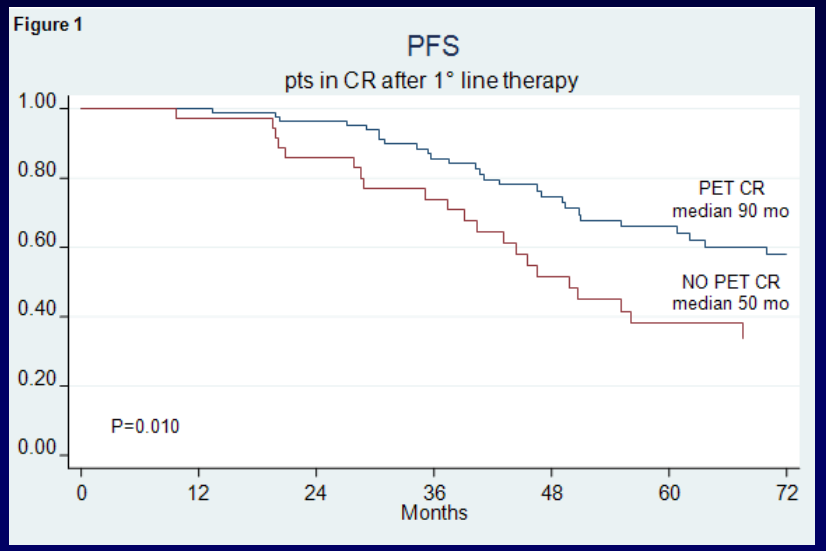
ASCT candidates (192 pts)

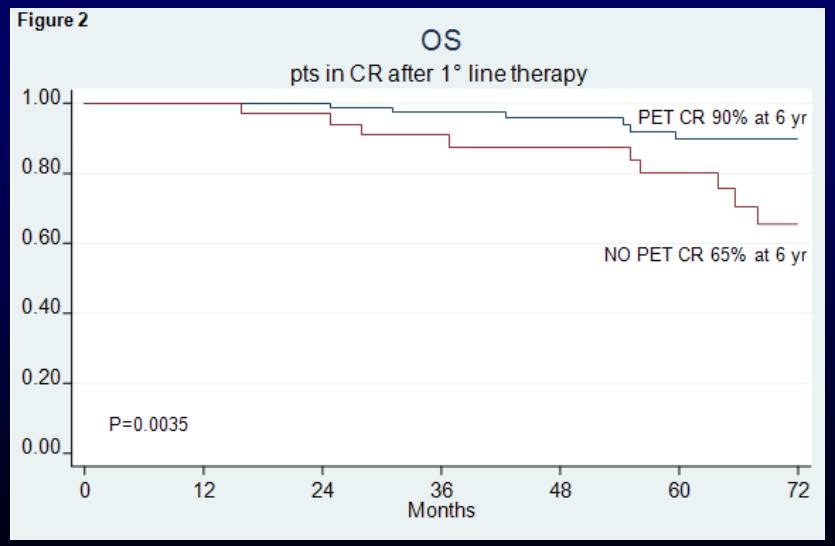


Zamagni E. et al, Blood 2011

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

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]

TO ASSESS MRD

- No stratification of CR patients[5] (US study, 45 pts)
- PFS and OS difference PET pos vs neg in CR patients[3,7] (retrospective study, 282 pts) and complementary with MFC[4]

[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, ASH 2015

[6] Korde N, JAMA Oncol 2015

[7] Zamagni E. et al, Clin Canc Res 2015

IMAGING TECHNIQUES AFTER TREATMENT: PET/CT

PROS

- Specificity
- Earlier post-therapy changes
- Prognostic significance in CR patients (MRD monitoring)
- Good correlation with biochemical response

CONS

- Lack of standardization
- Applicability in 75% of the patients
- Availability, cost

Zamagni E. et al, BJH 2012
Hillengass J. et al, Leuk and Lymphoma 2013
Mesguich C et al, EJR 2014

IMWG Criteria for MRD in Multiple Myeloma

	Response subcategory	Response criteria
IMWG MRD negativity criteria (Requires CR as defined below)	Sustained MRD negative	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)
	Imaging MRD-negative	MRD negative as defined below (Next-generation flow or Next-generation sequencing) PLUS Disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT[3]
	Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by next-generation flow cytometry[4] 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 10^5 nucleated cells or higher
	Sequencing MRD negative	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 10^5 nucleated cells[5] or higher

Kumar SK, et al. Lancet Oncology 2016

ROLE OF FDG PET/CT IN MULTIPLE MYELOMA

- Symptomatic MM
  - at diagnosis: staging and prognosis
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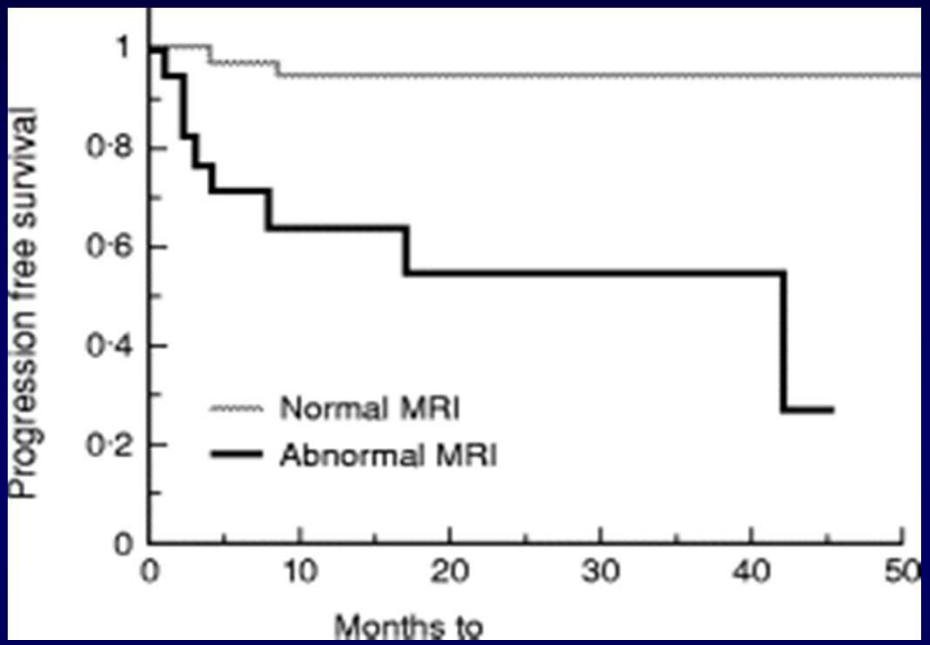
- **Early stage/smouldering MM**

IMAGING IN SMOLDERING MM
ROLE OF MRI

Axial MRI[1,2,3,4]



70% risk of progression to MM at 2 years if > 1 FL

WB-MRI[5]- LONGITUDINAL WB-MRI[6]

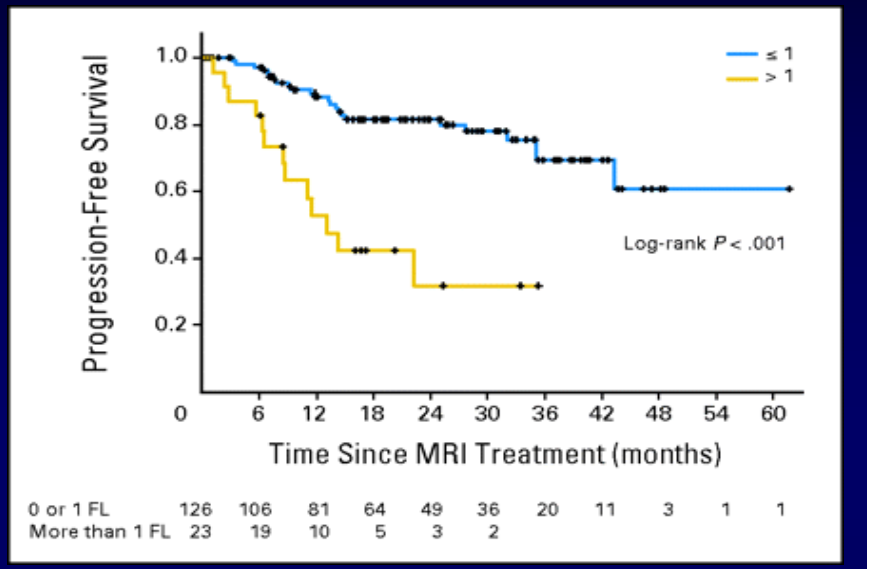


Table 3. Results of the Multivariate Analysis of All Variables and of Selected Variables for Progression-Free Survival

Variable by Multivariate Analysis Type	Hazard Ratio	*P*
Full model		
MRI-FL above cutoff point of one FL	3.01	.002
Diffuse bone marrow infiltration in MRI	2.37	.03
M protein concentration ≥ 40 g/L	1.87	.44
Presence of IgA	0.84	.71
Reduction of uninvolved Ig	1.03	.95
Presence of urinary Bence Jones protein	0.94	.87
Plasma cell infiltration in bone marrow ≥ 20%	1.30	.53
Final model after backward selection		
MRI-FL cutoff point	3.25	< .001
Diffuse bone marrow infiltration in MRI	2.64	.006

Abbreviations: MRI, magnetic resonance imaging; FL, focal lesion; Ig, immunoglobulin.

1.Moulopoulos L.A. et al, JCO 1995
2.Mariette X et al, BJH 1999
3.Vande Berg B.C et al, Radiology 1997
4. Kastritis E et al, Leukemia 2014
5. Hillengass J et al, JCO 2010
6. Merz M et al, Leukemia 2014

PET/CT

- Retrospective study on 188 pts with suspected SMM (122 observed)[1]
- Probability of progression at 2 years PET/CT pos 75%, 87% if underlying osteolysis (only 16 pts)
- Probability of progression at 2 years PET pos without underlying osteolytic lesions 61% (few pts)

- Prospective study on 120 pts[2]
- 16% pts with FLs, without underlying osteolytic lesions
- Probability of progression at 2 years PET pos pts vs neg: 58% vs 33%

[1]Siontis B. et al, Blood Cancer J 2015

[2] Zamagni E. et al., Leukemia 2015

OPEN ISSUES

- Do we need the same imaging technique at baseline and after treatment to evaluate metabolic response?
- How to incorporate imaging into risk-stratification at diagnosis (for both smoldering and symptomatic MM)
- What to do with persistent focal lesions after systemic therapy?
- German prospective study ongoing «Assessment of molecular disease heterogeneity in patients with MM by imaging guided biopsy»

OPEN ISSUES

- Quality of many studies hampered by a poor description of selection and execution criteria
- Major inconsistency in methodology between studies
- Need to define standardized criteria for imaging definitions and positivity cut-off

Zamagni E. et al, BJH 2012

Regelink JC et al, BJH 2013

Pianko MJ et al, Clin Canc Res 2014

Mesguich C et al, EJR 2014

Standardization of interpretative criteria

- **Italian trials: creation of descriptive criteria (EMN02 prospective trial):**
  - IMPeTUs, Nanni C et al, Eur J Nucl Med Mol Imaging, 2015: on the first 17 patients
  - to be **simplified** and correlated with outcome: on the whole group of 103 patients
  - to be **validated** on independent series of pts: italian FORTE prospective study
- **French trials**

OPEN ISSUES

- Which relationship between bone marrow MRD and imaging MRD?

- Bone marrow MRD will be repeated several times in the future during follow-up (MRD reappearance concept); what is the optimal follow-up with PET ?

- Should we tailor treatment (consolidation/maintenance) on imaging-defined minimal residual disease?

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
- **PET/CT and 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
- **Implementation of prospective clinical trials** with newer imaging techniques will help to adress several issues, standardize the interpretation of the results and optimize the use of these promising tools. This may improve disease management