CLÍNIC
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Hospital Universitari

UNIVERSITAT DE BARCELONA

Societat Catalana d'hematologia I hemoteràpia

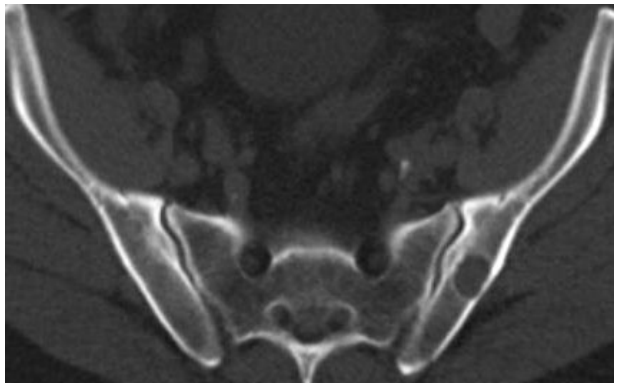
Tècniques de imatge en el mieloma multiple

1 juny, 2018

X. Setoain
Medicina Nuclear
H. Clínic, Barcelona

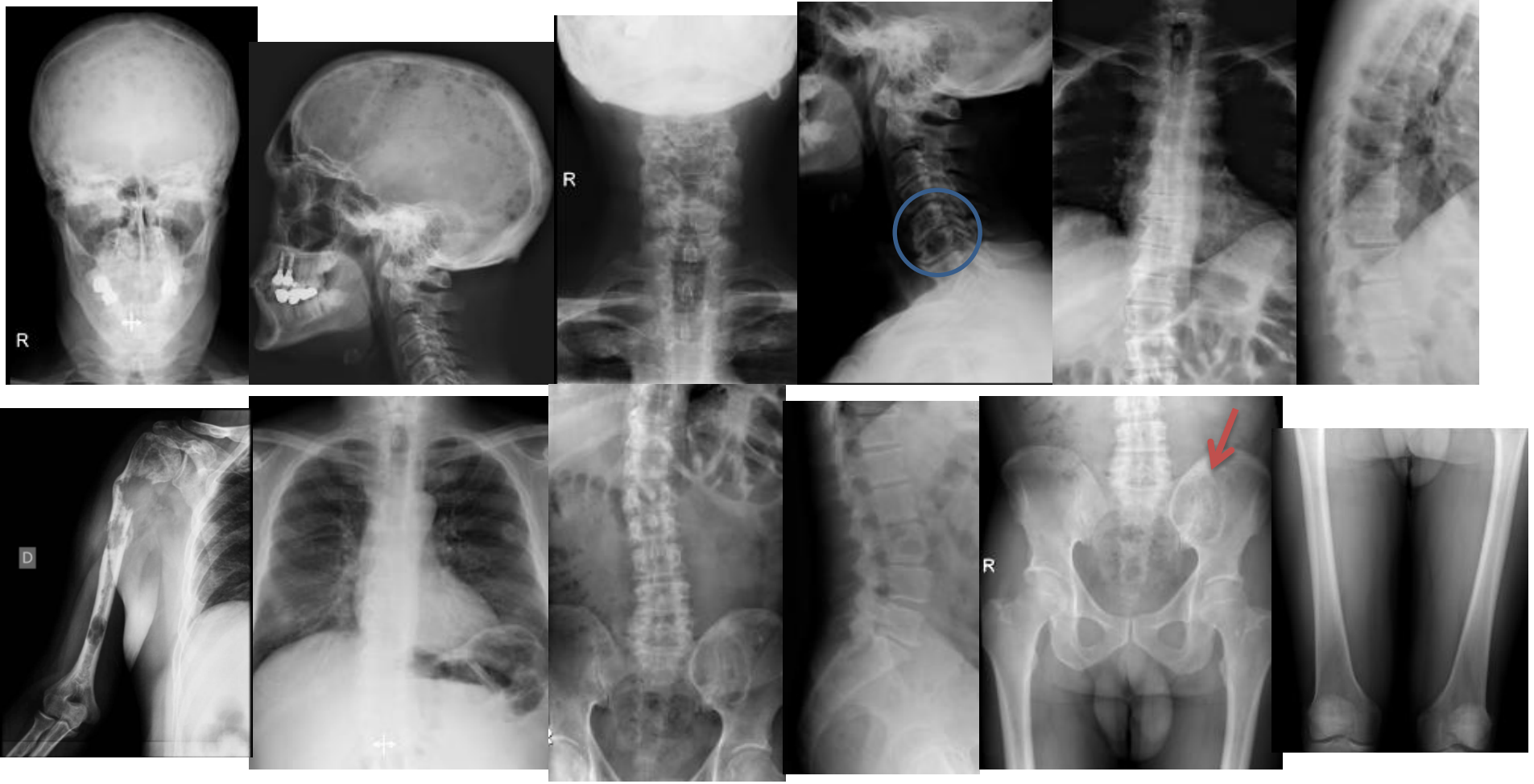
Imaging techniques: Multiple Myeloma

- Whole body X-ray (WBXR)
- WB CT
- WB MR or MR of the spine
- PET/CT

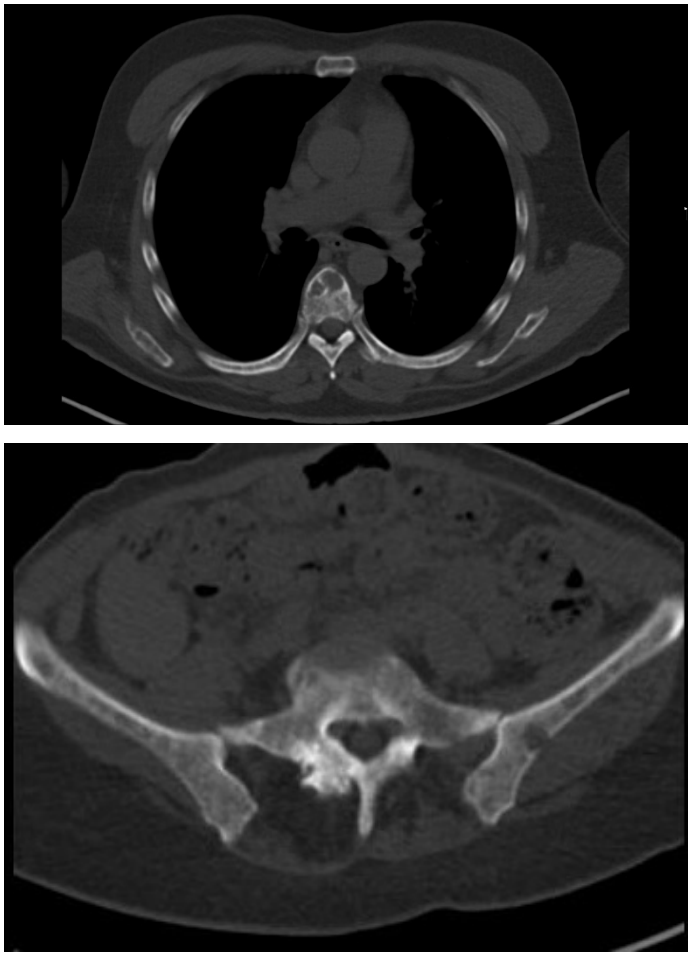


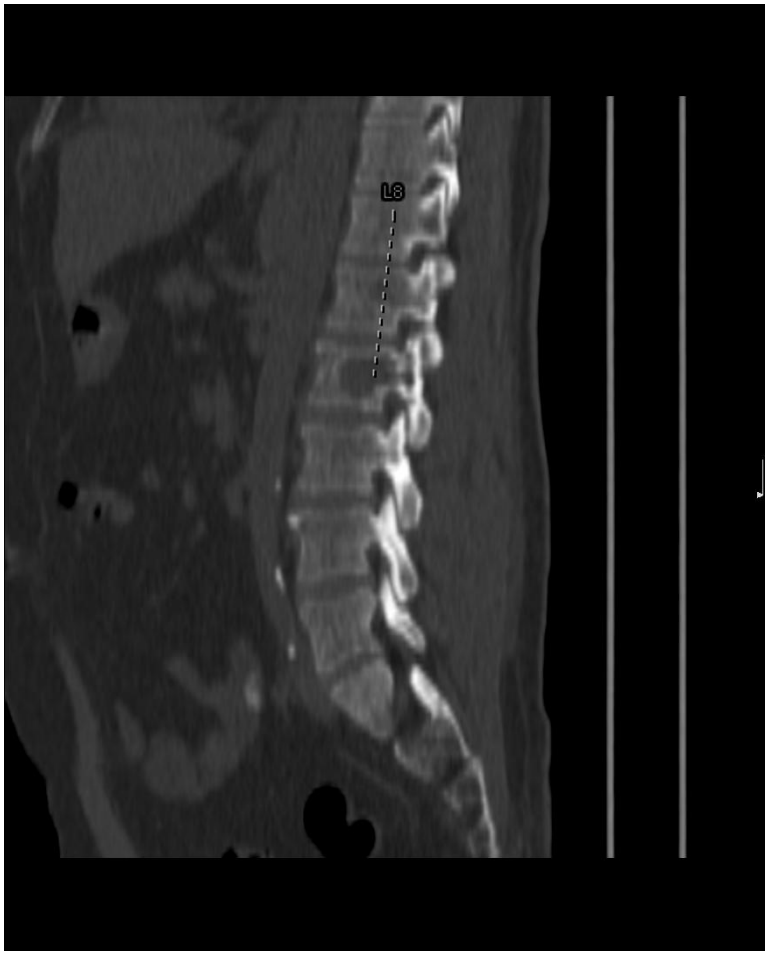
Whole body X-ray (WBXR)

- Osteolytic bone lesions “punched out”
- Endosteal scalloping “break out”
- Mass “plasmacytoma”



WBCT (low dose) replace WBRX





WBCT (low dose)

Hillengas et al. Blood Cancer J 2017: IMWG

WBCT vs XR 212 cases with MM and SM

212	WBCT +	WBCT -
XR +	43 / 20%	12 / 5%
XR -	54 / 25%	103 / 48%

Pelvis
Ribs
Vertebra
Sternum
Scapula

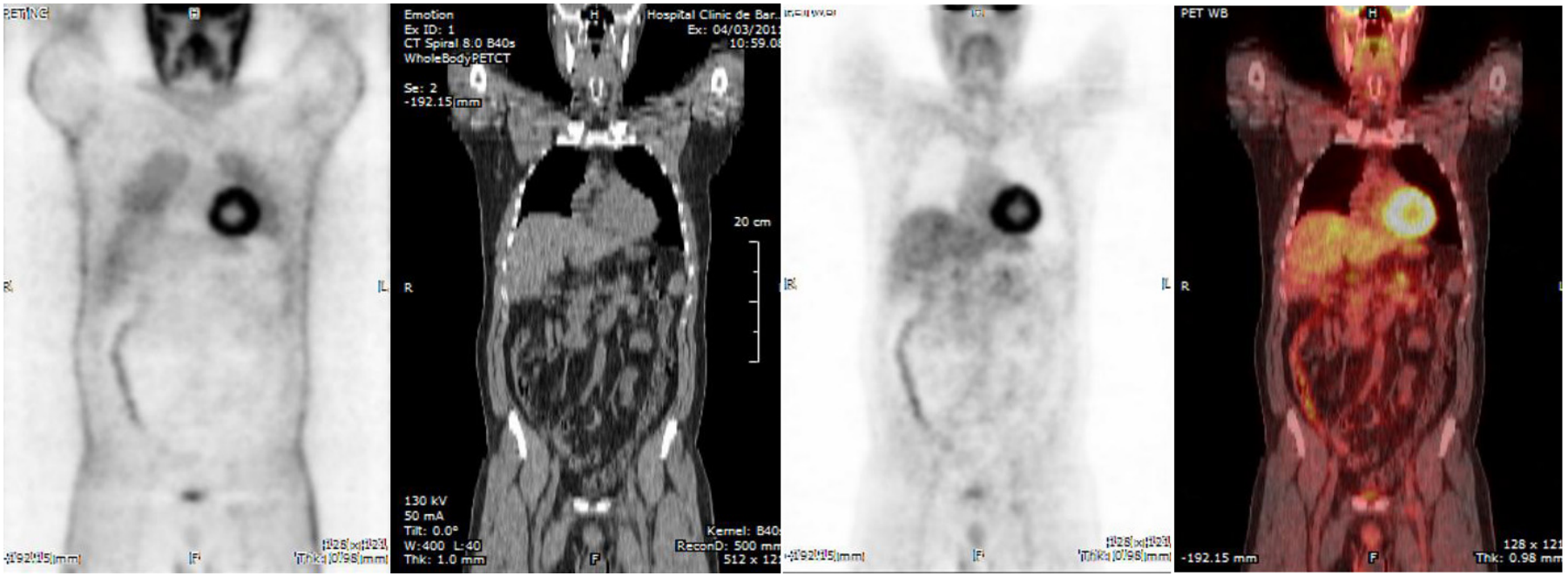
Skull
Humerus
Femur

WBLDCT > XR bone disease assesment in patients with SM and MM

PET/TC replace XR or CT

18F- FDG

PET without AC Low dose CT PET with AC Fusion PET/TC



Diagnostic imaging comparison

	X-Ray	CT	MR	PET/CT
Available	X			
Cost	X			
Radiation exposure			X	
Field of view		X		X
Acquisition time (min)	15	5	60	25
Renal failure	X	Iodine	Gd	X
Prognostic value				X
Treatment response				X
Sensitivity			X	

PET sensitivity - compared XR and MR

- *Systematic review: van Lammeren-Venema D et al,* *Cancer 2012;15:1971-81*
  - PET vs XR: PET > 46 – 63% (Lytic lesions XR > 30% bone mineral density)
  - PET vs MR: MR > PET
    - Diffuse bone marrow involvement
    - Spine: small size lesions MRI > PET 30%
    - PET > FOV of MR 30%

VOLUME 35 · NUMBER 25 · SEPTEMBER 1, 2017
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Prospective Evaluation of Magnetic Resonance Imaging and [^{18}F]Fluorodeoxyglucose Positron Emission Tomography-Computed Tomography at Diagnosis and Before Maintenance Therapy in Symptomatic Patients With Multiple Myeloma Included in the IFM/DFCI 2009 Trial: Results of the IMAJEM Study

Philippe Moreau, Michel Attal, Denis Caillot, Margaret Macro, Lionel Karlin, Laurent Garderet, Thierry Facon, Lotfi Benboubker, Martine Escoffre-Barbe, Anne-Marie Stoppa, Kamel Laribi, Cyrille Hulin, Aurore Perrot, Gerald Marit, Jean-Richard Eveillard, Florence Caillon, Caroline Bodet-Milin, Brigitte Pegourie, Veronique Dorvaux, Carine Chaleteix, Kenneth Anderson, Paul Richardson, Nikhil C. Munshi, Herve Avet-Loiseau, Aurelie Gaultier, Jean-Michel Nguyen, Benoit Dupas, Eric Frampas, and Françoise Kraeber-Bodere

134 patients (trial IFM/DFCI 2009):
– PET and MR spine and pelvis
- Staging
- Interim: 3 RVD
- EoT (before maintenance)

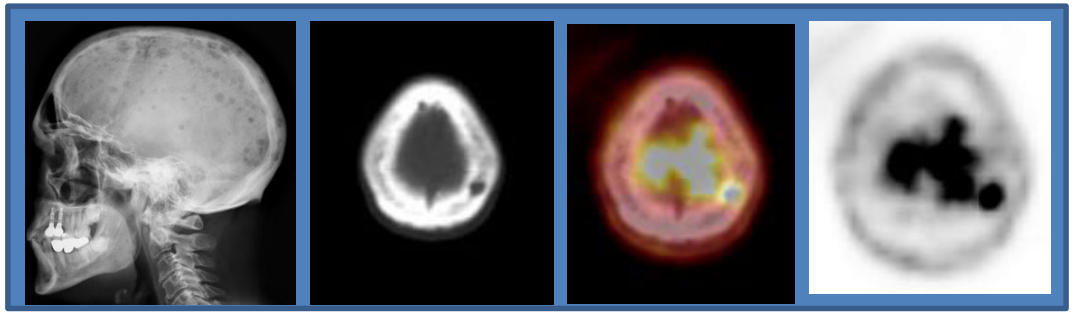
Staging	MR		PET	
	Pat. n	%	Pat. n	%
Normal	7	5	12	9
Focal lesions	46	34	44	33
Diffuse infiltration	41	31	12	9
Diffuse with FL (mixed)	25	26	66	49
Total	127	95	122	91

(P=0,33)

PET = RM

Diagnostic imaging comparison: Elective imaging technique

	X-Ray	CT	MR	PET/CT
Skull	X			
Spine/axial skeleton			X	
Bone marrow plasma cell infiltration			XX	X
Diffuse bone marrow involvement			X	
Osteoporosis			X	
Risk of vertebral fracture		X	X	
Spinal cord/nerve compression			X	
Extramedullary/soft tissue		X	X	XX
Guide for focal needle biopsy		X		X
Planning radiotherapy		X		



Indications of PET/CT in MM

- Staging:
  - Smoldering Myeloma
  - Solitary Plasmacytoma

- Multiple myeloma
  - Extramedullary disease
  - Prognostic value
  - Treatment response assessment

Smoldering Myeloma
Absence of bone lesions

Diagnosis criteria consensus of IMWG ; Lancet Oncology 2014;15:38-48

- WBTC
- WBMR or MR spine
- PET/TC

RM:

Hillengas et al, J Clin Oncol 2010;28:1606-1610

149 patients with SM with WBMR

- Focal lesions in 42 patients (28%)
- More than one focal lesion in 23 patients (15%) – Higher risk of progression to MM

PET:

No well evaluated.

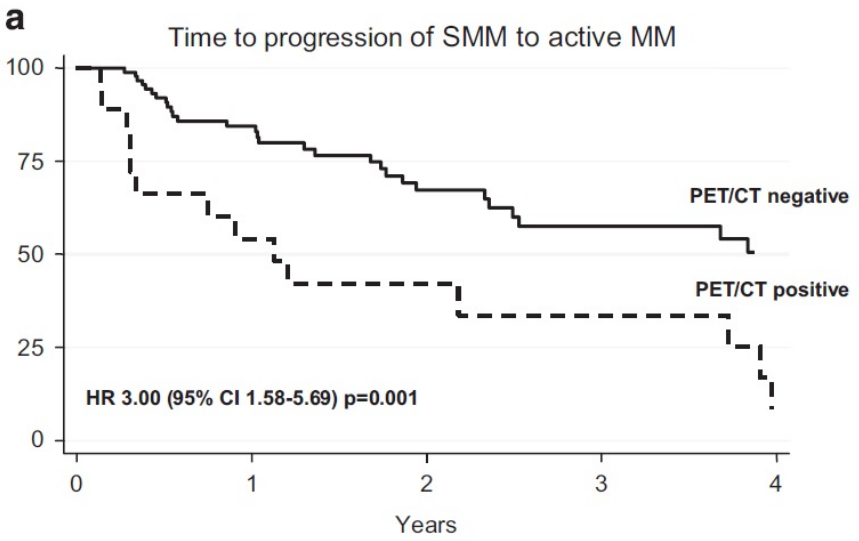
Smoldering MM- PET

Zamagni E, Leukemia 2016;30:417-422
Prospective study
PET : 120 patients with SMM
Without bone lytic lesions

Table 2. Baseline PET/CT characteristics

Patients with negative PET/CT, *N* (%)	101 (84%)
Patients with positive PET/CT, N (%)	19 (16%)
1 FL	8 (7%)
2 FLs	2 (2%)
⩾3 FLs	3 (2%)
Diffuse	6 (5%)
Median SUV_{max} (IQR)	4.7 (3.9–5.6)

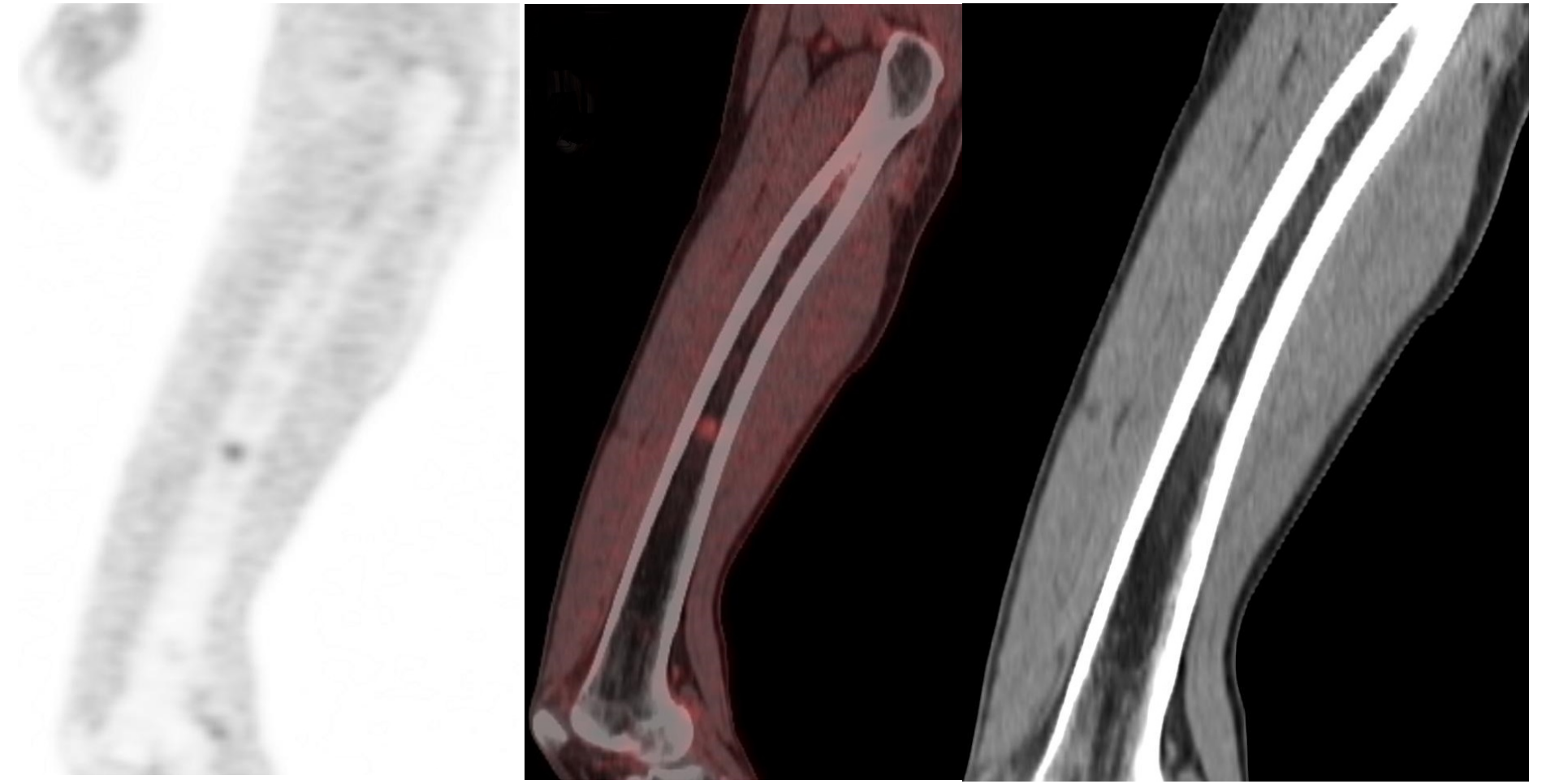
Abbreviations: CT, computed tomograpgy; FL, focal lesion; IQR, interquartile range; PET, positron emission tomography; SUVmax, maximum standardized uptake value.



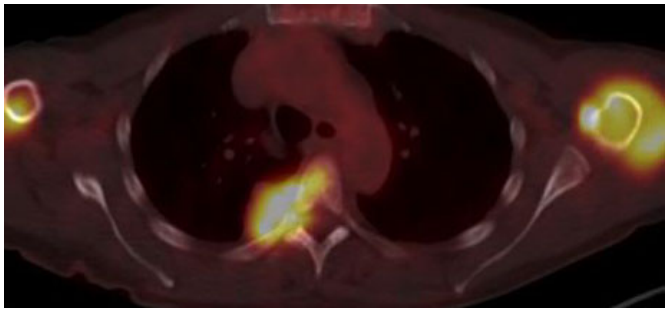
Risk of progression to MM

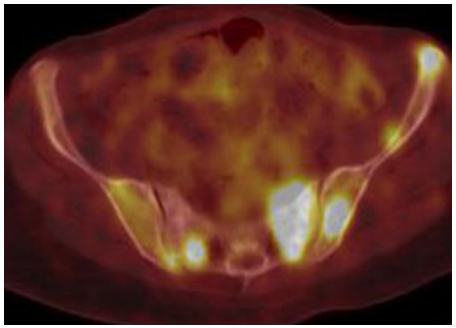
	PET -	PET +
2 years Time to Progression (y)	4,5	1,1
Probability of Progression (%)	33	58

Smoldering Myeloma
early stage



Solitary Plasmacytoma

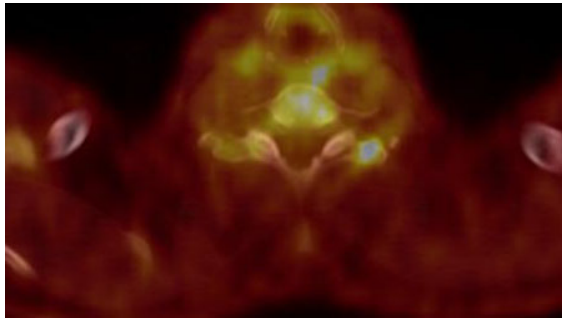


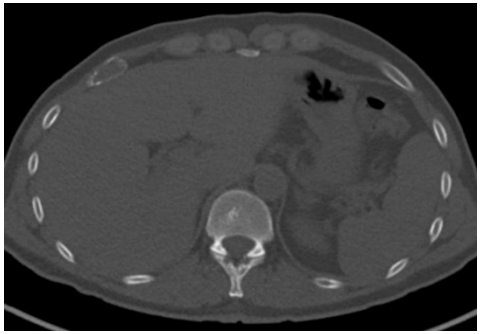


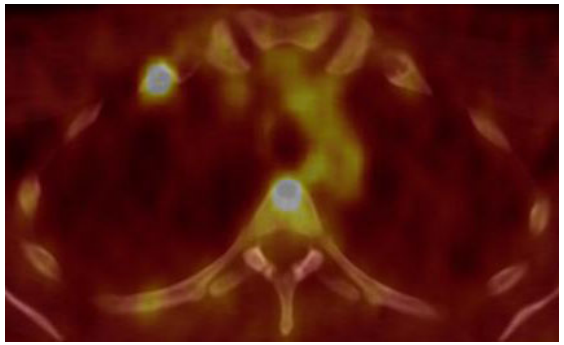
- PET:
  - **Absence of other lesions**
    - Second plasmacytoma
    - Lytic lesions – FDG uptake
  - Up-staging disease to MM
  - Change in prognostic and treatment
- *Fouquet G, Clin Cancer Res 2014;20:3254-60*
  - PET 43 patients with solitary plasmacytoma
  - ≥ 2 Focal lesions in 33% cases
  - ≥ 2 FL > risk of progression to MM (*23 vs 71 months*)

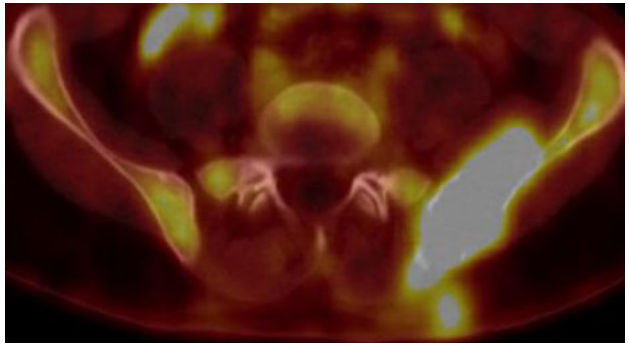
A 39 year-old male, with solitary plasmacytoma in left iliac crest

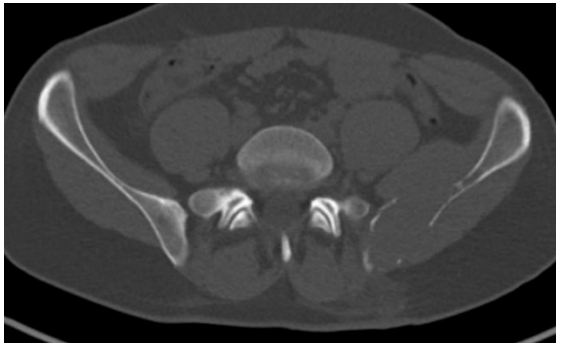
Baseline PET











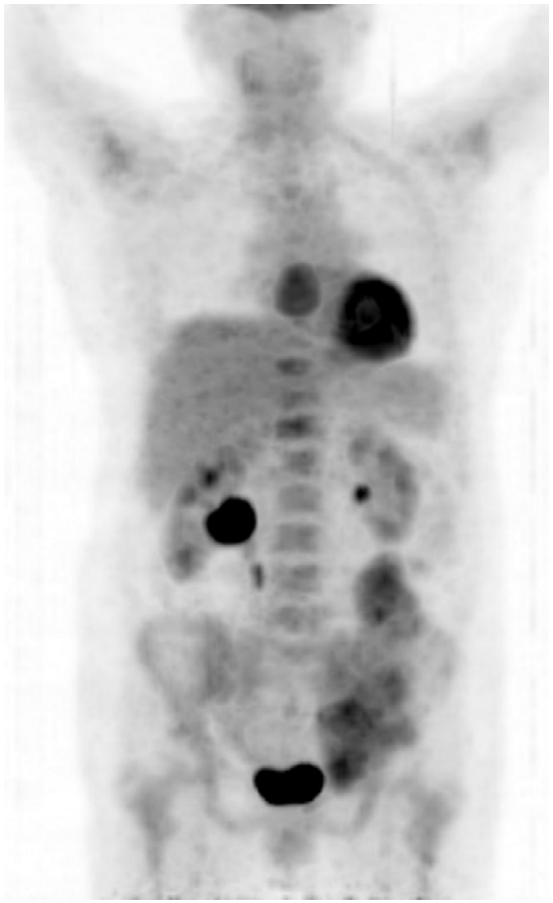
Extramedullary disease in MM

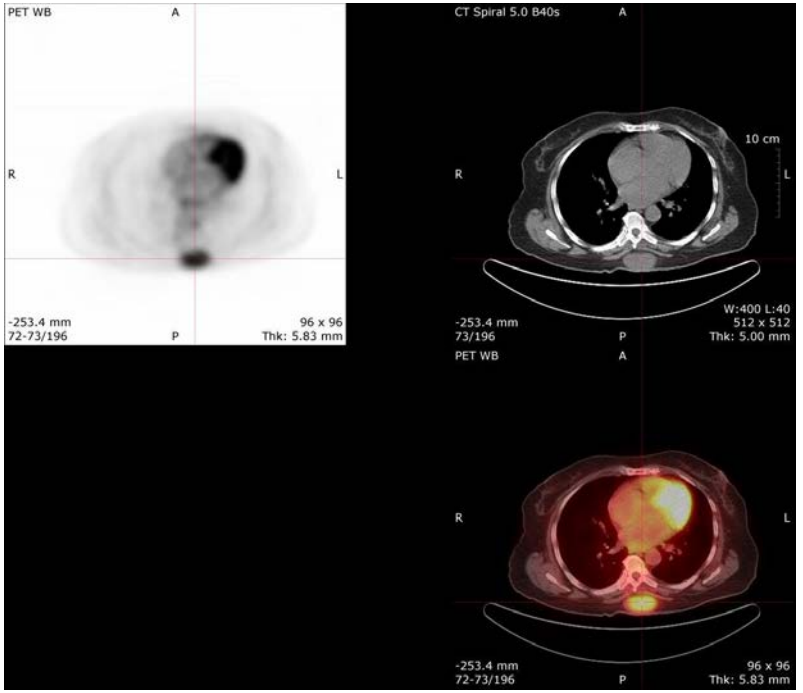
- PET:

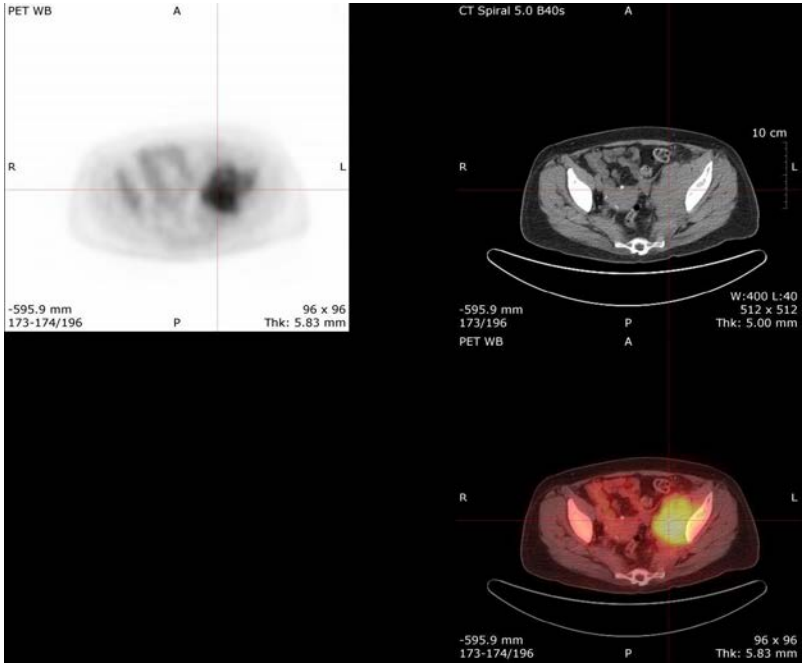
coexistence of additional hidden lesions:

  - Plasmacytoma not detected by X-Ray
  - Progression into MM with bone lytic lesions

Women with a recurrent extramedullary plasmacytoma in the back

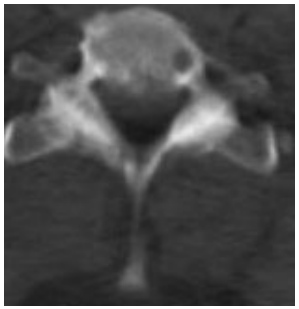
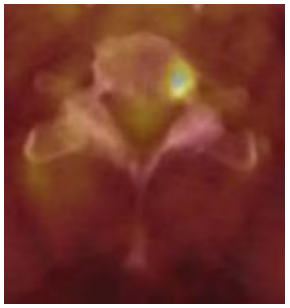
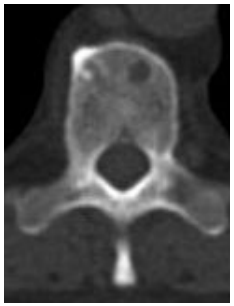


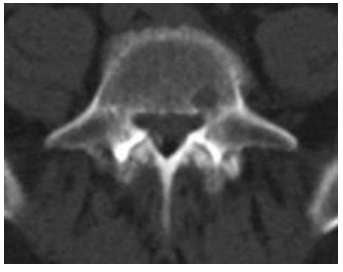
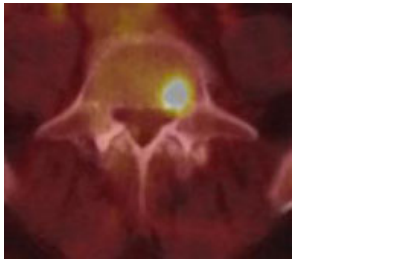
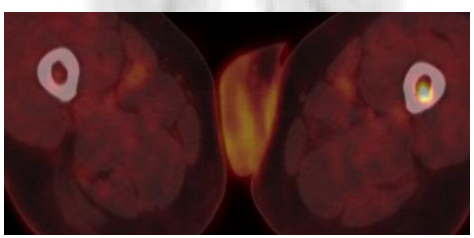
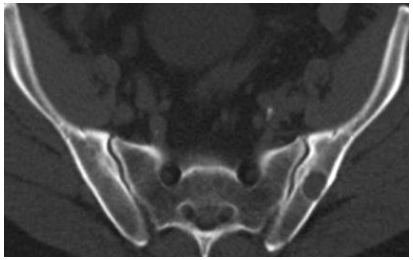
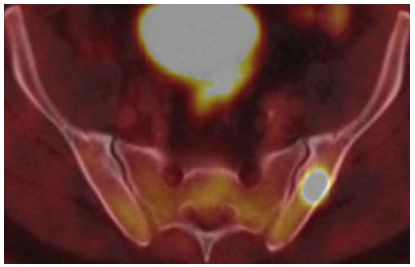
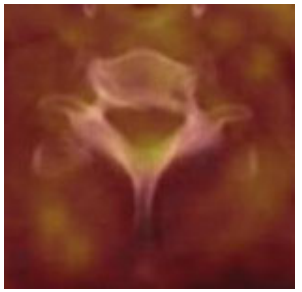


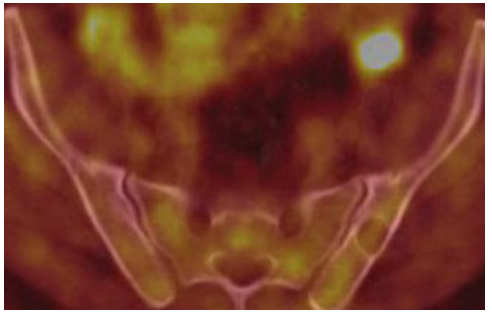


A 61 year-old male, with EMP in left submandibular lymph node, surgically removed, negative X-Ray

PET after chemotherapy

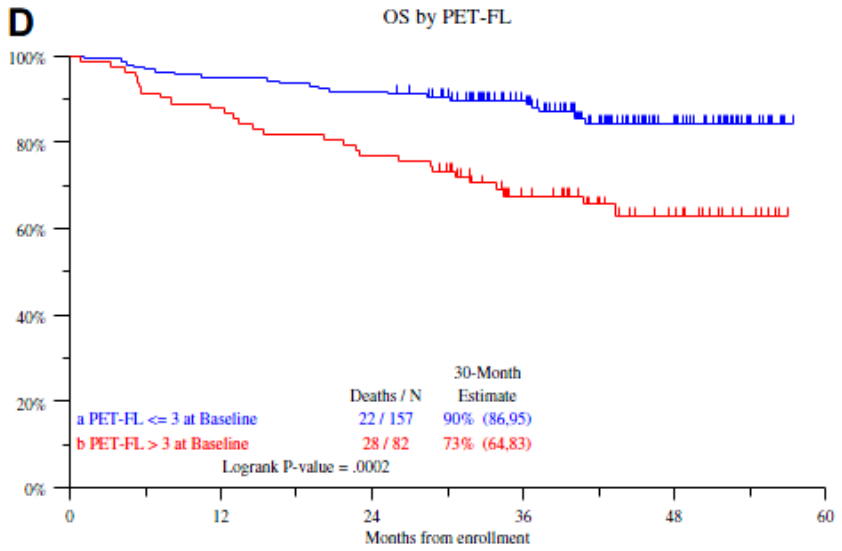









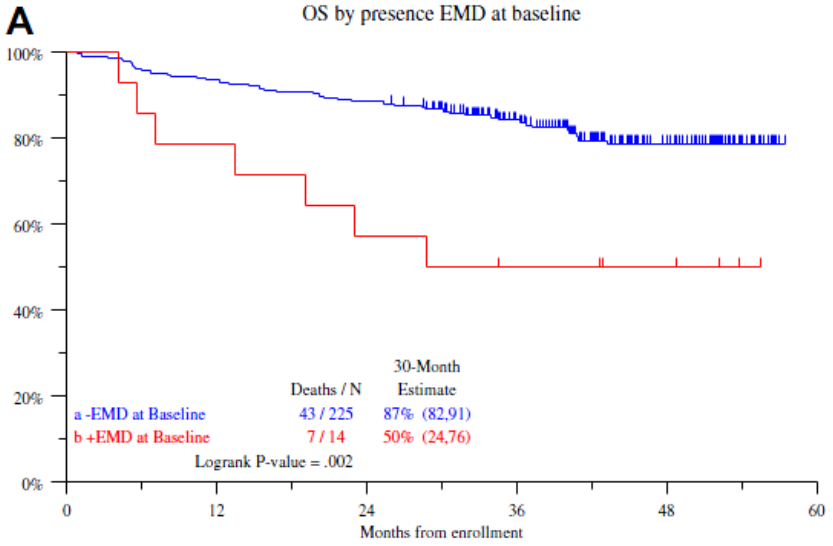
Prognostic value – PET/CT

Baseline PET:

Bartel et al, 239 patients
Blood 2009;114:2068-76
•Number of active lesions
≤ 3 FL
>3 FL



Zamagni et al, 192 patients
Blood 2011;118:5968-95
•Degree of FDG uptake
SUV ≤ 4.2
SUV > 4.2
•Extramedullary disease

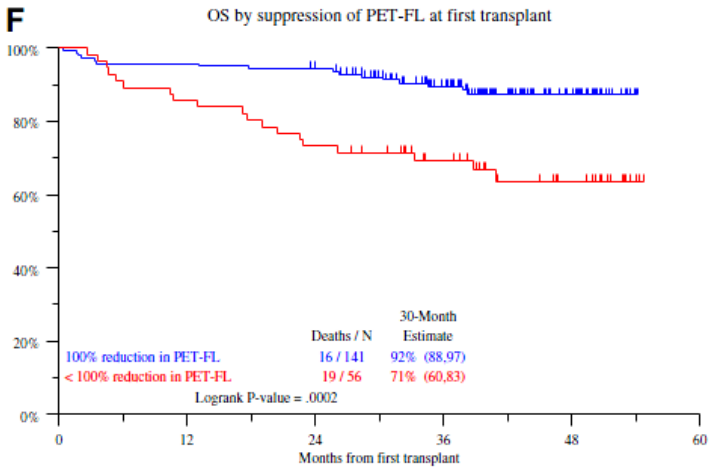


Prognostic value – PET/CT

Treatment response assessment

Bartel et al, Blood 2009

•PET 10 days from starting the first induction cycle of VDT-PACE

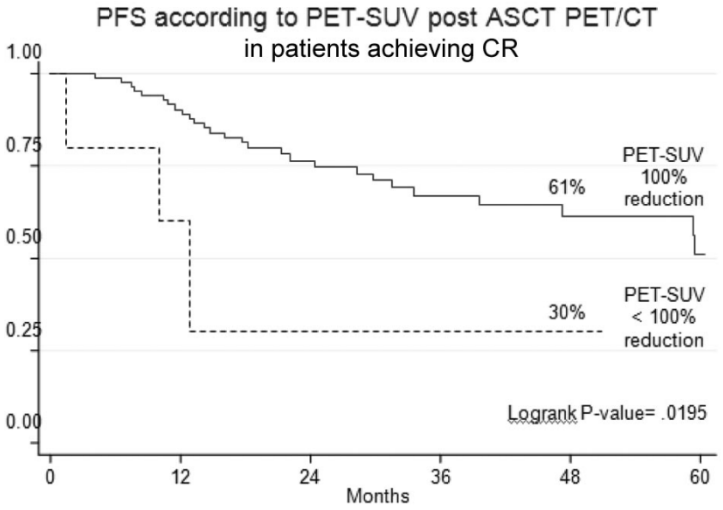


Zamagni et al Blood 2011

•PET 3 mounts post-ASCT

•Patients achieve CR with conventional criteria; 23% persistent PET/CT positive

- •PET + post - TAPH - - - - -
- •PET – post - TAPH _____



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134 patients (trial IFM/DFCI 2009):

– PET and RM spine and pelvis

- Staging
- Interim: 3 RVD
- EoT (before maintenance)

RM

P>0,05

PET

P<0,05

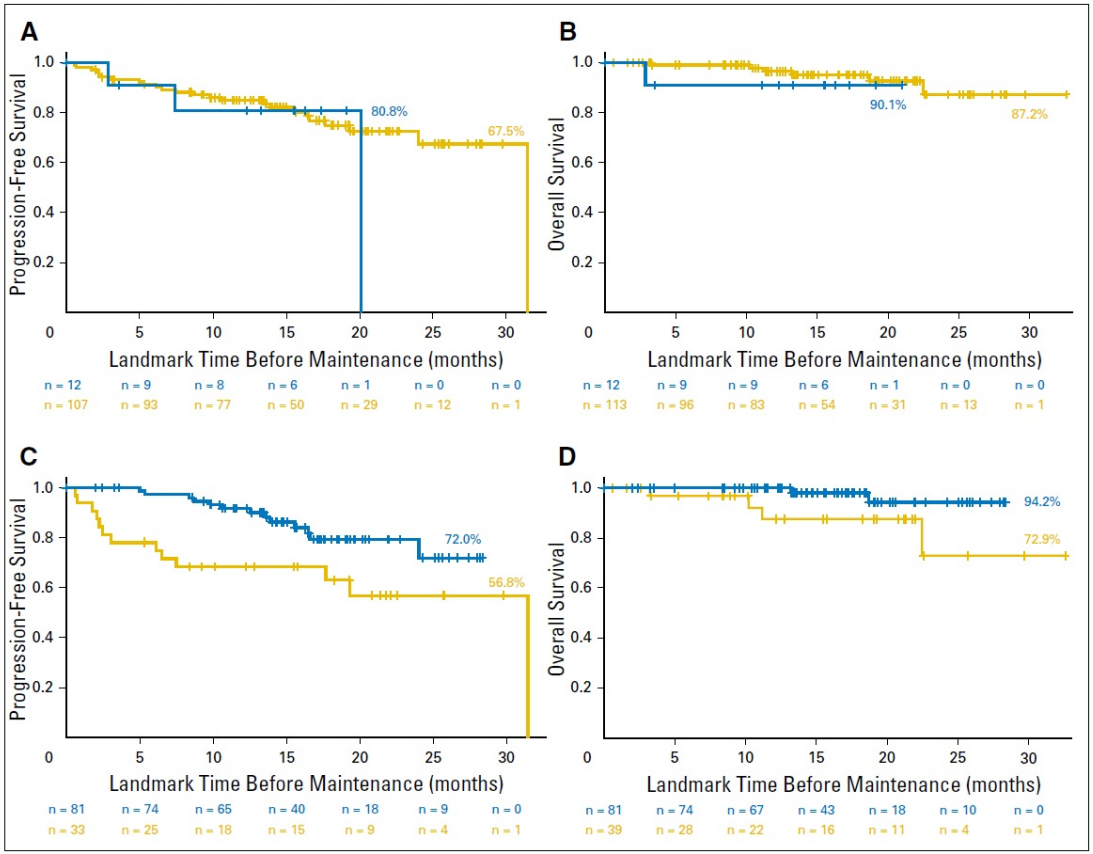
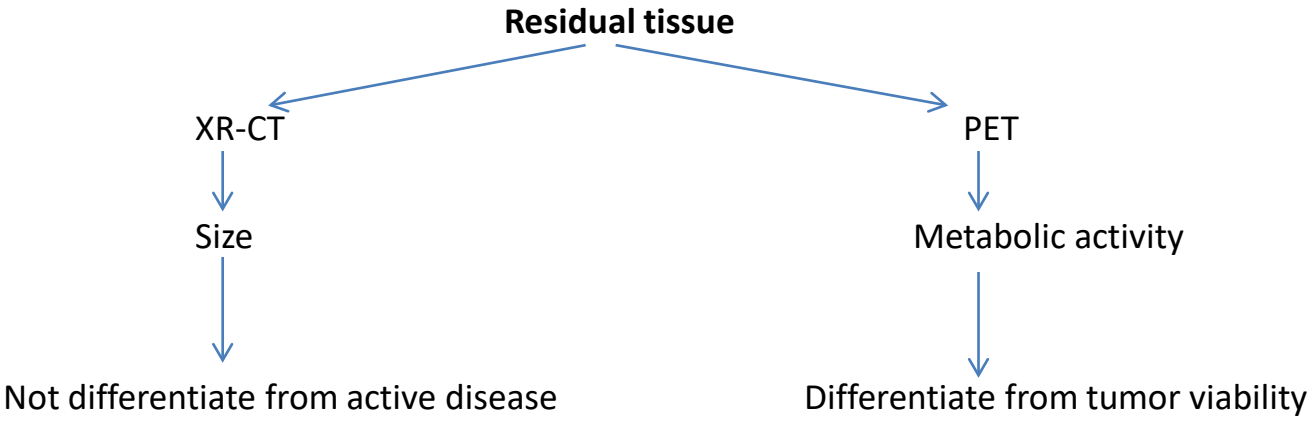


Fig 3. Progression-free survival (PFS) and overall survival (OS) according to normalization of magnetic resonance imaging (MRI) and positron emission tomography-computed tomography (PET-CT) before maintenance therapy. (A) PFS, MRI normalized versus positive ($P = .52$). (B) OS, MRI normalized versus positive ($P = .62$). (C) PFS, PET-CT normalized versus positive ($P = .011$). (D) OS, PET-CT normalized versus positive ($P = .033$).

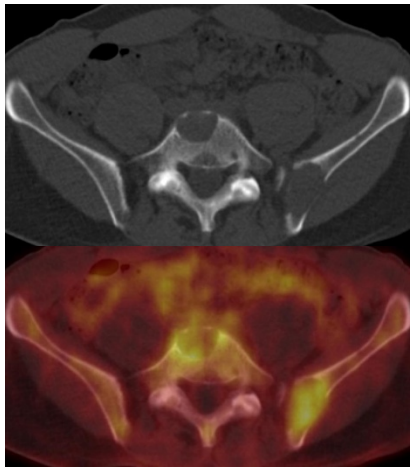
EoT	RM	PET
Become -	11%	62%
2 y. PFS (-)	73%	94%

Treatment response assessment

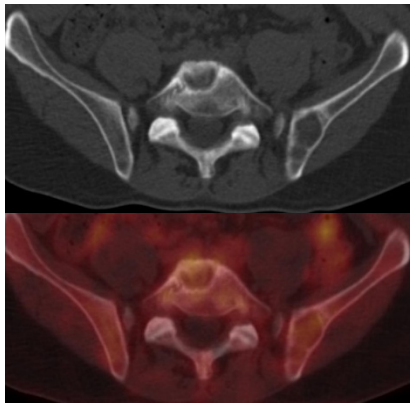
- **Lytic lesions XR and CT → sclerotic rim after treatment**



Baseline PET



PET after treatment



- **PET/TC could be useful in the assessment of treatment response:**
  - Extramedullary disease
  - After RDT, after induction, , before and after SCT, after consolidation
  - Metabolic Response: CMR; PMR; Non-MR, PMD

- **PET not indicated/validated to evaluate treatment response in MM**

International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma

Shaji Kumar, Bruno Paiva, Kenneth C Anderson, Brian Durie, Ola Landgren, Philippe Moreau, Nikhil Munshi, Sagar Lonial, Joan Bladé, Maria-Victoria Mateos, Meletios Dimopoulos, Efstathios Kastritis, Mario Boccadoro, Robert Orlowski, Hartmut Goldschmidt, Andrew Spencer, Jian Hou, Wee Joo Chng, Saad Z Usmani, Elena Zamagni, Kazuyuki Shimizu, Sundar Jagannath, Hans E Johnsen, Evangelos Terpos, Anthony Reiman, Robert A Kyle, Pieter Sonneveld, Paul G Richardson, Philip McCarthy, Heinz Ludwig, Wenming Chen, Michele Cavo, Jean-Luc Harousseau, Suzanne Lentzsch, Jens Hillengass, Antonio Palumbo, Alberto Orfao, S Vincent Rajkumar, Jesus San Miguel, Herve Avet-Loiseau

Treatment of multiple myeloma has substantially changed over the past decade with the introduction of several *Lancet Oncol* 2016; 17: e328–46

Next generation flow – Next generatrion sequence

Response criteria*	
IMWG MRD criteria (requires a complete response as defined below)	
Sustained MRD-negative	MRD negativity in the marrow (NGF or NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years)†
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by NGF‡ on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (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 NGS on bone marrow aspirate in which presence of a clone is defined as less than two 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§ or higher
Imaging plus MRD-negative	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue¶

Extramedulladry disease > 10% patients with MM at the time of relapse

Limitation PET/CT treatment response lack of an standardized level of FDG uptake

Mesguich C. et al, Eur J Radiol 2014; 83:2203-2223 (Mount Sinai, NY)

Recommendations

- Requirement after treatment:
  - Baseline PET/TC (before treatment)
  - to compare all focal lesions
    - **Non active focal lesion at baseline**:
      - No follow-up with PET
    - **Active focal lesions at baseline** :
      - PET remains positive: FDG uptake > **liver**
      - PET becomes negative: FDG uptake ≤ **liver**
- Validated in clinical trials: French criteria

Eur J Nucl Med Mol Imaging (2016) 43:414–421
DOI 10.1007/s00259-015-3200-9

ORIGINAL ARTICLE

Image interpretation criteria for FDG PET/CT in multiple myeloma: a new proposal from an Italian expert panel. IMPeTUs (Italian Myeloma criteria for PET USe)

Cristina Nanni[1] · Elena Zamagni[2] · Annibale Versari[3] · Stephane Chauvie[4] · Andrea Bianchi[5] · Marco Rensi[6] · Marilena Bellò[7] · Ilaria Rambaldi[1] · Andrea Gallamini[8] · Francesca Patriarca[9] · Francesca Gay[10] · Barbara Gamberi[11] · Michele Cavo[2] · Stefano Fanti[1]

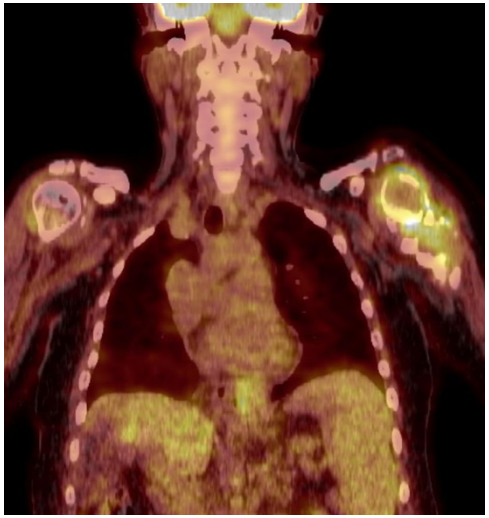
Lesion type	Site	Number of lesions (x)	Grading
Diffuse	Bone marrow[a]		Deauville five-point scale
Focal (F)	Skull (S)	x = 1 (no lesions)	Deauville five-point scale
	Spine (SP)	x = 2 (1 to 3 lesions)	
	Extraspinal (ExP)	x = 3 (4 to 10 lesions)	
		x = 4 (>10 lesions)	
Lytic (L)		x = 1 (no lesions)	
		x = 2 (1 to 3 lesions)	
		x = 3 (4 to 10 lesions)	
		x = 4 (>10 lesions)	
Fracture (Fr)	At least one		
Paramedullary (PM)	At least one		
Extramedullary (EM)	At least one	N/EN (nodal/extranodal)[b]	Deauville five-point scale

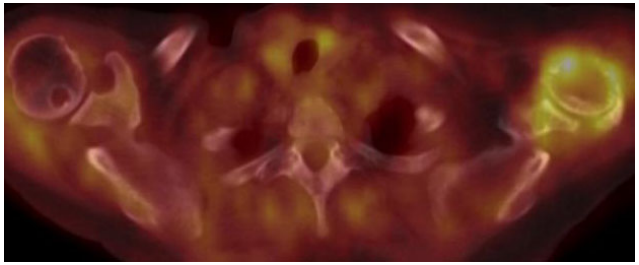
[a] "A" if hypermetabolism in limbs and ribs

[b] For nodal disease (N): *C* cervical, *SC* supraclavicular, *M* mediastinal, *Ax* axillary, *Rp* retroperitoneal, *Mes* mesenteric, *In* inguinal; For extranodal disease (EN): *Li* liver, *Mus* muscle, *Spl* spleen, *Sk* skin, *Oth* other

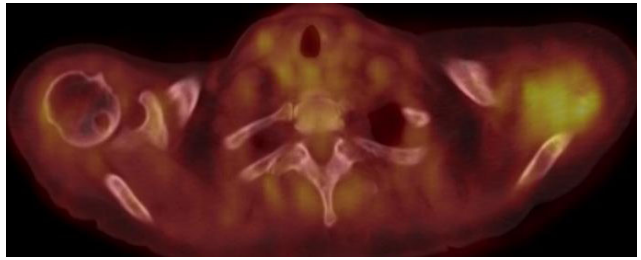
A 62 year-old female with left humerus plasmacytoma

PET baseline





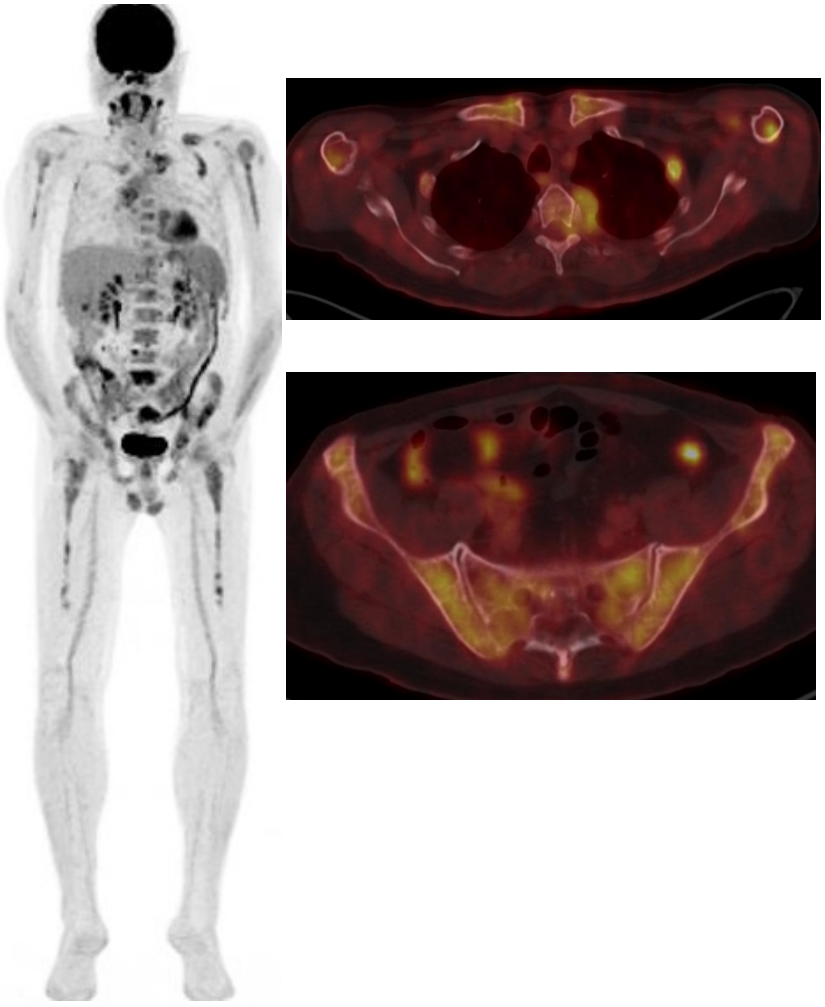
PET after treatment – Non-MR



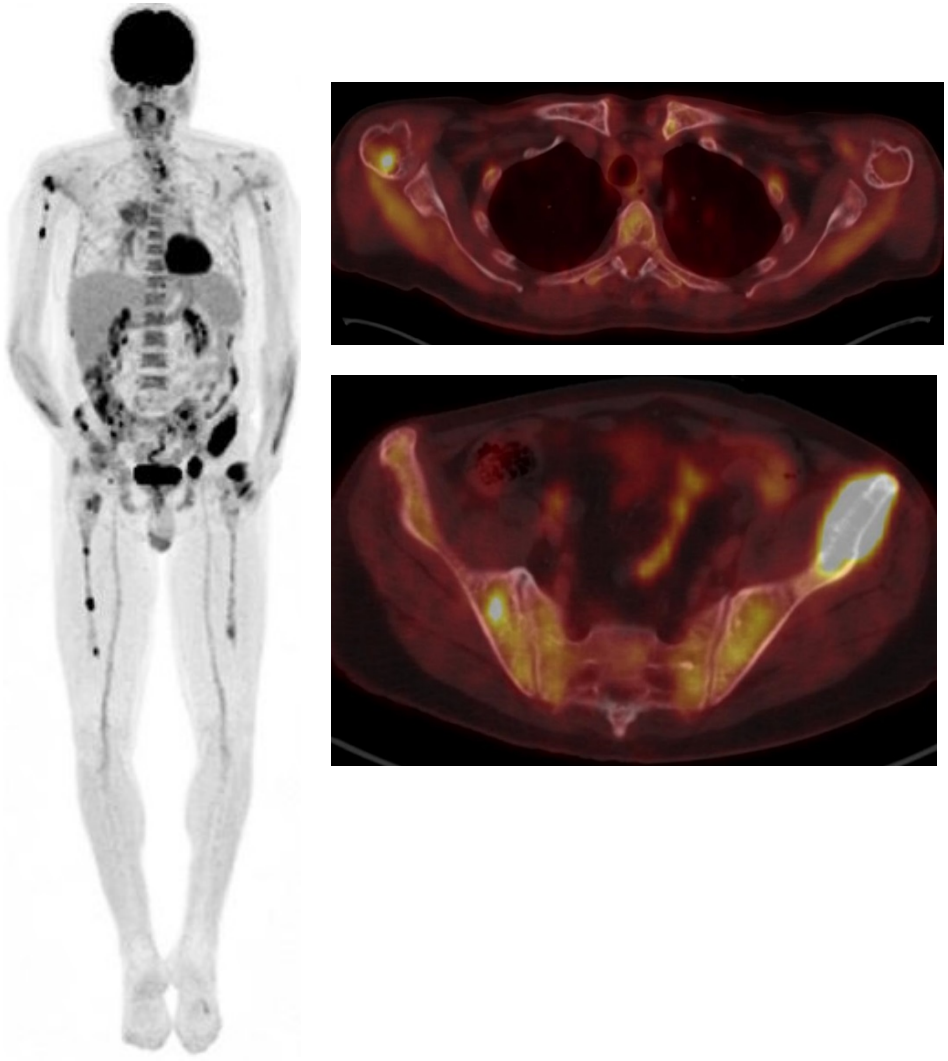
A 68 year-old male, with recurrence of MM

Diffuse bone marrow infiltration with multiple bone focal lesions and paravertebral plasmacytoma

Baseline PET/CT

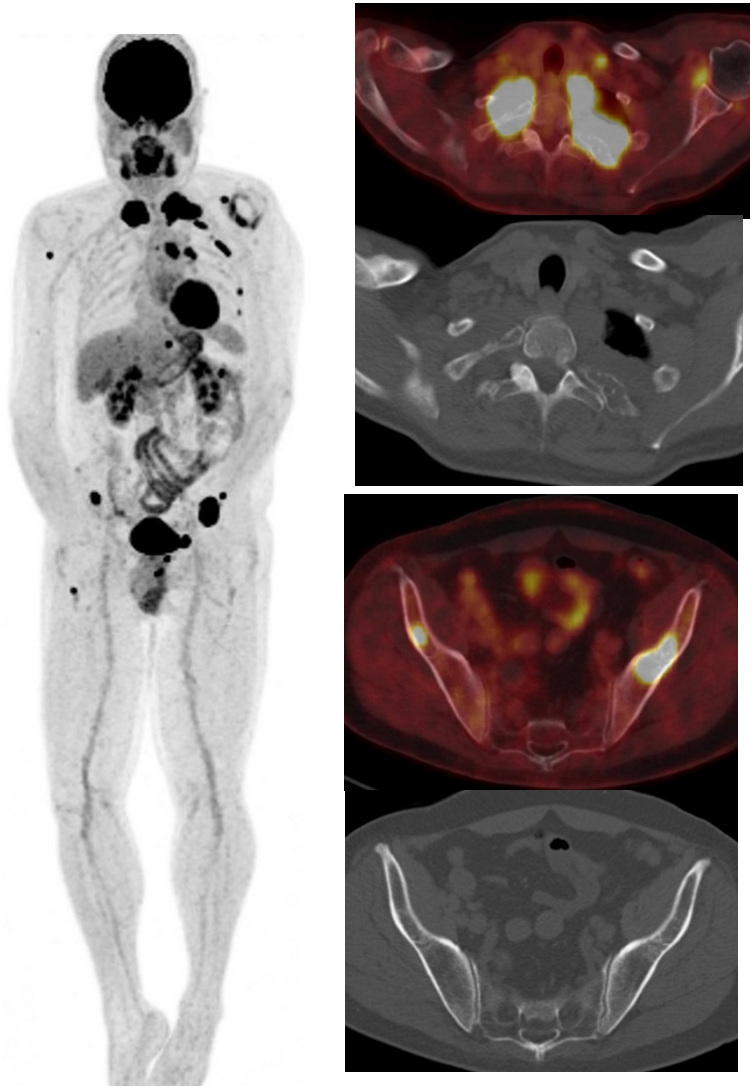


PET/CT after treatment (KRD) - PMD

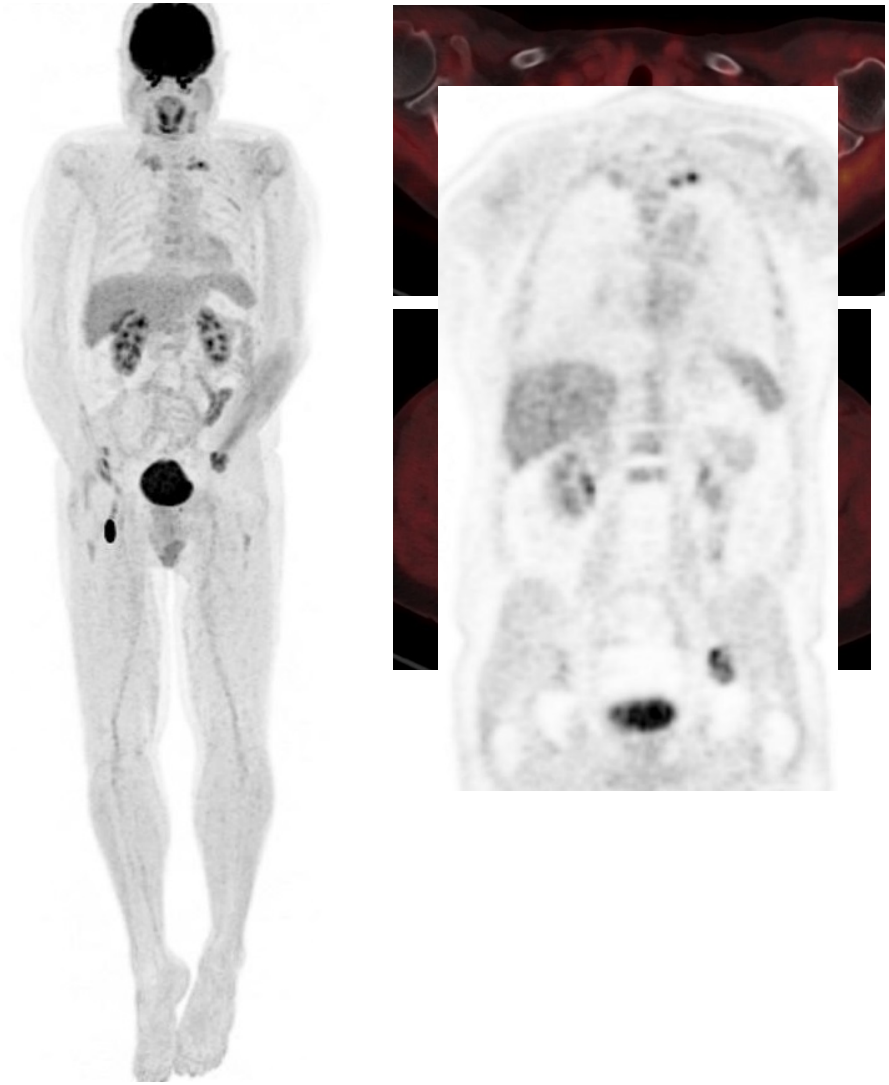


A 56 year-old male, with MM with recurrence after ASCT.
Plasmacytomas in ribs and focal lesions .

Baseline PET/CT

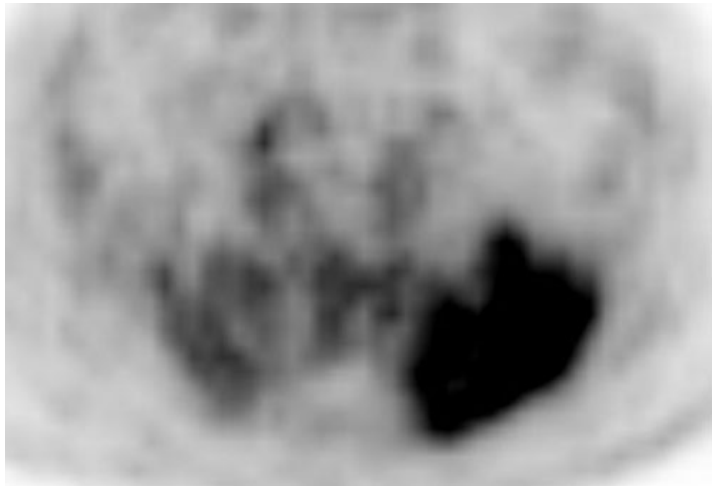


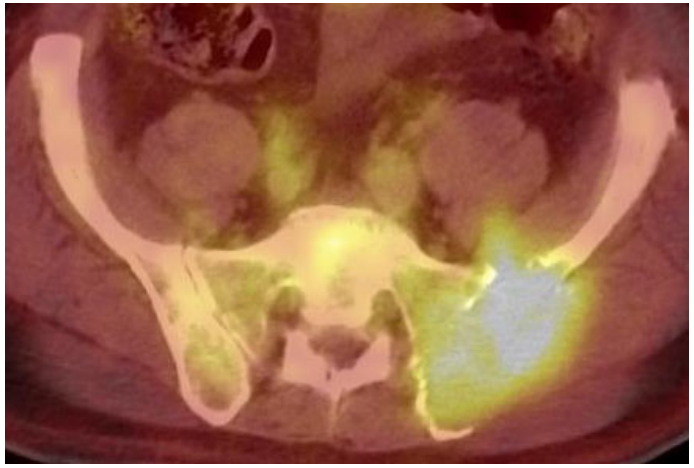
PET after chemo (KRD) - PMR



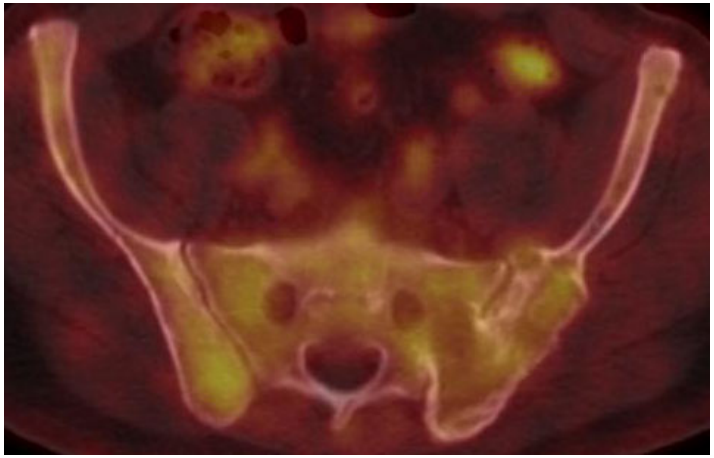
A 65 year-old male with left iliac crest plasmacytoma

Baseline PET/CT





PET after induction – before SCT - CMR



Non-standardization visual PET criteria lack of inter-observer reproducibility in reporting PET results

Systematic review: *van Lammeren-Venema D et al, Cancer 2012;15:1971-81*

- 18 studies y 798 patients with MM

Positive PET:

- SUV > 2.5
- Uptake > normal bone marrow
- Uptake > adjacent tissue
- Moderate increase uptake
- Significant increase uptake
- Non reported

Mesguich C. et al, (Mount Sinai) Eur J Radiol 2014;83:2203-2223

Recommendations for

Image description

Report scheme

Mesguich C. et al, Eur J Radiol 2014; 83:2203-2223

Image description: positive and negative PET lesion

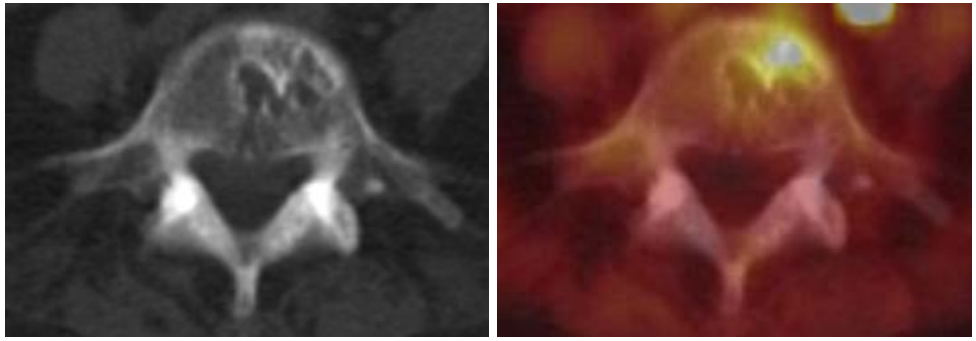
- **Diffuse** bone marrow uptake:
  - **Positive** > liver
  - Negative: ≤ liver

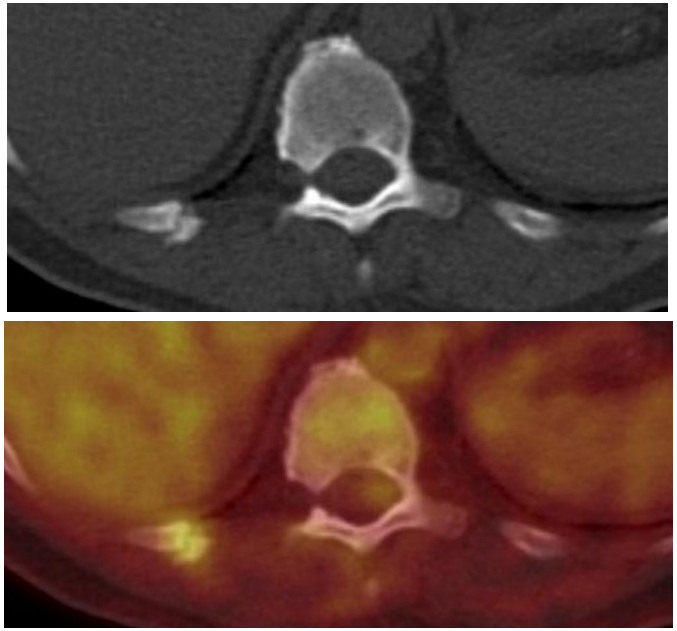
- **Focal** bone uptake
  - **positive**:
    - Uptake
      - > normal bone marrow (L4-L5)
      - and/or > liver
    - With or without corresponding CT finding

Mesguich C. et al, Eur J Radiol 2014; 83:2203-2223

Image description

- Focal bone uptake
  - **Equivocal**: FDG > liver localized:
    - Rib fracture
    - Bone fracture with sclerotic changes CT

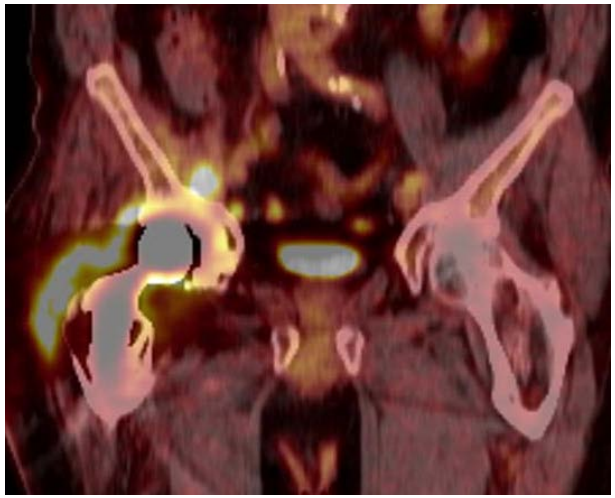


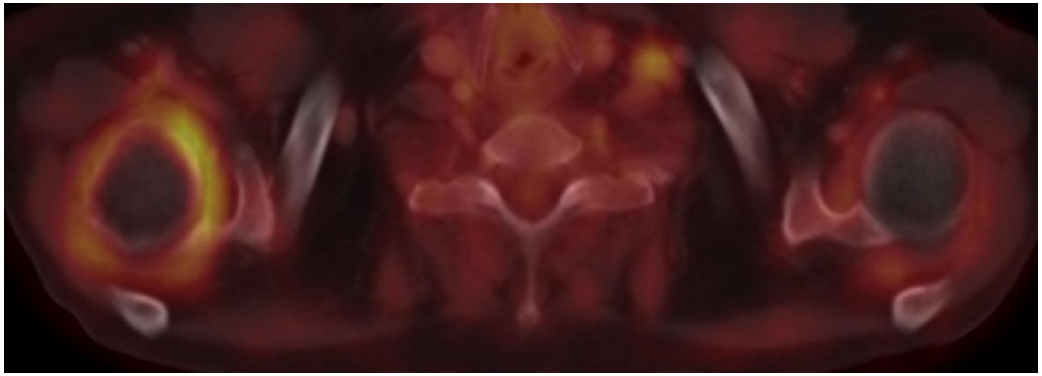


Mesguich C. et al, Eur J Radiol 2014; 83:2203-2223

Image description

- Focal bone uptake
  - **negative**: FDG > liver localized:
    - Osteoartritis, osteophites
    - Orthopedic devices
    - Vertebroplasty
    - …





Mesguich C. et al, Eur J Radiol 2014; 83:2203-2223

PET report

FDG uptake patterns:

Diffuse

Focal/Multifocal

Mixed

Mesguich C. et al, Eur J Radiol 2014; 83:2203-2223

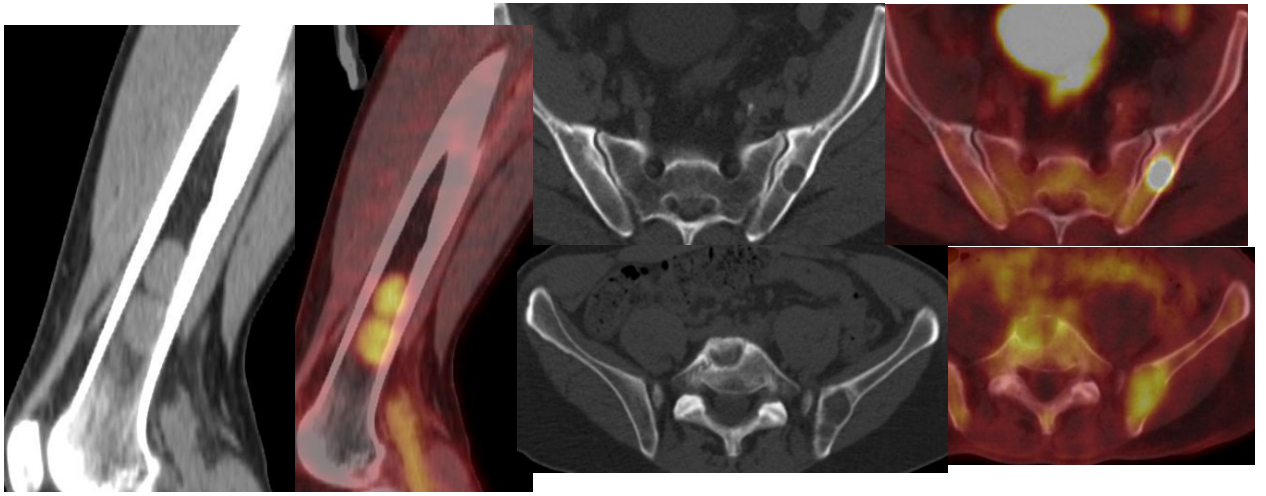
PET report

- **Number, localization and SUV of the focal lesions**
  - That allows a risk classification:
    - Durie & Salmon Plus
      - I < 4
      - II 5-20
      - III > 20

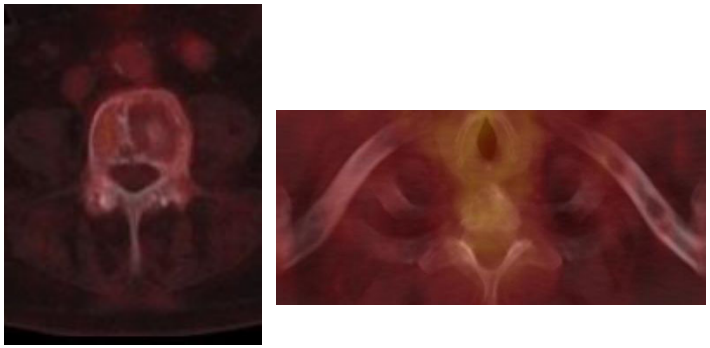
Mesguich C. et al, Eur J Radiol 2014; 83:2203-2223

PET report

- Description of abnormal underlying findings of CT:
  - FL corresponds:
    - osteolytic
    - osteosclerotic
    - osteoblastic



  - Lytic or sclerotic lesions on CT
    - Without FDG uptake

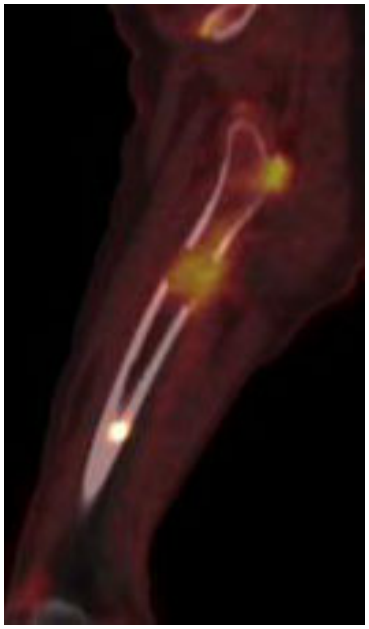


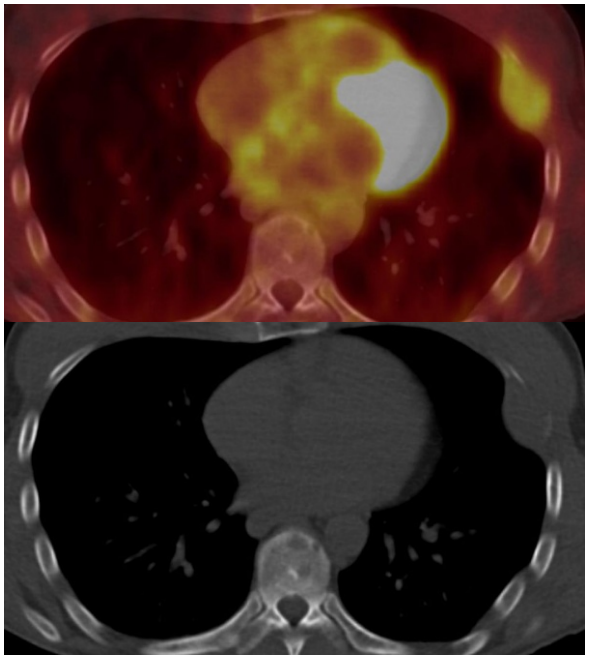
Mesguich C. et al, Eur J Radiol 2014; 83:2203-2223

PET report

Describe the **extramedullary expansion**:

- Lytic lesion with cortical disruption
- Cortical disruption and expansion into surrounding soft tissue "break out"
- Pure extramedullary soft tissue mass without bone involvement



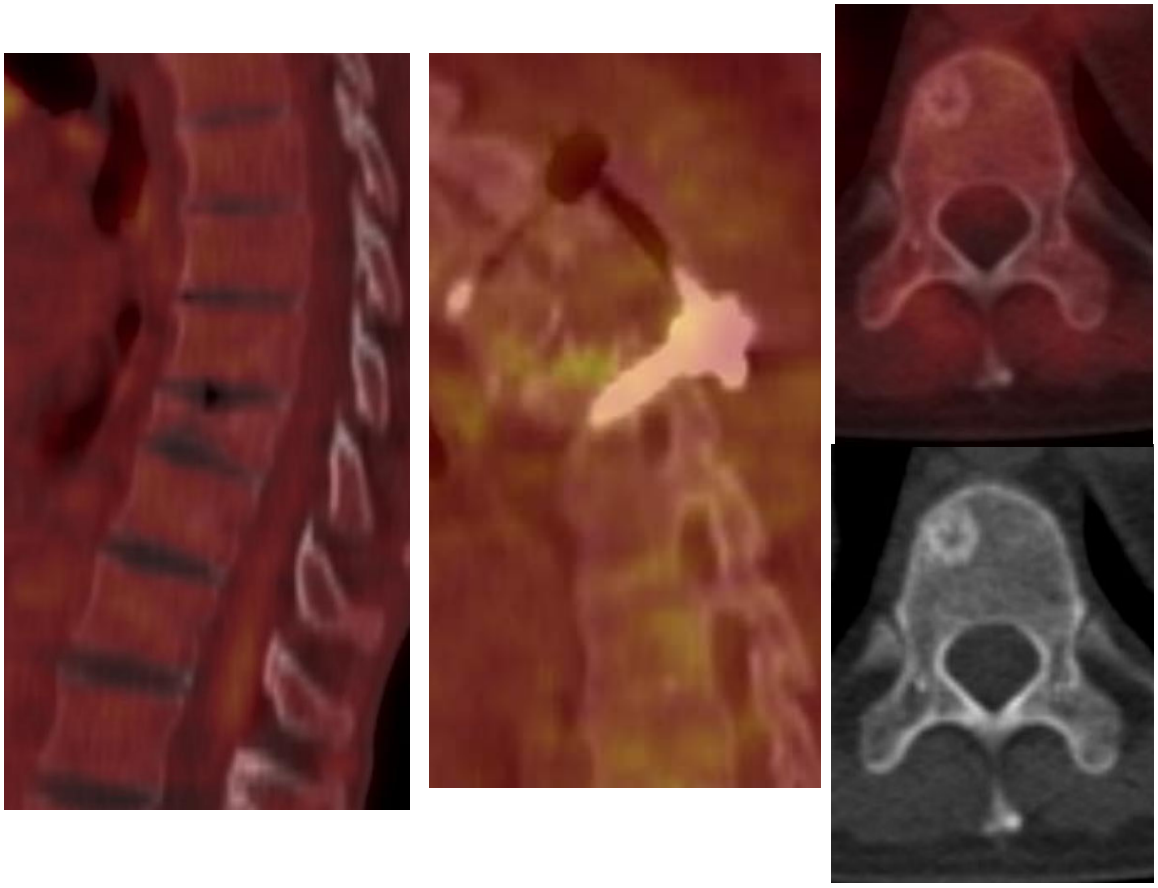


Mesguich C. et al, Eur J Radiol 2014; 83:2203-2223

PET report

Other bone lesions :

- Osteoartritis
- Fractures
- Osteophites
- Prosthesis
- Osteosyntesis
- Vertebroplasty
- Schmörl node



Conclusions
Role of PET in multiple myeloma

X-Ray remains a standard method for assessing bone disease
WBCT has replaced X-Ray

- PET: Allows a whole-body evaluation in a single session
  - Solitary Plasmacytoma
  - Extramedullary disease
  - Smoldering Myeloma
  - Multiple myeloma:
- Accurate stage of active disease
- Prognostic value
- Treatment response assessment:
  - Non validated
  - Non standardized
  - Role in the future