3es JFMN
Journées Francophones de Médecine Nucléaire

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

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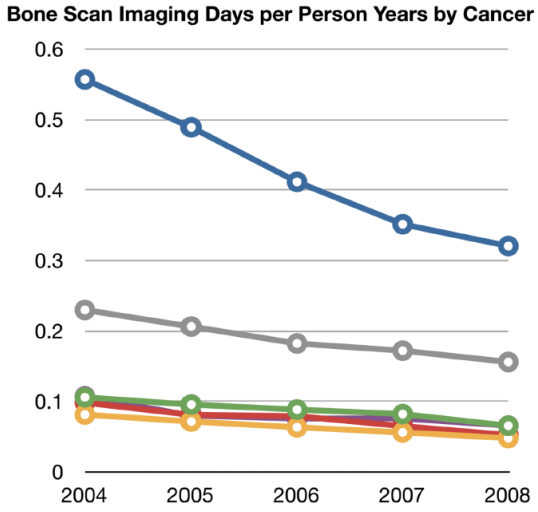
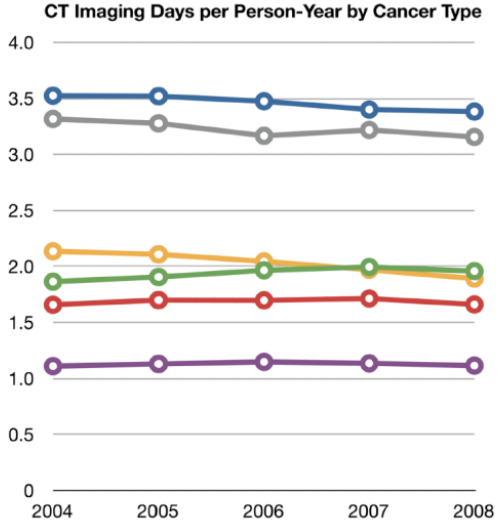
La Cité-Nantes
5 rue de Va

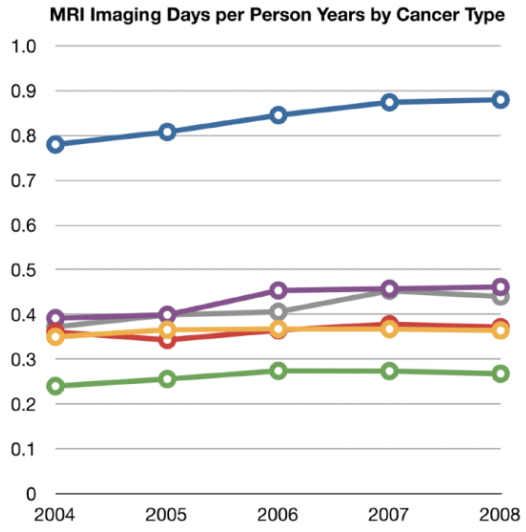
SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero-Universitaria di Bologna

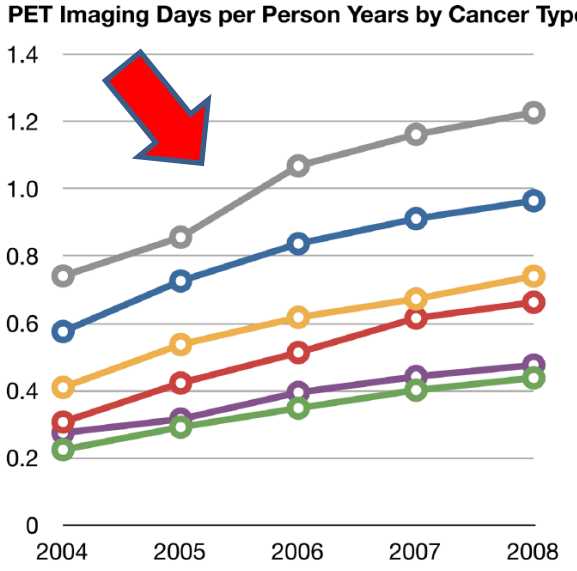
MNM

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









J Am Coll Radiol. 2012 Jan; 9(1): 33–41.

Why such an increase?

The fourth dimension….

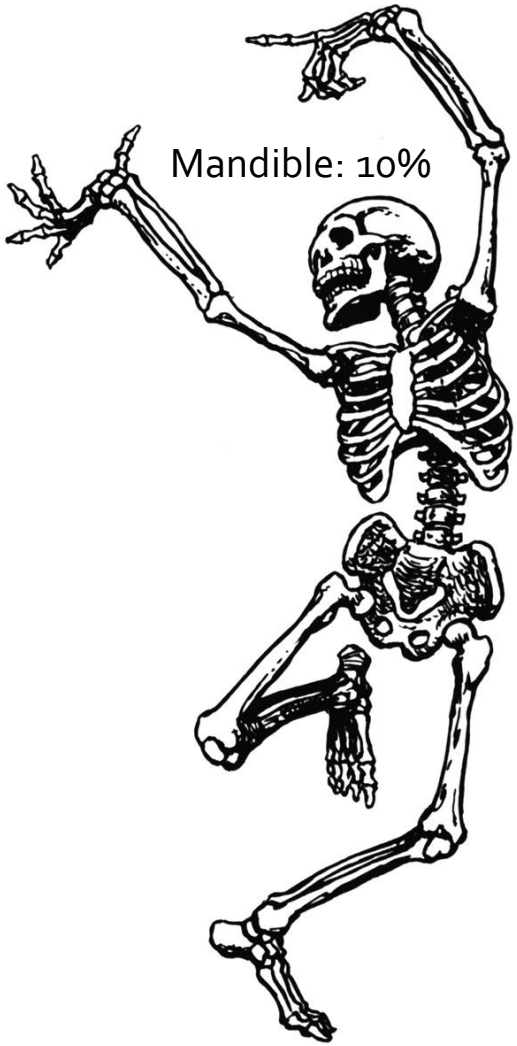
PET/CT provides a functional characterization of findings detected at tomographic morphological imaging .

- ✓Accurate staging
- ✓Function evaluation
- ✓Therapy assessment

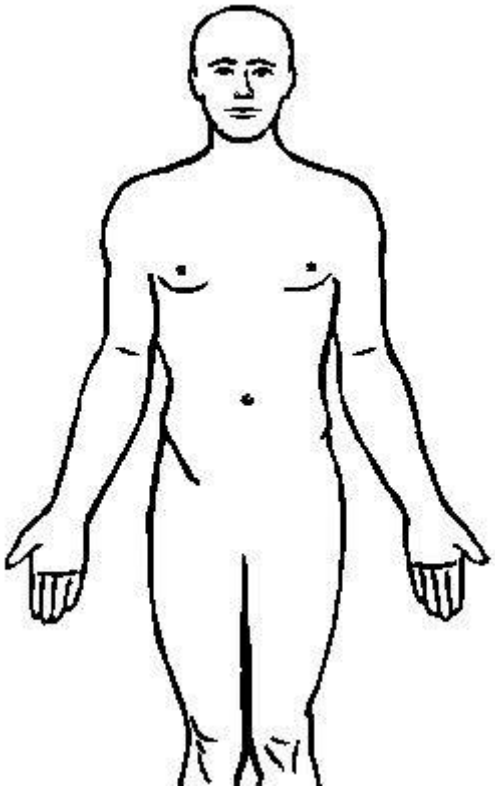
BETTER STRATIFICATION

Field of view

Distribution of bone lesions in MM patients



PET/CT FOV for MM



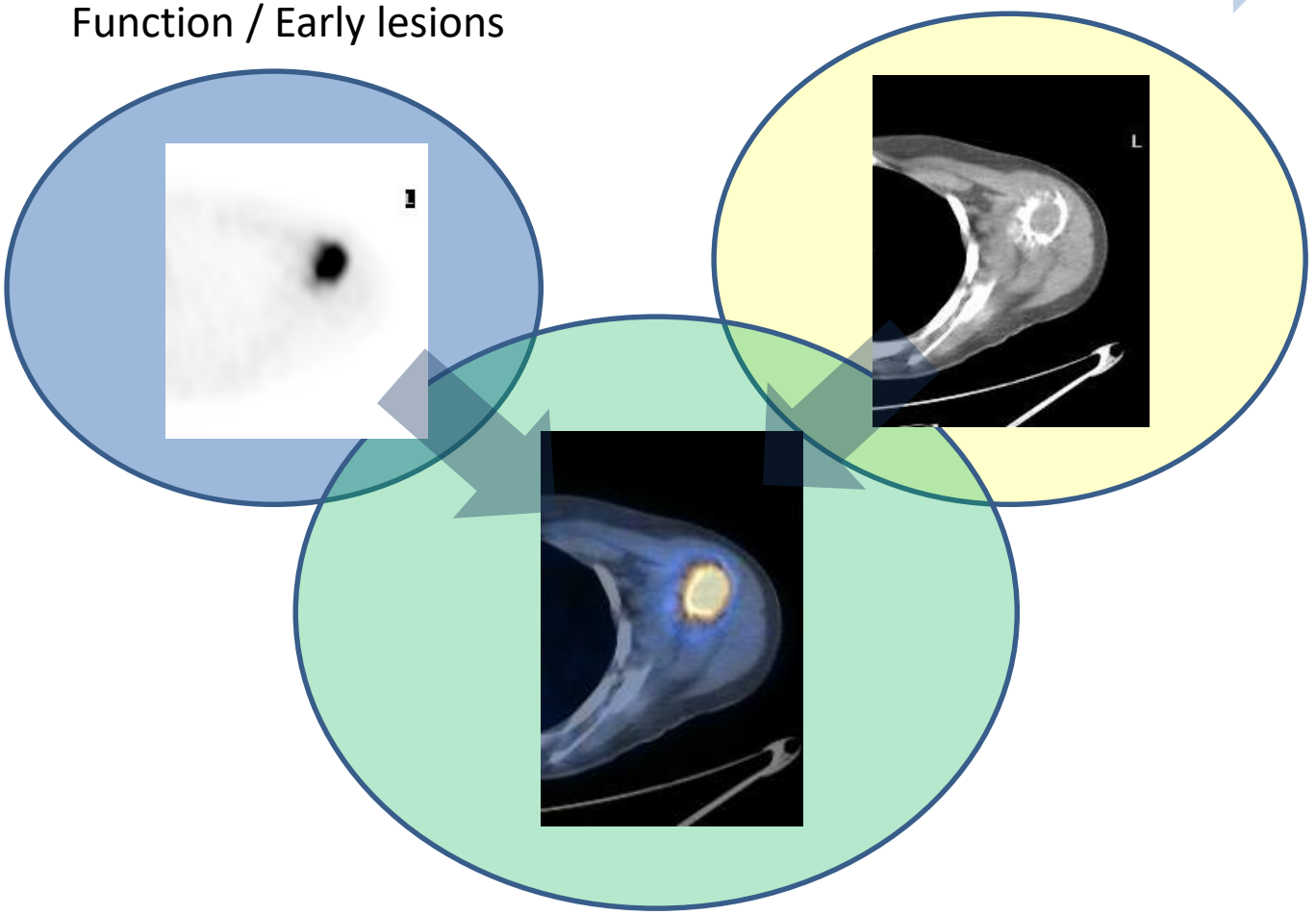
MOST OF THE BONES ARE INCLUDED

EXTRAMEDULLARY DISEASE CAN BE DETECTED

Function / Early lesions

Morphology

LDCT is accurate anough for the evaluation of bone in MM



Both

In symptomatic MM the bone evaluation is essential: CT contribution

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¶

CRAB criteria — Bone lesions, osteolytic or osteoporosis

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

Rajkumar V. et al., Lancet Oncology 2014

IMWG, BJH 2003

In symptomatic MM the bone evaluation is essential: PET contribution

Usually SUV max is high but not necessairly.

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

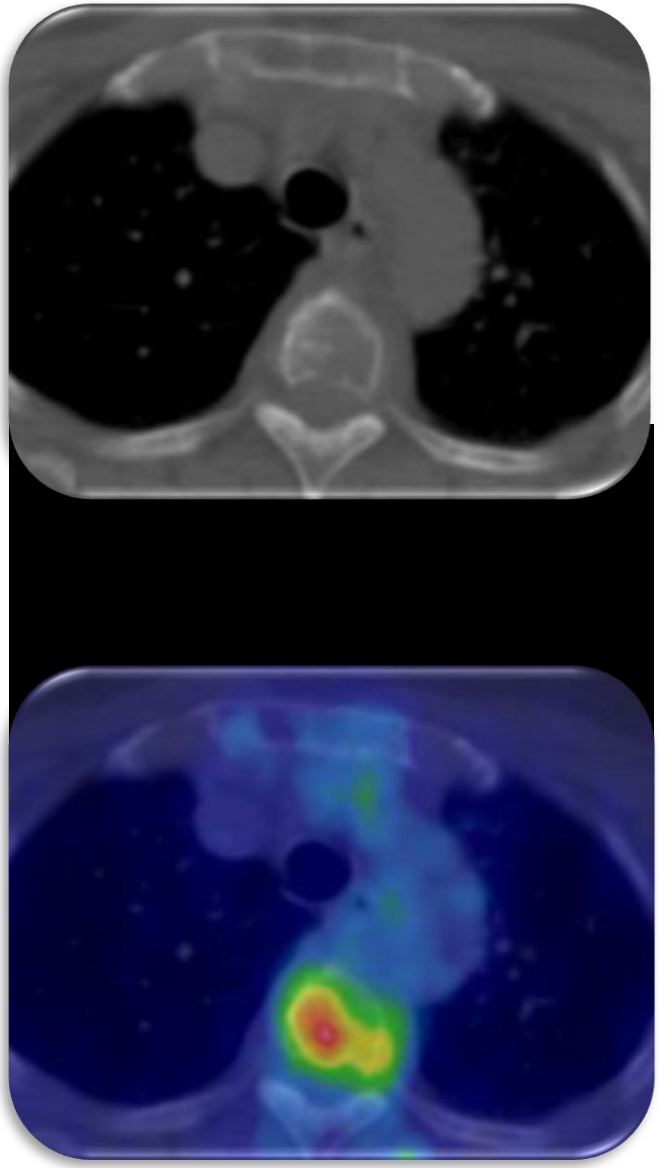
Focal uptake may be extramedullary

Table 2. SUV_{max} of the least and the most active lesion and disease stage for each patient

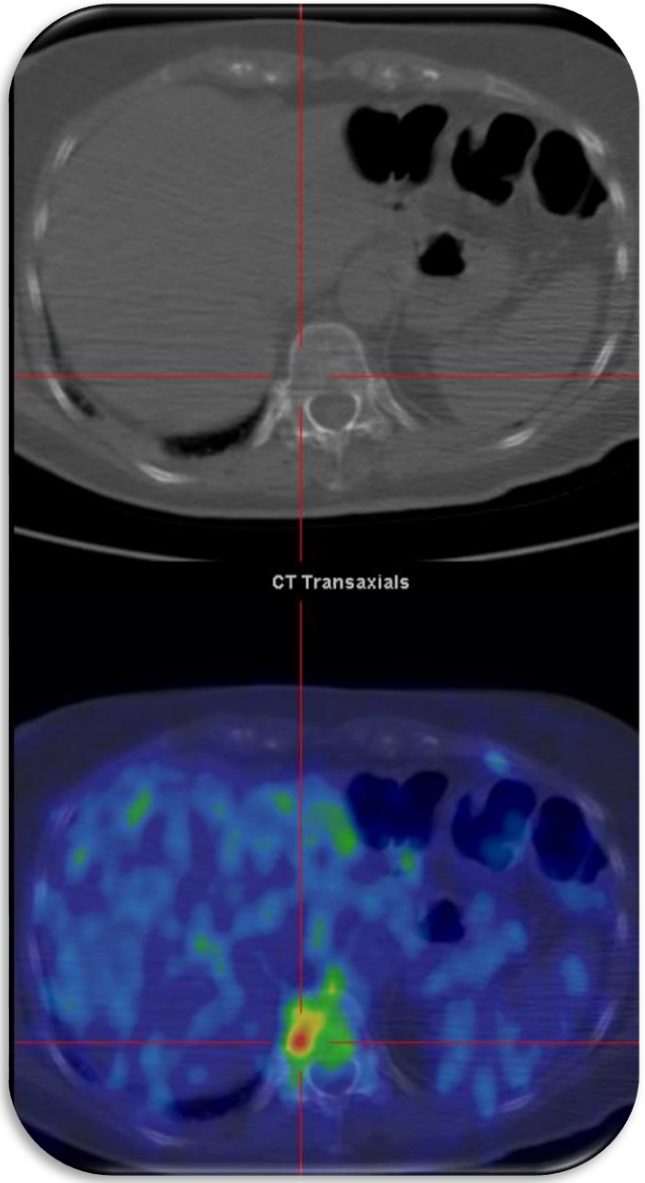
Patient no.	SUV_{max} of least active lesion	SUV_{max} of most active lesion	Stage
1	2.00	5.70	IIIA
2	3.20	4.70	IIIB
3	3.50	6.10	IIIA
4	3.00	4.10	IIIA
5	3.90		IIIA
6	1.90	6.80	IIIA
7	3.50	6.10	IIA
8			IIIA
9	2.10	7.20	IIA
10	5.10		SP
11	2.80	5.90	IIIA
12	2.00	2.50	IIIA
13	2.00	3.00	IIIA
14	2.30	5.40	PCL
15			IA
16	4.10	6.90	IIIA
17	2.30	2.90	IIA
18			IIIB
19	2.40	5.10	IIIA
20	5.50		IA
21	2.10	7.10	IIIA
22	4.30	6.00	IA
23	6.70		IIIA
24	3.60	5.80	IIIA
25			IIA
26	2.90	3.10	IIA
27	5.60		IIIA
28	6.60	6.80	IIIA

PCL plasma cell leukaemia, *SP* solitary plasmacytoma

Nanni C et al. Eur J Nucl Med Mol Imaging
DOI 10.1007/s00259-005-0004-3

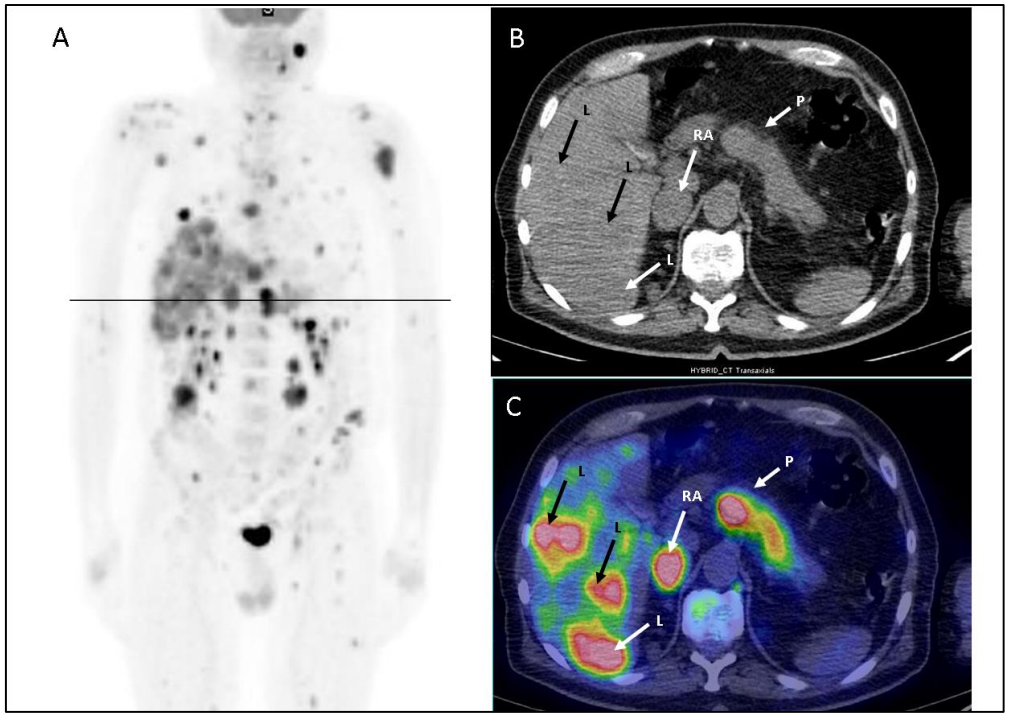


CT+; PET+

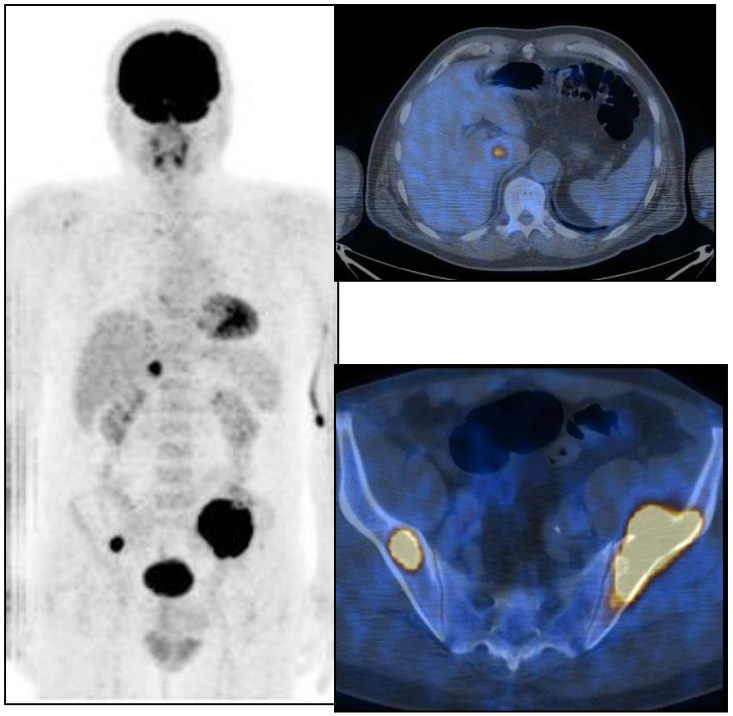


CT-; PET+

Extramedullary



Massive



Focal

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

SYMPTOMATIC

Zamagni, E. et al. Haematologica 2007;92:50-55

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

	Concordant results		*Discordant results*	
Comparative imagings	*N. of pts (%) with negative findings*	*N. of pts (%) with positive findings*	*N. of pts (%) with superiority of PET-CT*	*N. of pts (%) with inferiority of PET-CT*
PET-CT WB vs WBXR	9/46 (19)	12/46 (26)	21/46 (46)	4/46 (8)
PET-CT SP vs MRI SP	4/46 (8)	28/46 (61)	0/46	14/46 (30)
PET-CT WB vs MRI SP	4/46 (8)	15/46 (34)	13/46 (28)	14/46 (30)

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

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

SYMPTOMATIC

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

bjh research paper

SYMPTOMATIC

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

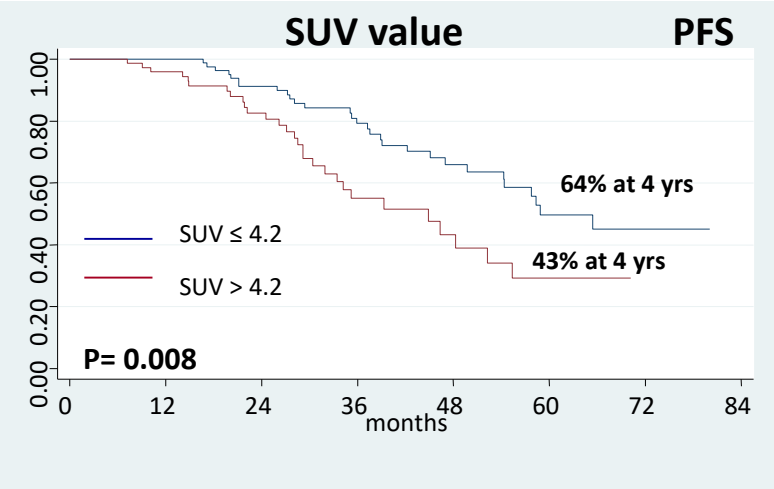
- 32 directly comparison studies, prospective and retrospective, 1661 patients
- Index test vs reference standard: detection rate
- Quality assessment of diagnostic studies
- All index tests had sensitivity above 0,9 as compared to WBXR (low false negative). Fewer additional lesions detected by PET/CT 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»

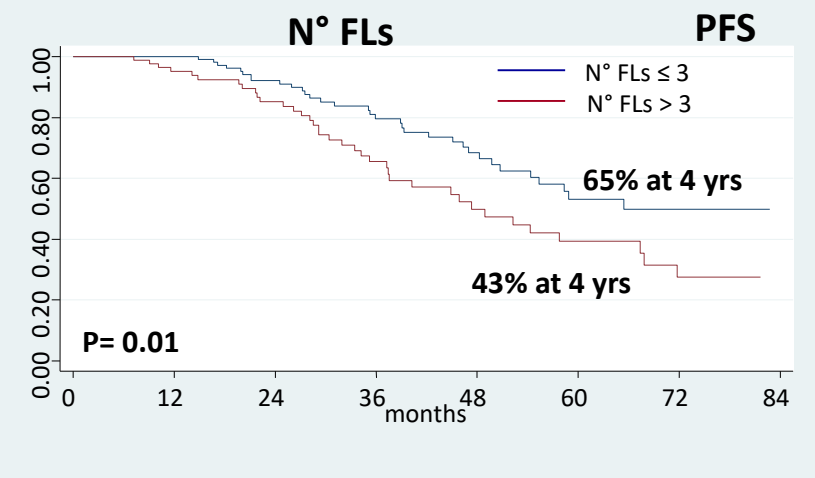
Regelink J. et al., BJH 2013

Staging symptomatic MM

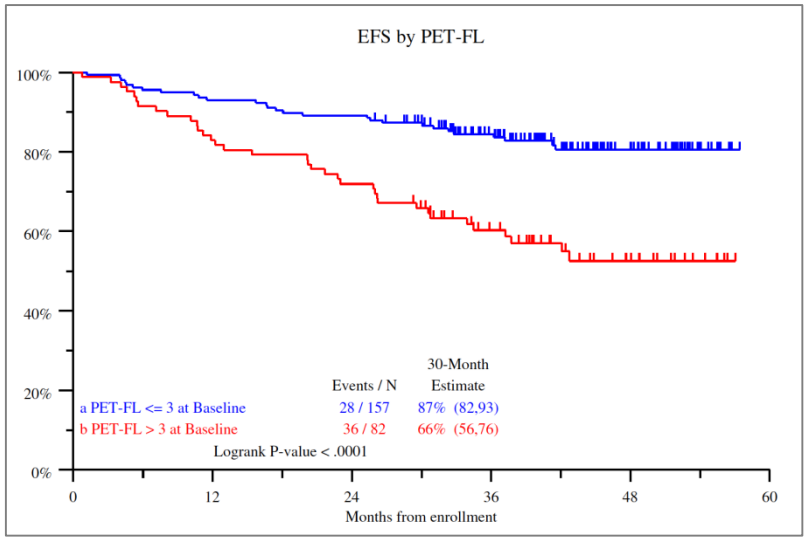
SYMPTOMATIC

N° OF FLs, SUV VALUE





Zamagni et al.

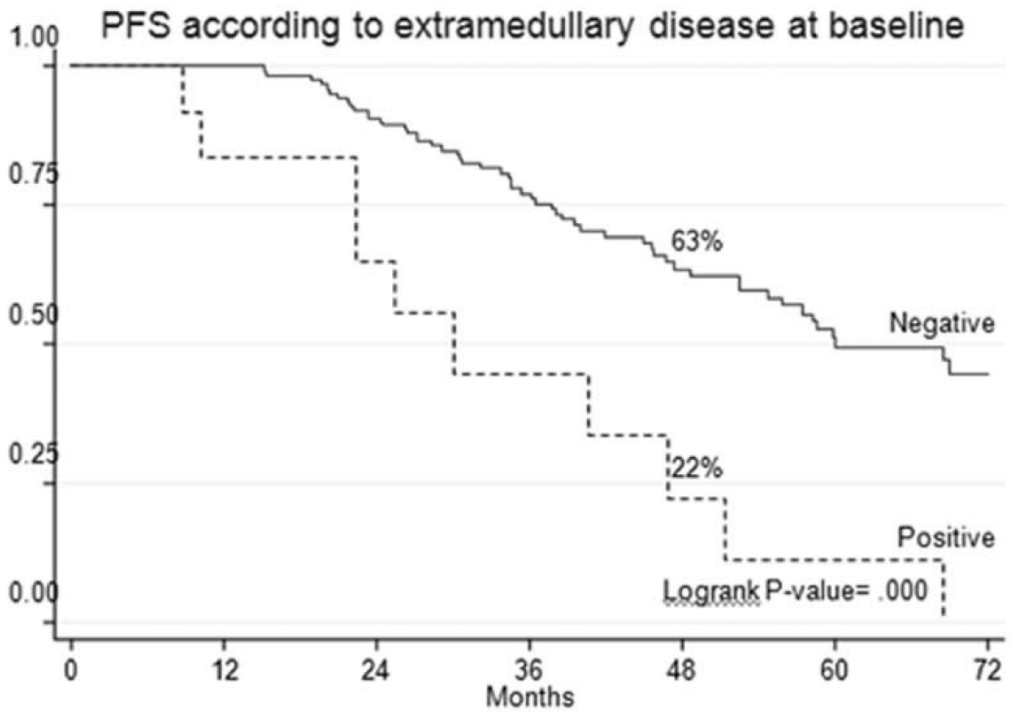


Bartel TB: Blood. 2009;114:2068-2076)

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

SYMPTOMATIC

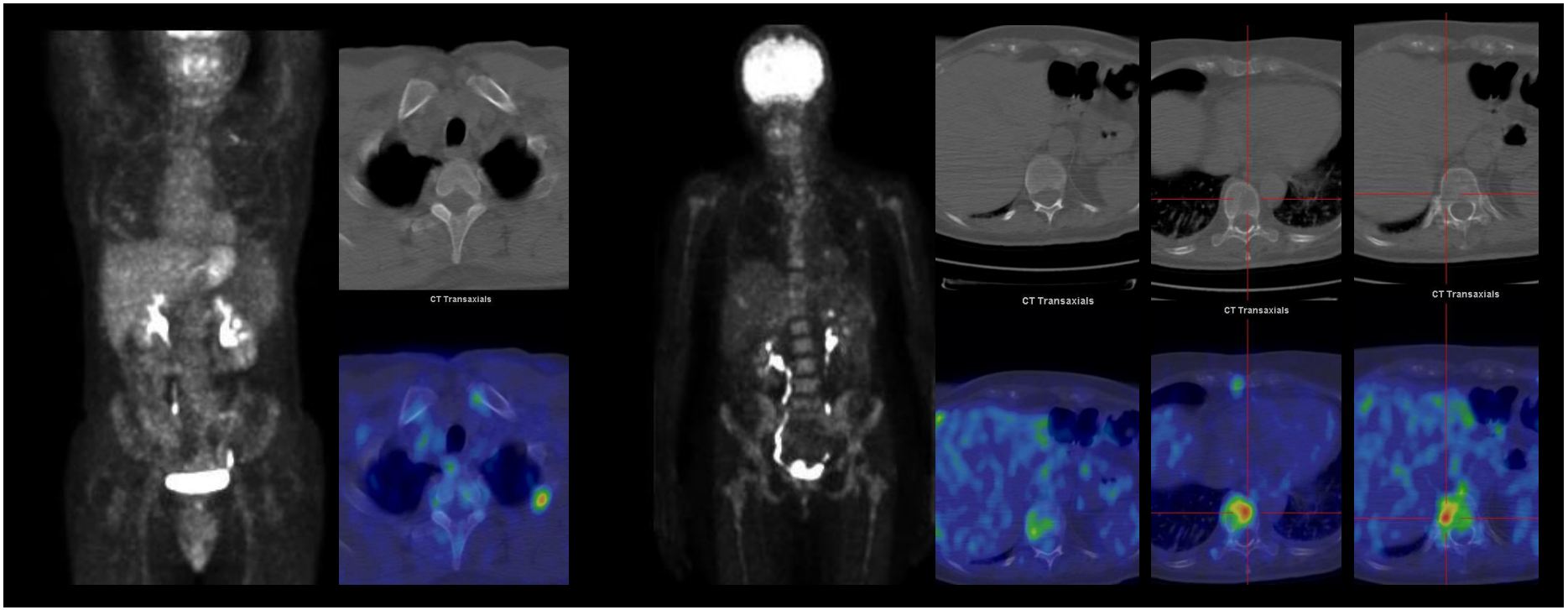
Variable	HR	95% CI		P
PFS				
EMD	3.81	1.93	7.50	.000
Postinduction PET SUV > 4.2	3.44	1.32	8.98	.007
Post-ASCT PET SUV > 100% reduction	2.69	1.15	6.28	.022
OS				
Relapse	9.31	2.78	31.16	.000
Post-ASCT PET SUV > 100% reduction	3.93	1.15	13.42	.029
EMD	3.91	1.55	9.88	.002
Postinduction PET SUV > 4.2	3.11	0.77	12.50	.09



Zamagni E.: Blood. 2011;118(23):5989-5995)

Staging: the bone in symptomatic MM

SYMPTOMATIC



1 lesion

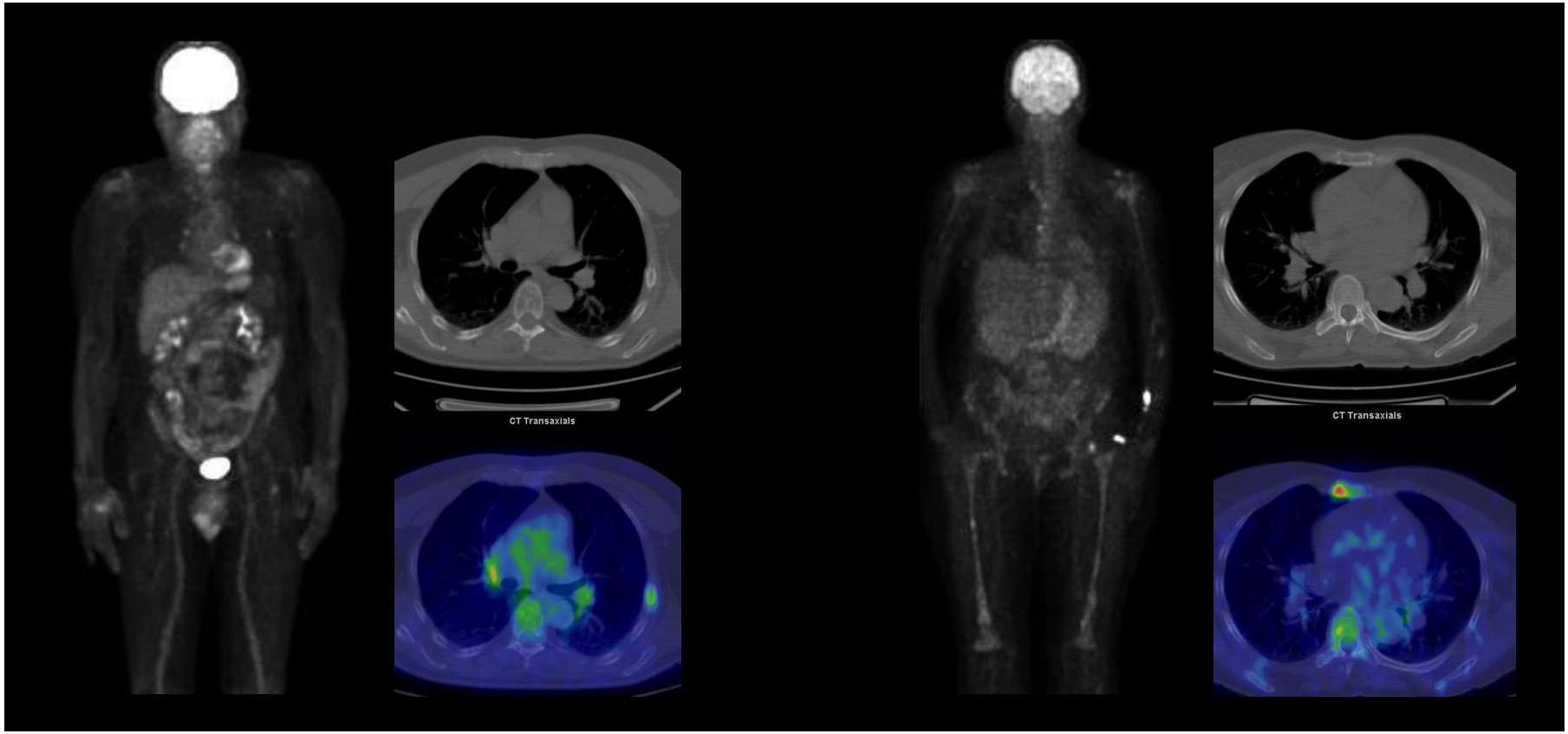
PFS 73 months

> 4 lesions

PFS 34 months

Staging: the bone in symptomatic MM

SYMPTOMATIC



SUV max 2,5

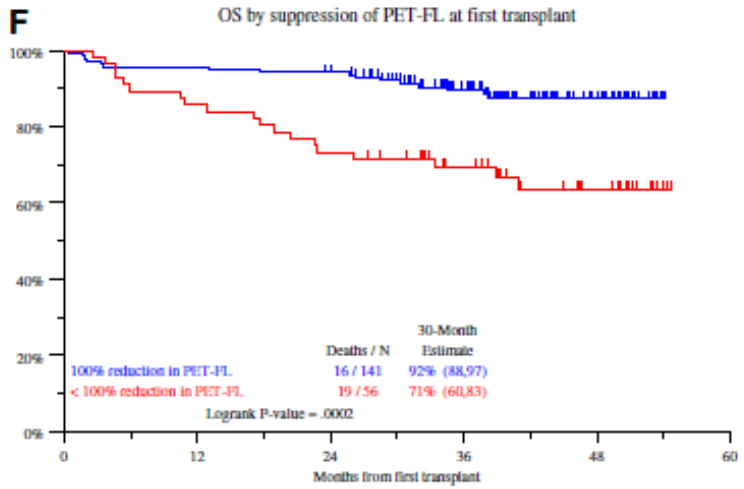
PFS 69 months

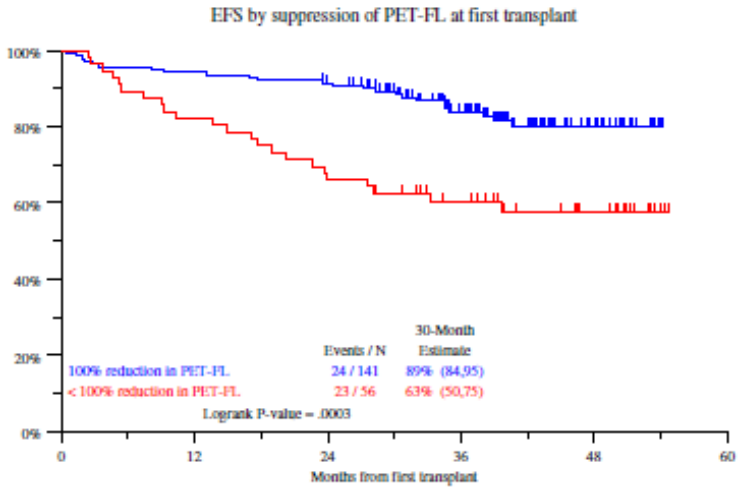
SUV max 7,9

PFS 39 months

PROGNOSTIC VALUE OF PET/CT BEFORE ASCT

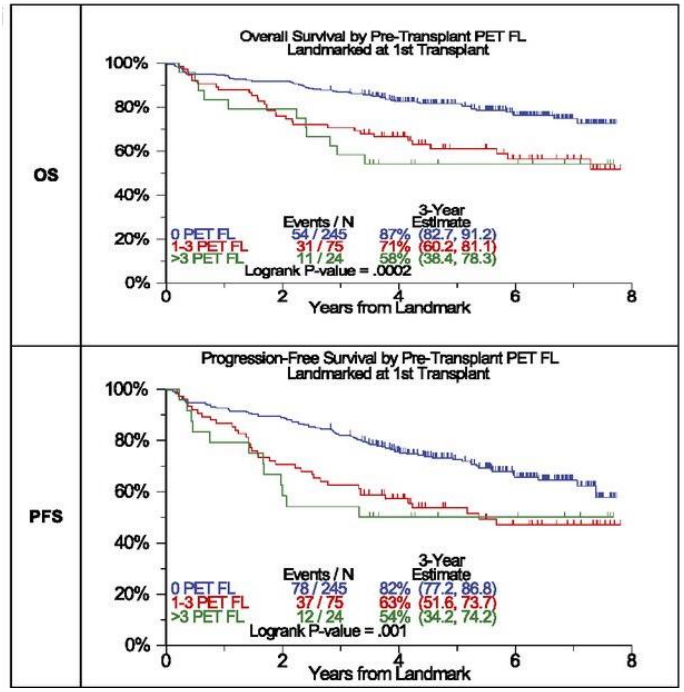
SYMPTOMATIC





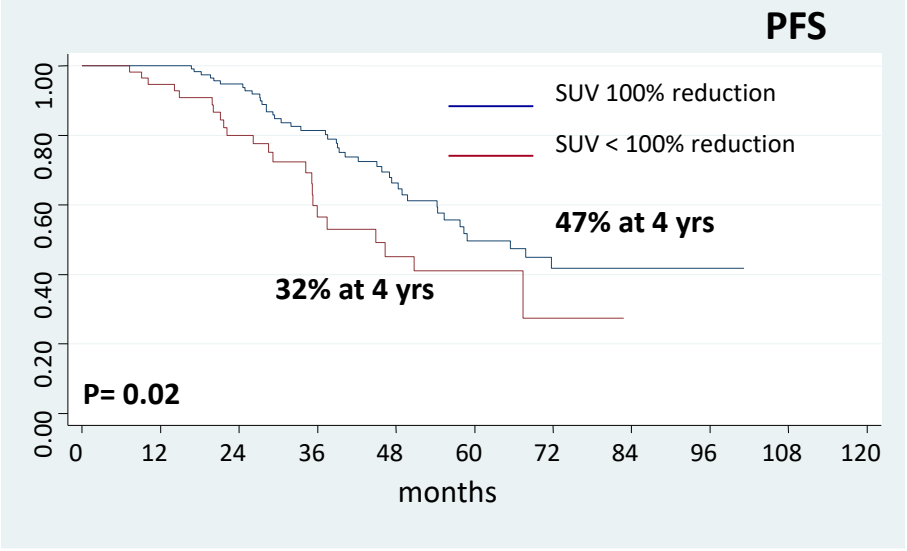
Bartel. TB et al, Blood 2009

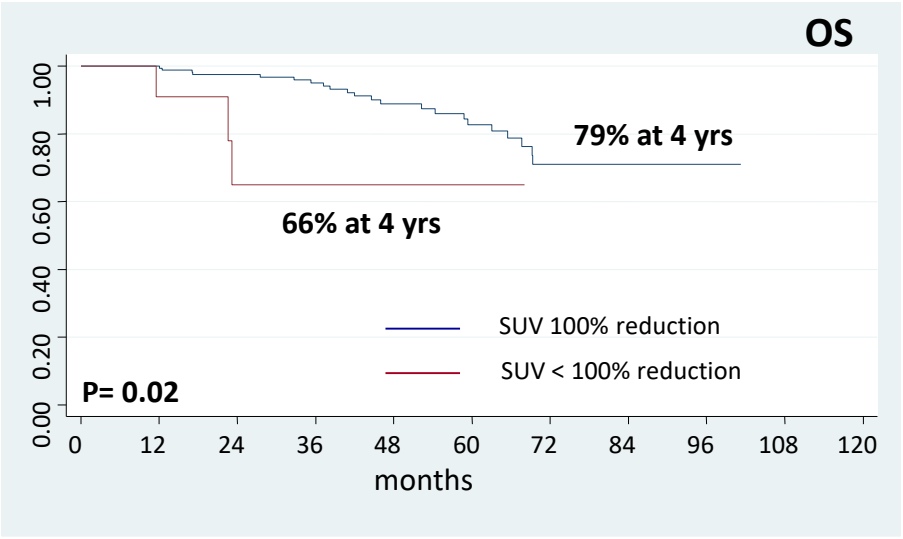
Complete FDG suppression retained independent prognostic value for PFS and OS in Cox regression analysis



PROGNOSTIC VALUE OF PET/CT AFTER ASCT

SYMPTOMATIC





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

PROGNOSTIC VALUE OF PET/CT AFTER ASCT

SYMPTOMATIC

Table 1. Patient characteristics at baseline and treatment received

Patients, *N*	282
Median age, y (range)	59 (22–83)
Median LDH (UI/L; range)	303 (99–2,020)
Patients with ISS stage 3 (%)	20
Patients with del (17p) and/or t(4;14) (%)	30
Patients receiving ASCT as first-line treatment (%)	73
Conventional chemotherapy-based	23
Thalidomide-based	43
Bortezomib-based	34
Patients not ASCT eligible (%)	27
Conventional chemotherapy	21
MPT	33
VMP	46
Patients receiving novel agents as first-line treatment (%)	77
Patients receiving bortezomib as first-line treatment (%)	37

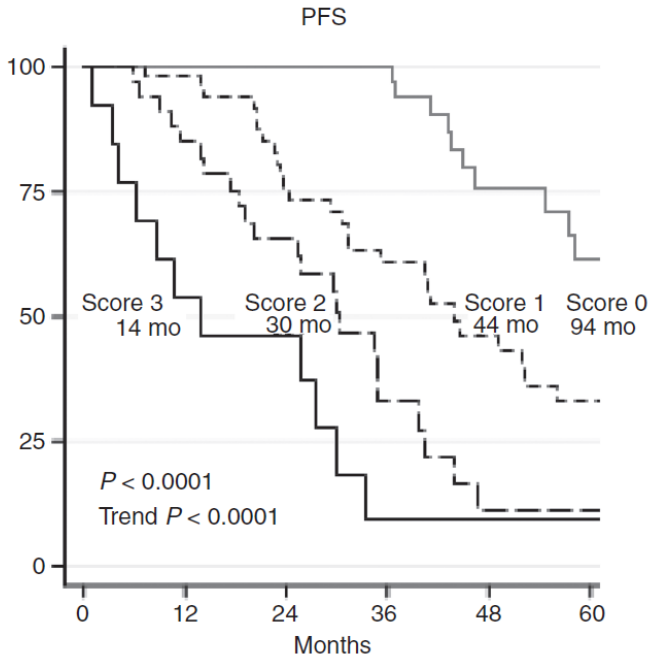
Abbreviations: del, deletion; ISS, international staging system; t, translocation.

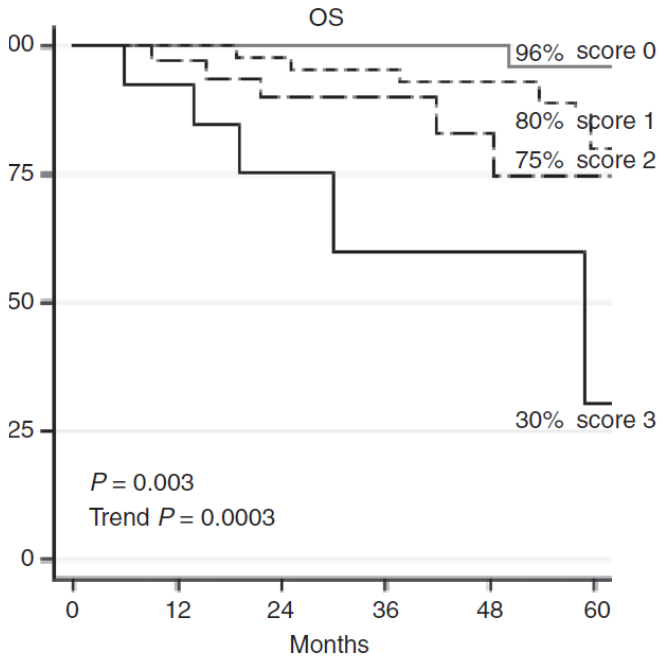
Table 2. PET/CT characteristics at baseline and after first-line treatment

PET/CT characteristics	Baseline	After treatment
Patients with negative PET/CT (%)	30	70
Patients with positive PET/CT (%)	70	30
1–3 FLs	28	15
>3 FLs or diffuse	42	15
SUV $\leq$ 4.2	25	18
SUV >4.2	45	12
Patients with EMD (%)	5	3

Table 3. PFS and OS according to ISS stage 3, failure to achieve best CR after first-line therapy, and PET/CT SUV_{max} >4.2 (Model 1, multivariate analysis) or according to their combination into a prognostic score (Model 2)

	HR (95% CI)	*P*
PFS		
Model 1		
ISS stage 3	1.49 (1.03–2.57)	0.041
Failure to achieve best CR	2.52 (1.51–4.21)	<0.001
SUV_{max} >4.2	1.90 (1.12–3.21)	0.017
Model 2		
Score 1 vs. 0	3.11 (1.52–6.35)	0.002
Score 2 vs. 0	5.70 (2.66–12.22)	<0.001
Score 3 vs. 0	7.17 (2.94–17.48)	<0.001
OS		
Model 1		
ISS stage 3	2.11 (1.04–5.15)	0.039
Failure to achieve best CR	1.61 (0.66–3.91)	0.295
SUV_{max} >4.2	3.65 (1.30–10.27)	0.014
Model 2		
Score 1 vs. 0	3.14 (0.79–12.48)	0.104
Score 2 vs. 0	6.01 (1.37–26.32)	0.017
Score 3 vs. 0	13.19 (2.71–64.09)	0.001





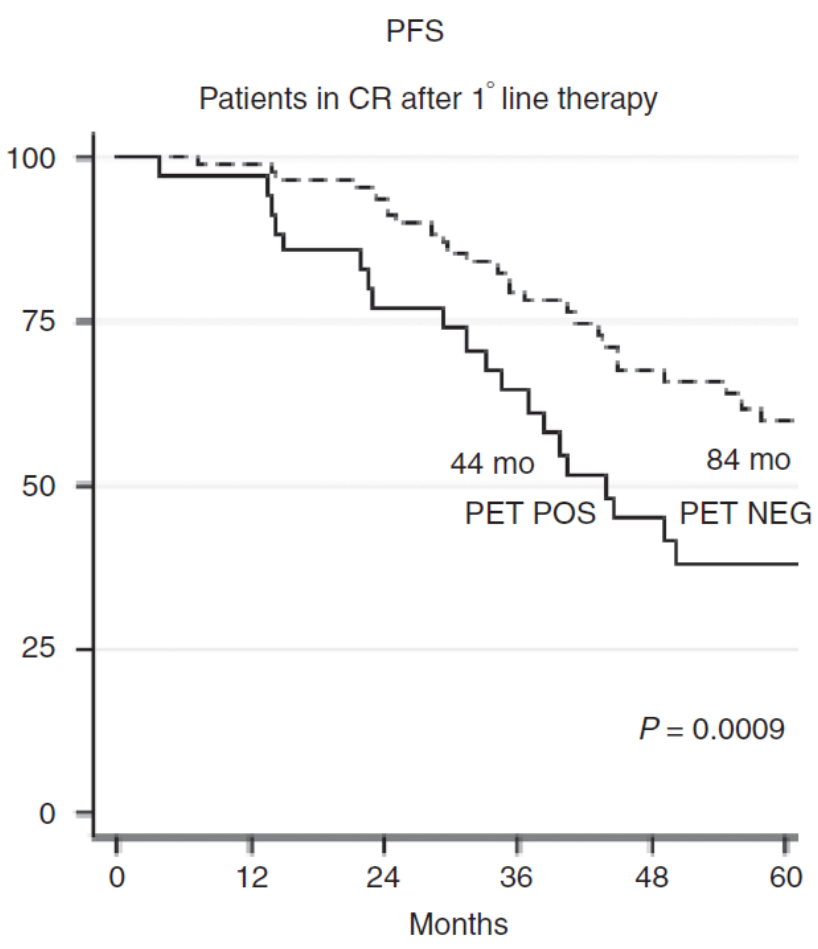
score 0: none of the 3 adverse factors, 30% of the patients
score 1: only 1 of 3, 36%
score 2: 2 factors, whichever, 25
score 3: all three risk factors, 9% of cases

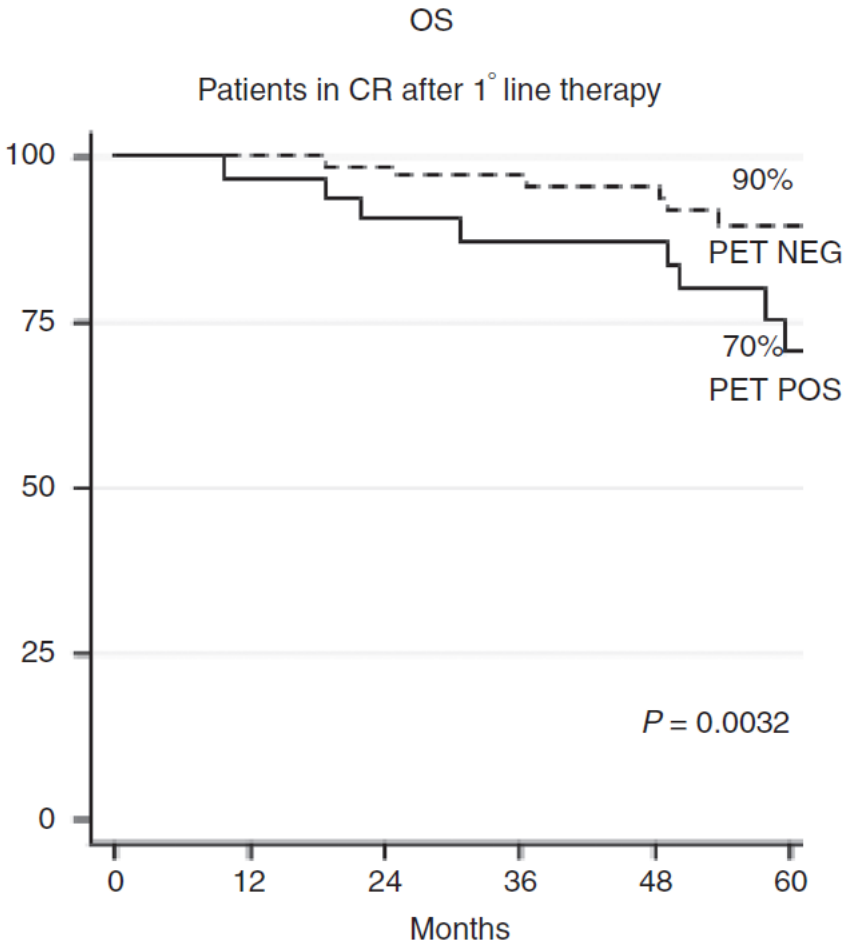
Zamagni et al. Clin Cancer Res; 21(19) October 1, 2015

PROGNOSTIC VALUE OF PET/CT AFTER ASCT

SYMPTOMATIC

PFS and OS according to PET/CT negativity or positivity in patients achieving conventionally defined CR after up-front therapy.



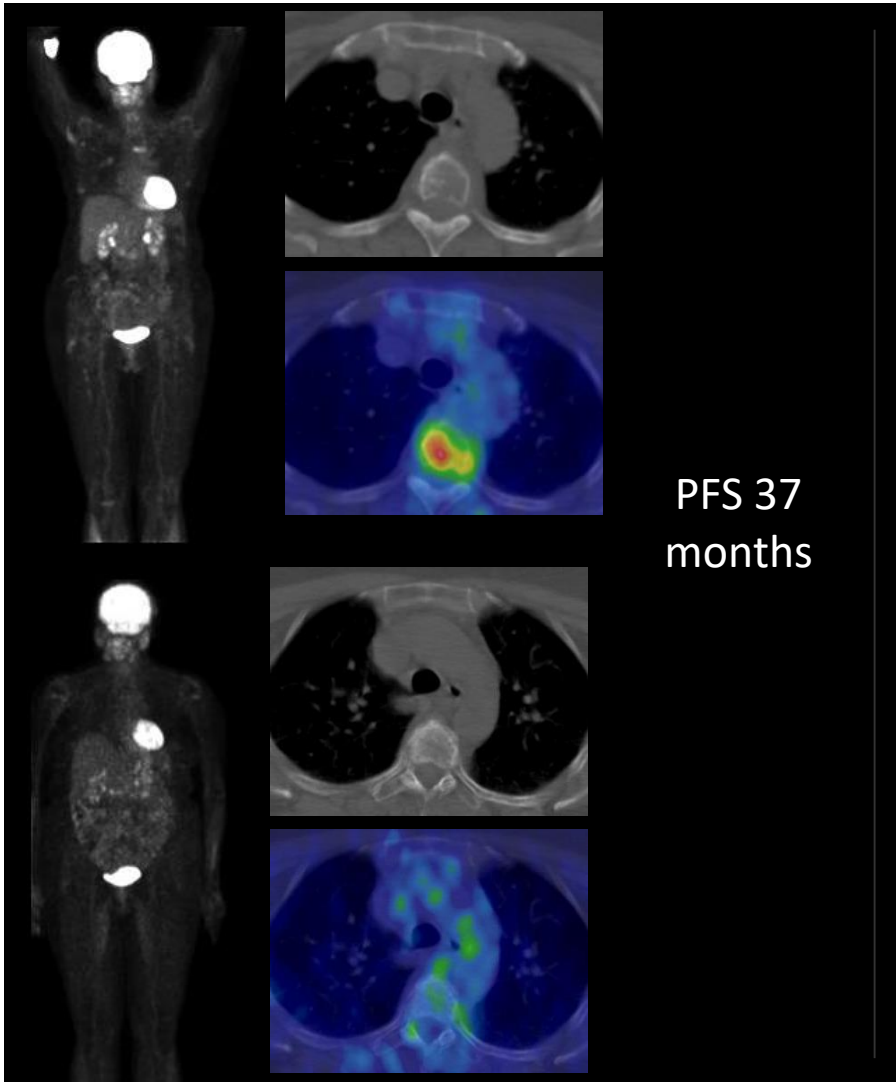


Interesting in non secretory MM

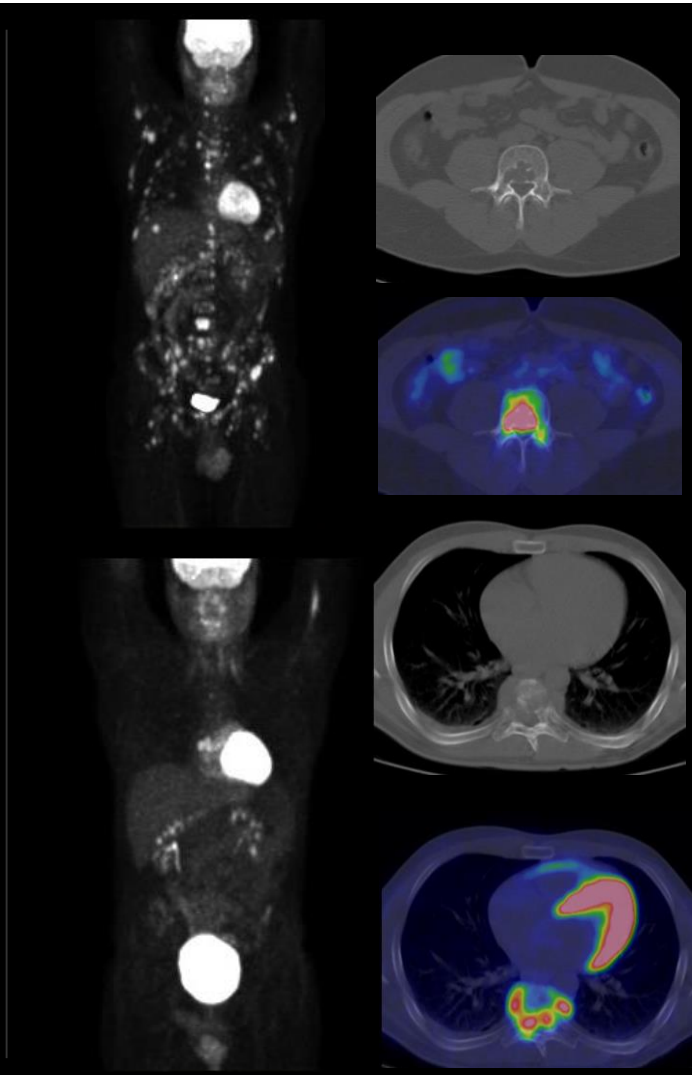
Zamagni et al. Clin Cancer Res; 21(19) October 1, 2015

PROGNOSTIC VALUE OF PET/CT in CR: MRD

SYMPTOMATIC



PFS 37 months

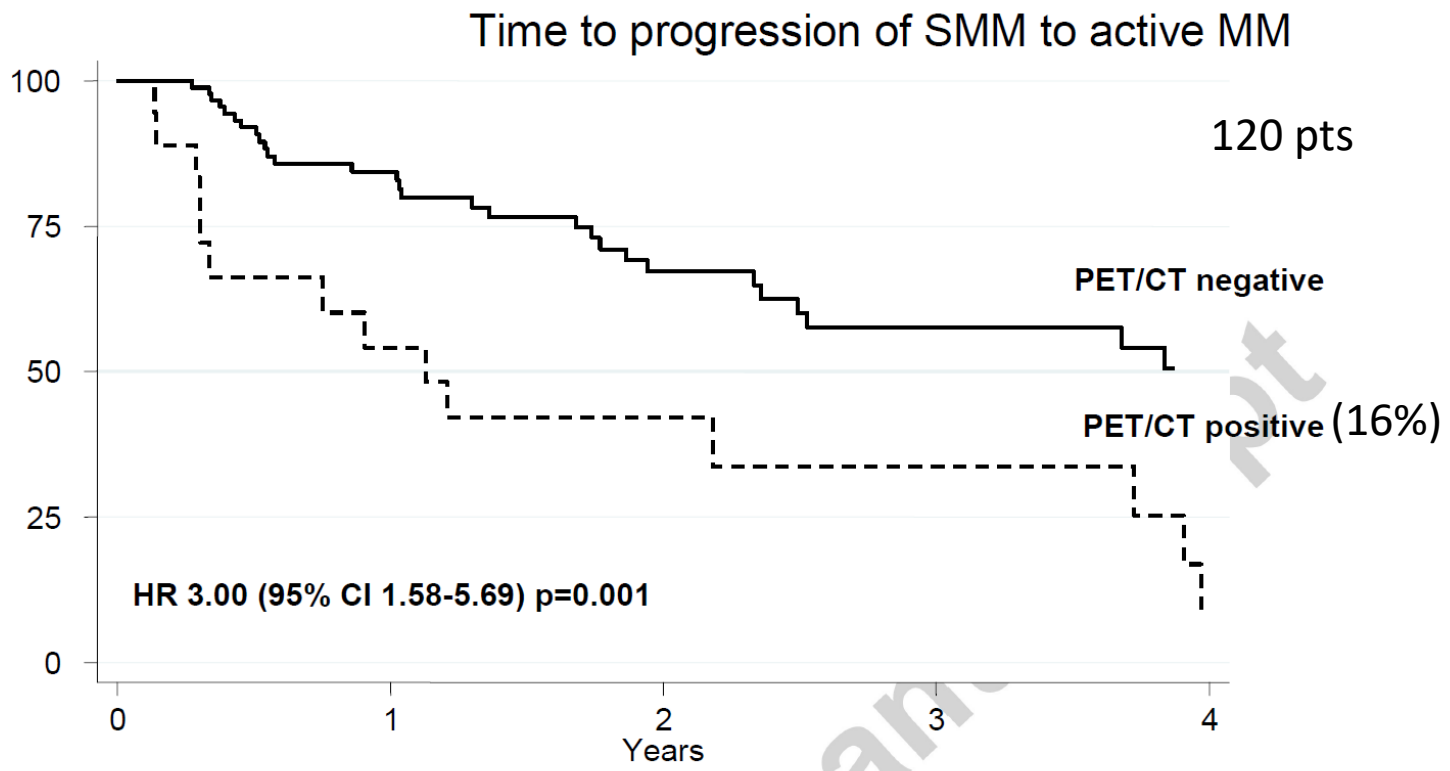


PFS 3 months

PROGNOSTIC VALUE OF PET/CT in smouldering MM

SMOULDERING

1. Focal utake 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



Leukemia. 2016 Feb;30(2):417-22

PROGNOSTIC VALUE OF PET/CT in smouldering MM

SMOULDERING

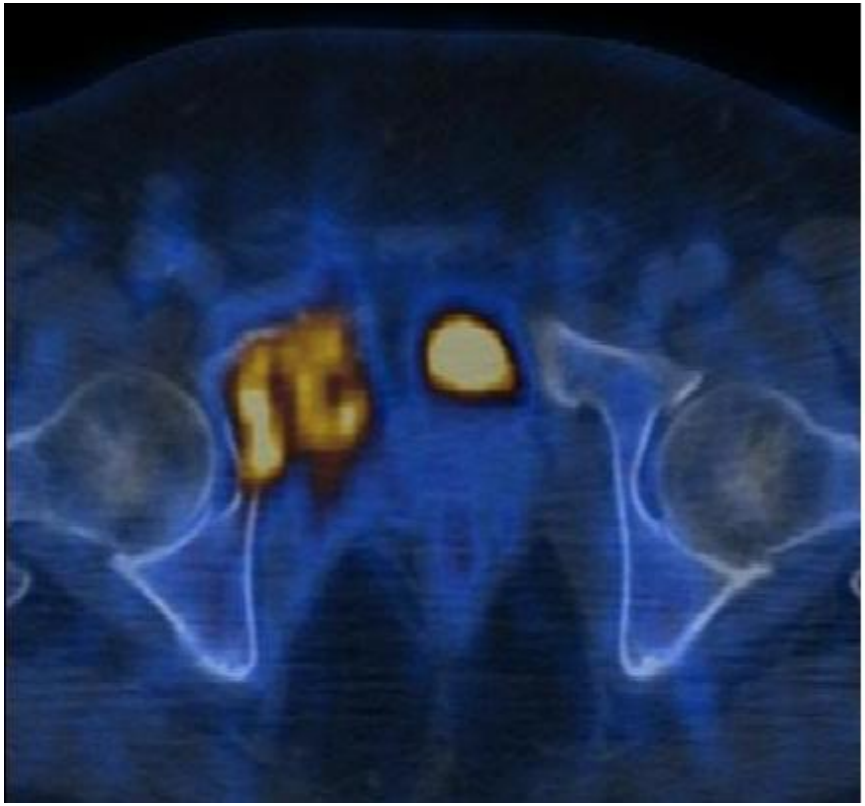
Univariate analysis of baseline variables adversely affecting time to progression of SMM into active MM (TTP)

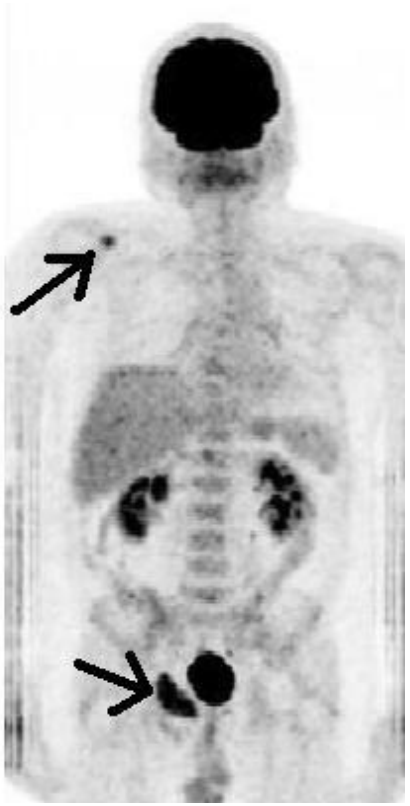
TTP			
Variables	HR	95% C.I.	
BMPC > 60%	3.7	1.5	9.1
MC	1.00	1.0	1.0
PET/CT pos	3.0	1.6	5.7
MRI pos	2.3	1.1	4.6
MRI diffuse	2.8	1.2	6.5

BMPC bone marrow plasma cells, MC M component, pos positive, HR hazard ratio, CI confidence interval

PET/CT in PLASMACYTOMA

PLASMACYTOMA





PET/CT in PLASMACYTOMA

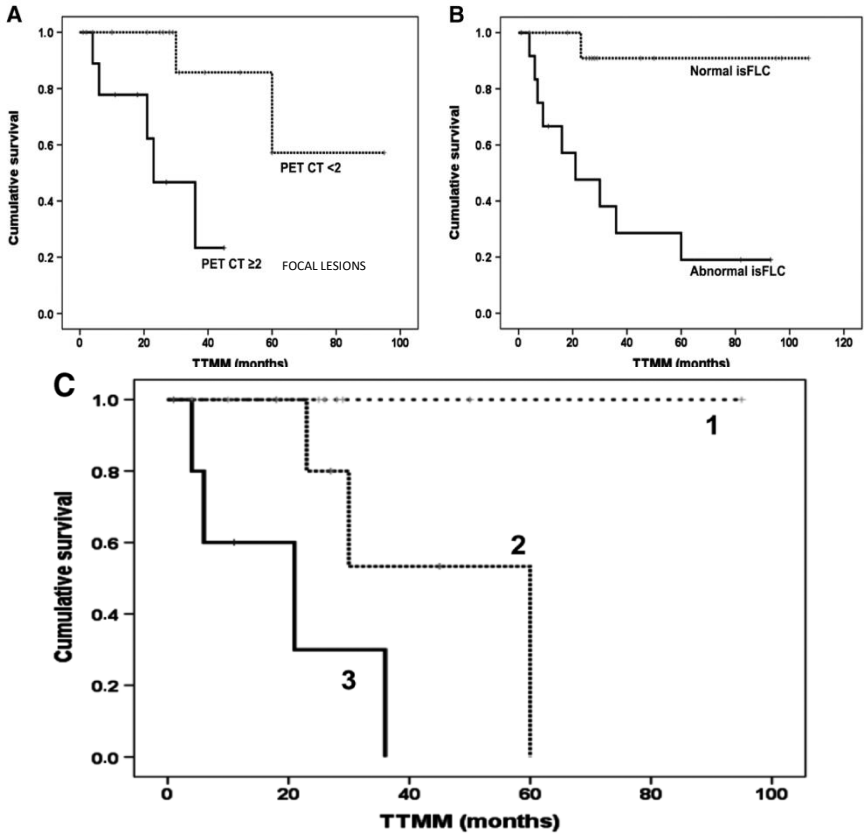
PLASMACYTOMA

Imaging, Diagnosis, Prognosis

Fouquet C.: Clin Cancer Res 2014; 20(12); 3254–60

Clinical Cancer Research

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



Time to multiple myeloma transformation

43 patients

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

serum-free light chain

PET/CT in PLASMACYTOMA

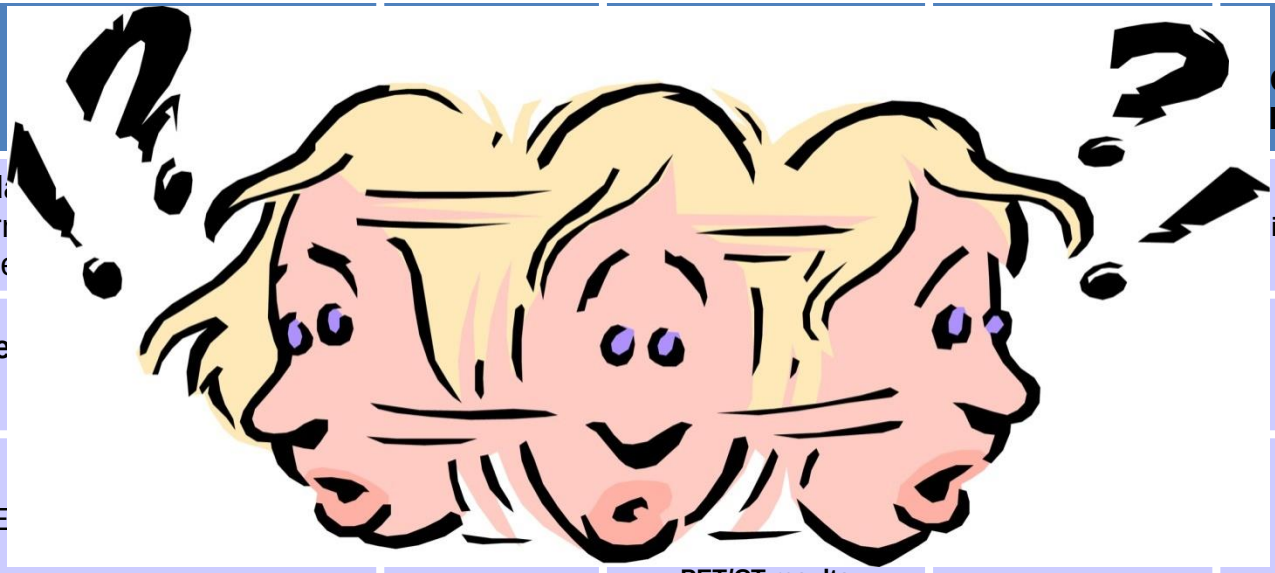
PLASMACYTOMA

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



				Prognostic Quantitative ET evaluation
Hazned Eur jour medicine				**ighest SUV max**
Falcone Recenti				**Not realized**
Elliott E				**Not realized**
		PET/CT results		
Bartel, Blood, 2009	**239**	**Visual** **Focal uptake higher than background**	**NO**	**Highest SUV max**
Derlin, Eur Radiol. 2013	**31**	**Visual** **Focal uptake higher than background**	**YES** uptake corresponding to CT abnormalities not attributable to benign bone conditions	**Highest SUV max**
Fonti, J Nucl Med, 2012	**47**	**Quantitative** **Focal uptake with SUV max**> 2,5	**YES** uptake corresponding to CT abnormalities not attributable to benign bone conditions	**MTV**
Zamagni , Blood, 2011	**192**	**Visual and/or Quantitative** **Depending on the size of the lesion**	**NO**	**Highest SUV max**

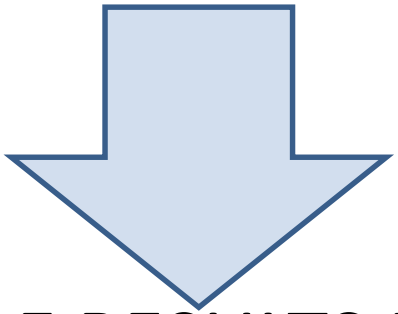
IN LITERATURE THERE ARE SEVERAL INTERPRETATION CRITERIA APPLIED BY VARIOUS RESERCH GROUP.

-SEMI-QUANTITATIVE

- VISUAL

- SEMIQUATITAVE + VISUAL

- DIFFERENT ARBITRARY CUT OFFs



VERY VARIABLE RESULTS ESPECIALLY IN BORDERLINE CASES

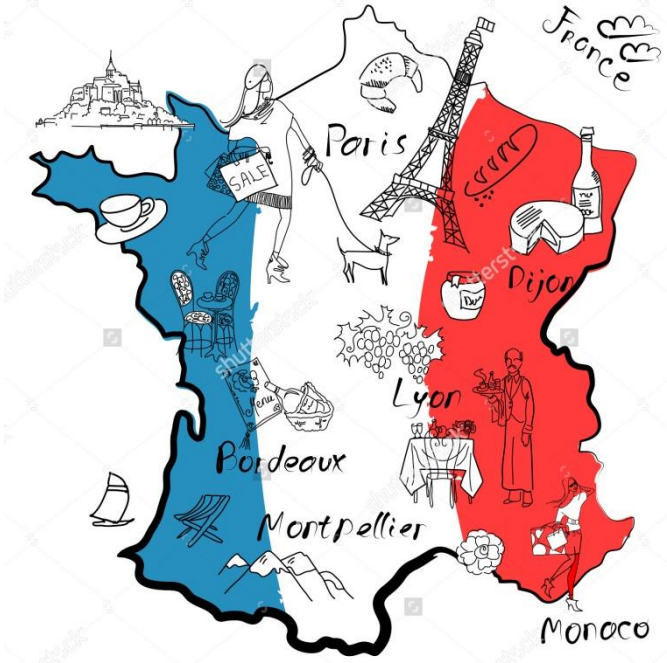
ALL THE CRITERIA ARE IN ACCORDANCE IN CASE OF:

- 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

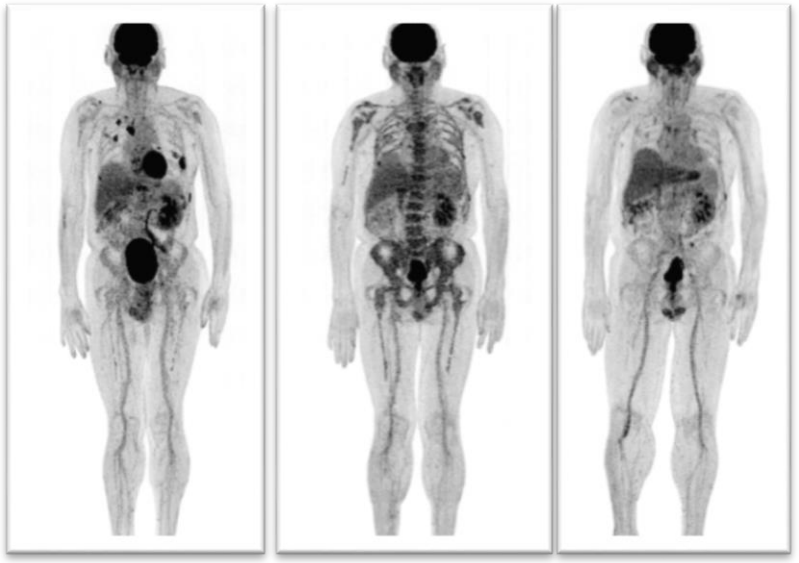
DIFFERENT CRITERIA PROVIDE A POS OR NEG RESULT IN BORDERLINE CASES

- 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


France
Paris
SALE
Dijon
Lyon
Bordeaux
Montpellier
Monoco


Italy



French Criteria

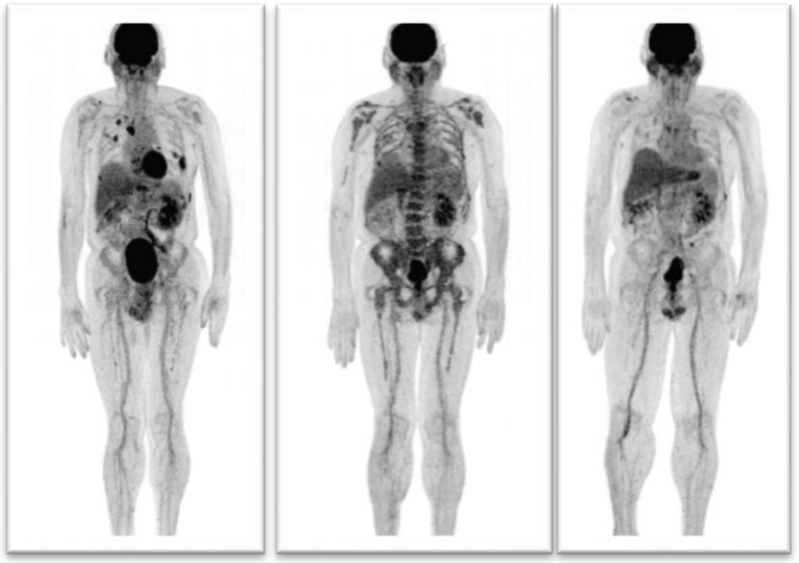
Francoise Kraeber-Bodéré, Caroline Bodet-Milin, Philippe Moreau

CENTRE HOSPITALIER UNIVERSITAIRE DE NANTES

CRCNA

iron labex

DHU ONCO-GREFFE



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

WHAT'S THE NEXT STEP?

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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