

6th International Workshop on PET in Lymphoma
Palais de l'Europe. Menton, France
September 20 -21, 2016



Organizing committee: M. Meignan (France), A. Gallamini (Italy), C. Haioun (France), S. Barrington (UK), B. Coiffier (France), E. Itti (France), S. Luminari (Italy), A. Versari (Italy), U. Dührsen (Germany), E. Zucca (Switzerland), L. Rigacci (Italy).

Summary: PET/CT IN MULTIPLE MYELOMA

Cristina Nanni, Annibale
Versari, Elena Zamagni,
Francoise Bodéré, Caroline
Bodet-Milin, Philippe Moreau,
Karim Belhadj, Laurent
Garderet, Alain Rahmouni,
Michel Meignan.



FDG-PET/CT in MM: WHY?

A LONG STORY: BACKGROUND

VERY CONCORDANT RESULTS ON THE VALUE
FDG PET/CT WERE FOUND BY THREE
INDEPENDENT GROUPS (LITTLE ROCK,
BOLOGNA, NANTES)

WHAT DO WE KNOW SO FAR ON FDG PET/CT

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
3. DETECTS EXTRAMEDULLARY DISEASE
4. PROVIDES METABOLIC **AND** MORPHOLOGICAL CHARACTERIZATION OF LESIONS (LDCT CAN REPLACE WBXR FOR CRAB CRITERIA)
Regelink J. et al., BJH 2013
5. IS SAFE, FAST AND HAS NO ABSOLUTE CONTRAINDICATIONS
6. SUB OPTIMAL FOR BONE MARROW DIFFUSE INFILTRATION

PROGNOSIS: AT BASELINE

blood

2009 114: 2068-2076
Prepublished online May 14, 2009;
doi:10.1182/blood-2009-03-213280

F18-fluorodeoxyglucose positron emission tomography in the context of other imaging techniques and prognostic factors in multiple myeloma

Twyla B. Bartel, Jeff Haessler, Tracy L. Y. Brown, John D. Shaughnessy, Jr, Frits van Rhee, Elias Anaissie, Terri Alpe, Edgardo Angtuaco, Ronald Walker, Joshua Epstein, John Crowley and Bart Barlogie



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2011 118: 5989-5995
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online September 6, 2011

Prognostic relevance of 18-F FDG PET/CT in newly diagnosed multiple myeloma patients treated with up-front autologous transplantation

Elena Zamagni, Francesca Patriarca, Cristina Nanni, Beatrice Zannetti, Emanuela Englaro, Annalisa Pezzi, Paola Tacchetti, Silvia Buttignol, Giulia Perrone, Annamaria Brioli, Lucia Pantani, Carolina Terragna, Francesca Carobolante, Michele Baccarani, Renato Fanin, Stefano Fanti and Michele Cavo

Prognosis value of PET vs MRI

- **PET number of FL > 3** at diagnosis were predictive on PFS and OS
- **IRM number of FL > 7** lésions were only predictive on **PFS**

At baseline Prognosis value of PET

- **Number of FL > 3**, SUV max > 4.2, and EMD were predictive on PFS and OS

FDG-PET/CT in MM

PROGNOSIS: DURING AND AFTER TREATMENT

blood

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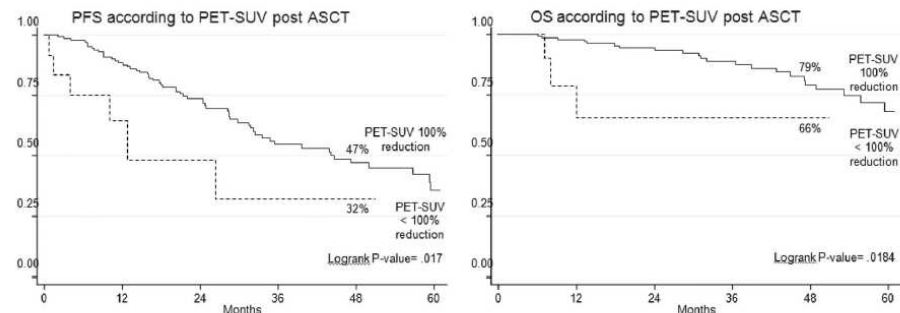
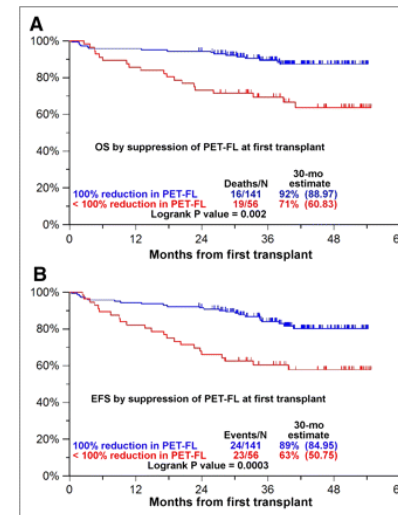
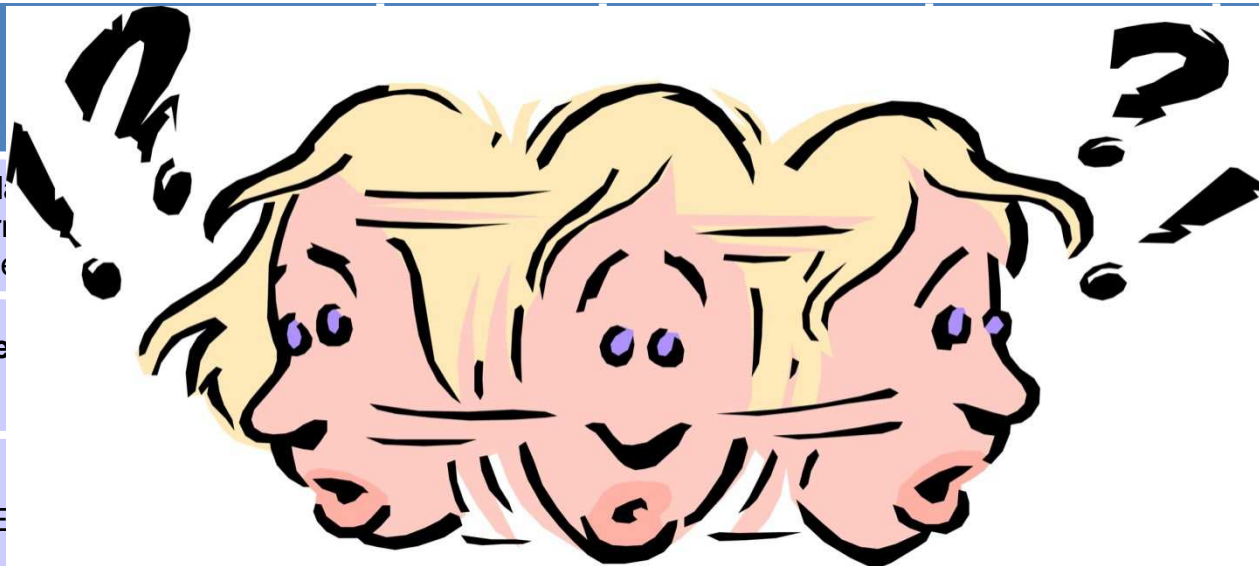


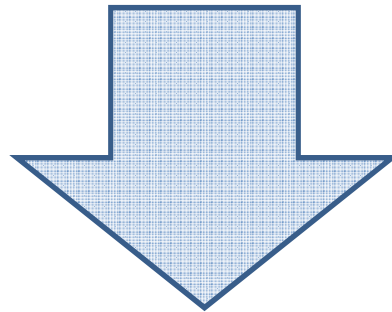
Figure 3. Outcome according to post-ASCT PET/CT.

				Prognostic Quantitative ET evaluation
Haznedar Eur journal medicine				Highest SUV max
Falcone Recenti				Not realized
Elliott E				Not realized
		<u>PET/CT results</u>		
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 <u>corresponding to CT abnormalities not attributable to benign bone conditions</u>	Highest SUV max
Fonti, J Nucl Med, 2012	47	Quantitative Focal uptake with SUV max > 2,5	YES uptake <u>corresponding to CT abnormalities not attributable to benign bone conditions</u>	MTV
Zamagni , Blood, 2011	192	Visual and/or Quantitative Depending on the size of the lesion	NO	Highest SUV max

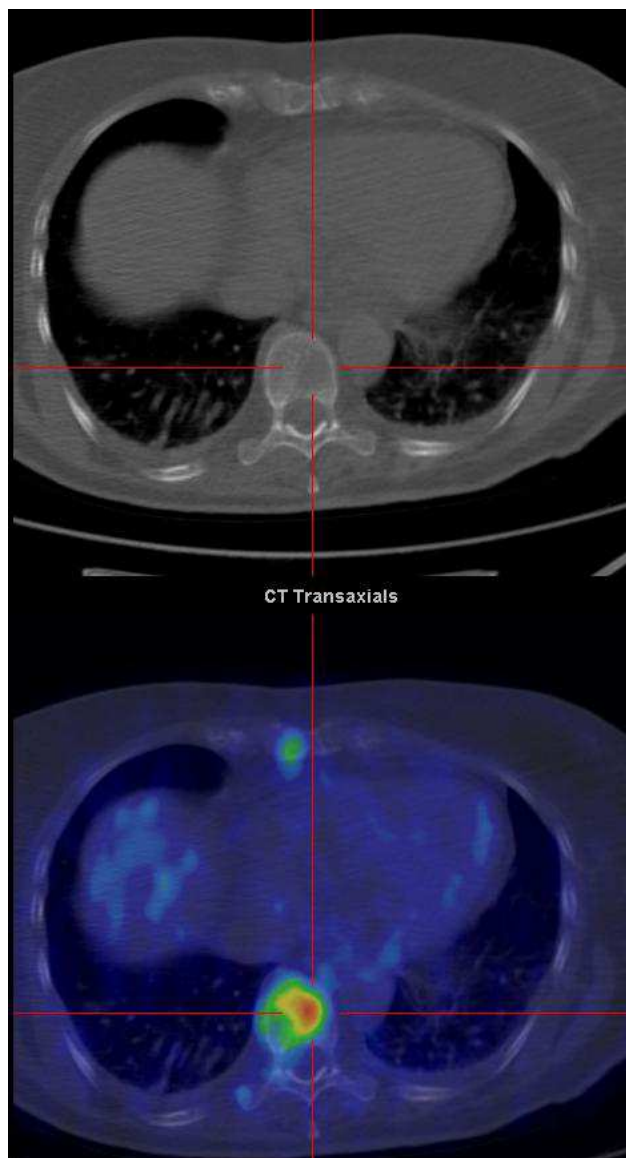


IN LITERATURE THERE ARE SEVERAL
INTERPRETATION CRITERIA APPLIED BY VARIOUS
RESEARCH GROUP.

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

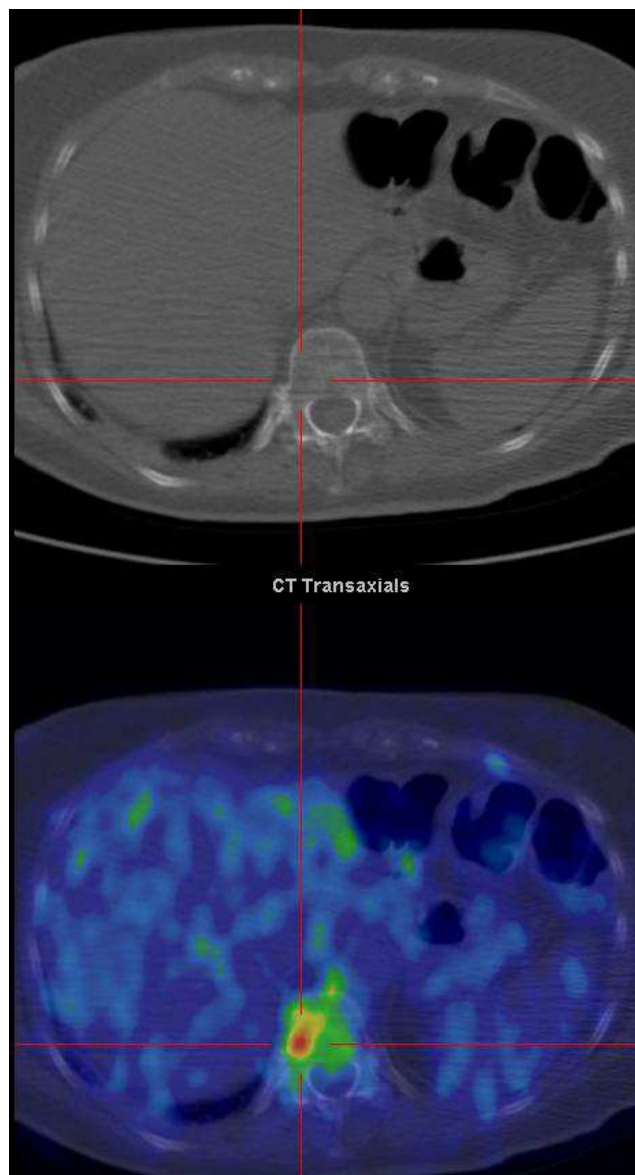


VERY VARIABLE RESULTS ESPECIALLY IN
BORDERLINE CASES



- Staging
- Focal uptake
- > 5mm
- Cold background
- High SUV max (9.3)
- Site consistent with MM lesion
- Clear lysis at CT images

***THIS IS MM
ACCORDING TO ALL
THE PROPOSED
CRITERIA***



- Focal uptake
- > 5mm
- Relatively cold background
- High SUV max (6.9)
- Site consistent with MM lesion
- No lysis at CT images, normal bone

***THIS IS NOT THE
CASE:
DISAGREEMENT!***

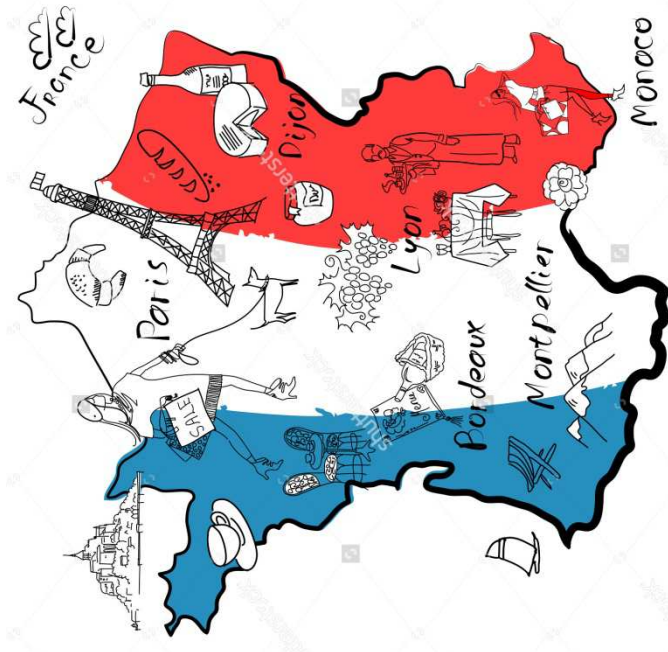
ALL THE CRITERIA ARE IN ACCORDANCE IN CASE OF:

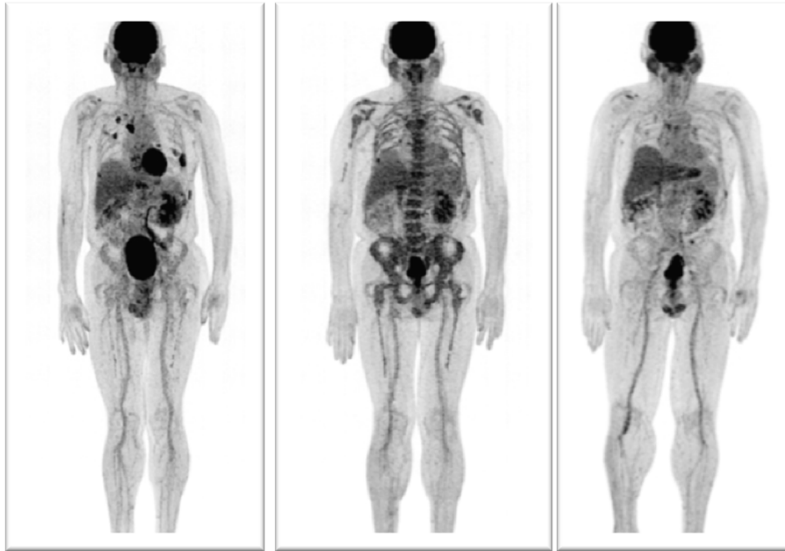
- Focal lesions > 5mm in cold background
- Litic lesions (inequivocal identification of the disease site)
- No increased background (no bone marrow activation)
- No recent vertebral fractures or collapse

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

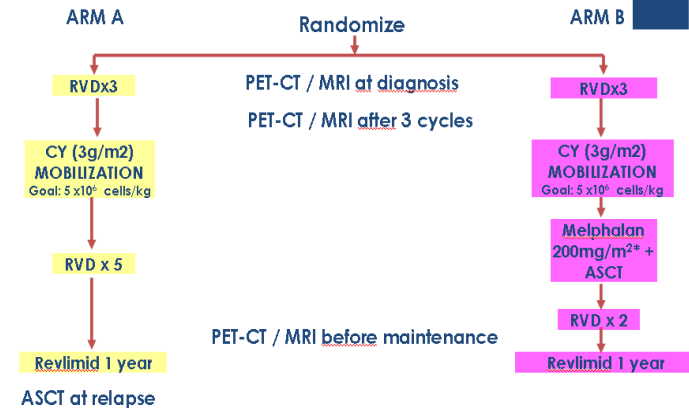


Criteria used for French Imajem study interpretation (2011-2014)

At diagnosis

PET interpretation:

- **FL**: uptake > regional background (with or without osteolytic lesion on CT)
- **Diffuse bone marrow involvement**: homogeneous uptake \geq liver background or heterogeneous uptake (regardless the intensity)
- **Extra-medullary lesion**



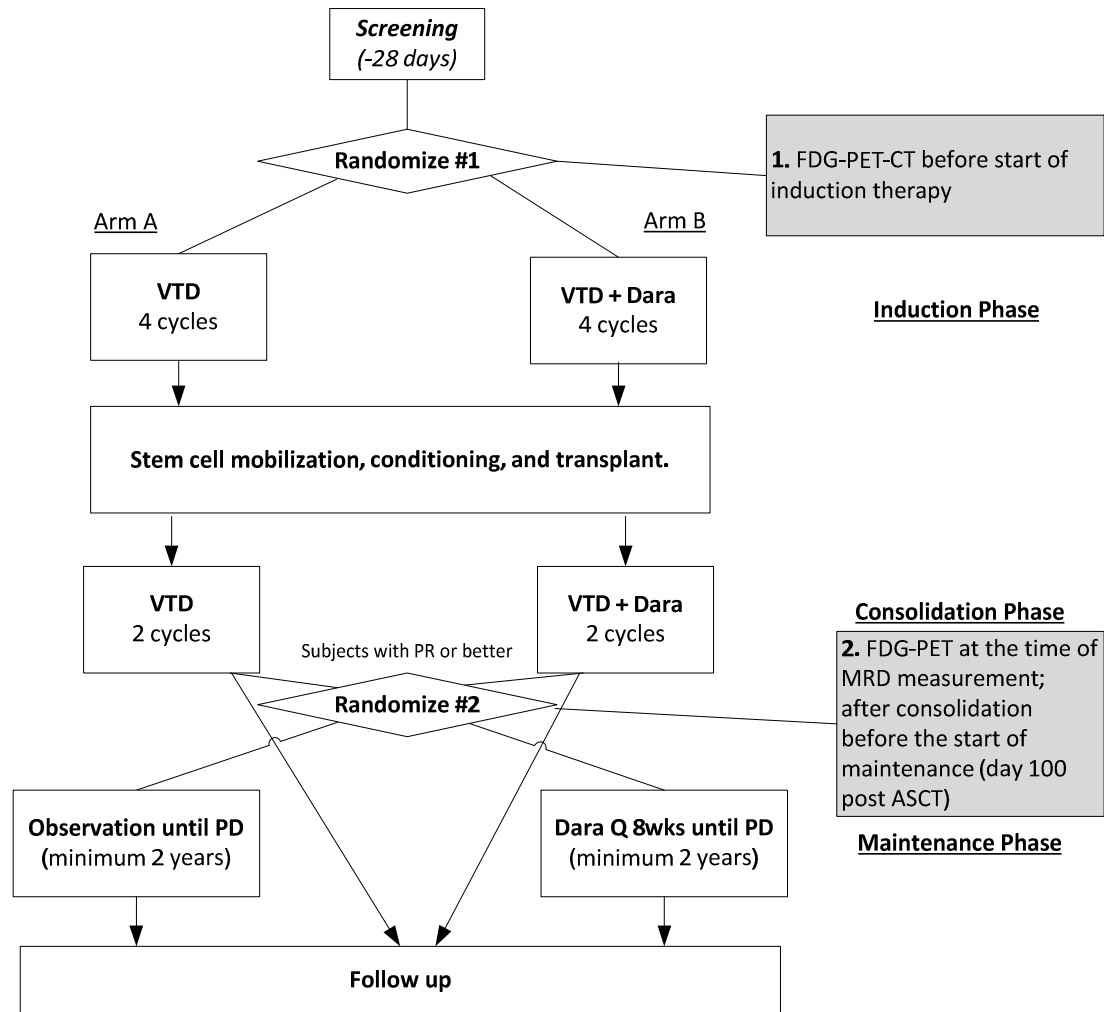
For therapeutic evaluation

FL: positive when residual uptake > liver background ~ level 4 on the “lymphoma Deauville scale”

Diffuse Bone marrow involvement: positive when “L4-L5” uptake > liver background (if positive at diagnosis)



Reactionnal diffuse bone marrow uptake and uptake in post-fracture (rib) or sclerotic bone reconstruction area



CASSIOPET study:

Assessment of the prognostic value of FDG PET-CT at diagnosis and follow up in patients treated in the Cassiopeia study

French criteria proposed for CassioPET study



At diagnosis

Bone Marrow uptake (BM): Evaluation of the bone marrow diffuse uptake, regardless focal lesions.

BM	
Visual analysis	SUVmax value (on L4-L5)
<input type="checkbox"/> 0 : no uptake
<input type="checkbox"/> 1: \leq mediastinal bloodpool	
<input type="checkbox"/> 2: $>$ mediastinal bloodpool \leq liver activity	
<input type="checkbox"/> 3 : $>$ liver activity	
<input type="checkbox"/> 4 : $>>$ liver activity	

Focal Lesion (FL): Focal increased FDG uptake in bone marrow as compared to surrounding bone marrow activity. An osteolytic lesion on CT is not a prerequisite. If osteolysis is not present, the focal lesion should be detectable at least in two adjacent slices. Excluded lesions: FDG uptake related to fractures; FDG uptake associated with joint surface.

FL	
Maximal or hottest SUVmax value	
Total number of FLs	
Number of FLs with uptake $>$ liver activity	
Number of FLs on peripheral skeleton	

For number of FLs: the response must be 0, 1, 2, 3, 4, 5-10 or >10 .

Paramedullary disease (PMD): Presence of a bone lesion involving surrounding soft tissues with bone cortical interruption

PMD	
Maximal or hottest SUVmax value	
Total number of lesions	
Number of lesions with uptake > liver activity	

Extramedullary disease (EMD): Soft tissue or nodal mass, not directly adjacent to MM bone localization

EMD	
Maximal or hottest SUVmax value	
Total number of lesions	
Number of lesions with uptake > liver activity	
Location:	
- Liver	
- Muscle	
- Spleen	
- Skin	
- Pleura	
- Other	

Proposed PET criteria for response monitoring

BM (only if > liver activity at baseline)	
Visual analysis	SUVmax value
<input type="checkbox"/> residual uptake ≤ liver activity	
<input type="checkbox"/> residual uptake > liver activity

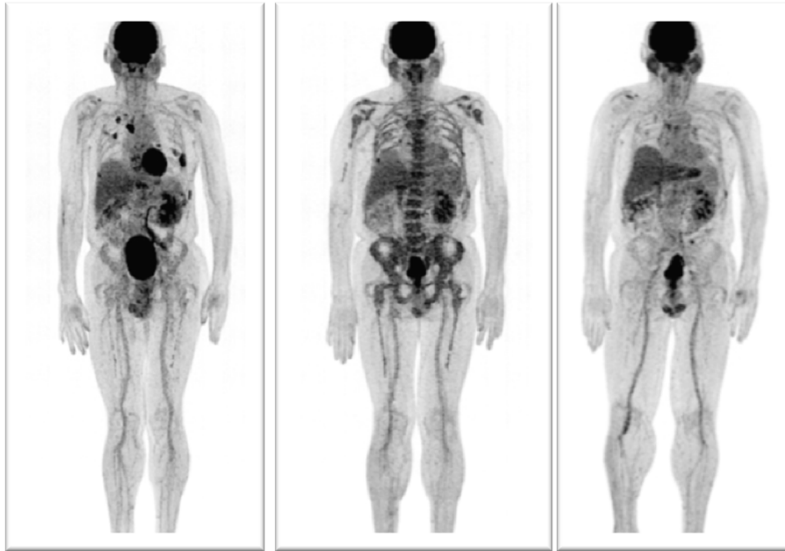
<p>FL (Excluded lesions: FDG uptake related to fractures; FDG uptake related to bone reconstruction (ie uptake associated with a previously lytic CT lesion with development of a sclerotic rim with FDG uptake corresponding to the sclerotic change); FDG uptake associated with joint surface)</p>	
Visual analysis	SUVmax value
<input type="checkbox"/> residual uptake ≤ liver activity	
<input type="checkbox"/> residual uptake > liver activity
Total number of focal lesions:	
New lesion : <input type="checkbox"/> Yes <input type="checkbox"/> No	

PMD	
Visual analysis	SUVmax value
<input type="checkbox"/> residual uptake ≤ liver activity	
<input type="checkbox"/> residual uptake > liver activity
Total number of lesions:	
New lesion : <input type="checkbox"/> Yes <input type="checkbox"/> No	

EMD	
Visual analysis	SUVmax value
<input type="checkbox"/> residual uptake ≤ liver activity	
<input type="checkbox"/> residual uptake > liver activity
Total Number of lesions:	
New lesion : <input type="checkbox"/> Yes <input type="checkbox"/> No	

Assessment of responses:

- FDG PET Complete metabolic response (CMR):
 - Uptake \leq liver activity in BM/FL/EMD/PMD
- FDG PET Partial metabolic response (PMR):
 - Decrease of number and/or activity of FL/EMD/PMD but persistence of lesion with uptake $>$ liver activity
- FDG PET Progression (PD):
 - New lesions (FL/EMD/PMD) compared to baseline FDG PET
 - Increase of FDG uptake in existing lesions (Excluding increasing FDG uptake related to fractures or related to bone reconstruction.*



Italian Criteria

Cristina Nanni, Elena Zamagni,
Annibale Versari, Stephane Chauvie,
Andrea Gallamini

ITALIAN APPROACH

PRELIMINARY COMMENTS

UNDEFINED PROGOSTIC VALUE OF MILD FOCAL FDG UPTAKE
UNDEFINED VALUE OF THE LESION SITE
SUV MAX IS NOT EXACTLY REPRODUCIBLE
PURELY VISUAL POSITIVITY DEPENDS ON BACKGROUND UPTAKE (VARIABLE SENS)

DESCRIPTIVE CRITERIA BASED ON DEUVILLE SCALE
MULTICENTER TRIAL WITH CENTRAL REVISION
GIMEMA
3 REVIEWERS
102 PTS REVISED (>300 PET/CT SCANS)
AGREEMENT ANALYSIS

POSITIVITY THRESHOLD A POSTERIORI BASED ON PROGNOSIS

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)

1. Descriptive
2. Cut-off to be defined a posteriori
3. To be simplified according to prognostic evaluation of parameters

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)	
Lytic (L)		x = 4 (>10 lesions)	
		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

IMPETUS Criteria: example

BM3, F2, Extra Sp2
(5), L, EM EN (5),

- 1 No uptake at all
- 2 \leq mediastinal blood pool uptake (SUV_{max})
- 3 $>$ mediastinal blood pool uptake, \leq liver uptake
- 4 $>$ liver uptake +10 %
- 5 \gg liver uptake (twice)

Focal bone lesions (F):

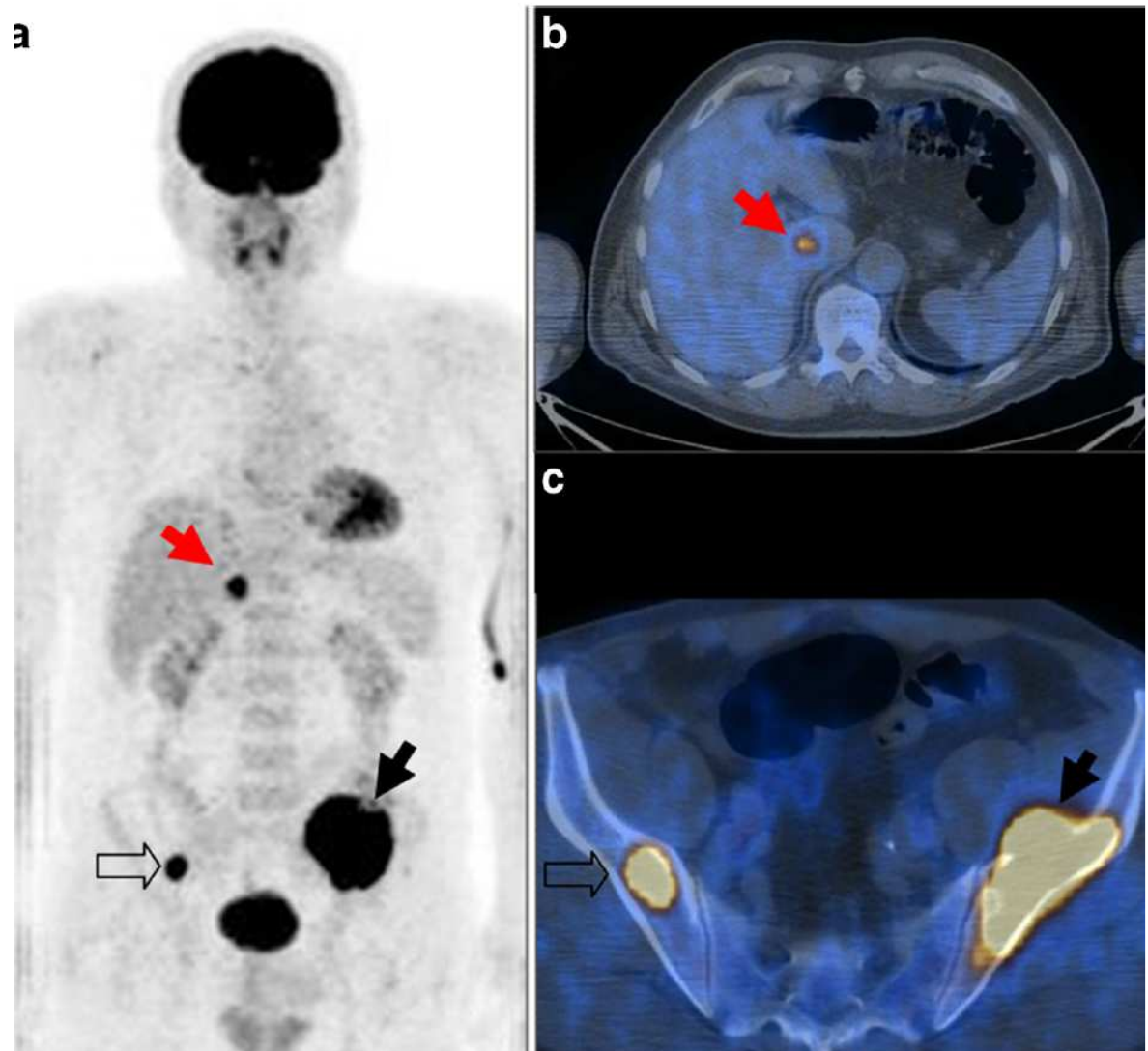
Lesion number group (x):

- x = 1: no lesions
- x = 2: 1 to 3 lesions
- x = 3: 4 to 10 lesions
- x = 4: $>$ 10 lesions

S: skull

Sp: spine

ExtraSp: all the rest



AGREEMENT

all reviewers, score 1-5

Nice concordance among the reviewers for all features and in all the disease phases. Agreement increased significantly after the training phase.

All*	BM	FS	EM	Fx	Lx	Sk	Sp	ExSp	Fr
Staging	0.50 (0.39-0.64)	0.61 (0.50-0.74)	0.05 (-0.04-0.14)	0.63 (0.52-0.76)	0.55 (0.43-0.69)	0.16 (-0.12-0.37)	0.58 (0.46-0.72)	0.64 (0.52-0.77)	0.14 (-0.06-0.31)
Post Ind	0.31 (0.17-0.45)	0.52 (0.39-0.68)	0.34 (0.19-0.55)	0.53 (0.36-0.74)	0.40 (0.23-0.62)	-0.01 (-1.01-0.02)	0.51 (0.37-0.66)	0.64 (0.53-0.80)	0.28 (0.08-0.48)
EOT	0.27 (0.13-0.40)	0.58 (0.45-0.73)	0.43 (0.17-0.73)	0.62 (0.50-0.79)	0.26 (0.05-0.46)	1.00 ()	0.36 (0.19-0.56)	0.69 (0.57-0.85)	0.40 (0.09-0.81)

* α



IMPeTuS vs PROGNOSIS

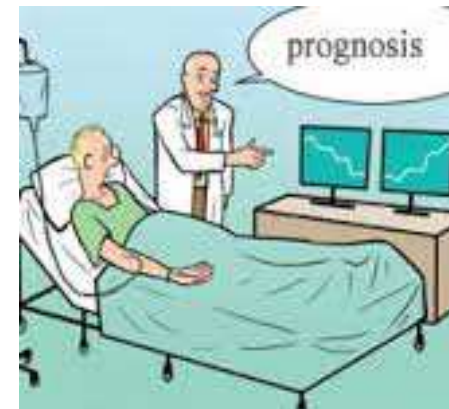
Definition of positivity cut-offs

Which metabolic features of MM are related to prognosis and are worthwhile to be reported? (i.d. focal SUV max 2.5???)

Positivity cut-offs on Deauville Scale

What change in FDG uptake is significant enough to call a response to therapy or progression?

What is a PET complete remission?



Abstract #93346 (ASH 2016)

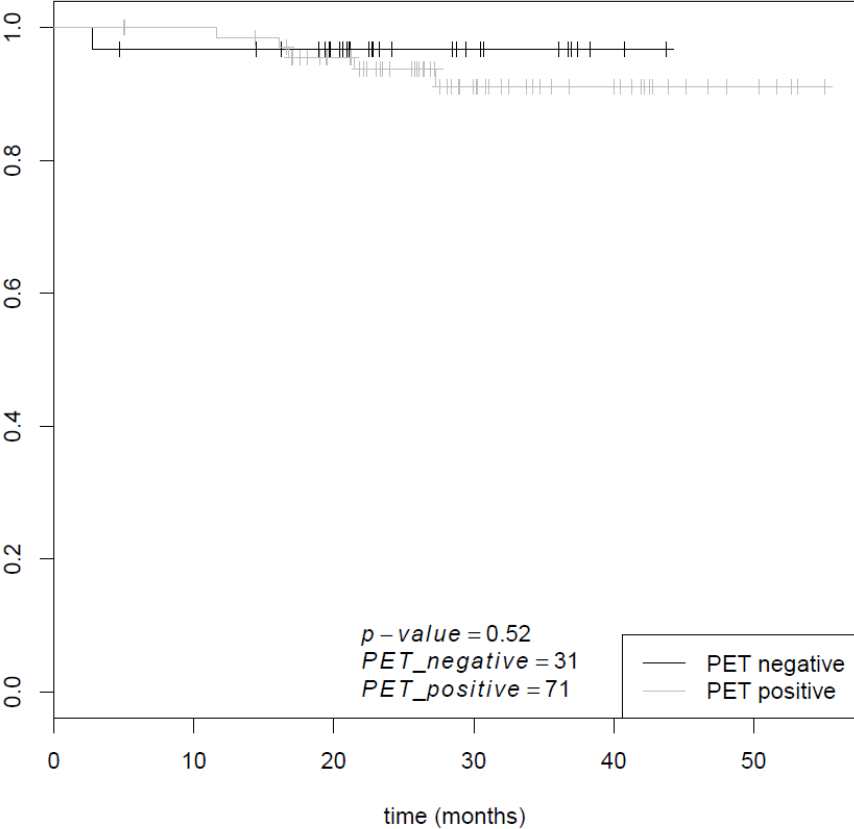
Prospective Evaluation of 18F-FDG PET/CT As Predictor of Prognosis in Newly Diagnosed Transplant Eligible Multiple Myeloma (MM) Patients: Results from the Imaging Sub-Study of the EMN02/HO95 MM Randomized Phase III Trial

	BM>2	Fx	FS	Sk	Sp	ExSp	Lx	Fr	EM
Staging	84%	78%	77%	0%	0%	6%	61%	0%	0%
Post Induction	66%	59%	60%	0%	0%	0%	39%	0%	2%
EOT	45%	34%	34%	0%	0%	1%	18%	0%	3%

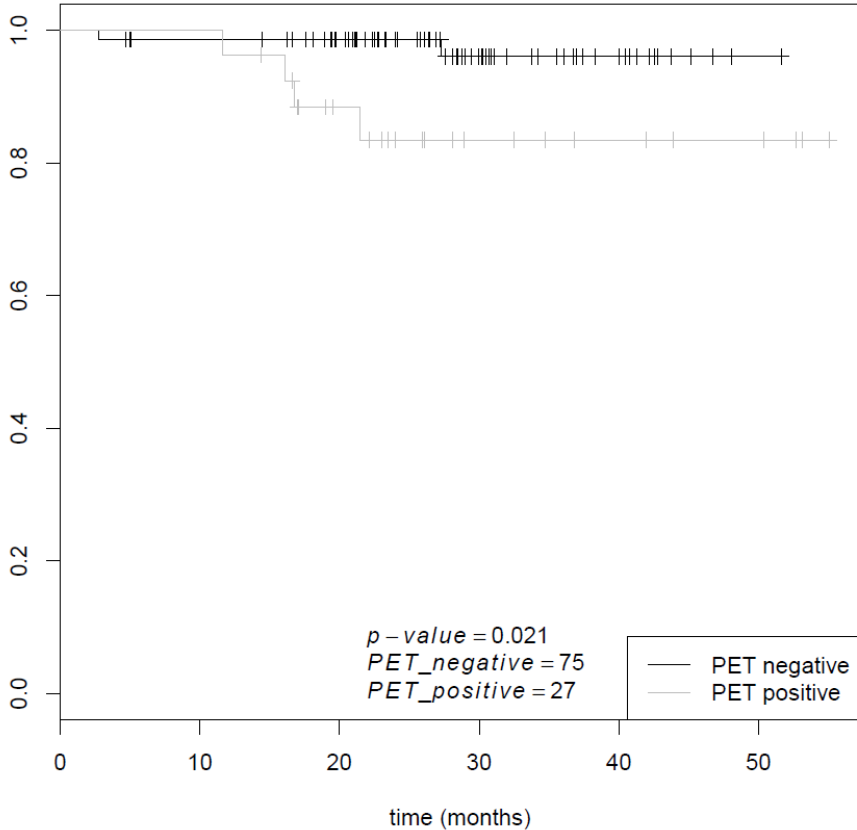
- Prognostic correlation for EOT PET/CT for PFS and OS

EXAMPLE OS: THRESHOLD 2 OF AT LEAST 1 PARAMETER, EoT, WITH AND WITHOUT BM

+BM

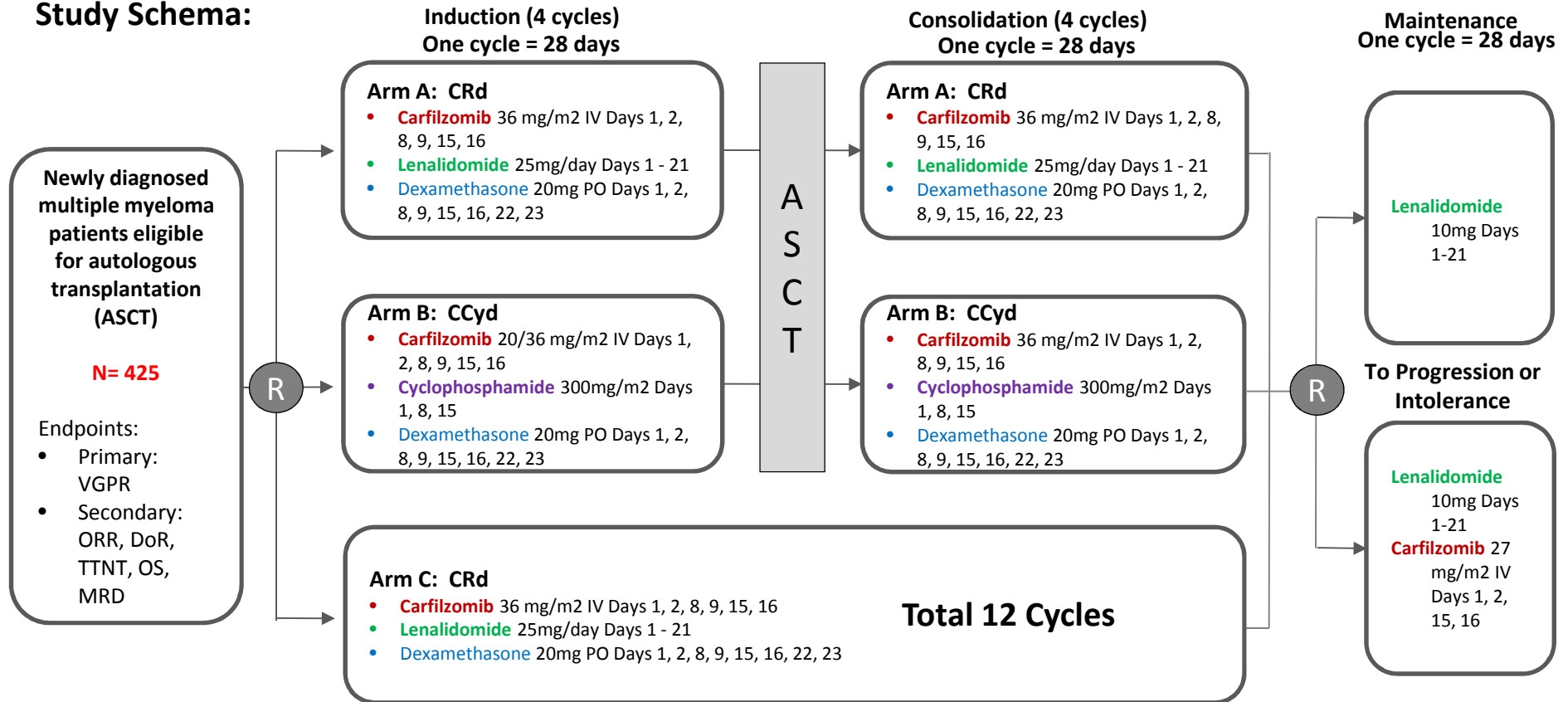


-BM



FORTE study design

Study Schema:



PET/CT: pre and post induction

PET/CT: pre maintenance

WHAT'S THE NEXT STEP?

(THANKS TO THE EXPERTS FOR SUGGESTIONS...😊)

ITALIANS: CUT-OFFs DEFINITION

SIMPLIFIED VERSION OF IMPetUs with proved prognostic meaning

ITALIANS and FRENCH: cross validation of French Criteria into Italian pt population and of Italian Criteria into French pt population

ITALIANS and FRENCH: merge pt population and provide prognostic factors derived by FDG PET/CT based on shared criteria (simplified IMPetUS + CassioPET)

1 - Definition of Focal Lesions at diagnosis > regional background, > liver, > mediastinum, SUV max of the hottest value

2 - Definition of high bone marrow uptake at diagnosis Homogeneous > liver uptake, Homogeneous > mediastinum, Homogeneous or Heterogeneous

3 - Definition of CR Focal lesion : 2 vs 3 vs 4 (+ number of FL at each score) Bone marrow : 2 vs 3 vs 4
EMD : yes / no ParaMD : yes / no, Global score

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.

WE WISH THE MYELOMA GROUPS A
SUCCESSFUL WORK

THANK YOU