Highlights from IMW 2021

1-2 febbraio 2022
Bologna
Royal Hotel Carlton

Work-up diagnostico e criteri di risposta alla terapia

Tecniche di imaging

Elena Zamagni

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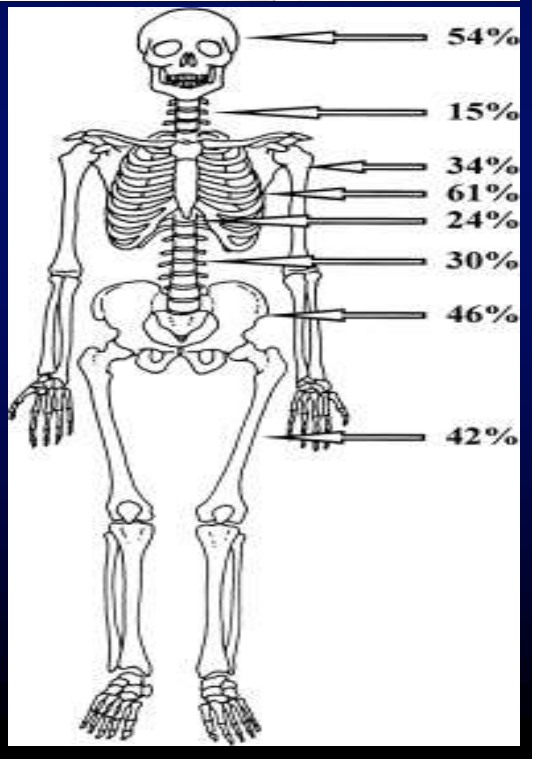
IRCCS-Azienda Ospedaliero-Universitaria S. Orsola-Malpighi

Employment	
Consultancy	
Equity/Ownership	
Honoraria	Janssen,BMS, Takeda, Sanofi, Amgen, GSK, Roche, Pfizer
Research Funding	
Patents/Royalties	
Speakers Bureau/Board of Directors	
Advisory Board	Janssen, BMS, Sanofi, GSK, Amgen, Pfizer, Roche

ROLE OF IMAGING IN PLASMA CELL DISCRASIAS

- **Early phases (MGUS, MM):**
  - exclude the presence of bone disease
  - predict the risk of progression

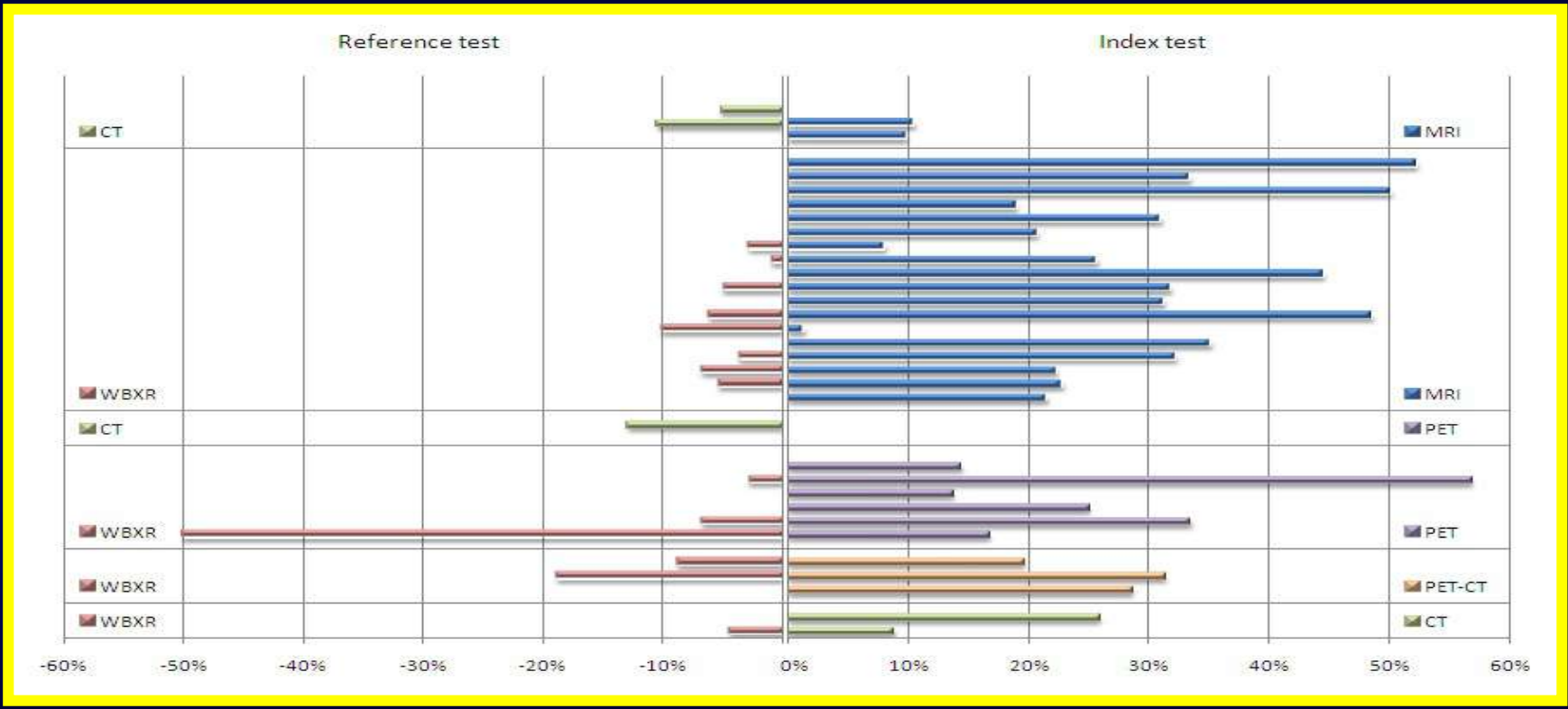
- **Multiple myeloma:**
  - **Assess bone disease**, as sign of organ damage and need to start treatment
  - **Assess sites of extra-medullary disease** (total body techniques)
  - **Assess bone stability:** correct identification of sites of bone disease at risk of complications (fractures, neurological complications)
  - **Assess tumor burden** (prognosis)
  - **Assess response to therapy:** correct follow up of the patients after treatment, in particular in non secretory MM



Zamagni E. et al, BJH 2012
Zamagni E et al, Blood 2018

SYSTEMATIC REVIEW

NEW IMAGING TECHNIQUES HAD A HIGHER DETECTION RATE AS COMPARED TO WBXR

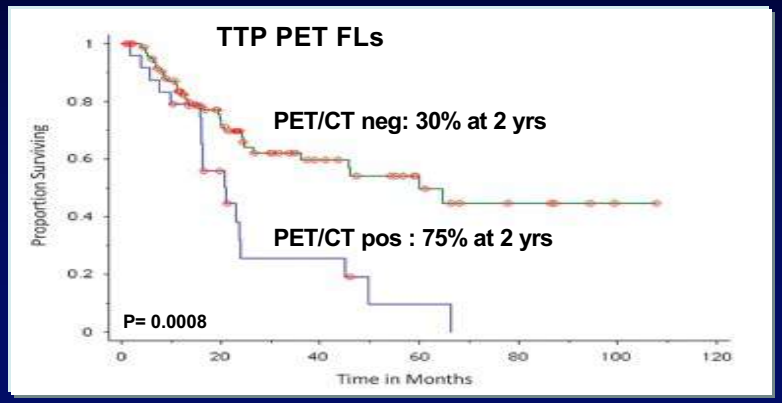


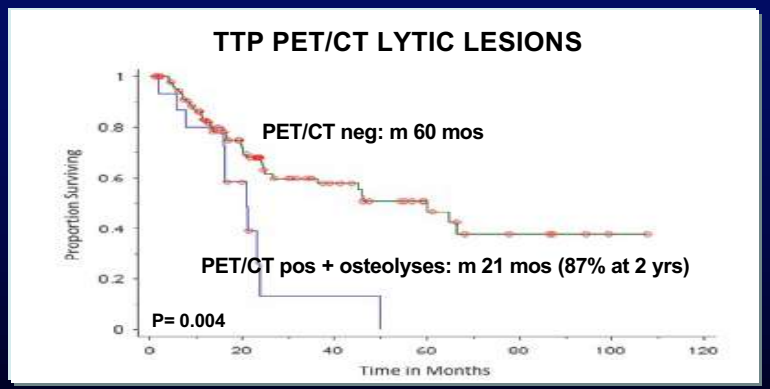
WBXR results in a frequent underestimation of MM bone disease

Regelink JC et al. BJH 2013;162:50-61.

IMAGING IN EARLY MM PHASES:

WBLDCT AND PET/CT vs WBXR: MM vs SMM
WBMRI for the RISK OF PROGRESSION





16/122 (13%) of patients having SMM according to WBXR had MM

Siontis B. et al, Blood Cancer J 2015

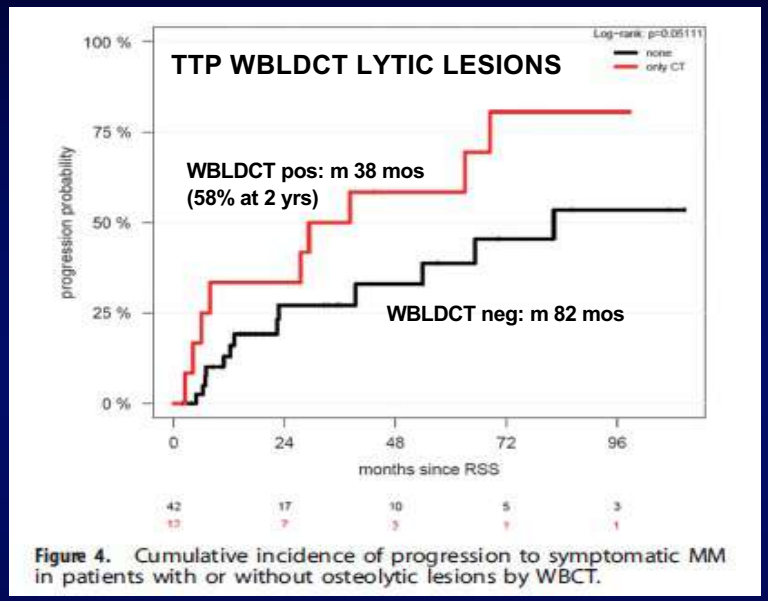
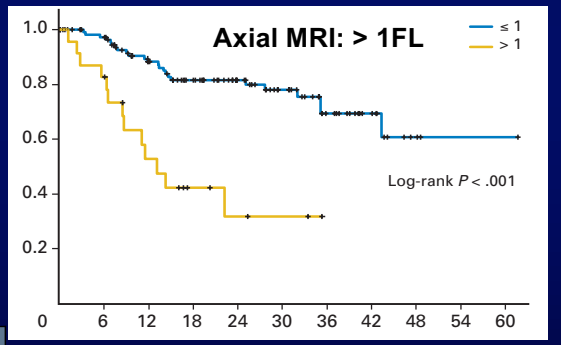


Figure 4. Cumulative incidence of progression to symptomatic MM in patients with or without osteolytic lesions by WBCT.

	CT neg	CT pos	total
CSS neg	103 (48.6%)	54 (25.5%)	157 (74.1%)
CSS pos	12 (5.7%)	43 (20.3%)	55 (25.9%)
total	115 (54.2%)	97 (45.8%)	212 (100%)

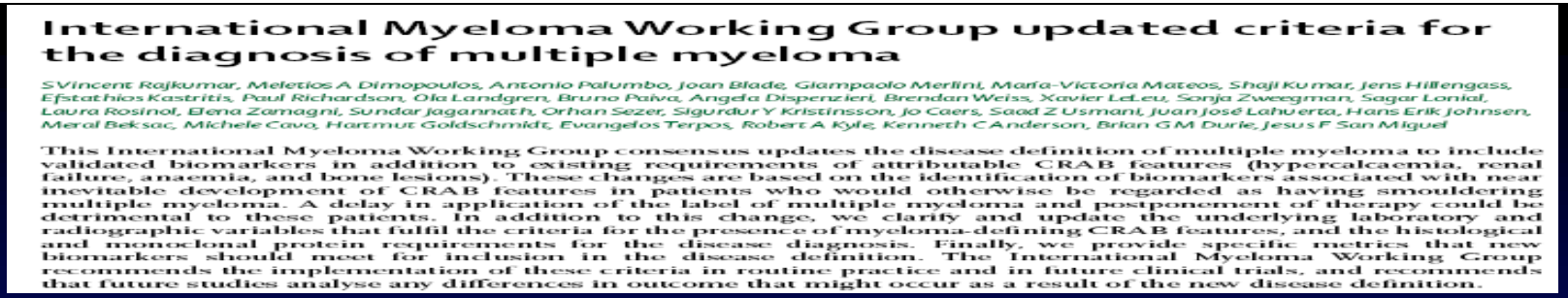
12/66 (25%) of patients having SMM according to WBXR had MM

Hillengas J et al. BCJ 2017



80% risk of progression to active MM if > 1 FL

Hillengass et al. 2010 JCO



International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma

S Vincent Rajkumar, Meletios A Dimopoulos, Antonio Palumbo, Joan Blade, Giampaolo Merlini, María-Victoria Mateos, Shaji Kumar, Jens Hillengass, Efstathios Kastritis, Paul Richardson, Ola Landgren, Bruno Paiva, Angela Dispenzieri, Brendan Weiss, Xavier LeLeu, Sonja Zweegman, Sagar Lonial, Laura Rosiñol, Elena Zamagni, Sundar Jagannath, Orhan Sezer, Sigurdur Y Kristinsson, Jo Caers, Saad Z Usmani, Juan José Lahuerta, Hans Erik Johnsen, Meral Beksac, Michele Cavo, Hartmut Goldschmidt, Evangelos Terpos, Robert A Kyle, Kenneth C Anderson, Brian G M Durie, Jesus F San Miguel

This International Myeloma Working Group consensus updates the disease definition of multiple myeloma to include validated biomarkers in addition to existing requirements of attributable CRAB features (hypercalcaemia, renal failure, anaemia, and bone lesions). These changes are based on the identification of biomarkers associated with near inevitable development of CRAB features in patients who would otherwise be regarded as having smouldering multiple myeloma. A delay in application of the label of multiple myeloma and postponement of therapy could be detrimental to these patients. In addition to this change, we clarify and update the underlying laboratory and radiographic variables that fulfil the criteria for the presence of myeloma-defining CRAB features, and the histological and monoclonal protein requirements for the disease diagnosis. Finally, we provide specific metrics that new biomarkers should meet for inclusion in the disease definition. The International Myeloma Working Group recommends the implementation of these criteria in routine practice and in future clinical trials, and recommends that future studies analyse any differences in outcome that might occur as a result of the new disease definition.

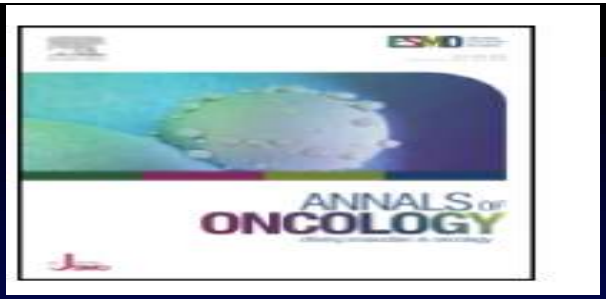
CURRENT DEFINITION OF MYELOMA BONE DISEASE

- **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

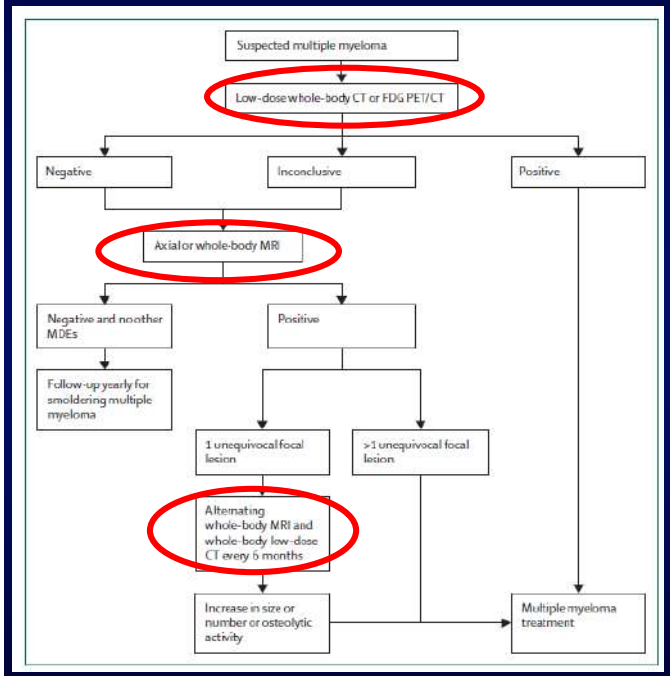
Rajkumar V. et al., Lancet Oncology 2014

International myeloma working group consensus recommendations on imaging in monoclonal plasma cell disorders

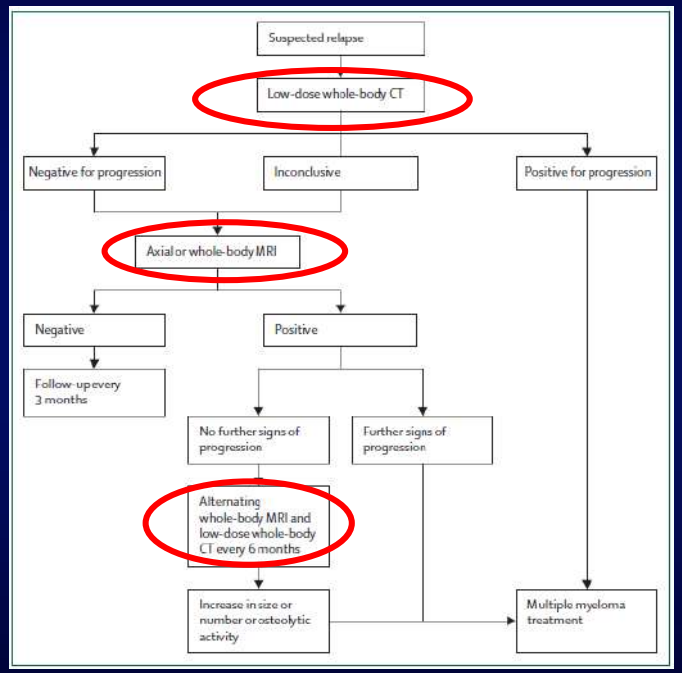
Jens Hillengass, Saad Usmani, S Vincent Rajkumar, Brian G M Durie, Maria-Victoria Mateos, Sagar Lonial, Cristina Joao, Kenneth C Anderson, Ramón García-Sanz, Elofsa Riva, Juan Du, Niels van de Donk, Jesús G Berdeja, Evangelos Terpos, Elena Zamagni, Robert A Kyle, Jesús San Miguel, Hartmut Goldschmidt, Sergio Giralt, Shaji Kumar, Noopur Raje, Heinz Ludwig, Enrique Ocio, Rik Schots, Hermann Einsele, Fredrik Schjesvold, Wen-Ming Chen, Niels Abildgaard, Brea C Lipe, Dominik Dytfeld, Baldeep Mona Wirk, Matthew Drake, Michele Cavo, Juan José Lahuerta, Suzanne Lentzsch



ALGORITHM IN MM AT DIAGNOSIS



ALGORITHM IN MM AT PROGRESSION



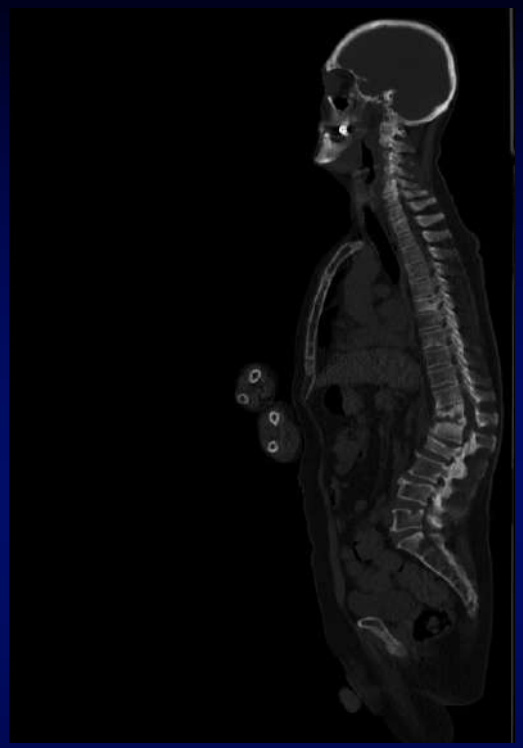
ESMO Recommendations on imaging at diagnosis, response assessment, during follow-up and at relapse of MM

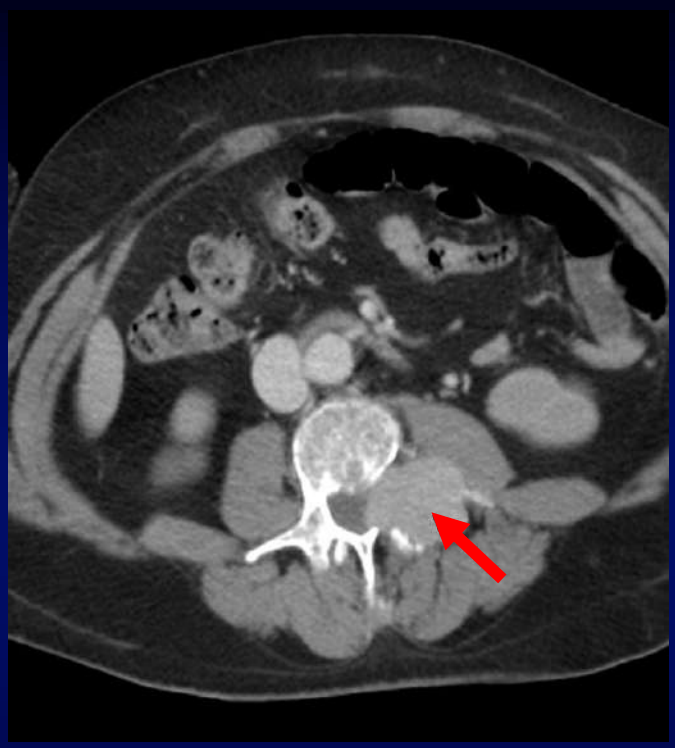
	Tool	Diagnosis	At response	At follow-up	At relapse
Imaging	WBLD-CT	Obligatory	Not required	When symptomatic (or CT of the symptomatic area)	Obligatory
	PET-CT	Optional (it may be performed instead of WBLD-CT	Obligatory to confirm Imaging MRD	Every 12 months in MRD-negative patients	Optional
	Whole-body MRI	Obligatory in WBLD-CT-negative cases and if PET-CT is not performed	Not required	When symptomatic	Optional

Hillengass J et al, Lancet Oncology 2019

Dimopoulos M et al ESMO Guidelines, Annals Oncology 2021

WHOLE BODY LOW-DOSE MULTIDETECTOR ROW-CT (WB-LDCT)





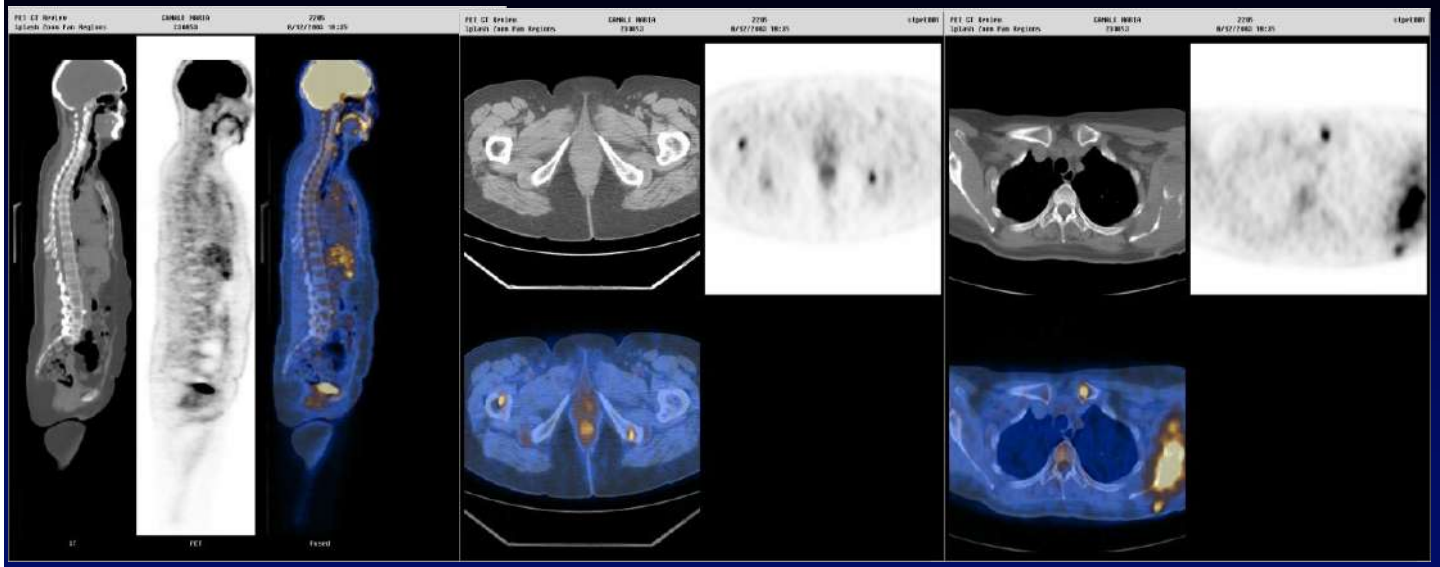
- Reveals lytic lesions in the skull, spine and long bones
- Basis for CT-guided biopsy, RT planning, evaluation of fracture risk
- Can reveal BM infiltration only in long bones (fatty BM) and not in trabecular bone, due to the trabeculae themselves

- Reveals extra-osseous lesions

Horger M., EJ Radiol, 2004
Hur J., J Comput Assist Tomogr, 2007
Gleeson TG et al, Skeletal Radiol 2009
Nishida Y et al, BJ Cancer 2015
Matsue K et al, Blood Advance 2018

Wolf MB et al, Eur Journal Radiology 2014
Pianko MJ et al, Clin Canc Res 2014
Shortt CP et al, Sem Musculoskel Radiology 2010
Ippolito D. et al, Eur J Radiol 2013

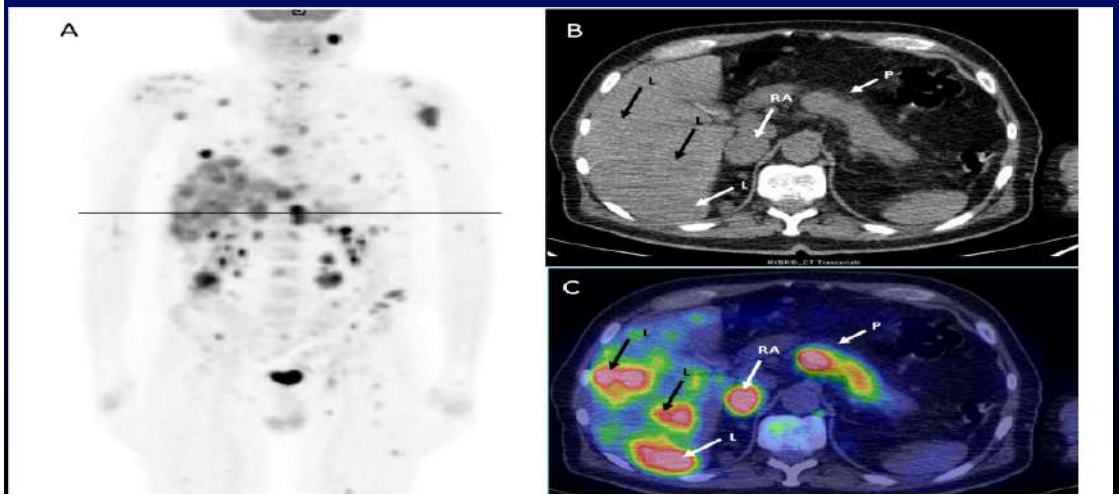
18F-FDG POSITRON EMISSION TOMOGRAPHY (PET/CT)



- Can depict lytic lesions (CT part)
- Can assess tumor burden and disease metabolism (PET part)

- Gold standard for the identification of extra-medullary (EMD) disease, due to hematogenous spread, associated with dismal clinical outcomes (PFS 20% at 5 years, median OS 6 years)
- Prognostic relevance for SUVmax, n° and size of FLs in newly diagnosed ASCT or ALLO candidates, non ASCT-eligible patients, at relapse

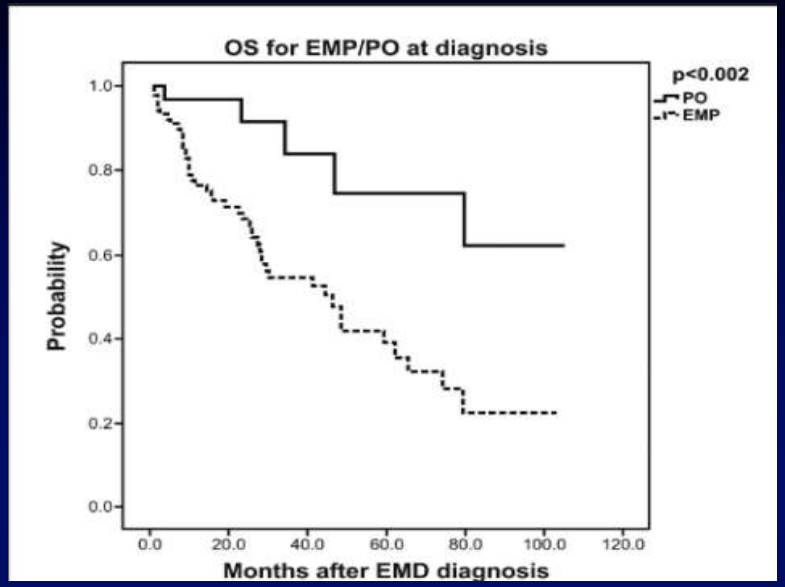
•PET/CT is positive in 80-85% of the patients at diagnosis



Van Lammeren-Venema D et al, Cancer 2011
Zamagni E. et al, Blood 2011
Bartel. TB et al, Blood 2009
Cavo M et al, Lancet Oncology 2017
Usmani S.Z. et al, Haematologica 2012
Lu Y.Y. et al, Clinical Nuclear Med 2012
Waheed S et al, Haematologica 2012
Usmani S.Z. et al, Blood 2013
Zamagni E et al, Clin Cancer Res 2015
Patriarca F. et al, Biol BMT 2015
Lapa C. et al, Oncotarget 2014
Derlin T. et al, EJNM Mol Imag 2011
Montefusco V et al, Haematolggica 2019
Beksac M et al, Haematologica 2019
Abe Y et al, AJR 2019
Moreau P, ASH 2019
Kaddoura M et al, Blood Advances 2021

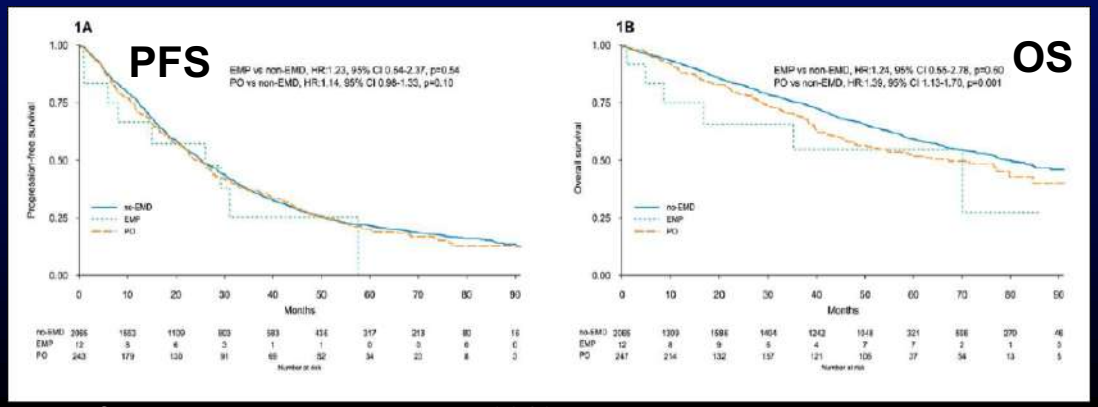
EXTRA and PARA-MEDULLARY DISEASE

EXTRAMEDULLARY vs PARA-MEDULLARY PLASMACYTOMA



Beksac M et al, Haematologica 2019

PARA-MEDULLARY PLASMACYTOMA



Montefusco V et al, Haematologica 2019

bjh review

Expert review on soft-tissue plasmacytomas in multiple myeloma: definition, disease assessment and treatment considerations

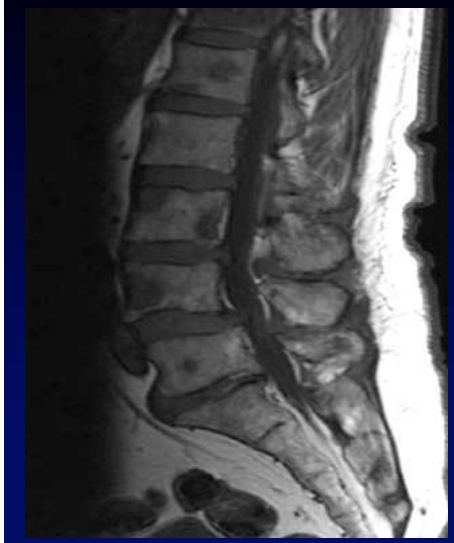
Laura Rosiñol,[1] Meral Beksac,[2] Elena Zamagni,[3] Niels W. C. J. Van de Donk,[4] Kenneth C. Anderson,[5] Ashraf Badros,[6] Jo Caers,[7] Michele Cavo,[3] Meletios-Athanasios Dimopoulos,[8] Angela Dispenzieri,[9] Hermann Einsele,[10] Monika Engelhardt,[11] Carlos Fernández de Larrea,[1] Gösta Gahrton,[12] Francesca Gay,[13] Roman Hájek,[14] Vania Hungria,[15] Artur Jurczyszyn,[16] Nicolaus Kröger,[17] Robert A. Kyle,[18] Fernando Leal da Costa,[19] Xavier Leleu,[20] Suzanne Lentzsch,[21] Maria V. Mateos,[22] Giampaolo Merlini,[23] Mohamad Mohty,[24] Philippe Moreau,[25] Leo Rasche,[10] Donna Reece,[26] Orhan Sezer,[27] Pieter Sonneveld,[28] Saad Z. Usmani,[29] Karin Vanderkerken,[30] David H. Vesole,[31] Anders Waage,[32] Sonja Zweegman,[4] Paul G. Richardson[5] and and Joan Bladé[1]

[1]Department of Hematology, Hospital Clínic, IDIBAPS, University of Barcelona, Barcelona, Spain, [2]Department of Hematology, Ankara University, Ankara, Turkey, [3]Istituto di Ematologia "Seràgnoli", Dipartamento di Medicina Specialistica Diagnostica e Sperimentale, Università degli Studi, Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy, [4]Department of Hematology, Amsterdam UMC, VU University, Amsterdam, the Netherlands, [5]Dana Farber Cancer Institute, Harvard Medical School, Boston, MA, [6]University of Maryland at Baltimore, Baltimore, MD, USA, [7]Department of Clinical Hematology, Centre Hospitalier Universitaire de Liège, Liège, Belgium, [8]Hematology and Medical Oncology, Department of Clinical Therapeutics, National and Kapodistrian University of Athens, Alexandra Hospital, Athens, Greece, [9]Division of Hematology, Mayo Clinic, Rochester, MN, USA, [10]Department of Internal Medicine II, University Hospital Würzburg, Würzburg, [11]Interdisciplinary Tumor Center, University of Freiburg, Freiburg, Germany, [12]Department of Medicine, Karolinska Institutet, Huddinge, Stockholm, Sweden, [13]Myeloma Unit, Città della Salute e della Scienza, University of Torino, Torino, Italy, [14]Department of Haematooncology, University of Ostrava, Ostrava, Czech Republic, [15]Clinica São Germano, São Paulo, Brazil, [16]Medical College Department of Hematology, Jagiellonian University, Krakow, Poland, [17]University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [18]Division of Hematology, Mayo Clinic, Rochester, MN, USA, [19]Instituto Português de Oncologia, Lisboa, Portugal, [20]Poitiers University Hospital, Poitiers, France, [21]Multiple Myeloma and Amyloidosis Service, Columbia University, New York, NY, USA, [22]IBSAL, Cancer Research Center, University Hospital of Salamanca, Salamanca, Spain, [23]Amyloidosis Research and Treatment Center, Department of molecular Medicine, University of Pavia, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy, [24]Department of Clinical Hematology and Cellular Therapy, Hospital Saint-Antoine, Sorbonne University, Paris, [25]Hematology Department, University Hospital Hotel-Dieu, Nantes, France, [26]Princess Margaret Cancer Center, University of Toronto, Toronto, Canada, [27]Berlin, Germany, [28]Erasmus MC Cancer Institute, Erasmus University of Rotterdam, Rotterdam, the Netherlands, [29]Department of Hematologic Oncology and Blood Disorders, Levine Cancer institute/Atrium Health, Charlotte, NC, USA, [30]Department Hematology and Immunology, Vrije Universiteit Brussel, Brussels, Belgium, [31]John Theurer Cancer, Hackensack Meridian School of Medicine, Hackensat, NJ, USA, and [32]Department of Clinical Molecular Medicine, St. Olavs Hospital, NTNU Trondheim, Trondheim, Norway

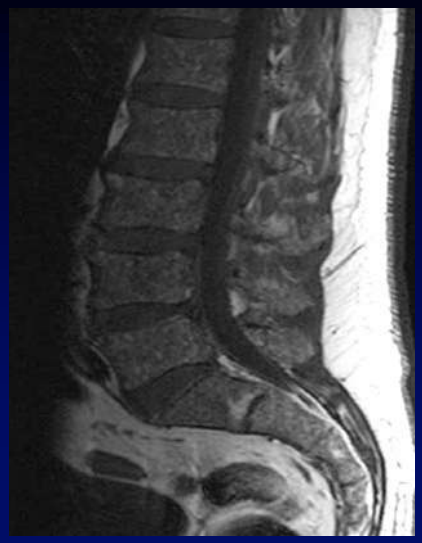
Rosinol L et al, BJH 2021

Bhutani M et al, Leukemia 2020

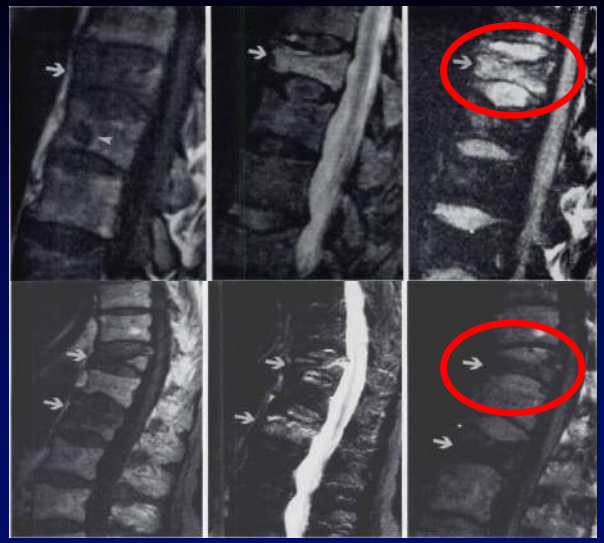
MAGNETIC RESONANCE IMAGING (MRI)



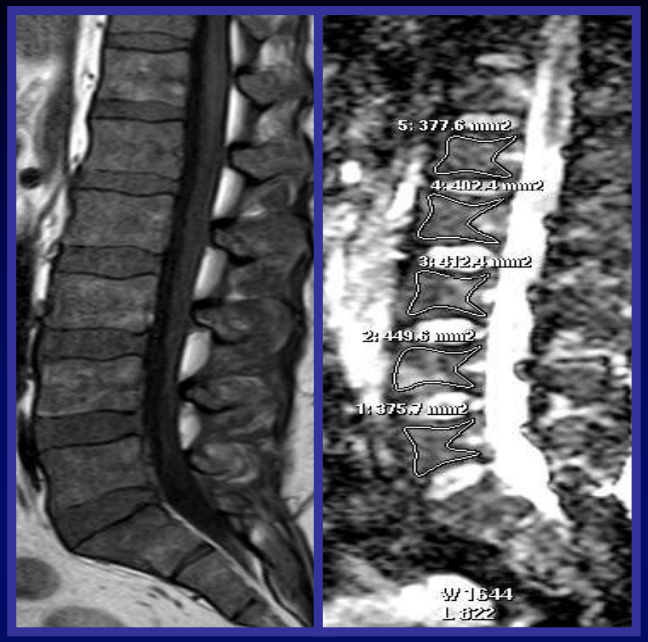
T1-weighted
Focal pattern



T1-weighted
Diffuse pattern



T1-weighted
MM vs osteoporotic fracture



DWI-WBMRI
Diffuse pattern

- MM lesions tipically hypo-intense on T1-and hyper-intense on T2-weighted images, enhanced with gadolinium injection . **DWI protocol for diffuse involvement**
- MRI shows infiltration **before** bone has been destroyed
- It has the highest resolution for soft tissue and bone marrow
- It differentiates between **benign** and **malignant** fractures, is the gold standard for cord compression
- Several independent retrospective or prospective studies showed a **prognostic relevance for MRI FLs**, diffuse pattern and correlation with other prognostic factors

•MRI is positive in 85-90% of the patients at diagnosis

Baur K et al, Radiology 1998
Dimopoulous M et al, JCO 2015

Koutoulidis V et al, Radiology 2017

Petralia G, Radiology 2018

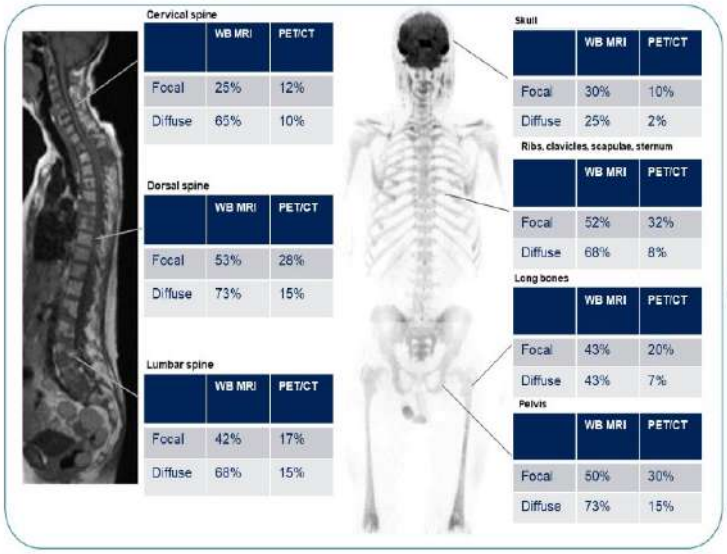
Pawlyn C et al, Leukemia 2016
Giles SL et al, Clinical Radiology 2015
Moulopoulos L.A. et al, Annals Oncology 2005
Mouolopulos L.A. et al, Leukemia 2010

Dutoit JC et al, Skeletal Radiol 2017
Messiou C et al, BJH 2015
Walker B et al, JCO 2007
Ippolito D et al, BJH 2017
Moulopoulos L.A. et al, AJH 2012
Mai EK. et al, Haematologica 2015
Terpos E et al, Ann Hematology 2017

PROSPECTIVE COMPARISON OF WHOLE BODY MRI AND FDG PET/CT FOR DETECTION OF MULTIPLE MYELOMA AND CORRELATION WITH MARKERS OF DISEASE BURDEN:

RESULTS OF THE ITIMM (IMAGEGUIDED THERANOSTICS IN MULTIPLE MYELOMA) TRIAL

Results: comparison WB MRI vs PET/CT



Cervical spine

	WB MRI	PET/CT
Focal	25%	12%
Diffuse	65%	10%

Dorsal spine

	WB MRI	PET/CT
Focal	53%	28%
Diffuse	73%	15%

Lumbar spine

	WB MRI	PET/CT
Focal	42%	17%
Diffuse	68%	15%

Skull

	WB MRI	PET/CT
Focal	30%	10%
Diffuse	25%	2%

Ribs, clavicles, scapulae, sternum

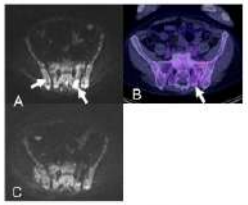
	WB MRI	PET/CT
Focal	52%	32%
Diffuse	68%	8%

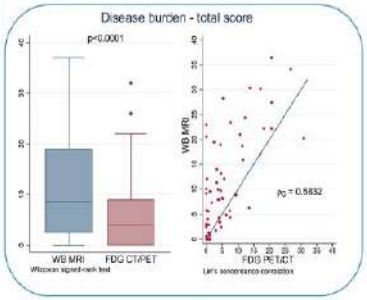
Long bones

	WB MRI	PET/CT
Focal	43%	20%
Diffuse	43%	7%

Pelvis

	WB MRI	PET/CT
Focal	50%	30%
Diffuse	73%	15%



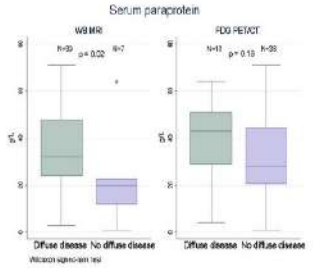


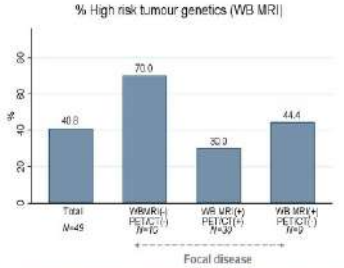
Higher sensitivity of WB MRI to detect focal and diffuse disease in all bone marrow areas

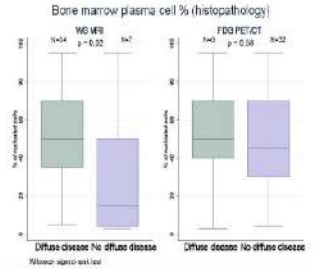
Presented By: Martin Kaiser, MD, FRCP, FRCPath
@MyMKaiser

2021 ASCO ANNUAL MEETING

Results: imaging disease burden and biology







Quantitative correlation between imaging and common markers
- Serum paraprotein
- Bone marrow plasma cells (histopathology)

in WB MRI diffuse positive vs negative

→ Potential for direct, spatial quantitation of MM by WB MRI

All tumours with high-risk genetics showed diffuse disease on WB MRI
Majority of tumours with diffuse pattern without focal disease high-risk

→ Potential for development of imaging markers for disease biology

Presented By: Martin Kaiser, MD, FRCP, FRCPath
@MyMKaiser

2021 ASCO ANNUAL MEETING

60 pts, recruited at Royal Marsden Hospital, London , UK 2015-2018

Kaiser M et al, ASCO 2021

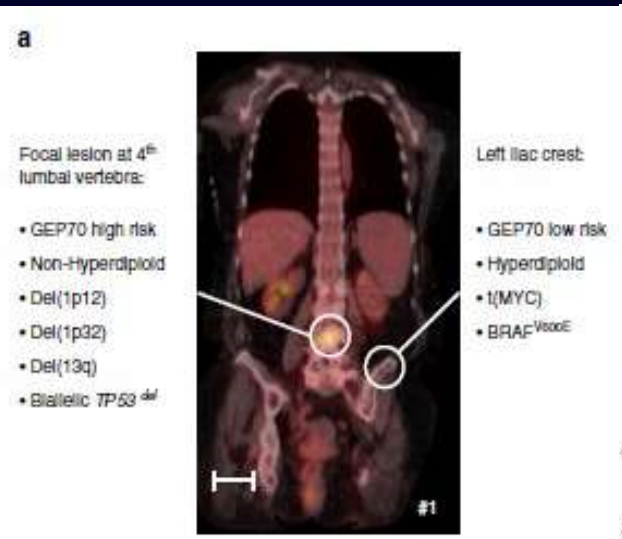
	WBLDCT	PET/CT	MRI
Ease of use	• Patient-friendly (fast scanning time, < 15 minutes) • Relatively cheap • Widely available	• Scanning time (including radiopharmaceutical injection) approximately 60 min • More expensive • Not always available	• Variable scanning time (30-60 min) • More expensive • Relatively available
Radiation exposure	• Relatively low radiation dose (3-4 mSv) • No need for iv contrast administration	Higher (6-10 mSv)	No radiation exposure
Bone damage	Depicts lytic bone lesions	Depicts contemporary lytic bone lesions and/or EMD, and disease metabolism	Highest sensitivity for early bone damage
Prognostic relevance	Not clear	Prognostic significance of FLs number and SUV_{max} value	Prognostic significance of FLs and diffuse pattern

Choice usually made according to local clinical practice, resources, expertise and national guidelines

Zamagni E. et al, Blood 2018

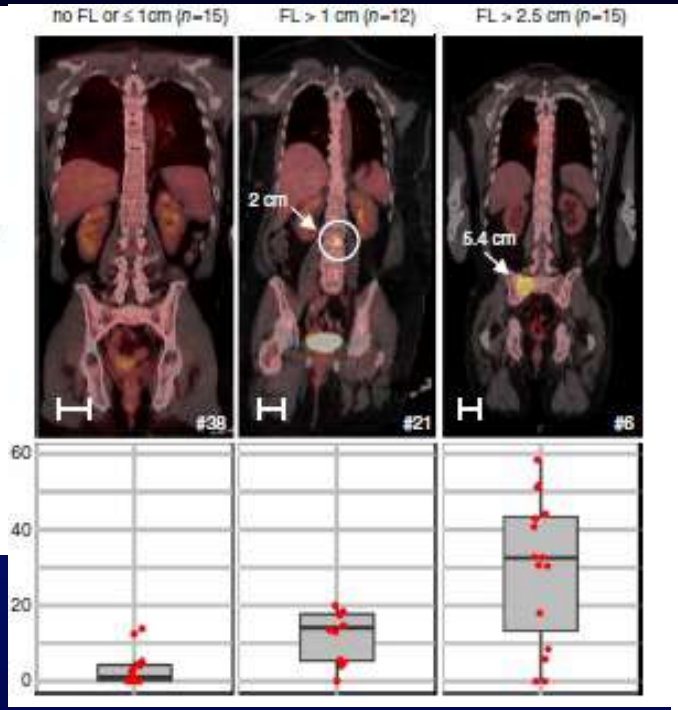
The impact of spatial heterogeneity on MRD diagnostic

Discrepancy between BM MRD and imaging: need for Imaging MRD category

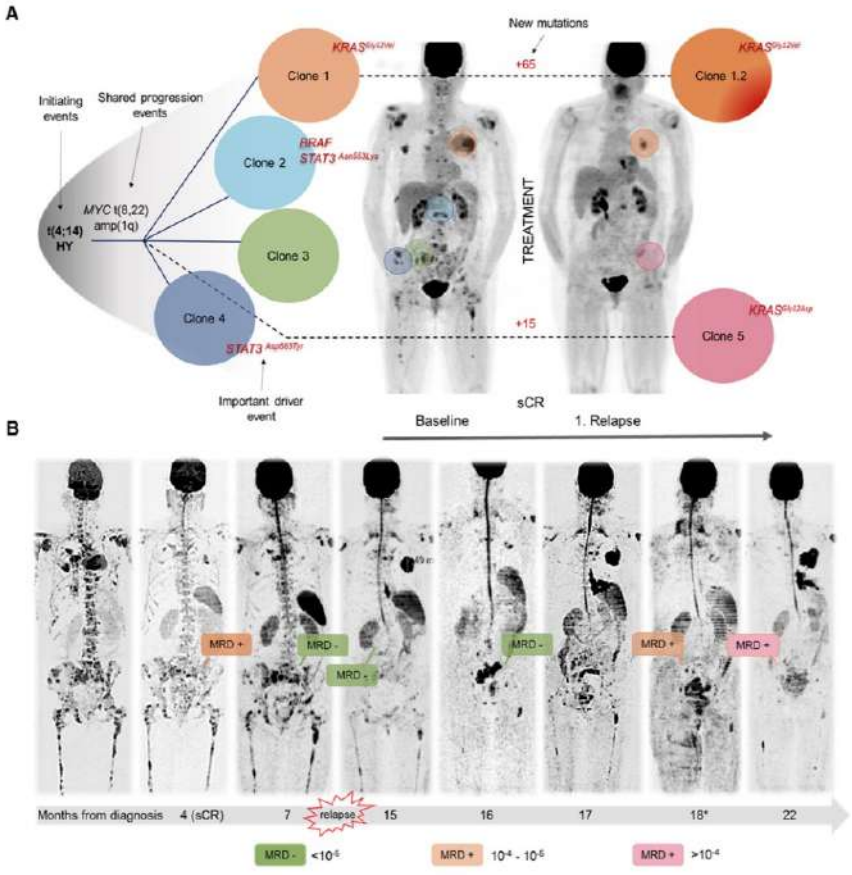


Different GEP profile between BM and FL

- **Patchy infiltration of the BM**
- **EMD**
- **Spatial heterogeneity**



Growing heterogeneity with growing size of the lesions

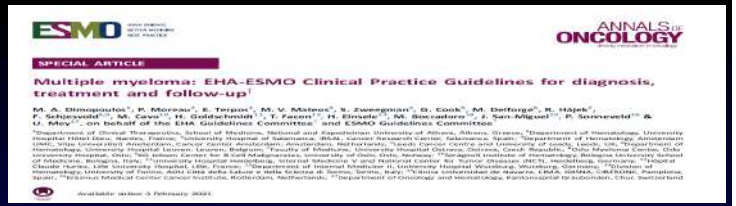


Rasche L et at, Nature Comm 2017
Rasche L et al, Blood 2018
Rasche L et al, Leukemia 2018
Moreau P et al, JCO 2017
Alonso R et al, AJH 2019

Imaging relapse while mantaining BM MRD negativity (MFC, $10^{-4}/10^{-5}$):
-12-15% by PET/CT
-higher risk in EMD/para-medullary disease and at relapse (50%)
-false negative FDG PET results (lack of exokinase): 10-12%

Role of ^{18}F-FDG PET/CT in the diagnosis and management of multiple myeloma and other plasma cell disorders: a consensus statement by the International Myeloma Working Group

International myeloma working group consensus recommendations on imaging in monoclonal plasma cell disorders



ESMO ANNALS OF ONCOLOGY

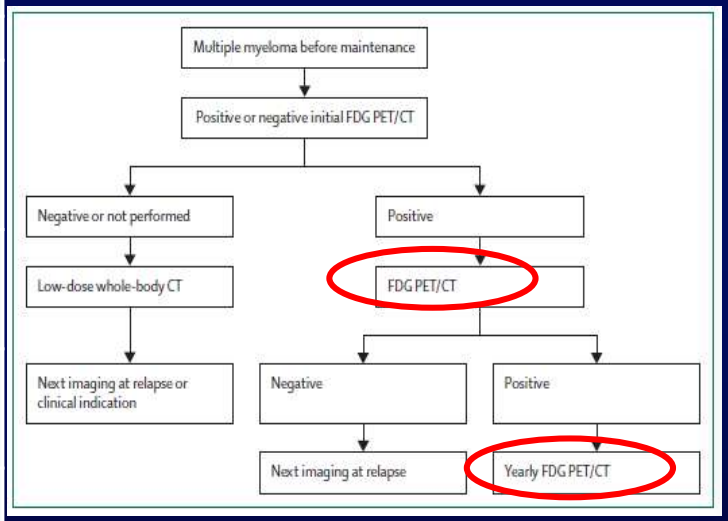
SPECIAL ARTICLE

Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

Recommendations for use of 18F-FDG PET/CT in MM

Recommendation	Grade
Active MM:	
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	B
In newly diagnosed MM, EMD and >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_{max}	B
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	A
18F-FDG PET/CT should be coupled with sensitive bone marrow-based assays as part of MRD detection inside and outside the bone marrow	B

ALGORITHM DURING FOLLOW-UP FOR RESPONSE EVALUATION



ALGORITHM AT RESPONSE

	Tool	Diagnosis	At response	At follow-up	At relapse
Imaging	WBLD-CT	Obligatory	Not required	When symptomatic or CT of the symptomatic area)	Obligatory
	PET-CT	Optional (it may be performed instead of WBLD-CT	Obligatory to confirm Imaging MRD	Every 12 months in MRD-negative patients	Optional
	Whole-body MRI	Obligatory in WBLD-CT-negative cases and if PET-CT is not performed	Not required	When symptomatic	Optional

Cavo M. et al, Lancet Oncology 2017

Hillengass J et al, Lancet Oncology 2019

Dimopoulos M et al, Annals Oncology 2021

STANDARDIZATION PROJECT FOR DEFINITION OF PET COMPLETE METABOLIC RESPONSE:
First use of Deauville criteria in MM-multivariable analysis

COMPLETE METABOLIC RESPONSE:

uptake ≤ liver activity in all localizations of the BM and FLs (including EMD and PMD) (DS 1-3)*

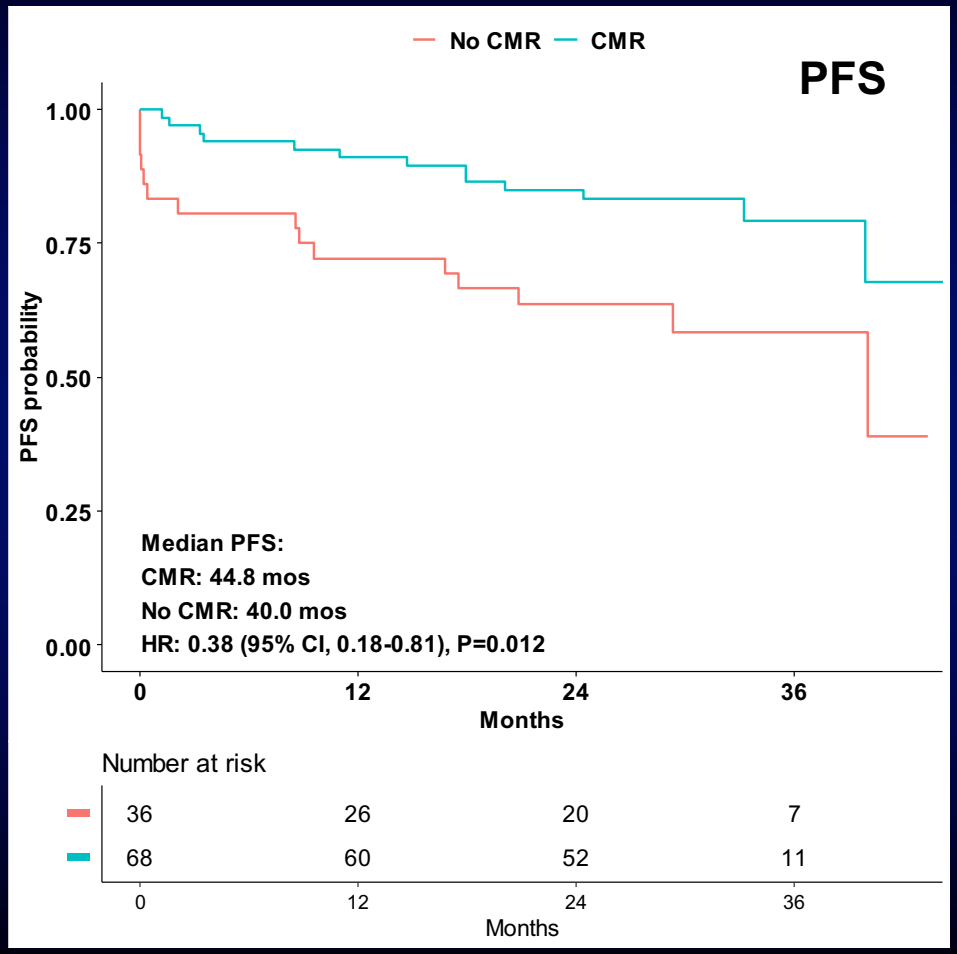
PFS	HR	95% CI	P-value
Baseline			
Absence of EMD	0.55	0.32 - 0.95	0.034
Beta2-mic < 5.5 mg/dL	0.61	0.39 - 0.96	0.034
Sex - Female	0.68	0.47 - 0.99	0.042
Pre-maintenance			
BM Score <4	**0.50**	0.26 - 0.97	**0.041**
FL Score <4	**0.60**	0.37 - 0.95	**0.030**

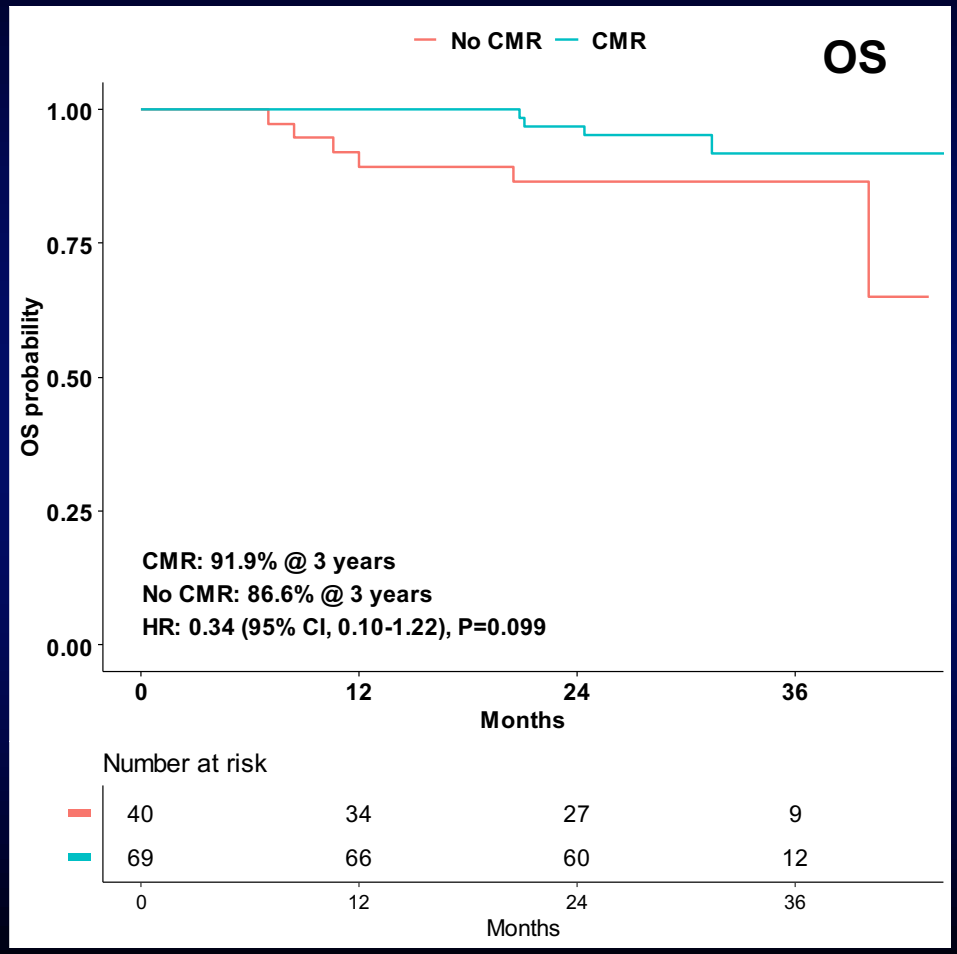
OS	HR	95% CI	P-value
Baseline			
BM SUV Max ≤ 3.5	0.33	0.13 - 0.84	0.014
LDH ≤ upper limit	0.33	0.15 - 0.77	0.024
SR cytogenetics	0.32	0.13 - 0.77	0.025
Pre-maintenance			
BM Score <4	0.25	0.10 - 0.66	**0.005**
FL Score <4	0.34	0.16 - 0.70	**0.004**
PLTS ≥ 150.000/mmc	0.33	0.14 - 0.78	0.012

Zamagni E et al, JCO 2021

IMPACT OF FDG-PET/CT COMPLETE METABOLIC RESPONSE ON PFS AND OS

CONFIRMATORY DATA IN INDEPENDENT SERIES OF PATIENTS (FORTE TRIAL)

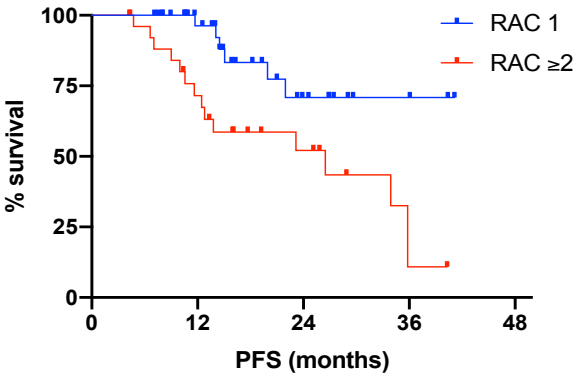




Zamagni E et al, ASH 2020, under publication

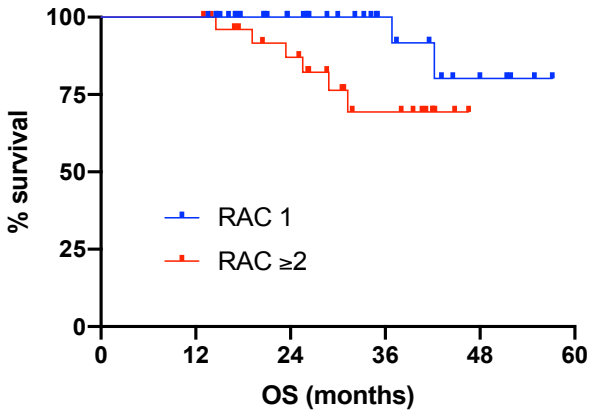
DWI-MRI to assess response after ASCT according to MY-RADS criteria

Post ASCT PFS according to imaging response



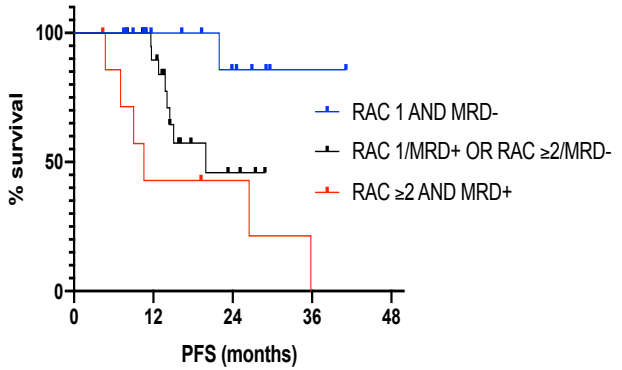
Median: NR vs 26.5 mos, HR 0.28, P= 0.004

Post ASCT OS according to imaging response



@ 3 yrs: 92% vs 69%, HR 0.24, P= 0.04

Post ASCT PFS according to MFC (10^{-5}) and imaging (46 pts)



Median PFS RAC1/MFC neg vs one pos vs both pos: NR vs 19.9 vs 10.6 mos, P= 0.007

MULTIVARIATE ANALYSIS

PFS	HR (95%CI)	P value
IMWG response: < CR	0,43 (0,17-1,03)	0,060
RAC ≥ 2	0,29 (0,11-0,75)	**0,011**
High Risk cytogenetic	0,39 (0,15- 0,99)	**0,048**

Retrospective analysis of 64 pts
Median follow-up 29 mos

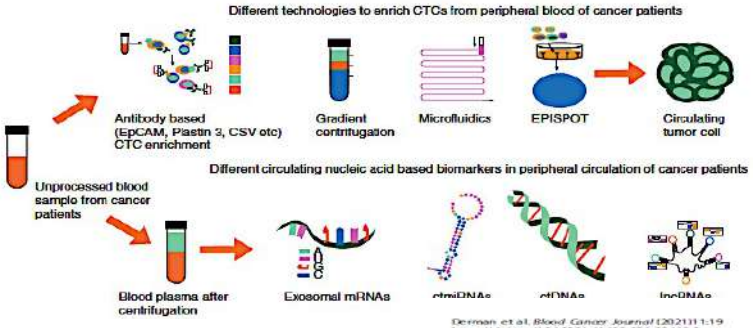
RAC 1 = complete imaging response
RAC 2 or higher = PR/stable/progressive imaging disease

Bellotti E et al, ASH 2020, adjourned at SIE 2021

Future directions of MRD testing

To convert some of the bone marrow/imaging tests into peripheral blood tests

MM samples processing for Liquid Biopsy studies



Batth IS et. al, Annals of Oncology 2017

Mass spectrometry

Murray et al. Blood Cancer Journal (2021)11:24
https://doi.org/10.1038/s41408-021-00408-4

Blood Cancer Journal

ARTICLE Open Access

Mass spectrometry for the evaluation of monoclonal proteins in multiple myeloma and related disorders: an International Myeloma Working Group Mass Spectrometry Committee Report

David L. Murray[1], Noemi Puig[2], Sigurdur Kristinsson[3], Saad Z. Usmani[4], Angela Dispenzieri[1,5], Giada Bianchi[6], Shaji Kumar[7], Wee Joo Chng[7,8,9], Roman Hajek[10], Bruno Paiva[11], Anders Waage[12,13], S. Vincent Rajkumar[1] and Brian Durie[14]

Derman et al. Blood Cancer Journal (2021)11:19
https://doi.org/10.1038/s41408-021-00418-2

Blood Cancer Jou

CORRESPONDENCE Open Acc

Measurable residual disease assessed by mass spectrometry in peripheral blood in multiple myeloma in a phase II trial of carfilzomib, lenalidomide, dexamethasone and autologous stem cell transplantation

Benjamin A. Derman[1], Andrew T. Stefka[1], Ken Jiang[1], Amanda McIver[1], Tadeusz Kubicki[2], Jagoda K. Jadelec, Andrzej J. Jakubowiak[1]

PFS

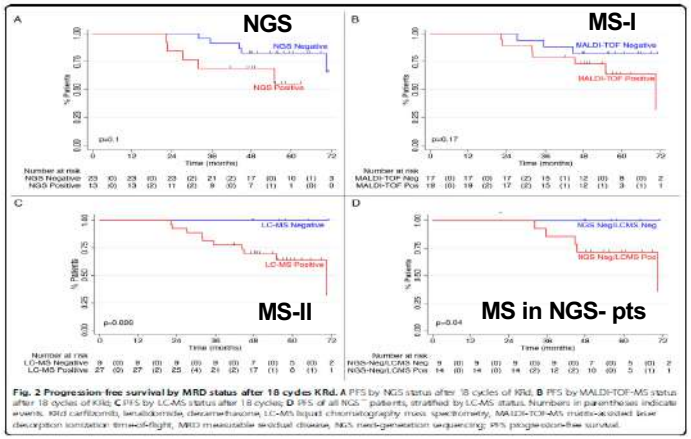


Fig. 2 Progression-free survival by MRD status after 18 cycles KRd. A PFS by NGS status after 18 cycles of KRd, B PFS by MALDI-TOF-MS status after 18 cycles of KRd; C PFS by LC-MS status after 18 cycles; D PFS of all NGS⁻ patients, stratified by LC-MS status. Numbers in parentheses indicate events. KRd carfilzomib, lenalidomide, dexamethasone, LC-MS liquid chromatography mass spectrometry, MALDI-TOF-MS matrix-assisted laser desorption ionization time-of-flight, MRD measurable residual disease, NGS next-generation sequencing, PFS progression-free survival.

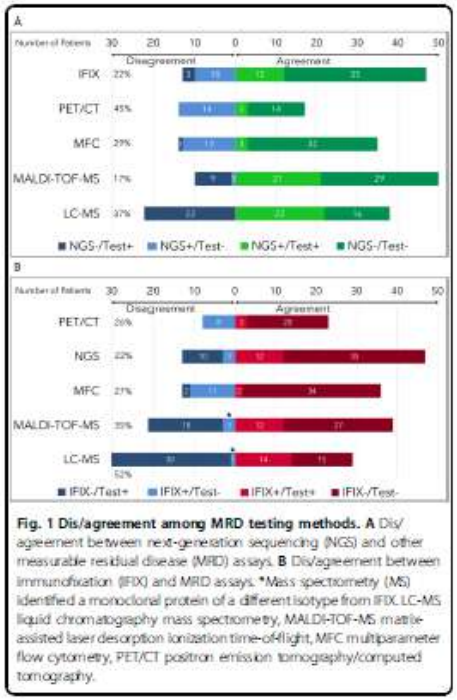


Fig. 1 Dis/agreement among MRD testing methods. A Dis/agreement between next-generation sequencing (NGS) and other measurable residual disease (MRD) assays. B Dis/agreement between immunofixation (IFIX) and MRD assays. *Mass spectrometry (MS) identified a monoclonal protein of a different isotype from IFIX. LC-MS liquid chromatography mass spectrometry, MALDI-TOF-MS matrix-assisted laser desorption ionization time-of-flight, MFC multiparameter flow cytometry, PET/CT positron emission tomography/computed tomography.

Derman B et. al, BCJ 2021

Panel: Recommendations on the reporting of imaging results in monoclonal plasma cell disorders

First diagnosis

A radiological report on whole-body imaging in patients with monoclonal plasma cell disorders should include:

- Infiltration and bone destruction pattern
  - Minimal (normal appearing)
  - Focal lesions
  - Diffuse infiltration and bone destruction
  - Mixed (focal lesions on diffuse background)
- Absolute number of focal lesions
  - For whole-body MRI: 0, 1, 2–7, or >7
  - For PET/CT: 0, 1–3, or >3
- Number of fractures (new *vs* old, location, and likelihood of malignant *vs* benign cause)
- Extramedullary disease
- Soft tissue masses growing out of the bone marrow into the surrounding tissue
- Infiltration of the long bones
- Evidence of surgical procedures at the skeletal system
- Incidental findings

In remission

Differentiate these findings with regards to response to therapy in imaging (guidelines papers for whole-body CT, whole-body MRI, and PET/CT):

- Response
  - Normalisation of bone marrow signal in previously affected areas
  - Decrease in the number and size of focal lesions
  - Resolution of severely infiltrated bone marrow infiltrate into focal lesions
  - Decrease in the of number and size of soft tissue tumours (paramedullary and extramedullary)
- No change
- Progression
  - Worsening of diffuse bone marrow signal or new appearance of infiltration in previously unaffected areas
  - Increase in the number and size of focal lesions
  - Merging of focal lesions into severely infiltrated bone marrow
  - Increase in the size or number of soft tissue tumours (paramedullary and extramedullary)

Specifics for MRI

Cystic or liquid transformation of focal lesions after therapy

Hillengass J et al, Lancet Oncology 2019

WBLDCT

Blood Cancer Journal

ARTICLE Open Access

Recommendations for acquisition, interpretation and reporting of whole body low dose CT in patients with multiple myeloma and other plasma cell disorders: a report of the IMWG Bone Working Group

Lia A. Moulopoulos[1], Vassilis Koutoulidis[1], Jens Hillengass[2], Elena Zamagni[3], Jesus D. Aquerreta[4], Charles L. Roche[5], Suzanne Lentzsch[6], Philippe Moreau[7], Michele Cavo[8], Jesus San Miguel[9], Meletios A. Dimopoulos[1], S. Vincent Rajkumar[10], Brian G. M. Durie[11], Evangelos Terpos[1] and Stefan Delorme[12]

MRI

Radiology

REVIEWS AND COMMENTARY • REVIEW

Guidelines for Acquisition, Interpretation, and Reporting of Whole-Body MRI in Myeloma: Myeloma Response Assessment and Diagnosis System (MY-RADS)

Christina Messiou, MD • Jens Hillengass, MD • Stefan Delorme, MD • Frédéric E. Lecouvet, MD • Lia A. Moulopoulos, MD • David J. Collins, BA • Matthew D. Blackledge, PhD • Niels Abildgaard, MD • Brian Østergaard, MD • Heinz-Peter Schlemmer, MD • Ola Landgren, MD • Jon Thor Asmussen, MD • Martin F. Kaiser, MD • Anwar Padhani, MD

FDG PET/CT

original reports

Standardization of ^{18}F-FDG–PET/CT According to Deauville Criteria for Metabolic Complete Response Definition in Newly Diagnosed Multiple Myeloma

Elena Zamagni, MD, PhD[1]; Cristina Nanni, MD[2]; Luca Dozza, MS[1]; Thomas Carlier, PhD[3]; Clément Bailly, MD, PhD[3]; Paola Tacchetti, MD[1]; Annibale Versari, MD[4]; Stephane Chauvie, PhD[5]; Andrea Gallamini, MD[6]; Barbara Gamberi, MD[7]; Denis Caillot, MD[8]; Francesca Patriarca, PhD[9]; Margaret Macro, MD[10]; Mario Boccadoro, MD, PhD[11]; Laurent Garderet, MD[12]; Simona Barbato, PhD[1]; Stefano Fanti, MD[2]; Aurore Perrot, MD[13]; Francesca Gay, MD[11]; Peter Sonneveld, MD, PhD[14]; Lionel Karlin, MD[15]; Michele Cavo, MD, PhD[1]; Caroline Bodet-Milin, MD[3]; Philippe Moreau, MD, PhD[16]; and Françoise Kraeber-Bodéré, MD, PhD[3]

Moulopoulos L et al, Blood Cancer Journal 2018

Messiou C, et al. Radiology 2019

Zamagni E. et al, JCO 2021

OPEN ISSUES-WORK IN PROGRESS

- DWI-MRI MRD after ASCT vs PET in prospective trials (on-going, iTIMM study and others)
- Prospective confirmation of new PET metabolic response criteria (on-going, FORTE trial, CASSIOPET trial)
- Refinition of imaging-response in plasmacytoma(s), based on metabolic (PET) or BM (DWI-MRI) criteria
- Imaging response criteria in patients receiving new immune therapies (experts group currently on-going)
- Relationship between imaging-MRD and BM MRD **at higher sensitivity** levels (10^{-6})/ liquid biopsy/mass spectrometry (on-going)
- Incorporation of imaging-MRD with BM-MRD after treatment: design of MRD-driven trials (on-going)

Zamagni E. et al, Blood 2018

CHALLENGES WITH CURRENT MM RESPONSE CRITERIA
DEFINITION OF IMAGING-PLASMACYTOMA RESPONSE (UNMET NEED!)

Issue	Recommendation
Response assessment	
Light chain myeloma (measurable urine M-protein)	Use only 24h urine M-protein, except for CR
IgG, IgD or IgA with “non-measurable” serum M-spike and measurable urine M-spike	Use only urine values except for CR and PD
Non-measurable values at baseline, M-spike “too small to quantitate”	All assessments not meeting CR or PD should be NE
Absence of 2 consecutive negative IFE and simultaneous <5% BMPCs	CR not assigned, assess as VGPR
Plasmacytoma	**Request functional and not morphological imaging**
Progressive disease	
Increase in a previously existing plasmacytoma or bone lesion as only source of PD	**Request functional imaging verification, before assigning PD**
New antimyeloma therapy before documented PD	Censor
Non pre-planned radiation therapy	Assess PD
PD based on M-protein increase with no confirmation	Censor, unless PD is considered “unequivocal”

BMPC, bone marrow plasma cell; CR, complete response; IFE, immunofixation electrophoresis non-evaluable; PD, progressive disease; VGPR, very good partial response

Bladé J, presented at IMW 2019, 2021

OPEN ISSUES-WORK IN PROGRESS

- DWI-MRI MRD after ASCT vs PET in prospective trials (on-going, iTIMM study and others)
- Prospective confirmation of new PET metabolic response criteria (on-going, FORTE trial, CASSIOPET trial)
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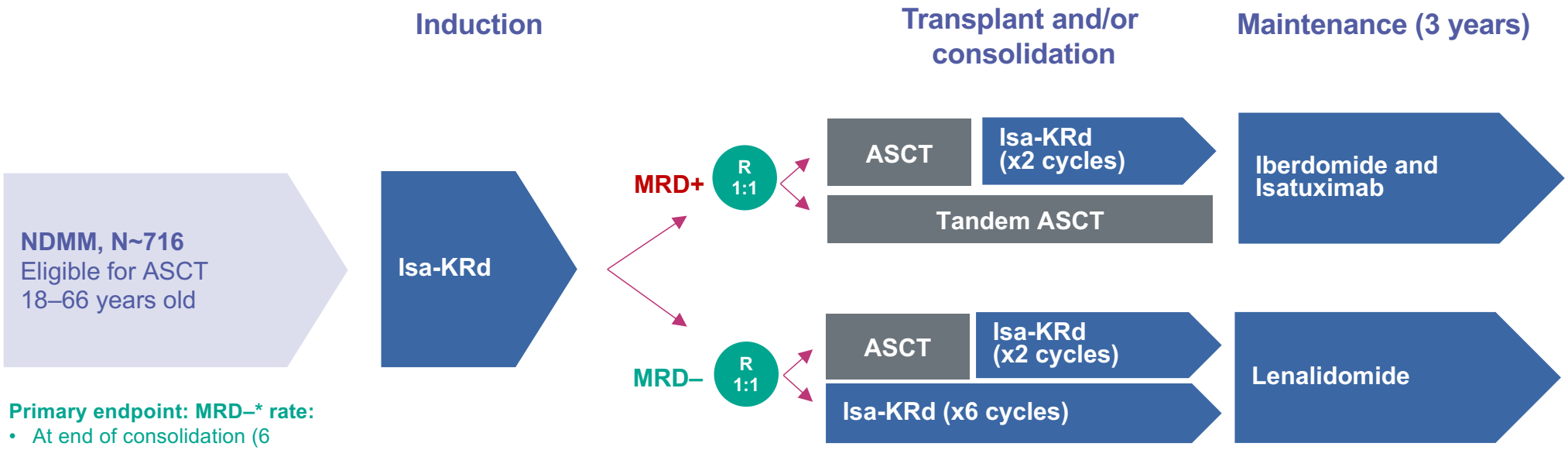
- Relationship between imaging-MRD and BM MRD **at higher sensitivity** levels (10^{-6})/ liquid biopsy/mass spectrometry (on-going)
- Incorporation of imaging-MRD with BM-MRD after treatment: design of MRD-driven trials (on-going)

Zamagni E. et al, Blood 2018

MRD status as driver of first-line therapy

Minimal Residual Disease Adapted Strategy (MIDAS)

Sponsor: Intergroupe Francophone du Myelome (IFM)
Estimated primary completion: September 2024



Primary endpoint: MRD–* rate:

- At end of consolidation (6 months)
- 1, 2, and 3 years post induction

*Primary analysis will evaluate MRD (NGS, 10^{-6} threshold)

Isa-KRd is an investigational combination that has not been approved by any regulatory authority. Sanofi does not recommend the use of their products outside the approved indication. Please consult your local label before prescribing

ASCT, autologous stem cell transplant; d, dexamethasone; Isa, isatuximab; K, carfilzomib; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; NGS, next-generation sequencing; R, lenalidomide

https://clinicaltrials.gov/ct2/show/NCT04934475

Carfilzomib-Lenalidomide-Dexamethasone Consolidation in Myeloma Patients with a Positive FDG PET/CT after Upfront Autologous Stem Cell Transplantation: A Phase II Study (CONPET)

Jakob Nordberg Nørgaard, MD[1,2,3], Niels Abildgaard, MD[4,5], Anna Lysén, MSc[1,3], Galina Tsykunova, MD[6], Annette Juul Vangsted, MD[7], Cristina João, MD, PhD, MSc[8], Nora Remen[1], James P Connelly, MD, PhD[9], Mona-Elisabeth R. Revheim, MD, PhD[2,9] and Fredrik H. Schjesvold, MD, PhD[1,3]

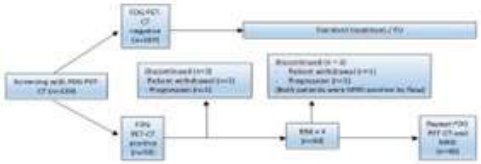
[1]Oslo Myeloma Center, Department of Hematology, Oslo University Hospital, Oslo, Norway. [2]Institute of Clinical Medicine, University of Oslo, Oslo, Norway. [3]KG Jebsen Center for B Cell Malignancies, University of Oslo, Oslo, Norway. [4]Department of Hematology, Odense University Hospital, Odense, Denmark. [5]Department of Clinical Research, University of Southern Denmark, Odense, Denmark. [6]Department of Hematology, Haukeland University Hospital, Bergen, Norway. [7]Department of Hematology, Rigshospitalet, Copenhagen, Denmark. [8]Department of Hematology, Champalimaud Centre for the Unknown, Lisbon, Portugal. [9]Division of Radiology and Nuclear Medicine, Oslo University Hospital, Oslo, Norway.

Introduction

[18F]-Fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) positivity after first line treatment with autologous stem cell transplantation (ASCT), is strongly correlated with reduced progression free survival and overall survival (Moreau *et al.*, JCO, 2017). However, FDG PET/CT positive patients who obtain FDG PET/CT negativity after treatment can have comparable outcomes to patients who were FDG PET/CT negative at baseline (Davies *et al.*, Haematologica 2018). Aiming for FDG PET/CT negativity may therefore be an important goal in myeloma treatment. The use of FDG PET/CT positivity as an indication for consolidation therapy after ASCT has not been studied before. We here present the final analysis of the primary endpoint of PET-CT negativity after KRd consolidation.

Methods

Patients with multiple myeloma who had received standard first line treatment including ASCT and achieved very good partial response (VGPR) or better, were examined by FDG PET/CT. Patients who were FDG PET/CT positive defined by the Italian Myeloma criteria for PET USe (IMPETUS) were included in the treatment phase of the study and were assessed for minimal residual disease (MRD) by Euroflow (sensitivity: 10^{-5}) before treatment. The treatment consisted of four 28-day cycles of KRd (carfilzomib 36 mg/m^2 day 1,2,8,9,15 and 16 (except 20 mg/m^2 day 1 and 2 first cycle), lenalidomide 25 mg day 1-21 all cycles and dexamethasone 40 mg day 1,8,15 and 22 all cycles). After four cycles, FDG PET/CT and Euroflow for MRD were repeated for response evaluation. Both patients with FDG PET/CT negativity and patients with FDG PET/CT positivity at baseline are followed for progression free survival (PFS) and overall survival (OS).



Results

- 159 patients were screened with FDG PET/CT. Fifty-three patients of 159 (33%) had a positive FDG PET/CT result. Among FDG PET/CT positive patients, a higher proportion had ISS score III and high-risk cytogenetics, and VCD induction was more common (Table 1).
- Forty-eight patients completed KRd treatment. Sixteen patients (33%) converted into FDG PET/CT negativity. More patients with previous VRd induction converted from FDG PET/CT positive to FDG PET/CT negative (Table 1). A patient example is showed in figure 1. No patients stopped treatment because of adverse events.
- Twenty-eight of 50 (56%) patients with a FDG PET/CT positive result were MRD negative before KRd consolidation. A higher proportion of MRD negative patients vs MRD positive patients before KRd treatment, converted into FDG PET/CT negativity, with 39% vs 23%, respectively. For the proportion of patients that after KRd treatment was both FDG PET/CT negative and MRD negative by EuroFlow, the difference was even higher (39% vs 4,5% in MRD neg vs MRD pos patients, respectively). In total, the MRD negativity rate increased from 56% to 74%. (Table 2).

	Before treatment		After treatment	
	PET negative (n=106)	PET positive (n = 53)	PET positive to negative (n=16)	PET positive to positive (n=32)
Median age (range)	62 (39-73)	60 (33-72)	62 (33-68)	61 (42-72)
ISS I:	40 (49%)	20 (45%)	4 (36%)	15 (52%)
ISS II:	28 (34%)	9 (20%)	3 (27%)	5 (17%)
ISS III:	14 (17%)	15 (34%)	4 (36%)	9 (31%)
ECOG 0	88 (83%)	40 (75%)	13 (81%)	24 (75%)
ECOG 1	18 (17%)	12 (23%)	3 (19%)	7 (22%)
ECOG 2	0 (0%)	1 (2%)	0 (0%)	1 (3%)
High risk FISH (17p-, t(4;14) or t(14;16))	14 (14%)	13 (25%)	5 (33%)	7 (22%)
Median eGFR (range)	90 (37-182)	91 (31-137)	89 (55-112)	91 (54-137)
VRD induction	93 (88%)	38 (72%)	14 (38%*)	23 (62%*)
VCD induction	12 (11%)	12 (23%)	2 (20%*)	8 (80%*)
VTD induction	1 (1%)	3 (6%)	0 (0%*)	1 (100%*)

Table 1: Description of patients who were FDG PET/CT negative and positive at screening. FDG PET/CT positive patients were further divided into patients who converted to FDG PET/CT negativity and patients who remained FDG PET/CT positive after treatment.
* of patients treated with the individual regimen

	Before KRd consolidation		
	All treated patients	MRD positive	MRD negative
After KRd consolidation	n(%)	n(%)	n(%)
PETpos/MRDpos	7 (14,0%)	6 (27,3%)	1 (3,6%)
PETpos/MRDneg	25 (50,0%)	9 (40,9%)	16 (57,1%)
PETneg/MRDpos	4 (8,0%)	4 (18,2%)	0 (0%)
PETneg/MRDneg	12 (24,0%)	1 (4,5%)	11 (39,3%)
Discontinued	2 (4,0%)	2 (9,1%)	0 (0%)
	50 (100%)	22 (100%)	28 (100%)

Table 2: FDG PET/CT and MRD results after KRd consolidation (rows) in all treated patients, MRD positive patients and MRD negative patients (columns).

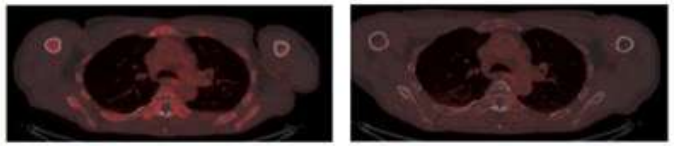


Figure 1:
FDG PET/CT before (left) and after (right) KRd treatment. Several osteolytic lesions show decreased uptake after treatment.

Conclusions

- Before KRd consolidation, 33% of patients in VGPR or better after first line treatment including ASCT were FDG PET/CT positive.
  - High-risk cytogenetics, ISS score III and VCD induction were more common in FDG PET/CT positive patients.
- After four cycles of KRd, 33% of patients converted from FDG PET/CT positivity to negativity.
  - A higher proportion in patients who were MRD negative before KRd treatment, and in patients who had received VRd
- KRd consolidation is feasible and converts a clinically significant proportion of FDG PET/CT positive patients to negativity
- Both FDG PET/CT positive and negative patients are followed to determine progression free and overall survival.

CONCLUSION

- WBLDCT is currently the minimum requirement to define active bone disease (diagnosis and re-staging at relapse)
- FDG PET/CT is currently considered the gold standard to monitor treatment response (demonstrated prognostic role and complementarity with BM techniques)
- DWI-MRI is challenging FDG PET/CT at diagnosis for sensitivity, identification of diffuse BM infiltration and correlation with biology and burden of the disease; at response evaluation, currently under evaluation
- The 3 imaging techniques are standardized