Descriptive cross-sectional study to assess the diagnostic and prognostic value of Whole-Body MRI with diffusion and 18F-FDG-PET/CT in patients with Multiple Myeloma

Final degree project

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A gigantic "thank you" to my mother, Eli; my father, Xavi; and my sister, Aïda; for supporting me and my dreams at all times. And to my partner, Àlex, for always supporting and loving me.

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3 ABBREVIATIONS

ADC	Apparent diffusion coefficient.
CEIC	Clinical Research Ethics Committee.
CMF	Flow cytometry.
CS	Cancer survival.
CS	Compressed sensing.
CT	Computed tomography.
DFS	Survival free of disease.
DWI	Diffusion weighted image.
FDG	F-fluorodeoxyglucose.
IMPeTUs	Italian Myeloma criteria for Pet Use.
IMWG	International Myeloma Working Group.
ISS	International Staging System.
MGUS	Monoclonal gammopathy of unknown significance.
MIP	Maximal intensity projection.
MM	Multiple Myeloma.
MMR	Macrophages mannose receptor.
MPR	Multi-planal reconstruction.
MRD	Minimal residual disease.
MY-RADS	Myeloma Response Assessment and Diagnosis System.
OS	Global survival.
PET	Positron emission tomography.
PFS	Survival free of progression.
ROI	Region of interest.
SMM	Smoldering multiple myeloma.
SUVmax	Maximum standardized uptake value.
TLG	Total lesion glycolysis.
ToF	Time of Flight.
VMT	Tumoral metabolic volume.
WB-MRI	Whole-body magnetic resonance imaging.

4 ABSTRACT

Title. Descriptive cross-sectional study to assess the diagnostic and prognostic value of Whole-Body MRI with diffusion and 18F-FDG-PET/CT in patients with Multiple Myeloma.

Background. Multiple myeloma (MM) is the second most frequent hematologic cancer, after Non-Hodgkin Lymphoma. Like most blood cancers, complete remission is a difficult task to achieve, therefore, prognostic factors such as treatment response and minimal residual disease (MRD) are important points to be assessed.

The most sensitive imaging technique to diagnose MM is Whole-Body MRI with diffusion using MY-RADS protocol. The most specific test to assess minimal residual disease is 18F-FDG-PET/CT using IMPeTUs guide. Since these are two different techniques, the pre-treatment acquisition with MRI, and the follow-up and post-treatment acquisition with PET/CT, cannot be compared.

Objective. To evaluate the sensitivity, specificity and predictive values of WB-MRI-DWI and 18F-FDG-PET/CT to diagnose and evaluate treatment response and MRD in patients with symptomatic Multiple Myeloma.

Methods. This protocol consists of a descriptive cross-sectional study in patients with symptomatic MM to whom WB-MRI-DWI and 18F-PET/CT will be performed to diagnose, to see the treatment response at the middle of the therapy and at the end of the therapy, and to assess MRD.

Keywords. Multiple Myeloma, Whole-Body MRI with diffusion, 18F-FDG-PET/CT, MY-RADS, IMPeTUs, treatment response, minimal residual disease.

5 INTRODUCTION

5.1 MULTIPLE MYELOMA

5.1.1 Introduction

Multiple Myeloma (MM) is an hematologic rare disease, being the second most common malignant hematologic disease. It is included in the definition of plasma cell dyscrasias, which evolves from a monoclonal gammopathy of unknown significance to plasma cell leukemia and extramedullary myeloma (1).

This disease is defined by the accumulation of **clonal malignant plasma cells** in the bone marrow that origins in a mutated germinal lymphoid B-cell lineage. This accumulation can be referred as different diseases depending on its malignancy, showing also the evolution of the illness (1–3):

- Monoclonal gammopathy of undetermined significance (MGUS): Asymptomatic premalignant proliferation of plasma cells defined by less than 10% of malignant cells. A rate of 1% a year evolves to MM. It does not require treatment.
- Smoldering multiple myeloma (SMM): A more advanced premalignant stage, clinically an asymptomatic Multiple Myeloma. This stage holds all the criteria for MM (more than 10% of malignant cells and more than 30g/l of M protein in serum or urine) but not end-organ damage. The rate of progression to MM is:
    - 10% per year for the first 5 years.
    - 3% per year the next 5 years.
    - 1% per year after the first 10 years.

  As seen, the progression of SMM to MM is very diverse, thus this stage is not treated outside clinical trials.
- Multiple Myeloma: Malignant disease with severe end-organ damage that causes significant patient morbidity and mortality.

Not all Multiple Myelomas follow the mentioned stages: all cases of MM come from MGUS; but MGUS does not always evolve to MM, in most cases it evolves to other lymphoproliferative disorders, Waldenström's macroglobulinemia or primary amyloidosis.

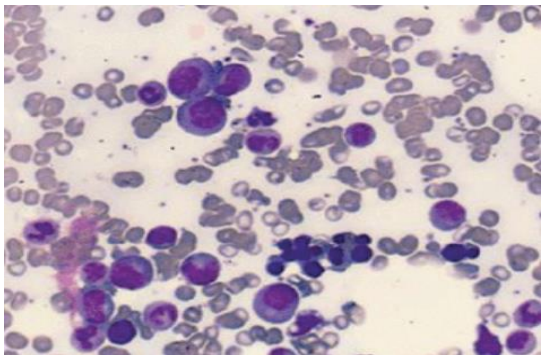

Fig 1. The larger cells with basophilic cytoplasm are myeloma cells (mutated plasma cells) (4).

5.1.2 Epidemiology

In 2018 there were 160.000 cases of MM globally, being 0'9% of all cancer diagnoses. Of these 160.000, about 90.000 were male and 70.000 female, having a sex-adjusted incidence of 2'1/100.000 and 1'4/100.000, respectively, making MM more frequent in man by 1'5. In 2016, MM cost 2'3 million disability-adjusted life years.

There is a higher incidence in the developed world, with the highest in Australia, Western Europe and in the US (in 2020, MM was the 14th most common neoplasm with 32.000 cases) (5).

MM is 10% of hematological malignancies, being black people affected twice as white people. Normally the diagnosis is on people above 65 year-old, even though there is a 3% of patients younger than 40 (1).

MM accounts for 1'1% of all cancer deaths, 59.000 male and 47.000 female, deducing a 0'15% risk of death among men and 0'10% among women.

From 1990 to 2016, the incidence of the disease increased by 126% worldwide; and in the same period, global death due MM increased by 96%. The increase of deaths is directly related to the increase of patients, but mortality has decreased: it is 18% below the maximum rate of mortality in 1994, which was 4/100.000 (5).

5.1.3 Etiology

It is still unknown what causes the disease. Studies show some risk factors, even though they lack of strong evidence (4,5):

- Radiation, although there is not an association with therapeutic radiation.
- Industrial/agricultural toxins.
- Viruses.
- Chromosomal abnormalities: these involve the immunoglobulin chain switch region on the long arm of chromosome 14.
- Family history: some studies have shown that there are family clusters of MM, especially among first-degree relatives, man and African American.

Genetic alterations are the main cause of the disease's pathogenesis, such as chromosomal translocations, aneuploidy, genetic mutations… All these aberrations may cause MGUS, SMM and MM (6).

Most of the translocations are related to the immunoglobulin heavy chain genes, most of which are in the chromosome 14. These result in the modifications of certain molecules from the cell cycle that are essential for it to progress:

- T(11;14) results in a high prevalence of CCND1 (cyclin D1).
- T(4;14) creates a high expression of NDS2 and FGFR3. Some studies have shown that this translocation holds a shorter life expectancy.
- Other translocations can be: t(14;16), t(6;14) and t(14;20).

Cytogenetic abnormality	Affected genes	Approximate frequency (%)
t(11;14)	CCND1	14-21
t(4;14)	NSD2, FGFR3	10-15
t(14;16)	MAF	3.5
t(6;14)	CCND3	1-4
t(14;20).	MAFB	1-2

Table 1. Primary chromosomal translocations related to 14q32 (6).

There are other abnormalities such as trisomy of chromosome 3, 5, 7, 9, 11, 15, 17, 18, 19 or 21. Most of them showed a protective effect on survival, except for 17,18 and 21 trisomy.

5.1.4 Diagnostic

At first, it can be difficult to diagnose MM since some patients may be presented as asymptomatic or with non-specific symptoms such as nausea, vomiting, weakness, infections, weight loss… In these cases, MM can be identified by laboratory alterations (7):

- Anemia (hemoglobin <12g per dL).
- Elevated creatinine >1’3 mg per dL.
- Hypercalcemia (calcium >10’1 mg per dL).

More advanced symptoms might be spinal cord compression, neuropathy and hyperviscosity (leading to dyspnea, heart attacks, transient ischemic attacks, and deep venous thrombosis).

It is important to do a proper differential diagnosis that involves the spectrum of plasma cell proliferative disorders; but other diseases such as metastatic cancer, benign bone lesions, and osteoporotic compression fractures, must be considered.

Laboratory parameters in serum	- Differential blood count, electrolytes, creatinine, LDH, CrP, B2-microglobulin. - Plasma coagulation, total protein, albumin. - Serum electrophoresis with densitometric determination of M protein (monoclonal protein). - Quantitative determination of Immunoglobulins (IgG, IgA, IgM, IgD). - Determination of free light chains, immunofixation electrophoresis.
Laboratory parameters in urine	- 24h urine collection with determination of free light chains. - Immunofixation electrophoresis, albumin.

Bone marrow diagnosis	Cytology and/or histology, cytogenetic investigation (chromosome analysis and FISH).
Diagnostic imaging	- Low dose whole-body computed tomography. - Supportive magnetic resonance imaging, positron emission tomography if needed.

Table 2. Tests to diagnose MM (8).

Definition of Multiple Myeloma based on International Myeloma Working Group (IMWG) criteria (9,10)

Criteria 1 and 2 must be fulfilled.

1. Clonal bone marrow plasma cells ≥ 10% or biopsy-proven bony or extramedullary plasmacytoma (lesion found in soft tissue, without bone or bone marrow being affected).
2. One or more of the items below:
    a. CRAB: evidence of end organ damage.
        i. Hypercalcemia: serum calcium >0’25mmol/L higher than the upper limit of normal or >2’75mmol/L.
        ii. Renal insufficiency: creatinine clearance <40mL/min or serum creatine >2mg/dL.
        iii. Anemia: hemoglobin <10g/dL or >2g/dL below the lower limit of normal.
        iv. Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT.
    b. Clonal bone marrow plasma cell percentage 60% or more.
    c. Involved/uninvolved serum FLC (free light chains) ratio of 100 or more.
    d. More than one focal lesion on MRI studies, at least 5 mm in size.

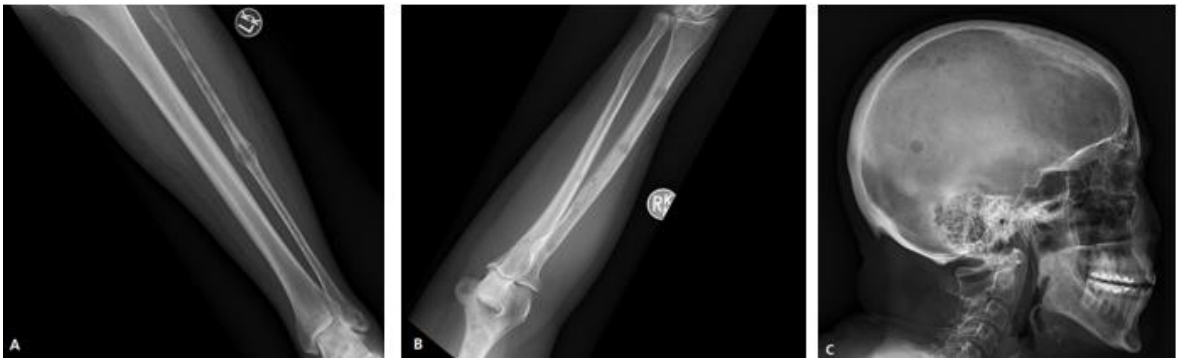

Fig 2. Lytic bone lesions in MM. A) left leg; B) right forearm; C) skull (7).

	MGUS	Smoldering myeloma	Symptomatic multiple myeloma
Proportion of plasma cells in bone marrow	<10%	≥10%	≥10%
M protein in serum	<30 g/l	≥30g/l	Detectable in serum and/or urine
End-organ damage (CRAB)	No	No	Present

Table 3. IMWG's diagnostic criteria (8).

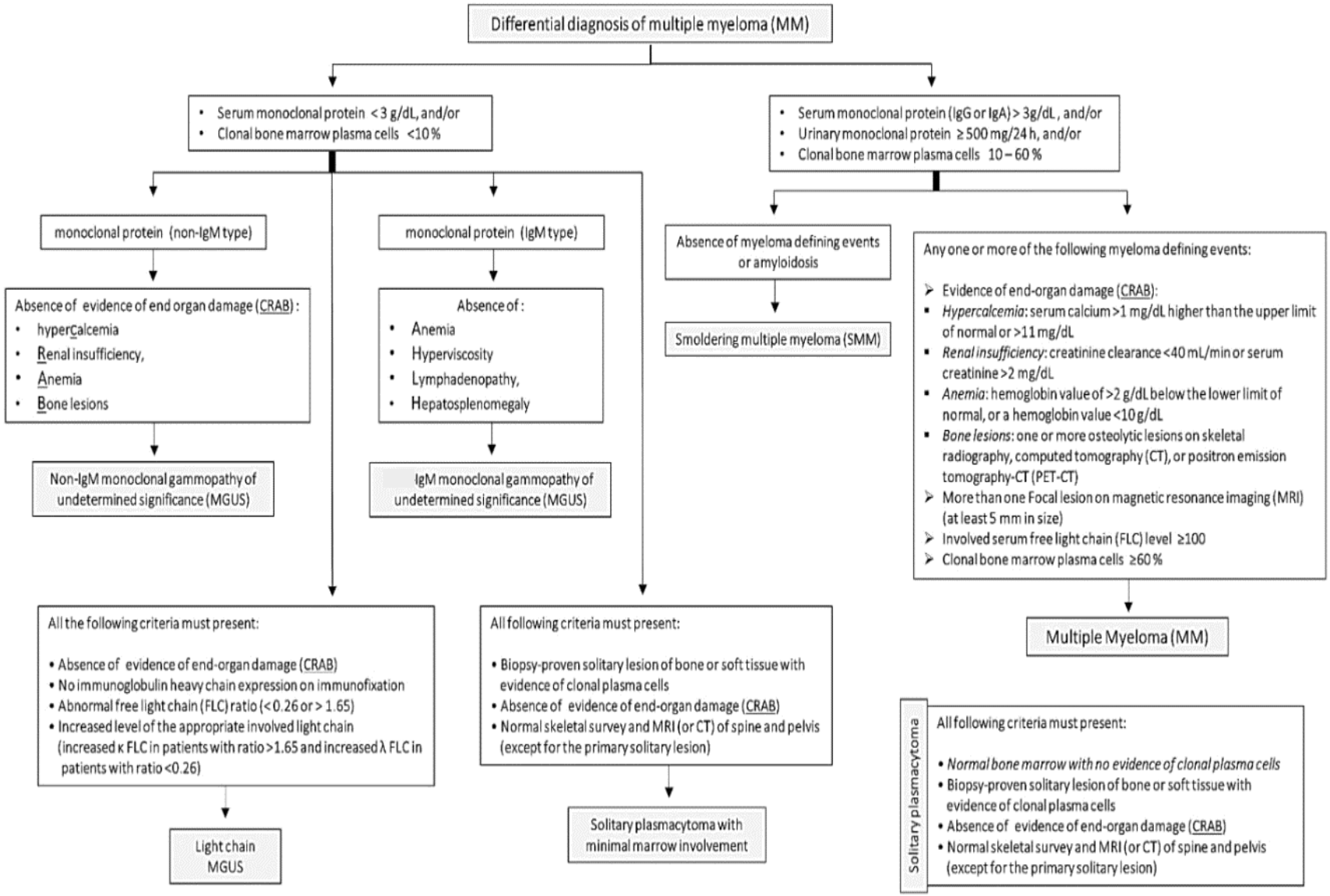

Fig 3. Differential diagnosis for MM (11).

MM can also be staged in order to express the size of the tumor mass and the number of clinical symptoms. The higher the stage, the lesser chances of survival. In actuality, the International Staging System (ISS) is used, which is not expensive and it is easy to apply (8):

Stage	Laboratory parameters	Median survival (months)
I	Serum albumin 35 g/L β2- Microglobulin <3'5 mg/l	62
II	Neither I nor III	44
III	β2-microglobulin >5'5 mg/L	29

Table 4. ISS - International Staging System (8).

5.2 IMAGING TECHNIQUES

5.2.1 Whole-Body CT

Computed tomography is a fast and available technique that uses radiation to get images of the body depending on the density of the tissues. It does not only give information of bone and muscle, but also allows to differentiate subcutaneous and visceral fat, and acquire detailed information of an organ or anatomic structure.

Normally, CT is used on a specific part of the body related to the disease to study. With only the image of a single region, it can estimate the body composition of the patient and gets an overall vision of the patient's health, but there are some limitations.

That is why whole-body (WB) CT exists; it allows to acquire a more specific body composition compared to the one that it has gotten from one single region (12).

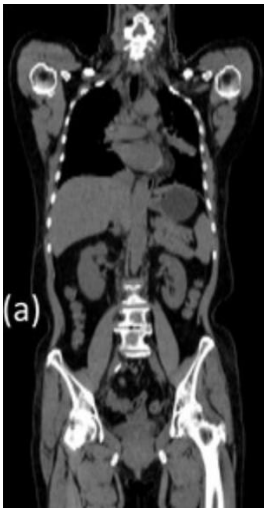

Fig 4. Whole-Body CT (12).

5.2.2 Whole-Body MRI

MRI stands for magnetic resonance imaging, a technique that uses radio waves and a powerful magnet to generate detailed pictures of the human body in a computer. It is one of the most used imaging modalities, especially for its capacity to give great images of soft tissue, the ability to use contrast (gadolinium) and the safeness of not using ionizing radiation.

The main obstacle of this technique is that these images are susceptible to artefacts due to movement, it requires a long acquisition time, and it is not as accessible as a CT.

In order to reduce the acquisition time, a compressed sensing (CS) special technique is used (13).

As well as there is WB-CT, WB-MRI also exists and it allows a more specific characterization of tissues, for example: the bone marrow. The existence of this technique allows to acquire images with all the advantages of an MRI within 45 minutes, but at the same time, to get additional morphologic and functional information of the whole body that is now crucial to evaluate the extent of systemic diseases and response to treatment.

Compared to other imaging tests (such as CT), the WB-MRI allows to get a **more sensitive** information of the disease and to use different sequences as needed, it is better for the assessment of treatment response and allows to detect metastases, which normally are unevaluable by conventional CT (unless there is soft-tissue component associated).

It is a non-invasive and well tolerated technique (excluding MRI's contraindications) that allows to do a long-term monitoring without radiation (14).

Whole-body MRI uses a special sequence called **diffusion weighted image** (DWI) to assess molecular diffusion of water, adding information about cellularity, integrity of the cell membrane and extra-cellular space. This allows to have more qualitative but also quantitative information thanks to reconstruction maps of ADC (apparent

diffusion coefficient). WB-MRI-DWI is much more sensitive to evaluate bone marrow than standard WB-MRI.

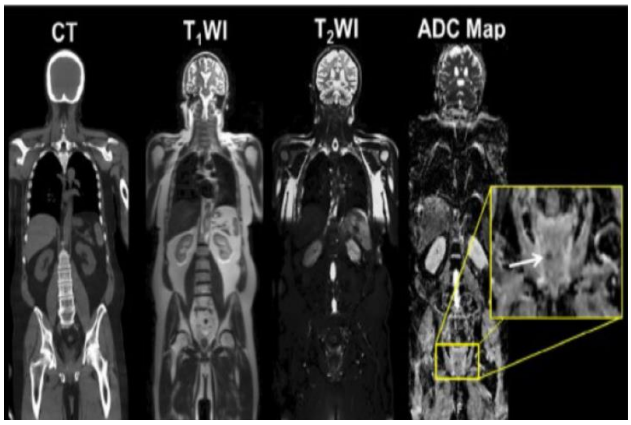

Fig 5. Example of WB-MRI-DWI in prostatic cancer (15).

Whole-body MRI is a very important technique to diagnose, assess and control MM, however a standardized methodology was needed to lessen variations in acquisition, interpretation, and reporting of the images. The protocol used is the **Myeloma Response Assessment and Diagnosis System** (MY-RADS (16)), which helps to categorize the disease and to guide patient care and treatment.

MY-RADS protocol recommends multisequence evaluations using DWI - MRI images and ADC maps (which are numeric values) (16).

5.2.3 18F-FDG-PET/CT

PET is a special type of imaging that uses a very small amount of radiopharmaceutical to track the tracer distribution in patients' bodies. Normally this technique is combined with another imaging such as CT or MRI, and the most used pharmaceutical is 18F-FDG (F-fluorodeoxyglucose).

PET alone has some limitations, such as covering only a limited part of the human body in a bed, which decreases image quality. Also, many aspects can affect its sensitivity.

A PET/CT scanner is a solution for those limitations. It can get scans with shorter acquisition time, total-body dynamic acquisition and it has the ability to detect small lesions and distant metastases (17).

There can be interpretation's problems of 18F-FDG-PET/CT, for example: there might be doubts when it comes to recent bone fractures, vertebral collapses, metallic bone implants… That is why it is important to have a standard system to interpret these images.

There is a defined visual descriptive criterion called **Italian Myeloma criteria for Pet Use** (IMPeTUs) that standardizes 18F-FDG-PET/CT readings in MM patients. It includes the visual interpretation of images to quantify FDG uptake and a morphological and anatomical aspect of FDG distribution in bone marrow non-focal lesion, focal bone lesion, para-medullary or extra-medullary.

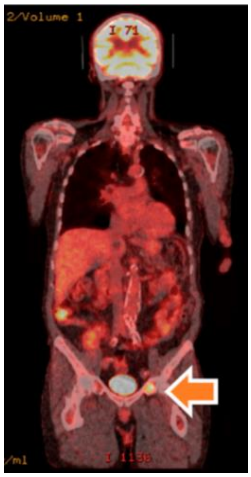

Fig 6. 18F-FDG-PET/CT (18).

IMPeTUs criteria includes: bone marrow metabolic state (BM), number and site of focal PET-positive lesions (Fx) with or without lytic characteristics (Lx), extra-medullary (EM) or para-medullary (PM) lesions and presence of fractures (Fr).

The FDG uptake is quantified using the **five-point Deauville scale** that is applied to PET scan in Lymphoma.

Even though IMPeTUs is only descriptive, it has proved to be highly reproducible for routine interpretation of 18F-FDG-PET/CT in MM and to have very good concordance between different specialists (19).

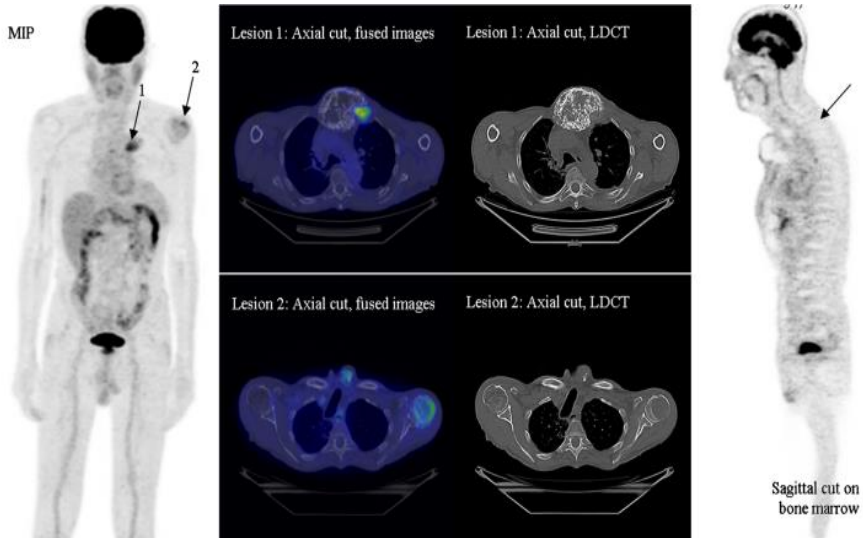

Fig 7. 18F-FDG-PET/CT of a 77-year-old patient with a 100% concordance of interpretation between reviewers using IMPeTUs: BM 2 (bone marrow affection grade 2), 2 extra-spinal hypermetabolic lesions, PM (para-medullary lesion), L2 (2 lytic lesions) (19).

5.2.4 Role of Whole-body MRI and 18F-FGD-PET/CT on the diagnosis and follow up of Multiple Myeloma

To diagnose MM, it is important to follow the criteria previously described, which includes the need to have one or more lesions of at least 5 mm in MRI studies. Only lesions detected by MRI or PET will be considered focal lesions (which are different from lytic lesions that are detected by CT, where bone destruction has already happened) (3,9,10).

At first, skeletal survey was used for the diagnose of the bone disease, given it was cheap, simple, and available. Nowadays, it is only used in case all the other techniques are not available.

Whole-body MRI is the recommended imaging technique to **diagnose** the disease (if not available, the alternative would be MRI of the spine and pelvis) because it is considered to be more sensitive than other techniques. PET/CT can be used instead of whole-body CT (as long as it fulfills the criteria of diagnostic whole-body CT).

18F-FDG-PET/CT and whole-body MRI are different techniques, but both give information of the investigated tissue: the first one, informs of its metabolic activity; whereas the second one, informs of the water and fat composition (3).

- PET/CT is considered better to assess focal lesions viability and more specific for treatment response and minimal residual disease's assessment.
- MRI is considered better to assess diffuse infiltration and more sensitive for the disease's diagnosis.

<u>Recommendations</u> (3)

MGUS

- Whole-body CT is recommended to rule out MM if there is the suspect of high risk MGUS. If whole-body CT is not available, whole-body MRI or conventional skeletal survey are alternatives.
- If there are findings, whole-body MRI is recommended, and PET/CT should be done.
- It is not recommended imaging follow-up unless clinical progression.

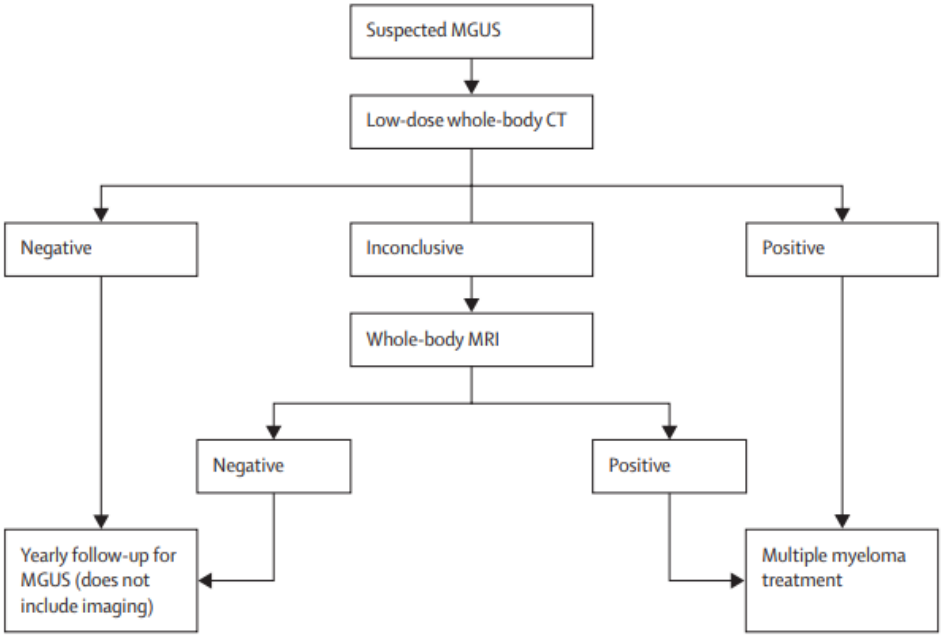

Fig 8. Imaging algorithm for MGUS (3).

Smoldering MM

- Conventional skeletal survey is not recommended to determine if there is or not bone disease.
- Whole-body CT is the choosing imaging technique to exclude osteolytic lesions. If negative, it is recommended the use of whole-body MRI. PET/CT can be used in place of both techniques if they are not available or if there are contradictions for their usage.
- Imaging follow-up should be done every year for 5 years, with the same imaging technique used for its diagnosis.

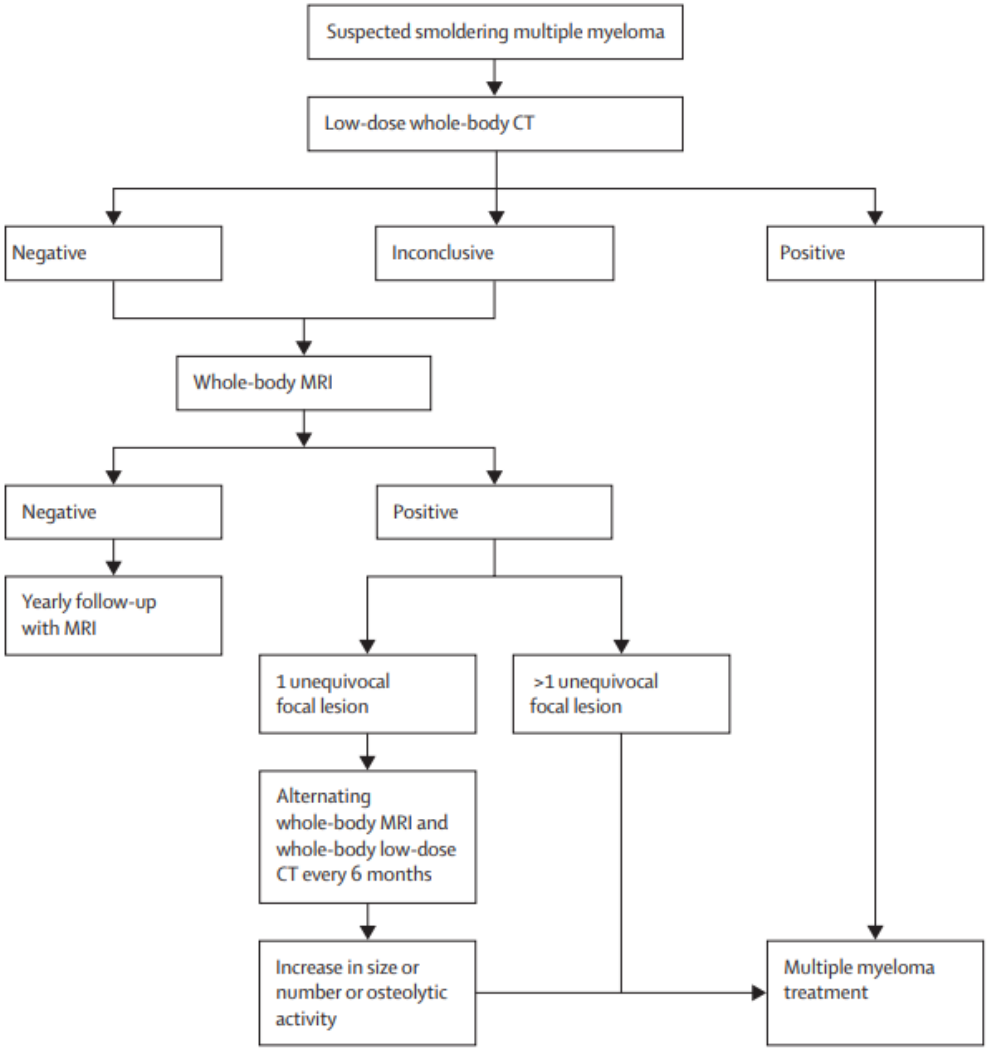

Fig 9. Imaging algorithm for Smoldering Multiple Myeloma (3).

Multiple Myeloma

- Conventional skeletal survey is not recommended to diagnose the disease.
- Whole-body CT is the imaging of choice to exclude osteolytic lesions. PET/TC can be used in its place.
- If whole-body CT is negative, whole-body MRI should be used (it is more sensitive). PET/CT can be used if not available or if there are contraindications for MRI.

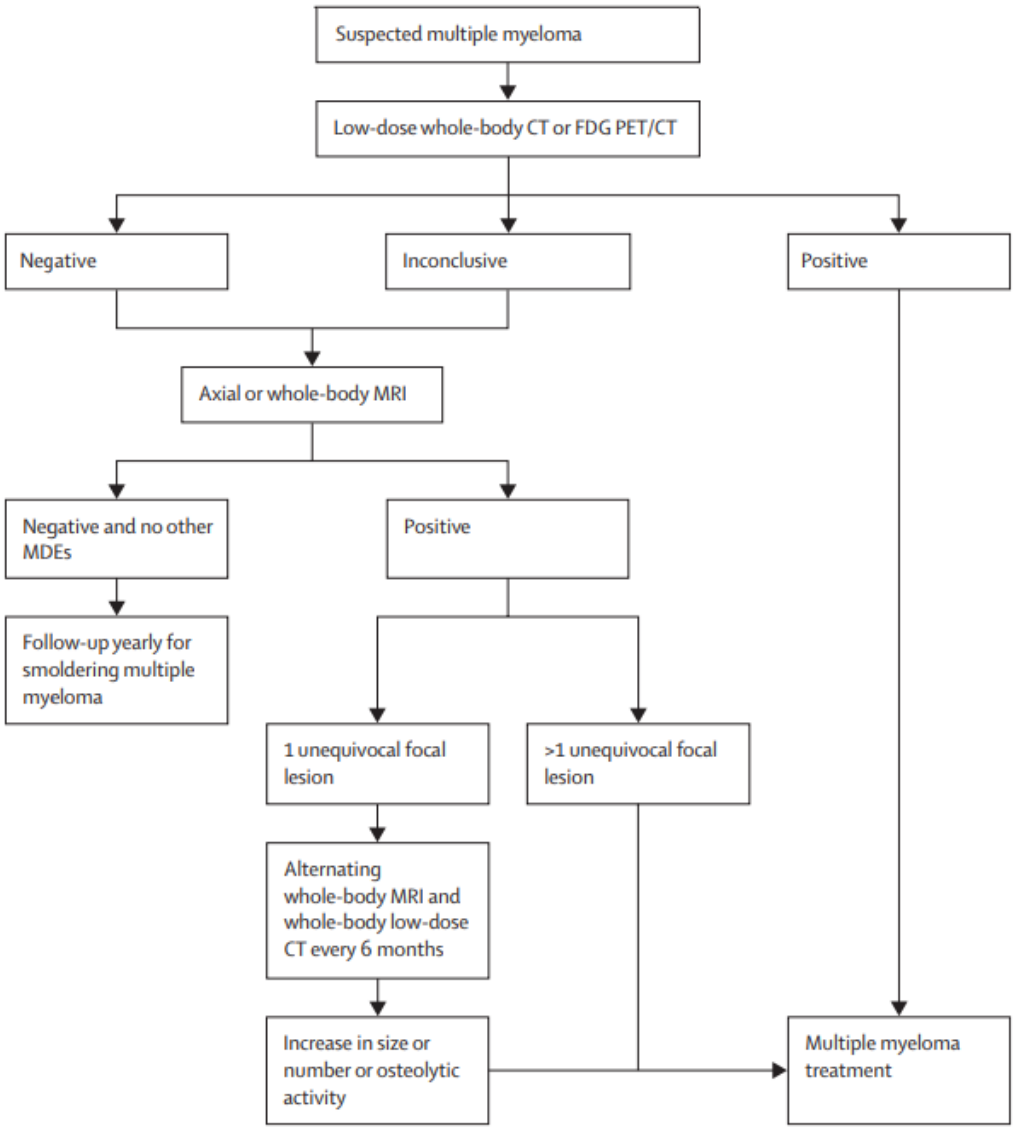

Fig 10. Imaging algorithm for Multiple Myeloma (3).

5.3 DIAGNOSTIC ALGORITHM

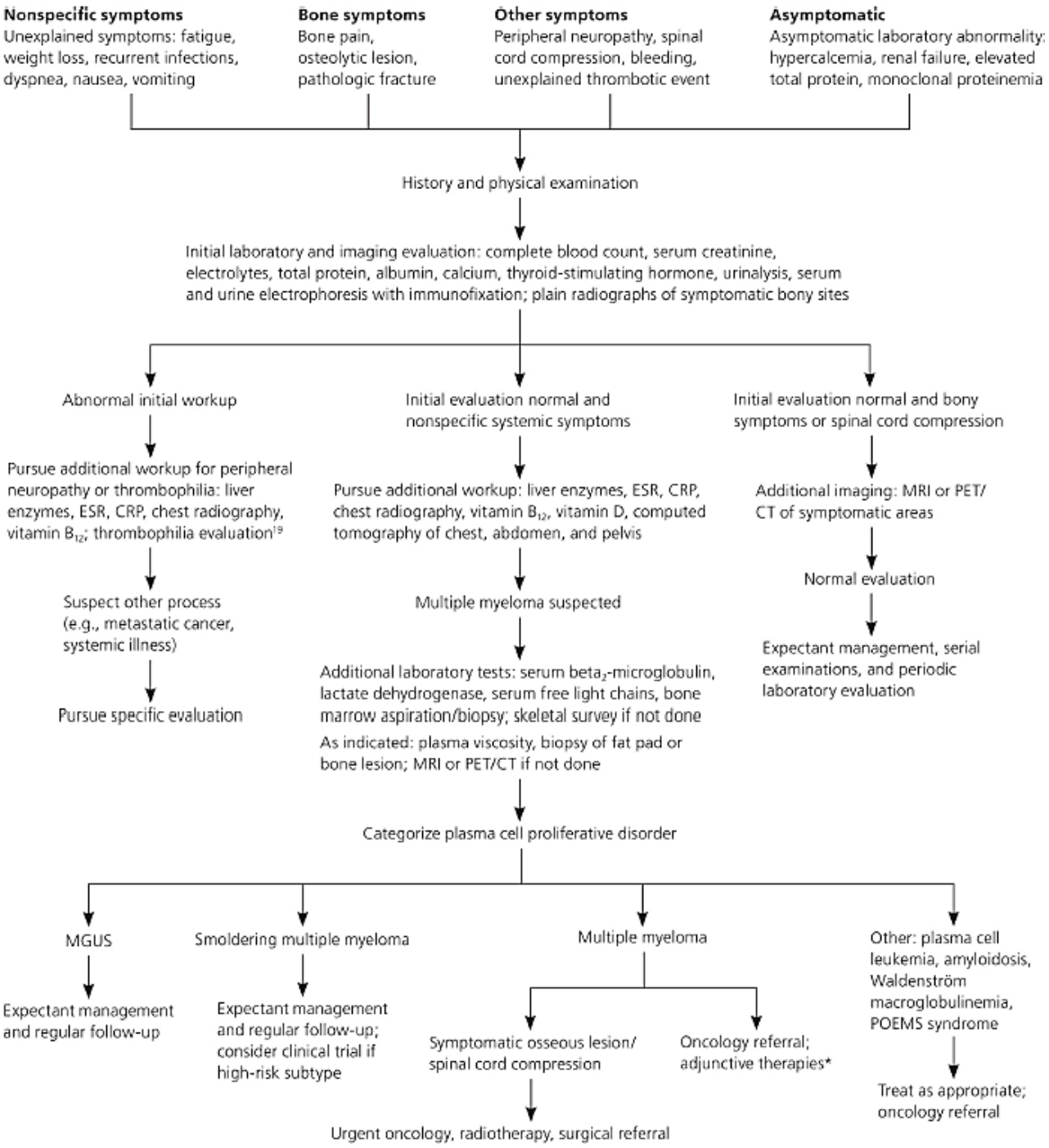

Fig 11. Evaluation and management of Multiple Myeloma (7).

5.4 IMAGING DURING FOLLOW-UP

Treatment response is defined by the measurement of M protein in serum and urine, combined with the evaluation of plasmatic cells in a bone marrow's aspirate. However, most patients categorized as full response will relapse, which can be interpreted as the persistence of the disease even when it cannot be detected by criteria and conventional techniques (minimal residual disease - MRD).

Different studies have shown that those patients that get a full response but have positive minimal residual disease, relapse sooner and have less progression-free survival than those who do not have minimal residual disease. Therefore, MRD is an important prognostic value.

The accepted techniques by IMWG to assess if there is **minimal residual disease** are multiparameter flow cytometry, next generation sequencing (NGS) and **18F-FDG PET/CT.**

However, there are still some un-solved problems such as if a WB-MRI with diffusion can be as useful (if not more) as 18F-FDG PET/CT when it comes to response evaluation and minimal residual disease, and if it has prognostic value during the follow-up.

Technically PET-CT is superior to standard MRI when it comes to treatment response, although the studies that have shown this result did not use ADC of diffusion sequence of the MRI to compare it with 18F-FDG-PET/CT. Most of the studies done in order to compare both imaging techniques were done without having standardized criteria in neither of them, even though they are available (MY-RADS and IMPeTUs).

Another question to consider is how often and when is more optimal to check for imaging techniques, and whether if the kinetics of the disease can affect the patient's evolution (depending on how much time is needed to see treatment's response).

It would also be needed to resolve whether if sex, age or other comorbidities that make professionals select one treatment or another, can affect patients' evolution (20–22).

More studies are needed in order to answer all these questions with larger samples, as several studies published at the moment comparing PET-CT and MRI were done with a small sample.

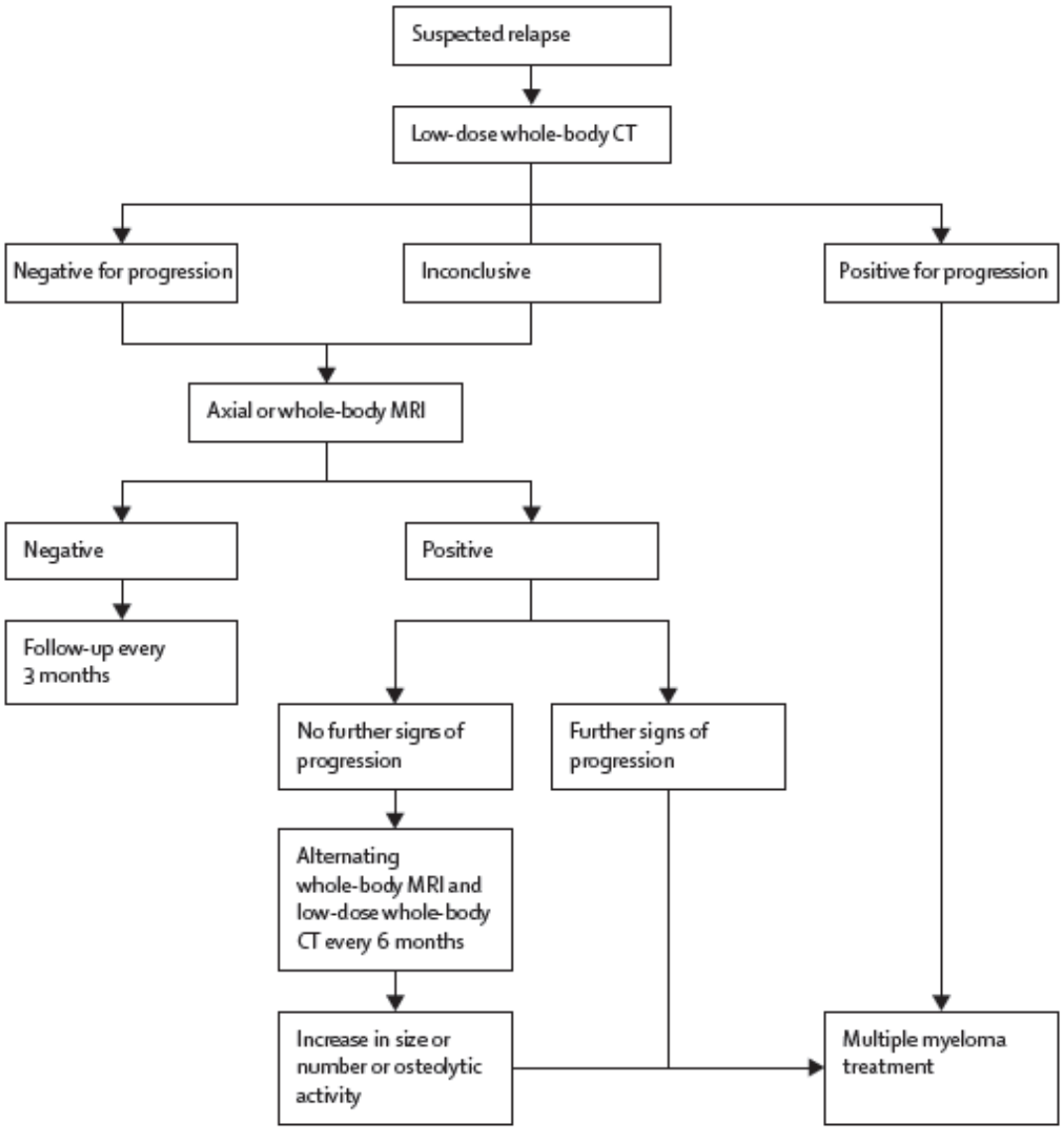

Fig 12. Imaging algorithm for suspected relapse (10).

6 JUSTIFICATION

Multiple myeloma (MM) is a type of bone marrow cancer in which there is an abnormal proliferation of plasma cells. Recent new treatments have shown increased survival of MM, and because of that, there is a need to have an early diagnosis. One **important criteria to diagnose MM** is the detection of **more than one focal lesion >5mm with whole-body MRI** even if the lesion cannot be seen with low-dose whole-body CT.

WB-MRI-DWI and 18F-FDG-PET/CT have a specific guide for its interpretation: MYRADS for whole-body MRI with diffusion, and IMPeTUs for 18F-FDG-PET/CT. There have been some studies comparing both techniques but without using the standardized criteria that they both have or with a very small sample size, thus they are not really representative on the use of the techniques and of how beneficial their usage can be to get an early diagnosis and a proper follow-up using both techniques.

Therefore, comparative studies with the standardized criteria for both of the imaging techniques are needed.

At the same time, WB-MRI with diffusion is not one of the imaging techniques approved by the IMWG to assess if there is minimal residual disease (MRD), which is an important prognostic parameter. The accepted technique by IMWG to assess MRD is 18F-FDG-PET/CT.

The problem is that if WB-MRI-DWI is the chosen one to diagnose, and 18F-FDG-PET/CT is the chosen one to assess MRD, it is not possible to know exactly the progression or evolution of the disease because two images from two different techniques cannot be compared. Therefore, to be able to compare the evolution of the disease, both items (diagnosis and MRD) should be detected by the same imaging technique.

Thus, there is not only the need to compare both techniques when it comes to the diagnosis, but also to see if they are both as useful to search for minimal residual disease, or if one of them is superior to the other.

7 HYPOTHESIS

The hypothesis of this project is that WB-MRI-DWI is better than 18F-FDG-PET/CT in the detection of Multiple Myeloma, evaluation of treatment response and detection of minimal residual disease.

8 OBJECTIVES

The main objective of this final degree project is to compare the diagnostic accuracy of the Whole-body MRI with diffusion and 18F-FDG-PET/CT in the diagnosis, treatment response and minimal residual disease.

Secondary objectives:

- To evaluate the usefulness of the standardized criteria of MY-RADS for WB-MRI with diffusion and IMPeTUs for 18F-FDG-PET/CT in the diagnosis and evaluation of the treatment response, measured with the IMWG criteria for response assessment including criteria for MRD.
- To determine the convenience and correlation between the ADC values of the WB-MRI with diffusion and the quantification values (SUVmax/VMT/TLG) of the 18F-FDG-PET/CT in treatment response, according to the IMWG criteria.
- To assess the variability between readers of the WB-MRI with diffusion and 18F-FDG-PET/CT. The studies will be interpreted by 2 professionals in each technique: 2 radiologists will interpret the WB-MRI with diffusion's images, and 2 nuclear doctors will interpret the 18F-FDG-PET/CT's images.

9 MATERIALS AND METHODS

9.1 STUDY DESIGN

Descriptive cross-sectional study in a series of patients with diagnosis or diagnostic suspicion of symptomatic MM to whom WB-MRI-DWI and 18F-FDG-PET/CT will be performed to see the treatment response half therapy, in the end of the therapy and to assess MRD (an important prognostic value). The collection of data will be prospective.

WB-MRI-DWI's images will be analyzed by 2 radiologists; 18FDG-PET/CT's images will be analyzed by 2 nuclear medicine doctors. Results of both techniques will be compared to a **bone marrow's flow cytometry**, which will be the **gold standard** for this study.

With the collected data, a statistical analysis will be performed in order to define which technique has been more accurate in the diagnosis of MM, evaluation of treatment response and MRD.

9.2 STUDY POPULATION

Patients with diagnostic suspicion or diagnosis of symptomatic MM that require imaging diagnostic for staging in order to determinate the possible diffuse and focal skeletal and extramedular affection.

9.2.1 Inclusion criteria

- Patients with diagnosis of symptomatic MM.
- Patients with suspicion of symptomatic MM.
- Patients that had not been treated yet for MM.
- Patients ≥ 18 years old.
- Signed consent form.

9.2.2 Exclusion criteria

- Patients with solitary plasmacytoma, whether it is on the bone or extra-skeletal.

- Patients with known MM already treated who have relapsed.
- Patients with background of others solid cancers.
- Patients with comorbidities that do not allow treatment for MM.
- Pregnant patients.
- General contraindications in MRI and FDG-PET/CT.
    - MRI absolute contraindications (23): cardiac pacemaker, cardiac defibrillator, cochlear implants, internal pacing wires, clips (cerebral, carotid, aortic aneurysm…), implants held in by magnet, Swan-Ganz catheter.
    - 18F-FDG-PET/CT contraindications (24): there are no absolute contraindications. Relative contraindications might be pregnant people (for the radiation), patients who breastfeed, contrast allergies if contrast is needed and elevated sugar blood levels (glucose levels will be checked prior the test).

9.3 SAMPLING

9.3.1 Sample selection

A non-probabilistic consecutive sampling method will be used. Patients with diagnosis or suspicion of symptomatic MM that require imaging diagnostic admitted in *Hospital Universitari Doctor Josep Trueta* and fulfill the inclusion and exclusion criteria will be asked to participate in the study and given an informed and consent form (*see in annex 1)*.

9.3.2 Sampling size

It is estimated that the annual incidence of MM's cases in Girona is of 45 patients per year (25). Of these, according to professionals of the *Hospital Universitari Doctor Josep Trueta*, 35 patients per year are diagnosed in this hospital.

Approximately, WB-MRI-DWI sensitivity's is 87% and 18F-FDG-PET/CT's is 64% (26) in evaluation of treatment response. Using this data and a p=q=0'5 in treatment response, *Epidat App* calculated a sample size of 108 patients. To achieve this number of participants, the study will need to last at least 3 years.

9.4 VARIABLES

9.4.1 Independent variables

The independent variables for this study will be the results of each imaging technique (evaluated by 2 professionals each: the WB-MRI-DWI will be interpreted by 2 radiologists and the 18F-FDG-PET/CT will be described by 2 nuclear medicine doctors) and the result of the flow cytometry (CMF) given by a clinical biochemistry doctor. This last technique will be the *gold standard* of this project.

The professionals will express if the results are positive or negative for the disease. These variables are qualitative, nominal and dichotomous.

9.4.2 Dependent variables

As dependent variables, the project will evaluate the survival free of disease (DFS), survival free of progression (PFS), cancer survival (CS) and global survival (OS). These variables are directly linked to the capacity of the imaging technique to evaluate treatment response and MRD: if the imaging technique cannot detect MRD, all these variables will be affected (less cancer survival, less survival free of progression…).

They will be valued by months-years, being quantitative and continuous variables.

9.4.3 Other variables

In this study other variables may alter the result, so the following will be taken into consideration:

- Co-variables: clinical data (age, symptomatology, comorbidities, staging) and laboratory parameters.
- Stratification variable: sex.

	Variable	Measurement	Description
Independent variables	Results of the imaging techniques and flow cytometry	Positive or negative	Qualitative, nominal dichotomous
Dependent variables	Survival free of disease	Months – years	Quantitative continuous
	Survival free of progression	Months – years	Quantitative continuous
	Cancer survival	Months – years	Quantitative continuous
	Global survival	Months – years	Quantitative continuous
Co-variables	Age	Years	Quantitative continuous
	Symptomatology	Bone pain: pain scale from 0 -10	Quantitative discrete
		Anemic syndrome (apathy and weakness): positive or negative	Qualitative, nominal dichotomous
		Recurrent infections: positive or negative	Qualitative, nominal dichotomous
		Renal failure: positive or negative	Qualitative, nominal dichotomous
		Pathological fractures: positive or negative	Qualitative, nominal dichotomous

		Spinal cord compression: positive or negative	Qualitative, nominal dichotomous
	Comorbidities	Comorbidities suffered by the patient	Quantitative discrete
	Staging	ISS	Qualitative, ordinal
	Laboratory	Analytical values	Quantitative continuous
Stratification variable	Sex	Female or male	Qualitative, nominal dichotomous

Table 5. Description of the main variables included in the study.

9.5 METHODOLOGY

9.5.1 Collecting clinical and laboratory data (based of the IMWG of 2014)

The diagnosis and follow-up / evaluation of the treatment response will be done in the middle and in the end of the treatment:

- Age and sex.
- Symptomatology and comorbidities.
- Analytical data: hemogram, calcium, creatinine, proteinogram in plasma and urine, urine 24 hours and quantitative nephelometry (dosage of IgG, IgM, IgD and IgA). Protein fixation in plasma and urine 24 hours. Serum free light chain and ratio in serum. Myelogram (bone marrow aspiration).

9.5.2 Imaging techniques' protocols

WB-MRI with diffusion

MRI: Philips Intera (1'5T, Release 5.7). 3 coils (1 cranium-neck and 2 for the body).

Minimum 5 stations of work depending on the patient and the possibility of changing the parameters.

With the Mobiview technique, multiple segments will be fused automatically. The sequences will be done following the recommendation of MY-RADS (*see in annex 2)*: T1 TSE coronal, T2 Dixon sagittal of the whole column, T1 Dixon sagittal of the whole column, T2 TSE axial single shot, whole-body diffusion sequence.

A coronal multi-planal reconstruction (MPR) and a maximal intensity projection (MIP) in 3D radial inverted of the diffusion b900 sequence and ADC (apparent diffusion coefficient) map will be done.

18F-FDG-PET/CT

Tomograph PET/CT (Philips Ingenuity-64TF) PIXELAR detection system, ring of 28.3360 LYSO crystals, 3D acquisitions mode and list mode, technology Astonish Time of Flight (ToF), detection system of 64 crowns (64 real cuts for a rotation of 360º), with a system of modulation and reconstruction iDose of 4th generation.

The local protocol of acquisition and European guidelines of the EANM will be followed. Fasting of 4 hours will be required.

Previous to the administration of the radiopharmaceutical, glucose in blood will be measured. If glucose is above 200mg/dl, the radiopharmaceutical will not be administered. Insulin will not be able to be administered 2 hours prior the test. Oral contrast will not be administered.

60 minutes after the administration of 3-7MBq/Kg of 18F-FDG, the whole-body acquisition will be done (head to toes, arms next to the core).

9.5.3 Image evaluation

The evaluation will be done in the diagnosis, follow-up / evaluation of the early and final treatment response, according to the criteria described in 9.5.2.

WB-MRI-DWI

Diagnosis

- It will be classified positive or negative according to the bone or extramedular affection.
- Each patient will be classified depending on the affectation pattern of the bone marrow and number of lesions according to MY-RADS (*Fig 12)*: normal – micronodular – diffuse infiltration – focal lesion (determining 5 target lesions that will be followed quantitatively with ADC) – mixt (determining 5 target lesions that will be followed quantitatively with ADC).
- Others: lesions to control because they are unspecific, or they need biopsy.
- Patients with focal lesions or mixt pattern will be registered by the number of affected areas (cervical-dorsal-lumbar column, cranium, pelvis, large bones of superior and lower extremities).
- Diffusion study will be valued qualitatively and quantitatively, registering the ADC values of 5 target lesions (the biggest or more representatives). ADC values of the diffuse affection of the bone marrow (in column and large bones) will be also registered. The higher the value, better diffusion of water, therefore lesser chances of malignancy.
- Osteopenic and pathological vertebra collapses will be registered.
- Extra-medullar affectation will be registered.
- Registration of the iliac crest trephine in order to compare its affectation with the affectation detected in the MRI.

Follow-up

- Treatment response will be classified according to MY-RADS response criteria (*see in annex 3*). RAC 1 and 2 will be considered response, meanwhile RAC 3, 4, 5 will be considered no response.

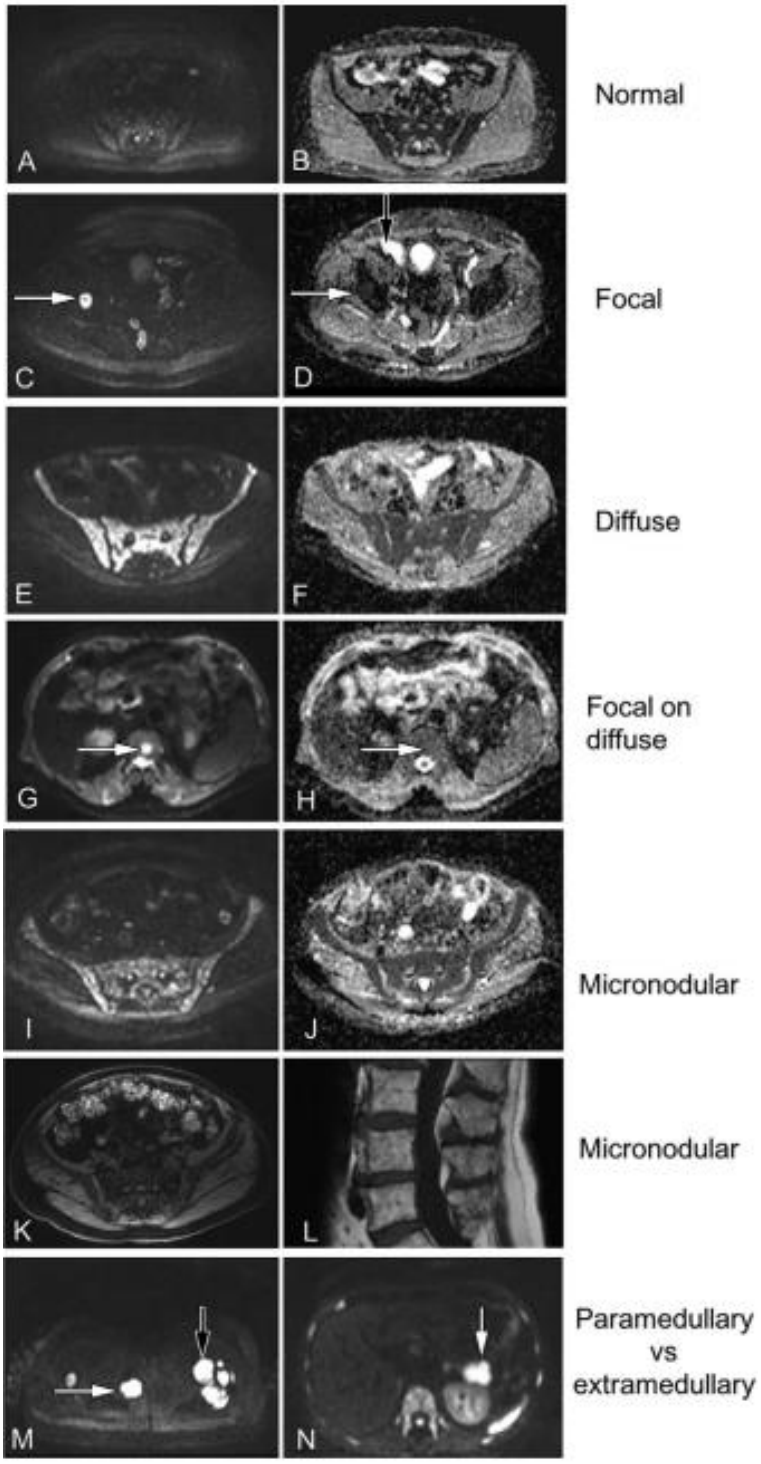

Fig 13. Affectation patterns (16).

18F-FDG-PET/CT

All studies will be evaluated following the IMPeTUs criteria and Deauville Score (*see in annex 4)*, in the diagnostic and the follow – up, according to the next criteria:

- Metabolic grade of the bone marrow.
- Number and location of metabolically active focal lesions (with or without osteolytic lesion).
- Extramedullary or paramedullary lesions. Presence and number of fractures.
- Activity grade of the FDG captures, following the 5 points of Deauville score criteria.
- Evaluation semi-quantitative of the maximum standardized uptake value (SUVmax) of the physiological captures of reference organs such as mediastínic, vascular and liver, using an area of interest (ROI) of 3 cm. These parameters will be registered and used to compare with lesions in order to have more visual analysis in doubtful cases (the comparation can also be numeric): if the SUVmax of the lesion is higher than the reference organs, it will be considered pathological. Tumoral metabolic volume (VMT) and total lesion glycolysis (TLG) calculations of the more active lesions in each territory will be done.
- If there are radiological doubts between both techniques, new explorations will be done (new sequences of MRI or CT). Biopsy can also be performed (according to criteria) to confirm the diagnosis.
- Registration of the SUVmax value of the iliac crest in order to compare with the aspirate.

All lesions detected with WB-MRI-DWI and 18F-FDG-PET/CT will be described, registered, and quantified (ADC, SUVmax).

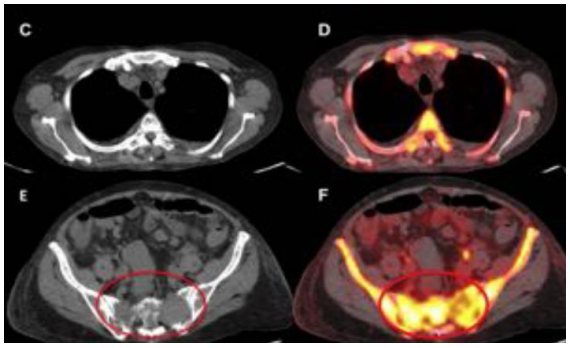

Fig 14. PET/CT showing intense metabolism of 18F-FDG in patient with MM. The circle indicates a plasmacytoma in the sacrum (27) .

9.5.4 Flow cytometry

In the diagnosis and follow-up, a bone marrow's aspirate will be performed. The sample will be processed with the flow cytometry, which will be the *gold standard* of this project to which the images will be compared to.

Samples of 1'5-2ml of bone marrow in an EDTA tube will be collected and proceed to study macrophages mannose receptor (MMR) with a sensitivity of 10-5-10-6, with a panel of 8 colors including recommended markers by Euroflow (*see annex 5)*.

9.5.5 Definition of response and relapse

The treatment response and progression will be valued according to the IMWG criteria, which includes the standardized response criteria and MRD response criteria for each technique (*see annex 6)*.

10 STATISTICAL ANALYSIS

The lesions detected in the imaging techniques will be considered **true positives** if the flow cytometry (gold standard) detects them too.

If there is no lesion in the imaging techniques and the gold standard does not detect it as well, the result will be considered a **true negative**.

The lesions detected by the imaging techniques but not by the flow cytometry, will be considered **false positives**.

If the imaging technique does not detect lesions, but the flow cytometry does, the result will be considered a **false negative**.

	Flow cytometry	
Imaging techniques	Presence of disease	No presence of disease
Presence of disease	*True positive*	*False positive*
No presence of disease	*False negative*	*True negative*

Table 6. How to calculate true positive, false positives, true negatives, false negatives.

WB-MRI-DWI

Sensitivity of WB-MRI-DWI	$\frac{true\ positives}{true\ positives\ +\ false\ negatives}$
Specificity of WB-MRI-DWI	$\frac{true\ negatives}{false\ positives\ +\ true\ negatives}$
Positive predictive value of WB-MRI-DWI	$\frac{true\ positives}{true\ positives\ +\ false\ positives}$
Negative predictive value of WB-MRI-DWI	$\frac{true\ negatives}{false\ negatives\ +\ true\ negatives}$

Table 7. Table to calculate sensitivity, specificity, positive predictive value, and negative predictive value of WB-MRI-DWI.

18FDG-PET/CT

Sensitivity of 18F-FDG-PET/CT	$\frac{true\ positives}{true\ positives\ +\ false\ negatives}$
Specificity of 18F-FDG-PET/CT	$\frac{true\ negatives}{false\ positives\ +\ true\ negatives}$
Positive predictive value of 18F-FDG-PET/CT	$\frac{true\ positives}{true\ positives\ +\ false\ positives}$
Negative predictive value of 18F-FDG-PET/CT	$\frac{true\ negatives}{false\ negatives\ +\ true\ negatives}$

Table 8. Table to calculate sensitivity, specificity, positive predictive value, and negative predictive value of 18F-FDG-PET/CT.

The imaging techniques will be interpreted by two specialist each: 2 nuclear medicine doctors for 18F-FDG-PET/CT and 2 radiologists for WB-MRI-DWI.

To avoid interobserver variability between the professionals interpreting the results, **Kappa statistic** will be used. This statistic studies the concordance between each reader. The higher the percentage, the more concordance there will be.

	Interpreter 1	
Interpreter 2	Presence of disease	No presence of disease
Presence of disease		
No presence of disease		

Table 9. Table to calculate interobserver variability.

Considering that the independent variable of the study is qualitative nominal, and the dependent variables are quantitative continuous, ***Kaplan Meier*** will be used to compare bivariate medians between positive and negative results of the imaging techniques.

In addition, a multivariate ***Cox regression analysis*** (Cox proportional-hazards model) will be performed including all co-variables for each dependent variables to avoid alterations in the main association the study analyzes.

11 ETHICAL AND LEGAL CONSIDERATIONS

This protocol will be reviewed by ***The Clinical Research Ethics Committee*** *(CEIC) of the Hospital Universitari Doctor Josep Trueta*. All the corrections and annotations given will be taken into consideration and introduced to the study. In order to start, CEIC'S approval must be received.

Each participant will be given a consent form in order to be able to participate. Patient's must have read, understood, and signed the consent form (*see annex 1)*, previously evaluated and approved by the CEIC.

The study will follow the ethical principles of the ***Declaration of Helsinki***, last revised at the World Medical Association's 64th General Assembly (Fortaleza, Brazil, October 2013). It will also follow the ***Principles of Biomedical Ethics by Beauchamp and Childress of 1979****,* last reviewed in 2009. This project must also obey the "*Ley 14/2007 de 3 de Julio de Investigación Biomédica, que regula las investigaciones relacionadas con la salud humana".*

- Beneficence: Obligation to act for the benefit of others. This protocol will have potential benefits for MM patients. If WB-MRI-DWI is considered more useful than 18F-FDG-PET/CT, it will allow patients to have imaging controls with a non-invasive and non-radioactive technique, which will benefit them since they will need multiple imaging controls.
- Autonomy: The respect of any personal decisions of the individual. All patients' decisions will be respected in order to protect their autonomy. Participants will be informed accordingly and will be provided a consent form, accepting or refusing to participate in the study as well as abandon it.

  Patient's autonomy will be protected and respected according to the "*Ley 41/2002, de 14 de noviembre, básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica".*

  All personal data will be protected and used accordingly to the "*Reglamento (UE) 679/2016 del Parlamento Europeo y del Consejo, de 27 de abril de 2016, relativo a la protección de las personas físicas en lo que respecta al*

tratamiento de datos personales y a la libre circulación de estos datos", and "*Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales".*

- Justice: Equitable distribution of well-being benefits avoiding any discriminatory treatment. Neither positive nor negative discrimination for any reason will be present in the study. As long as the patients fulfill the inclusion and exclusion criteria, they will have access to the study.
- Non-maleficence: No malicious acts will be done. The supplementary tests outside of protocols that will be applied won't cause damage to our participants as long as they do not have contraindications for its usage (in which case they would be excluded from the study).

This project will be using sanitary products (the imaging techniques), therefore it will follow *"La Regulación (EU) 2017/745 del Parlamento Europeo y el Consejo del 5 Abril 2017 sobre los productos sanitarios"* and "*Real Decreto 1/2015 del 24 de Julio sobre la Ley de garantías y uso racional de los medicamentos y productos sanitarios".*

All the researchers in this study will be asked to sing a non-conflict declaration.

12 STUDY LIMITATIONS

The main limitation of this project is the low prevalence of the disease and the long treatment time. The disadvantages of these are that the data collecting and the following will be longer, and this can cause information loss.

Another limitation could be the exclusion criteria since not every patient with MM will be included, only those who are symptomatic and serious enough to go to the hospital. This will cause that even though there are approximately 35 cases of MM in the *Hospital Universitari Doctor Josep Trueta* per year, not all of them will be included in the study.

Other characteristics of the patients, such as the advanced age and comorbidities, might influence the tolerance of the treatment: if it is not well tolerated, this might delay the chemotherapy administration, changing the homogeneity of the sample and the times of the response valuation. This can happen up to 10-15% of the patients.

The limited access to MRI and its susceptibility to artefacts are other limitations to consider in this study. This would not apply to 18F-FDG-PET/CT since it is more accessible (there are less indications for its usage, so the waiting list is not as long as the MRI's), even though it uses radiation and is more expensive.

13 WORKING PLAN AND CHRONOGRAM

13.1 RESEARCH TEAM

The research team will be composed by the following members:

- ***Director of the research.*** This member will be responsible of the execution of the project, as well as the application of the proper protocol.
- ***Coordinator of the research.*** The coordination of the researchers and physicians will be the main task of this member.
- ***Principal investigator.*** This researcher will be the responsible of the main idea of the study and its planning: will be the one to create the study and the protocol as well as presenting the project to CEIC. This member will also recruit the rest of the research team and the patients and work together with the director and the coordinator to make sure that the protocol planned is well applied and respected.
- ***Hematology doctor.*** This doctor will be the responsible of explaining the study to the patients and to present and collect the consent form, as well as performing all the tests and visits stablished in the disease's protocol.
- ***Nuclear medicine doctors.*** Two nuclear medicine doctors will be needed to interpret the results of the 18F-FDG-PET/CT.
- ***Radiologists.*** Two radiologists will be needed to interpret the results of the WB-MRI-DWI.
- ***Clinical biochemistry doctor.*** This member will be needed to perform the bone marrow's aspirate, analyze the sample and process it with the flow cytometry. This doctor will process other samples of the patients, such as blood samples.
- ***Health personnel.*** Nuclear medicine technicians, radiology technicians, nurses and laboratory technicians will be needed in order to carry out this project properly.
- ***Statistician***. This member will perform the statistical analysis of the results.
- ***Data manager***. Responsible of the data collecting, processing and report writing.

13.2 WORKING PLAN

This study will be conducted in different stages, with a total duration of 3 years, starting November 2023 and finishing in April 2027.

Stage 0. Study design (November 2023 - December 2023)

In this stage, the main protocol will be created. In order to do so, extensive bibliographic research will be done, and the current project will be written.

Stage 1. Protocol review (December 2023 – February 2024).

The protocol will need to be evaluated by the Clinical Research Ethic Committee (CEIC) of the *Hospital Universitari Doctor Josep Trueta* for its approval before its application.

Stage 2. Initial coordination (February 2024 – March 2024)

During this period, the firsts meetings with the whole research team will be done. This will allow to do a proper application of the protocol and a proper coordination of each researcher. The dates of each of the following stages will be decided and any doubts of the project will be revised.

Stage 3. Sample recruitment (March 2024 – December 2026)

During this period of time, patients with MM that fulfill the inclusion and exclusion criteria will be added to the study. The first battery of tests will be performed in order to diagnose and assess the severity of the disease. This stage includes:

- Hematology visit: to explain the study and collect the consent form.
- Carrying out the imaging techniques in order to have an initial assessment (WB-MRI-DWI and 18F-FDG-PET/CT). Laboratory samples will also be collected.
- Patient codification and introduction of the data in the data base.

Stage 4. Clinical follow-up of patients and data collection (March 2024 – March 2027)

In this stage, patients will have another visit to the hematology doctor that is responsible for their treatment in order to evaluate treatment response clinically and analytically.

Patients will have an early and final treatment evaluation with both imaging techniques and the flow cytometry.

Stage 5. Statistical analysis and data interpretation (February 2027 – March 2027)

From February 2027 to March 2027, the statistician will use statistical test to analyze it and facilitate its comprehension.

The research team will meet in order to discuss the results.

Stage 6. Final report configuration and study publication (March 2027 – April 2027)

The principal researcher will complete the project with all the discussion and conclusions in order to publish them in a scientific journal and being able to present it in any lecture or talk about Multiple Myeloma.

13.3 CHRONOGRAM

Stage	Task	Period																			
		2023		2024												2025	2026	2027			
		Nov	Dec	Jan	Feb	Mar	Apr	May	Jn	July	Aug	Sep	Oct	Nov	Dec	J-D	J-D	Jan	Feb	Mar	Apr
Stage 0	Study design																				
Stage 1	Protocol review																				
Stage 2	Initial coordination																				
Stage 3	Sample recruitment																				
Stage 4	Follow – up																				
	Data collection																				
Stage 5	Statistical analysis																				
	Data interpretation																				
Stage 6	Final report																				
	Study publication																				

14 BUDGET

In this project, the following budget will be followed:

- ***Personnel expenses***. The researchers and other professionals participating in this study will not receive extra remuneration since their participation will be included during their normal working hours.

  The principal investigator cost will not be included in the budget to avoid financial incentive to join the study.

  A statistician will be hired for 25 € per hour, with approximately 70 hours of work, costing 1.750€.
- ***Diagnostic and follow-up expenses***. Imaging techniques can be expensive, but there are special prices for studies included in projects making the cost more affordable.
  - WB-MRI-DWI scan: each patient will need 3 WB-MRI-DWI: one for the diagnosis, one for the early response and one for the late response and MRD. The cost of one WB-MRI-DWI is estimated to be around 250€, therefore, the cost per patient would be 750€. Since WB-MRI-DWI are already tests performed by the hospital in the disease's protocol, the cost of them will not be included in the study's budget.
  - 18F-FDG-PET/CT scan: a total of 3 PET/CT per patient will be needed: one for the diagnosis, one for the early response and one for the late response and MRD. The cost of one PET/CT is 350€, therefore, the cost per patient would be around 1.050€.
  - Other analysis tests: such as blood work, bone marrow's aspirate, flow cytometry... will not be included in the budget since these tests are already standardized in the disease's protocol.
- ***Material expenses***. Printing the protocol once, and the consent and information forms for each patient, will be included in the budget. Each side is printed at 0'06€.
- ***Assistance to an International Congress***. The average cost for assisting an International Congress is 2000€.

- ***Publication expenses***. The cost of publishing one study in an international Open Access Medical Journal is estimated to be around 1.500€.
  An additional cost for the edition, formatting, revision, and translation will be of 1.000€. In total, publication expenses will cost around 2.500€.

Expenses		**Cost per unit**	**Number of units**	**Subtotal**
Personnel expenses	Investigators	-	-	0€
	Statistician	25€/hour	70 hours	1.750€
Diagnostic and follow-up expenses	WB-MRI-DWI scan	-	-	0€
	18F-FDG-PET/CT scan	1.050€/patient	108	113.400€
	Other analysis tests	-	-	0€
Material expenses: printing		0’06€	823	50€
International Congress’ assistance		2.000€	1	2.000€
Publication expenses		2.500€	1 publication	2.500€
			TOTAL	119.700€

Table 10. Budget.

15 FEASIBILITY

All the professionals involved in the project have experience within Multiple Myeloma and their diagnostic techniques to manage properly the disease. This protocol is considered feasible because of the high expertise and professionalism of the responsible team.

The *Hospital Universitari Doctor Josep Trueta* provides all the technical resources and reporting rooms with all the available working stations to read and process the imaging acquisition from all the examinations.

Concerning the budget, the hospital will provide economic cooperation. Moreover, the research team will apply to different national and international calls in order to receive grants to afford the budget of the project.

16 CLINICAL IMPACT

Due to the change in expectations regarding survival that has recently been improved in patients with Multiple Myeloma (thanks to the introduction of new drugs), research in this field is of great importance to improve the quality of life of these patients.

Important clinical impact would be:

- To have an early diagnosis, a correct assessment of the response to treatment and determine which tests provide a greater prognostic value at different time points of the disease. Thus, it will allow to begin treatment early and subsequently adapting it to the specific situation of each patient according to their evolution.
- To detect minimal residual disease because it can change completely the prognosis of the patient. If the most sensible test is used to assess MRD, a negative answer will determine higher chances of full remission, cancer survival, time free of progression.

Our study will facilitate the availability of more appropriate and simplified diagnostic algorithms that indicate the use of the same imaging test in the diagnosis and monitoring of the disease. It would be of great importance and benefit for the patient, minimizing the stress caused by duplication and change of diagnostic tests, and at the same time it would be more cost-effective with whichever of the tests is decided to perform (according to the results of the study): in case of WB-MRI-DWI, it would be cost-effective because it is the most economical test of the two (and radiation would also be avoided); but the selection of 18F-FDG-PET/CT would also be economical if it meant avoiding duplication of diagnostic tests.

The result and, consequently, the recommendation of a standardized management of patients with MM would be of direct applicability in our centers, given that the researchers, that are also healthcare physicians, would carry out the transmission between the rest of the responsible professionals through the Care Committee and the Functional Multiple Myeloma Unit of the hospital, in which the professionals and several of the researchers participate.

On the other hand, the study would be transferable by introducing and discussing the results in future updates to the Multiple Myeloma Oncological Guides of our autonomous community.

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18 ANNEXES

ANNEX 1: CONSENT AND INFORMATION FORMS

The following documents will be available in Catalan and Spanish.

Hoja de información al paciente

Estudio: Evaluación del valor diagnóstico y pronóstico de la Resonancia magnética de cuerpo entero con difusión y el 18F-FDG-PET/TC en pacientes con Mieloma Múltiple.

Investigadores principales: Dr. Kai Vilanova Busquets y Yaël Fibla Esteban.

Centro: Hospital Universitario Doctor Josep Trueta.

Introducción

Nos dirigimos a usted para informarle sobre un estudio de investigación en el cual se le invita a participar. Nuestra intención es que reciba la información adecuada para que pueda decidir si acepta o no participar. Tómese el tiempo necesario para leer y entender el documento, y pregunte cualquier aspecto que le provoque dudas o que no sea de su comprensión.

Si decide participar, solicitaremos que firme el consentimiento informado. Le proporcionaremos una copia de ambos documentos y los originales quedaran archivados con la documentación del estudio.

El protocolo ha sido aprobado por el Comité de Ética de la Investigación, conforme la "*Ley 14/2007, de 3 de julio, de Investigación biomédica*". También ha sido diseñado con las recomendaciones éticas descritas en la *Declaración de Helsinki de 1964* y en el *Convenio de Oviedo del Consejo de Europa de 1977, ratificado en 1999.*

Participación voluntaria

Deseamos hacerle saber que la participación en el estudio es completamente voluntaria y puede decidir participar o no sin alterar su relación con su médico o

cualquier perjuicio hacia usted o su atención sanitaria. En caso de aceptar, puede retirar el consentimiento en cualquier momento y por cualquier motivo.

Los investigadores podan retirarlo del estudio si consideran oportuno. En dicho caso, usted recibiría una explicación adecuada del motivo causante de su retirada.

Objetivo del estudio

Se le invita a participar en este estudio porque le han diagnosticado Mieloma Múltiple, una enfermedad maligna de unas células sanguíneas llamadas células plasmáticas.

El objetivo de este estudio es la función diagnóstica i pronóstica de la resonancia magnética de cuerpo entero con difusión y el 18F-FDG-PET/TC en pacientes con Mieloma Múltiple. Esto permitirá en un futuro adecuar las pruebas diagnósticas para poder usar aquella que muestre mejor resultado en la detección de la enfermedad y en la valoración de respuesta del tratamiento o enfermedad mínima residual.

Descripción del estudio

Este estudio se realizará en el *Hospital Universitario Doctor Josep Trueta,* participando aproximadamente 108 personas afectadas de Mieloma Múltiple.

Al padecer la enfermedad, se someterá a una serie de visitas médicas y pruebas que están consensuadas para el diagnóstico y tratamiento de su enfermedad, entre ellas la resonancia magnética de cuerpo entero con difusión. Si decide participar en el estudio, se le hará de forma complementaria el 18F-FDG-PET/TC en el momento de diagnóstico, a mitad de tratamiento y al final del tratamiento.

Este estudio durará aproximadamente 3 años, en el cual se le realizará un seguimiento de su enfermedad según establece el protocolo del Mieloma Múltiple, a la vez que las pruebas de imagen previamente comentadas en el momento de diagnóstico, a mitad de tratamiento y al final del tratamiento. Todas estas pruebas serán aplicadas en las instalaciones del *Hospital Universitario Doctor Josep Trueta.*

Riesgos y molestias de su participación en el estudio

La resonancia magnética tiene bajo riesgo de complicaciones y no aplica radiación. Lo más habitual son molestias por la incomodidad que supone estar quieto durante mucho rato mientras la prueba de imagen se está realizando. También puede sentir incomodidad por el ruido que hará la máquina, o por estar metido dentro del tubo, sobre todo si padece de claustrofobia (miedo a los espacios cerrados).

El PET/TAC es una prueba segura y fácil de hacer, pero que emite radiación, aunque esta será de baja dosis y no representará ningún perjuicio hacia su salud. Para esta prueba se le administrará un isotopo radioactivo (18F-FDG) de forma endovenosa. Este isótopo tiene una radiación muy baja, que no afectará en su salud. En caso de que se quedara embarazada, no podría participar en el estudio ya que la radiación podría afectar al feto.

Precauciones

El 18F-FDG es un isótopo radiactivo que no afectará a su salud ni a la de sus convivientes, por lo cual no deberá realizar ningún tipo de aislamiento.

Se recomienda que las horas posteriores a la administración, hasta el día siguiente, no se acerque a niños o embarazadas.

Beneficios

No verá beneficios directos por su participación. No obstante, los conocimientos adquiridos gracias a ella pueden ayudar al avance médico y a otras personas.

Advertencia sobre el embarazo

Si usted está embarazada no podrá participar este estudio por el riesgo a la exposición de radiación dañina para el embrión/feto, siendo esta situación un criterio de exclusión.

Procedimientos alternativos

Si usted decide no participar en el estudio, se le aplicaría el protocolo diagnóstico y de tratamiento ya establecido en el hospital para el Mieloma Múltiple. No se le haría

el 18F-FDG-PET/TC en el momento de diagnóstico, a mitad de tratamiento y al final del tratamiento; pero si todo el resto de las pruebas.

Derecho a la revocación del consentimiento

Deseamos hacerle saber que su participación es voluntaria y que puede retirar su consentimiento en cualquier momento del estudio sin que haya un perjuicio a la relación con su médico o hacia su atención sanitaria. No obstante, los datos obtenidos hasta el momento de la revocación podrán ser conservados y utilizados para el estudio.

Protección de datos personales

El promotor y el centro se comprometen al cumplimiento del "*Reglamento (UE) 2016/679 de 27 de abril relativo a la protección de las personas físicas en relación con el tratamiento de sus datos personales*" y a la normativa española de aplicación: "*Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales*" y "*Ley Orgánica 15/1999, de 13 de diciembre, de Protección de Datos de Carácter personal y en su reglamento de desarrollo, aprobado por el Real decreto 1720/2007, de 21 de diciembre*".

Todos los datos que se recojan se utilizarán única y exclusivamente con la finalidad previamente expuesta en este documento.

Los datos recogidos serán identificados con un código, de manera que no haya forma de relacionar la información con su persona. Los datos codificados pueden ser compartidos con terceros u otros países con la finalidad del estudio o para su publicación, siempre manteniendo su información personal confidencial para que usted no pueda ser identificado.

El promotor adoptará las medidas necesarias para garantizar la protección de su privacidad y no permitirá que sus datos crucen con otras bases de datos que pudieran permitir su identificación.

El acceso a dicha información queda reservada a los profesionales sanitarios (Médicos, enfermeras, auxiliares y técnicos), las autoridades sanitarias, el Comité

de Ética de la Investigación y el personal autorizado por los investigadores principales. El acceso será permitido para comprobar datos, procedimientos, y para un buen cumplimiento de la práctica clínica. Su identidad solo sería revelada en caso de urgencia médica para su salud o requerimiento legal.

El investigador principal y el centro son responsables de su protección de datos y, para lograrlo, se comprometen a cumplir la normativa mencionada.

En caso de retirada del estudio, no se recogerá ni procesará nueva información sobre usted, pero los datos recogidos hasta el momento serán conservados y podrían utilizarse si ya han sido analizados o publicados. En cualquier caso, usted puede exigir su destrucción o anonimización.

Compensación económica

No percibirá ninguna compensación económica por su participación en este estudio.

Otra información relevante

Cualquier nueva información que se descubra durante su participación y que se estime que puede afectar a su disposición a participar, le será comunicada por su médico lo antes posible.

Al firmar la hoja de consentimiento adjunta, se compromete a cumplir con los procedimientos del estudio previamente expuestos.

Contacto en caso de dudas

Si presenta algún tipo de duda a través de la lectura de este documento, puede preguntar al personal sanitario que se lo ha administrado.

Si en cualquier momento de su participación desea obtener más información o tiene alguna duda, contacte con Yaël Fibla Esteban.

Consentimiento informado

Estudio: Evaluación del valor diagnóstico y pronóstico de la Resonancia magnética de cuerpo entero con difusión y el 18F-FDG-PET/TC en pacientes con Mieloma Múltiple.

Yo, _____,
con DNI_____, de nacionalidad _____,
mayor de edad, con domicilio _____.

Declaro que:

- He recibido y he leído la Hoja de información al paciente.
- He recibido la información necesaria para entender:
    - Los objetivos del estudio y sus procedimientos.
    - Los beneficios y perjuicios del estudio.
    - El trato y la finalidad de mis datos personales.
- He podido hacer todas las preguntas necesarias para una mejor comprensión y que dichas preguntas han sido contestadas de forma suficiente y satisfactoria por el investigador responsable.
- He estado informado/da por el investigador _____.
- Entiendo que mi participación es voluntaria y que en cualquier momento puedo revocar mi consentimiento.
- Doy permiso para el uso de los datos obtenidos con el estudio y de mi historia clínica para los fines de este proyecto.
- Entiendo la confidencialidad de mis datos y el uso que estos tendrán.
- Se me ha entregado una copia de la hoja informativa y de este consentimiento informado.

Acedo a que los médicos responsables del estudio contacten conmigo en un futuro si se encuentra oportuno añadir nuevos datos a los recogidos: SI NO

Al firmar este documento, presto voluntariamente mi consentimiento a participar en el estudio y al acceso y utilización de mis datos según se describe en la Hoja de información que se me ha entregado.

Recibiré una copia firmada y fechada de este documento de consentimiento informado.

_____ de _____, 20_____.

Firma del investigador Firma del participante

Revocación del consentimiento

Yo, _____,
con DNI _____, revoco el consentimiento previamente signado para la participación del estudio previamente especificado.

_____ de _____, 20_____.

Firma del investigador Firma del participante

ANNEX 2: MY-RADS

No.	Sequence Description	Core Clinical Protocol	Comprehensive Assessments for Research
1	Whole spine: sagittal, T1-weighted, fast spin-echo, section thickness of 4–5 mm	Yes	Yes
2	Whole spine: sagittal, T2, STIR or fat-suppressed T2-weighted, section thickness of 4–5 mm	Yes	Yes
3	Whole body (vertex to knees): T1-weighted, gradient-echo Dixon technique. Fat and water image reconstructions are mandatory and should be used to generate fat fraction maps (FF = F/(F+W) × 100%). (A 3D fast spin-echo T1-weighted sequence offering multiplanar capability may be performed as an alternative to replace sequences 1 and 3.)	Axial or coronal (5 mm)*	Axial and coronal
4	Whole body (vertex to knees): axial, diffusion-weighted, STIR fat suppression, 5 mm contiguous sectioning, multiple stations.	2 *b* values (50–100 sec/mm^2 and 800–900 sec/mm^2)	3 *b* values (additional 500–600 sec/mm^2)
	ADC calculations with monoexponential data fitting		
	3D MIP reconstructions of highest *b*-value images†		
5	Whole body (vertex to knees): axial, T2-weighted, fast spin-echo without fat suppression, 5-mm contiguous sectioning, multiple stations, preferably matching the diffusion-weighted images	Optional	Yes
6	Regional assessments: for example, symptomatic or known sites outside standard field of view, through sites of suspected cord compression, nerve root involvement, extramedullary disease	Usually not	Optional

Note.—ADC = apparent diffusion coefficient, MIP = maximum intensity projection, STIR = short inversion time inversion-recovery, 3D = three-dimensional.

* 5-mm axial imaging may be chosen to match section thickness of diffusion-weighted imaging to facilitate image review.

† Whole-body 3D MIP images displayed as a sequence of coronal or sagittal MIP images rotating in the axial plane (≤3 degrees of rotation per frame) by using an inverted gray scale.

Fig 15. MY-RADS' sequence components (16)

Clinical Reporting Template	Notes
Indication	
Technique	Core or comprehensive protocol, additional sequences and deviations
Findings	
Dates of previous examinations	
Evaluation of bones	Spine and then head to thighs in descending order
Measurements of up to five focal lesions and document pattern of marrow infiltration	Normal, focal, focal on diffuse, diffuse, micronodular*
Paramedullary or extramedullary sites	Measure size
Vertebral fractures	Document presence and use a combination of morphologic and functional imaging to characterize as benign versus malignant. Source.—Reference 52.
RAC for each anatomic region†	Cervical spine, thoracic spine, lumbar spine, pelvis, long bones, skill, ribs or other
1: Highly likely to be responding	
2: Likely to be responding	
3: Stable	
4: Likely to be progressing	
5: Highly likely to be progressing	
Posterior iliac crests	Is trephine likely to be representative?
Incidental findings	Incidental lesions including avascular necrosis, which may be a complication of myeloma treatment. Source.—Reference 53.
Conclusion	
Summary statement, RAC score, heterogeneity, recommendations including for investigation of equivocal findings	State level of concern regarding incidental findings

Fig 16. MY-RADS' clinical reporting template (16).

ANNEX 3: MY-RADS' RESPONSE CRITERIA

RAC Descriptions*
1: Highly likely to be responding
Return of normal fat containing marrow in areas previously infiltrated by focal or diffuse myelomatous infiltration
Unequivocal decrease in number or size of focal lesions
Conversion of a packed bone marrow infiltrate into discrete nodules, with unequivocal decrease in tumor load in the respective bone marrow space
Decreasing soft tissue associated with bone disease
Emergence of intra- or peritumoral fat within/around focal lesions (fat dot or halo signs)
Previously evident lesion shows increase in ADC from ≤1400 μm^2/sec to >1400 μm^2/sec
≥40% increase in ADC from baseline with corresponding decrease in normalized high *b*-value signal intensity; morphologic findings consistent with stable or responding disease
For soft-tissue disease, RECIST version 1.1 criteria for PR/CR
2: Likely to be responding
Evidence of improvement but not enough to fulfill criteria for RAC 1. For example:
Slight decrease in number/size of focal lesions
Previously evident lesions showing increases in ADC from ≤1000 μm^2/sec to <1400 μm^2/sec
>25% but <40% increase in ADC from baseline with corresponding decrease in high *b*-value signal intensity; morphologic findings consistent with stable or responding disease
For soft-tissue disease, RECIST version 1.1 not meeting requirements for PR
3: No change
No observable change
4: Likely to be progressing
Evidence of worsening disease, but not enough to fulfill criteria for RAC 5
Equivocal appearance of new lesion(s)
No change in size but increasing signal intensity on high *b*-value images (with ADC values <1400 μm^2/sec) consistent with possible disease progression
Relapsed disease: reemergence of lesion(s) that previously disappeared or enlargement of lesion(s) that had partially regressed/stabilized with prior treatments
Soft tissue in spinal canal causing narrowing not associated with neurologic findings and not requiring radiation therapy
For soft-tissue disease, RECIST version 1.1 criteria not meeting requirements for PD
5: Highly likely to be progressing
New critical fracture(s)/cord compression requiring radiation therapy/surgical intervention; only if confirmed as malignant with MRI signal characteristics
Unequivocal new focal (>5 to 10 mm)/diffuse area(s) of infiltration in regions of previously normal marrow
Unequivocal increase in number/size of focal lesions
Evolution of focal lesions to diffuse neoplastic pattern
Appearance/increasing soft tissue associated with bone disease
New lesions/regions of high signal intensity on high *b*-value images with ADC value between 600–1000 μm^2/sec

Fig 17. MY-RADS' response criteria (16).

ANNEX 4: IMPETUS AND DEAUVILLE SCORE

Lesion type	Site	Number	Grading
Diffuse	Bone marrow		5-PS
	"A" if hypermetabolism in limbs and ribs		
F	S (Skull)	X_1 (None)	5-PS
(Focal)	SP (spine)	X_2 ($N = 1$ to 3)	
	Ex-Sp (extra-spine)	X_3 ($N = 4$ to 10)	
		X_4 ($N > 10$)	
L		X_1(None)	
(Lytic)		X_2 ($N = 1$ to 3)	
		X_3 ($N = 4$ to 10)	
		X_4 ($N > 10$)	
Fr (Fracture)	At least one		
PM (Para-medullary)	At least one		5-PS
EM (Extra-medullary)	At least one	N /EN (Nodal/Extranodal)*	

*For nodal disease: *C* cervical, *SC* supraclavicular, *M* mediastinal, *Ax* axillary, *Rp* retroperitoneal, *Mes* mesentery, *In* inguinal; For ENS: *Li* liver, *Mus* muscle, *Spl* spleen, *Sk* skin, *Oth* other)

5-PS Deauville 5-point scale

Fig 18. IMPeTUs criteria (19).

Deauville 5-point scale	
Score	Grade of uptake
1	No uptake
2	Uptake ≤ mediastinum
3	Uptake > mediastinum and ≤ liver
4	Uptake moderately increased above liver at any site
5	markedly increased uptake above liver and/or new sites of disease

FDG, fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography.

Fig 19. Deauville 5-point scale (28).

ANNEX 5: EUROFLOW

Euroflow is a database that allows to assess MRD in different bone marrow samples. It is a complex data analysis that uses different immunophenotypic markers and classifies them in 8 colors.

In the data base there are multiple donor samples which are normal/healthy. When the "patient sample" is evaluated, it will be compared to the healthy samples registered, allowing to identify anomalies (if there is MRD or not) (29).

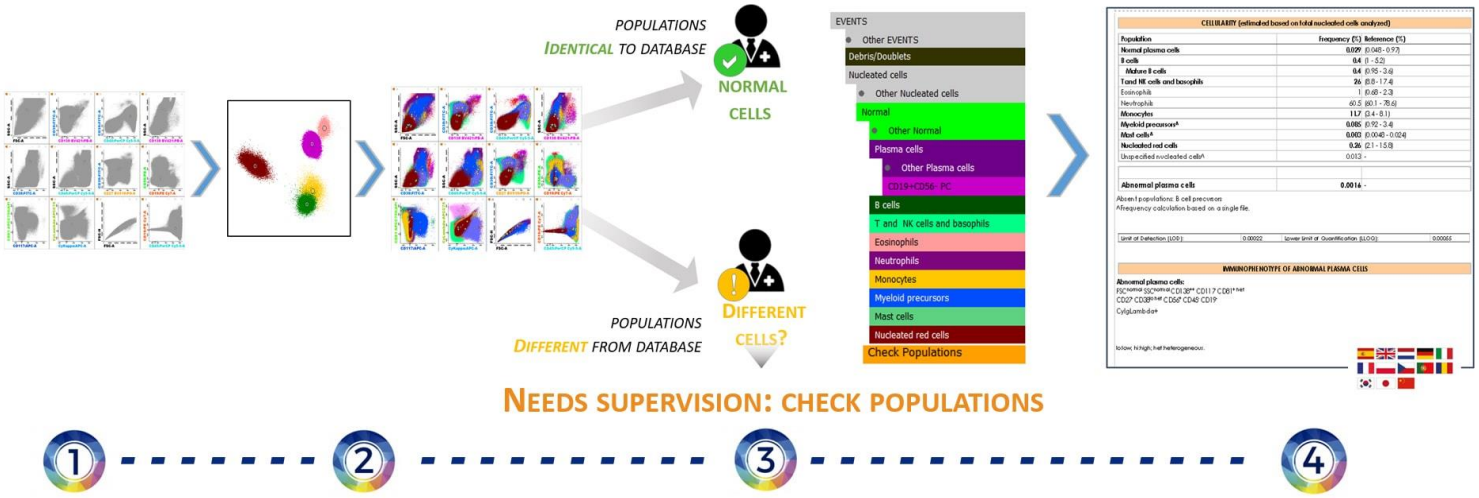

Fig 20. Euroflow (29).

ANNEX 6: IMWG CRITERIA FOR RESPONSE AND MINIMAL RESIDUAL DISEASE

	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¶
Standard IMWG response criteria‖	
Stringent complete response	Complete response as defined below plus normal FLC ratio** and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells)††
Complete response	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates
Very good partial response	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 h
Partial response	≥50% reduction of serum M-protein plus reduction in 24 h urinary M-protein by ≥90% or to <200 mg per 24 h; If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria; If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥30%. In addition to these criteria, if present at baseline, a ≥50% reduction in the size (SPD)§§ of soft tissue plasmacytomas is also required
Minimal response	≥25% but ≤49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50–89%. In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size (SPD)§§ of soft tissue plasmacytomas is also required
Stable disease	Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for complete response, very good partial response, partial response, minimal response, or progressive disease
Progressive disease ¶¶,‖‖	Any one or more of the following criteria: Increase of 25% from lowest confirmed response value in one or more of the following criteria: Serum M-protein (absolute increase must be ≥0·5 g/dL); Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥5 g/dL; Urine M-protein (absolute increase must be ≥200 mg/24 h); In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL); In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥10%); Appearance of a new lesion(s), ≥50% increase from nadir in SPD§§ of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis; ≥50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease
Clinical relapse	Clinical relapse requires one or more of the following criteria: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder. It is not used in calculation of time to progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice; Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression); Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥1 cm) increase as measured serially by the SPD§§ of the measurable lesion; Hypercalcaemia (>11 mg/dL); Decrease in haemoglobin of ≥2 g/dL not related to therapy or other non-myeloma-related conditions; Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma; Hyperviscosity related to serum paraprotein
Relapse from complete response (to be used only if the end point is disease-free survival)	Any one or more of the following criteria: Reappearance of serum or urine M-protein by immunofixation or electrophoresis; Development of ≥5% plasma cells in the bone marrow; Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcaemia see above)
Relapse from MRD negative (to be used only if the end point is disease-free survival)	Any one or more of the following criteria: Loss of MRD negative state (evidence of clonal plasma cells on NGF or NGS, or positive imaging study for recurrence of myeloma); Reappearance of serum or urine M-protein by immunofixation or electrophoresis; Development of ≥5% clonal plasma cells in the bone marrow; Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcaemia)

Fig 21. IMWG's response criteria (22).