New diagnostic criteria for myeloma

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International Myeloma Working Group (IMWG) define...

Diagnostic criteria

Definitions of response

Definitions of relapse

OLD CRITERIA

Table 2- Diagnostic criteria for MGUS, asymptomatic myeloma and symptomatic myeloma (adapted from International Myeloma Working Group, 2003)

** 1% are non-secretory

MGUS	Asymptomatic myeloma	Symptomatic myeloma
M-protein in serum <30 g/l	M-protein in serum ≥30 g/l and/or	M-protein in serum and/or urine**
Bone marrow clonal plasma cells <10 % and low level of plasma cell infiltration in a trephine biopsy (if done)	Bone marrow clonal plasma cells ≥10 %	Bone marrow (clonal) plasma cells* or biopsy proven plasmacytoma
No related organ or tissue impairment ((no end organ damage including bone lesions)	No related organ or tissue impairment (no end organ damage including bone lesions) or symptoms	Myeloma-related organ or tissue impairment (including bone lesions)

BIGGEST CHANGE Any one or more of the following biomarkers of malignancy:

- **Clonal bone marrow plasma cell percentage* ≥60%**
- **Involved:uninvolved serum free light chain ratio§ ≥100 (tumour FLC>100)**
- **>1 focal lesions on MRI studies¶**

OLD CRITERIA

Table 3 - Myeloma-related organ or tissue impairment (ROTI) (adapted from International Myeloma Working Group, 2003)

Clinical effects due to myeloma	Definition
*Increased calcium levels	Corrected serum calcium >0.25 mmol/l above the upper limit of normal or >2.75 mmol/l
*Renal insufficiency	Creatinine>173 µmol/l
*Anaemia	Haemoglobin 20 g/l below the lower limit of normal or haemoglobin <100 g/l
*Bone lesions	Lytic lesions or osteoporosis with compression fractures (MRI or CT may clarify)
Other	Symptomatic hyperviscosity, amyloidosis, recurrent bacterial infections (> 2 episodes in 12 months)

Problem with definitions

Based on expert opinion on cut-offs ie 10% pcs, 30g/L pp (not biology) and now expert opinion on biomarker predictiveness

Clinically most important decision is when to treat. Traditionally based on

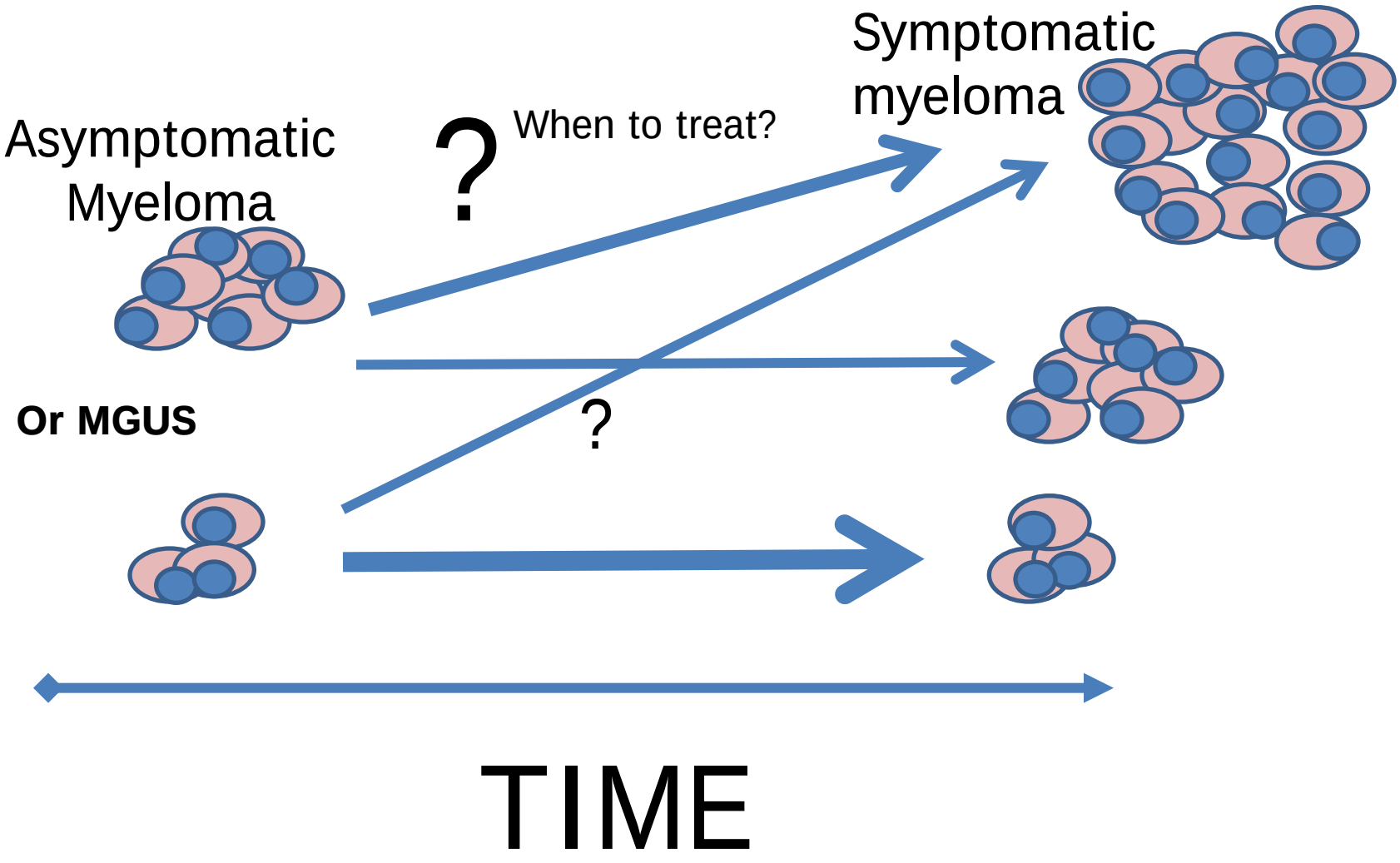
1) the presence or absence of myeloma related organ damage
2) Significant sequential rise in M-protein before symptoms occur (not defined at all)

However high risk of progression from asymptomatic to symptomatic disease for a subgroup of patients

Risk of waiting greater than risk of early treatment for very high risk subgroup

All multiple myelomas are preceded by a pre-malignant phase

BUT most patients with MGUS do not develop myeloma



blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

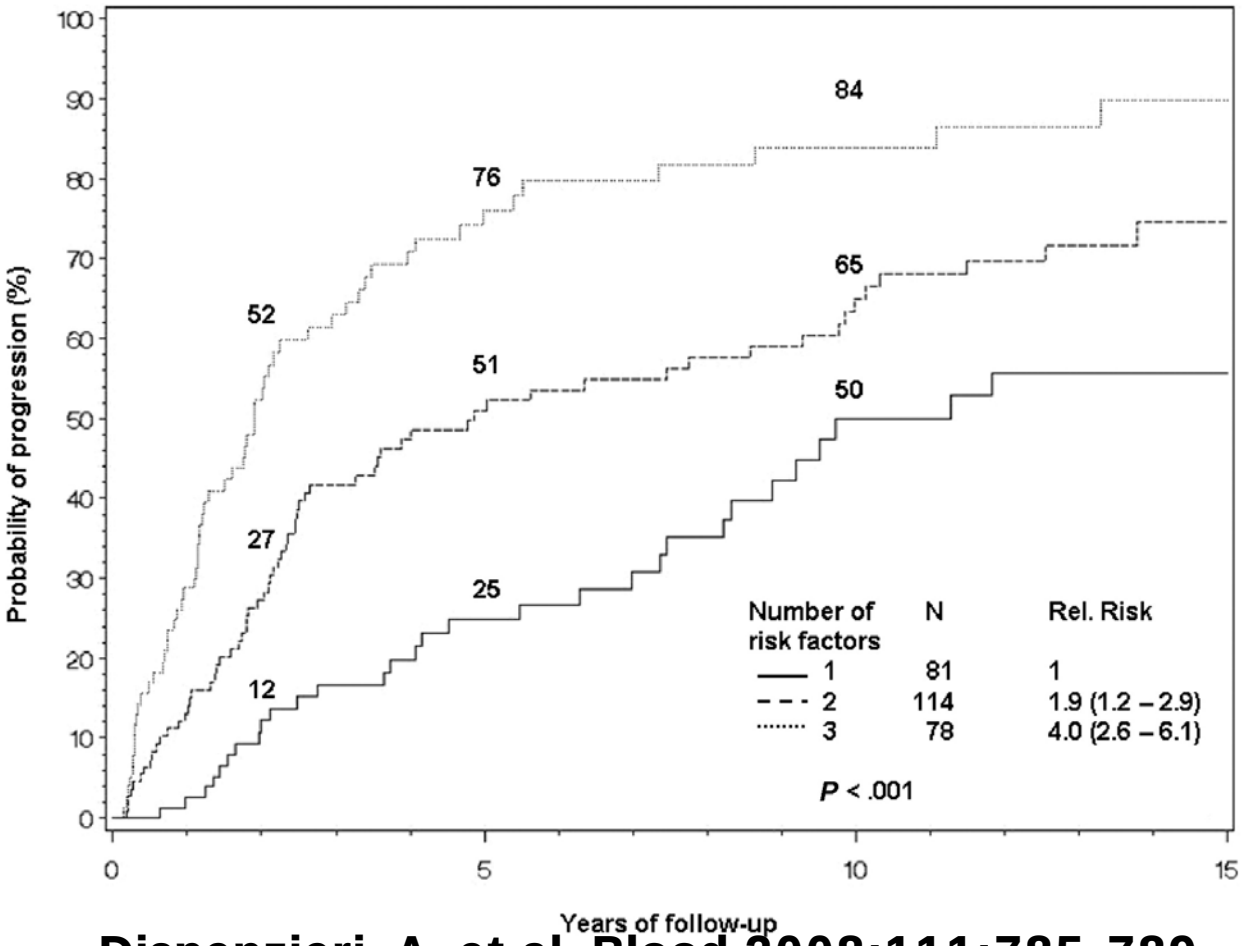
Smouldering or asymptomatic multiple myeloma

Risk factors for progression

BMPCs greater than or equal to 10%

serum M protein greater than or equal to 30 g/L

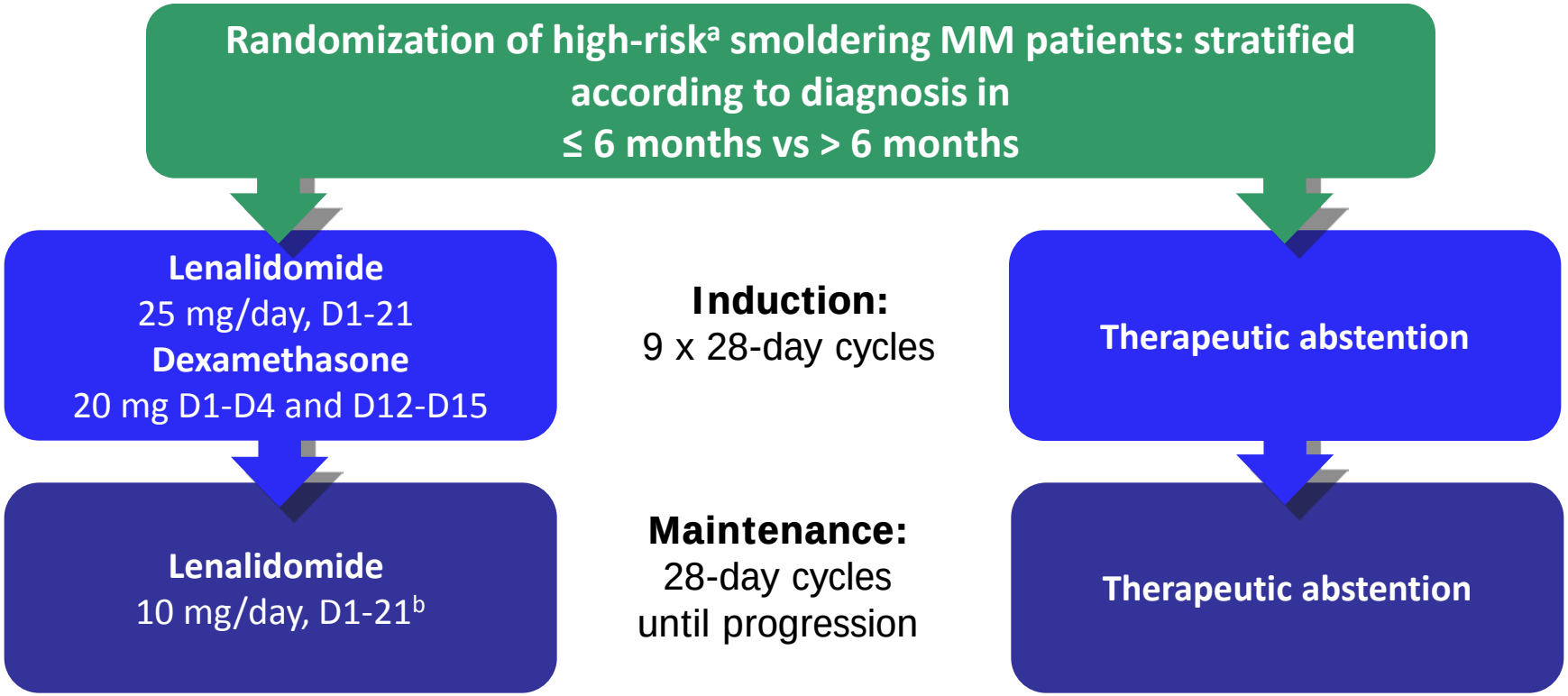
serum immunoglobulin FLC ratio either less than 0.125 or more than 8.



Dispenzieri, A. et al. Blood 2008;111:785-789

High risk smouldering myeloma

QUIREDEX Study



Objectives: compare efficacy and safety of Len treatment vs therapeutic abstention in patients with high-risk smoldering MM

[a] PCs BM ≥ 10% plus M-protein ≥ 30 g/L or PCs BM ≥ 10% or M-protein ≥ 30 g/L, but BM aPC/nPC > 95% plus immunoparesis.
[b] Low-dose Dex added at the moment of biological progression.
aPC, abnormal PC; BM, bone marrow; Dex, dexamethasone; Len, lenalidomide; MM, multiple myeloma; nPC, normal PC; PC plasma cell.

Mateos MV, et al. *Haematologica.* 2011;96(s1):S82 [poster presentation].

High risk smouldering myeloma QUIREDEX Study

- Patients in observation arm more likely to develop symptomatic disease (76 vs 23%)

- 30% withdrawal rate from lenalidomide arm due to toxicity

- With a median follow-up of 40 months, the treated patients had a superior 3-year survival without progression to symptomatic disease (77% vs 30%; P =0.001) and a superior 3-year OS (94% vs 80%; P 0.03)

- Trial could be criticised- observation arm needed to develop symptoms (CRAB criteria), escalation of treatment in lenalidomide not censored, withdrawal not clear, higher than expected mortality in control group (?access to lenaldiomide, need to have CRAB criteria, monitoring?)

Smoldering multiple myeloma requiring treatment: time for a new definition?

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Patients with the highest risk smouldering multiple myeloma should be treated

These include –

Patients with >60% bone marrow plasma cell infiltrate (2-3% of patients)

Patients with serum free light chain ratio >100 (7-15% of patients)

Patients with >1 lesion on whole body MRI scan (15% of patients)

...as risk of progression is >80% at 2 years

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 Rosinol, 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

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New definition of myeloma based on early treatment of a small group of patients who are asymptomatic but have a high risk of progression (approx 80% in 2 years) to end-organ damage and are now upstaged

Definition of multiple myeloma

Clonal bone marrow plasma cells **≥10% or biopsy-proven bony or extramedullary plasmacytoma*** and any one or more of the following myeloma defining events or any one or more of the following biomarkers of malignancy.

Myeloma defining events:

Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder as follows:

• Hypercalcaemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)

• Renal insufficiency: **creatinine clearance <40 mL per min† or serum creatinine >177 µmol/L (>2 mg/dL) due to myeloma**

• Anaemia: haemoglobin value of >20 g/L below the lower limit of normal or a haemoglobin value <100 g/L

• Bone lesions: one or more osteolytic lesions on skeletal radiography, **CT, or PET-CT‡**

OR Any one or more of the following biomarkers of malignancy:

- **Clonal bone marrow plasma cell percentage* ≥60%**
- **Involved:uninvolved serum free light chain ratio§ ≥100**
- **>1 focal lesions on MRI studies¶**

*Clonality should be established by showing κ/λ-light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used.

‡If bone marrow has less than 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement.

§These values are based on the serum Freelite assay (The Binding Site Group, Birmingham, UK). The involved free light chain must be ≥100 mg/L.

¶ Each focal lesion must be 5mm or more in size

Definition of smouldering multiple myeloma

Both criteria must be met:

- Serum monoclonal protein (IgG or IgA) ≥30 g/L or urinary monoclonal protein ≥500 mg per 24 h and/or **clonal bone marrow plasma cells 10–60 %**

- Absence of myeloma defining events **including biomarkers of malignancy** or amyloidosis

Biomarkers of risk: Lack of concordance and prospective studies

IMWG have picked 3.....

Bone marrow infiltrate >60%.

Uncommon in asymptomatic patients (only 5%) as usually symptomatic with this degree of infiltration but very predictive of progression (95% progression in Mayo series).

Two smaller series (one Greek) showed the same

?reproducibilty of estimating % infiltration

sFLC ratio >100 (note involved FLC needs to be >100mg/L)

Larsen et al (2013) Mayo
586 patients with smouldering multiple myeloma and identified that a sFLC ratio of >100 was found in 90 patients (15%) and was associated with a 79% risk of progression at 2 years.

Using a cut-off of involved sFLC >100 mg/l and a sFLC ratio >100, then 82% of patients progressed by 2 years and 93% by 3 years but adding a cut-off reduced sensitivity

Two smaller studies (one Greek) confirmed high risk of progression although only 64% at 2 years in Waxman et al study

>1 unequivocal focal lesion on cross-sectional imaging

Hillengass et al
(2010) evaluated whole body MRI in 149 patients with smouldering myeloma and found focal bone lesions in 42 patients (28%) with more than one focal lesion in 23 patients (15%). For patients with more than one focal lesion the median time to progression was 13 months, with 70% of patients progressing at 2 years.

Kastritis et al Greek group (2014) identified 9/65 (14%) of patients with smouldering myeloma to have >1 focal lesion on spinal MRI and the median time to progression for this group was 15 months, with 69% of patients progressing by 2 years and 85% by 3 years.

What will be the impact of these changes?

Only a small number of patients (20% of previously asymptomatic disease)
These patients will start treatment earlier and may have prolonged therapy (?toxicity, cost effectiveness)

BUT impact more wide ranging

More advanced imaging being done (whole body low dose CT, MRI or PET)

More bone marrows performed

Diagnosis of renal disease

Impact on clinical trials

Impact on patients with existing asymptomatic myeloma

Changing terminology

Terminology

The terminology of symptomatic and asymptomatic multiple myeloma is increasingly confusing given that more patients without overt symptoms are going to be recommended to start on treatment based on the presence of a biomarker.

Recommendation:

It is recommended to use the terminology of **multiple myeloma** and **smouldering multiple myeloma** as they are defined and no longer use the terminology symptomatic or asymptomatic disease.

Clinical trials

Currently patients without the conventional CRAB criteria but with one of the biomarkers of malignancy will be excluded from trials that have not amended the entry criteria to include the new IMWG definition i.e. Myeloma XI

These patients would be expected to have a longer overall survival/PFS determined from time of treatment as they are being treated earlier than historically identical patients (lag time effect) so will skew results

Clinical trials

Recommendations:
Future trials will need to incorporate the new definition and importantly account for and stratify the group of patients without the CRAB criteria and with one of the three biomarkers of malignancy.

It is imperative that biomarker evaluation becomes incorporated into large clinical trials to develop better predictors of risk.

The new definition of myeloma requires a plasma cell infiltrate >10% and this may have implications in terms of having to repeat a bone marrow biopsy or biopsy of a bony lesion in a small minority of patients where initial biopsy shows <10% plasma cells in order to enter a trial (?More bone marrows being done as the cut-offs of 10% and 60% may direct investigation (imaging) and treatment)

Definition and investigation of renal disease

New definition of renal failure based on estimated GFR in the revised CRAB criteria and the definition of renal insufficiency due to myeloma being defined as renal insufficiency due solely to light chain cast nephropathy.

Recommendation:
The IMWG recommend a renal biopsy in patients to clarify the underlying cause of the renal failure in patients with suspected cast nephropathy, especially if the serum involved FLC levels are less than 500 mg/L.

What about patients already diagnosed with Smouldering myeloma?

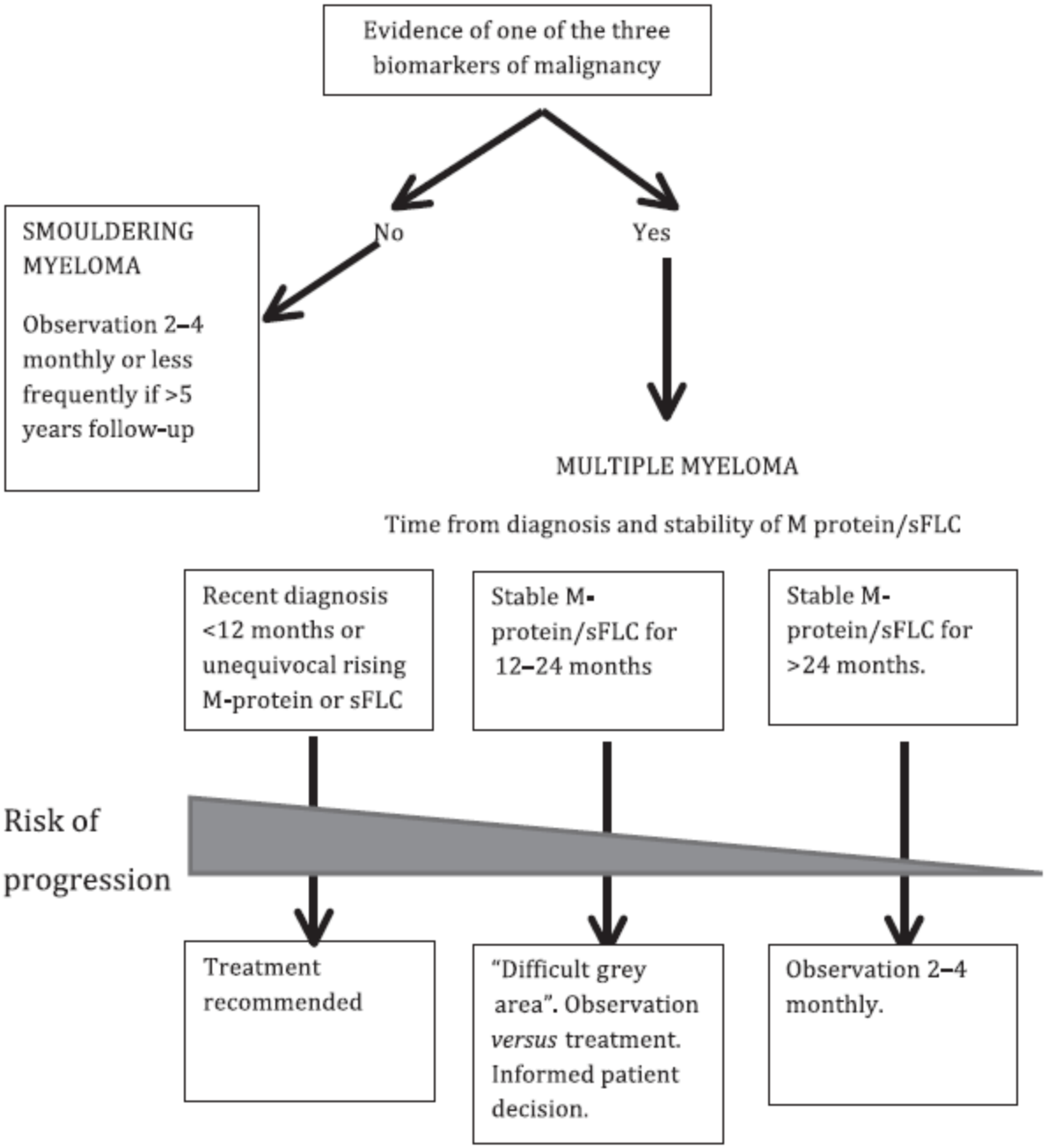

Fig 1. Algorithm for patients with multiple myeloma lacking CRAB (hypercalcaemia, renal impairment, anaemia, bone disease) criteria. sFLC, serum free light chain

Role of imaging in Myeloma and MGUS in 2015

As a diagnostic tool (especially new definition by IMWG)

In evaluating spinal disease for management (conservative vs surgery, vertebro/kyphoplasty, radiotherapy)

In evaluating non-spinal disease for management (conservative, radiotherapy, surgery)

Baseline for monitoring especially non-secretory, oligo-secretory, plasmacytoma, extramedullary disease

Could identify potential complications

Prognostic information

Skeletal survey, whole body MRI, whole body low dose CT scan, FDG-PET

Skeletal survey (=£100).

Standard of care for decades.
Numerous plain radiographs
Requires patient to move in various positions.
Takes time.
Lacks sensitivity compared to newer techniques
Cannot distinguish cause of vertebral wedge fractures and osteopenia

Whole body MRI (=£200)

Limited capacity and limited experience in most units. Takes time
The best in terms of sensitivity –picks up infiltrative disease as well as focal disease.
Presence of infiltrative disease – can be difficult to assess. Does not alter management currently
Picks up extramedullary disease
No radiation
Some patients not suitable
Not very useful for follow up or assessment of response
Newer techniques = Diffusion weighted MRI (see Messiou and Kaiser, BJH 2015)

Skeletal survey, whole body MRI, whole body low dose CT scan, FDG-PET

Whole body low dose CT scan (£150)

?Probably more capacity
Will pick up focal disease ?as good as MRI but not good for infiltrations
Picks up extramedullary disease
Some radiation
Not useful for follow up or assessment of response

FDG-PET in myeloma (£650)

Less experience, still need to confirm if positive lesion an osteolytic lesion on the CT portion
?higher false positive rate, some false negative result. Radiation, capacity
Better for monitoring especially non-secretory or oligosecretory disease or major extramedullary disease

For detection of focal disease IMWG has not specified which cross sectional imaging technique to use

Focal lesion >5mm so all techniques (?PET especially) may pick up equivocal activity

Advanced imaging is more sensitive for detecting myeloma bone disease than conventional radiology and it is probably inevitable that it will eventually replace plain radiography for assessing patients with multiple myeloma (but not for MGUS).

Recommendation:
Currently available techniques for advanced imaging (MRI, low dose CT and PET) are felt to be broadly equivalent and choice is currently more dependent on accessibility, cost and convenience. It is important to liaise closely with local radiologists to discuss the impact of these changes and develop appropriate protocols.

Accurate and consistent reporting is essential and a clear description of the patterns of myeloma involvement is required particularly as currently only the presence of > 1 unequivocal focal lesions >5mm is defined as a biomarker of malignancy. Increased uptake on PET-CT alone is not adequate for the diagnosis of multiple myeloma and evidence of underlying osteolytic bone destruction is needed on the CT portion of the examination to indicate unequivocal disease.

Follow up imaging is required for patients with equivocal lesions, a solitary lesion and evidence of marrow infiltration typically in 3-6 months' time. If diagnostic doubt exists about a lesion then a biopsy may be required.

New IMWG definition of myeloma

Will effect a relatively small number of patients with a biomarker of malignancy but without traditional CRAB criteria who are now recommended to start on treatment

However implications are wider.

Will accelerate the use of advanced imaging in suspected myeloma

Will focus us to look at biomarkers of risk such as sFLC

Will focus us to look at extent of bone marrow infiltration

Will alter eligibility criteria for future trials and skew results relative to older studies

Should change our terminology