Consensus guidelines for Diagnostic Criteria and Indication for treatment and retreatment in plasma cell disorders

On behalf of the members of the Consensus Panel 2

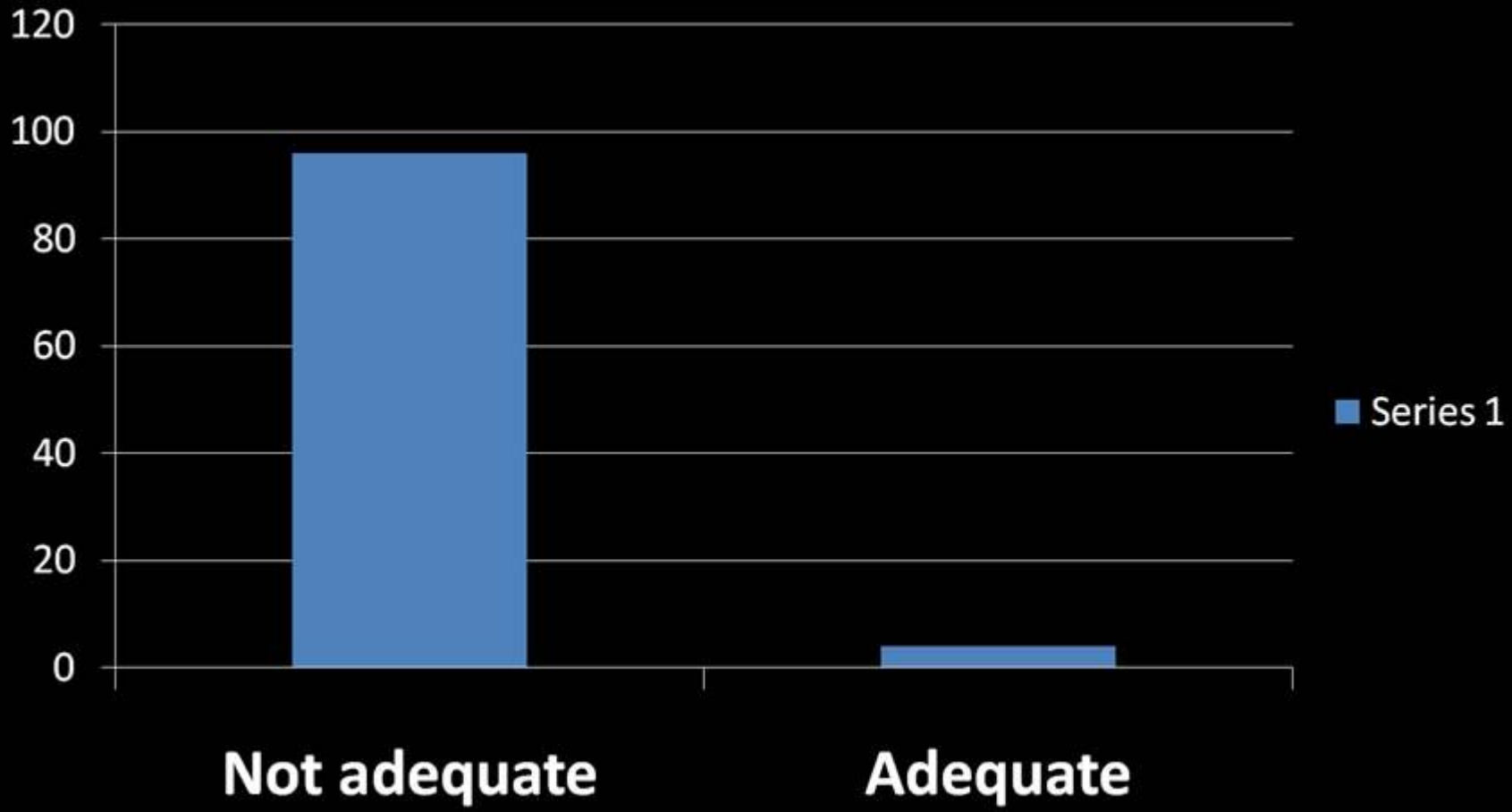
Purposes

- To review the current diagnostic criteria.

- To incorporate newer diagnostic methods, now routinely used, in the criteria.

- To develop criteria to decide whether to treat or not.

Opinion about need to modify current criteria



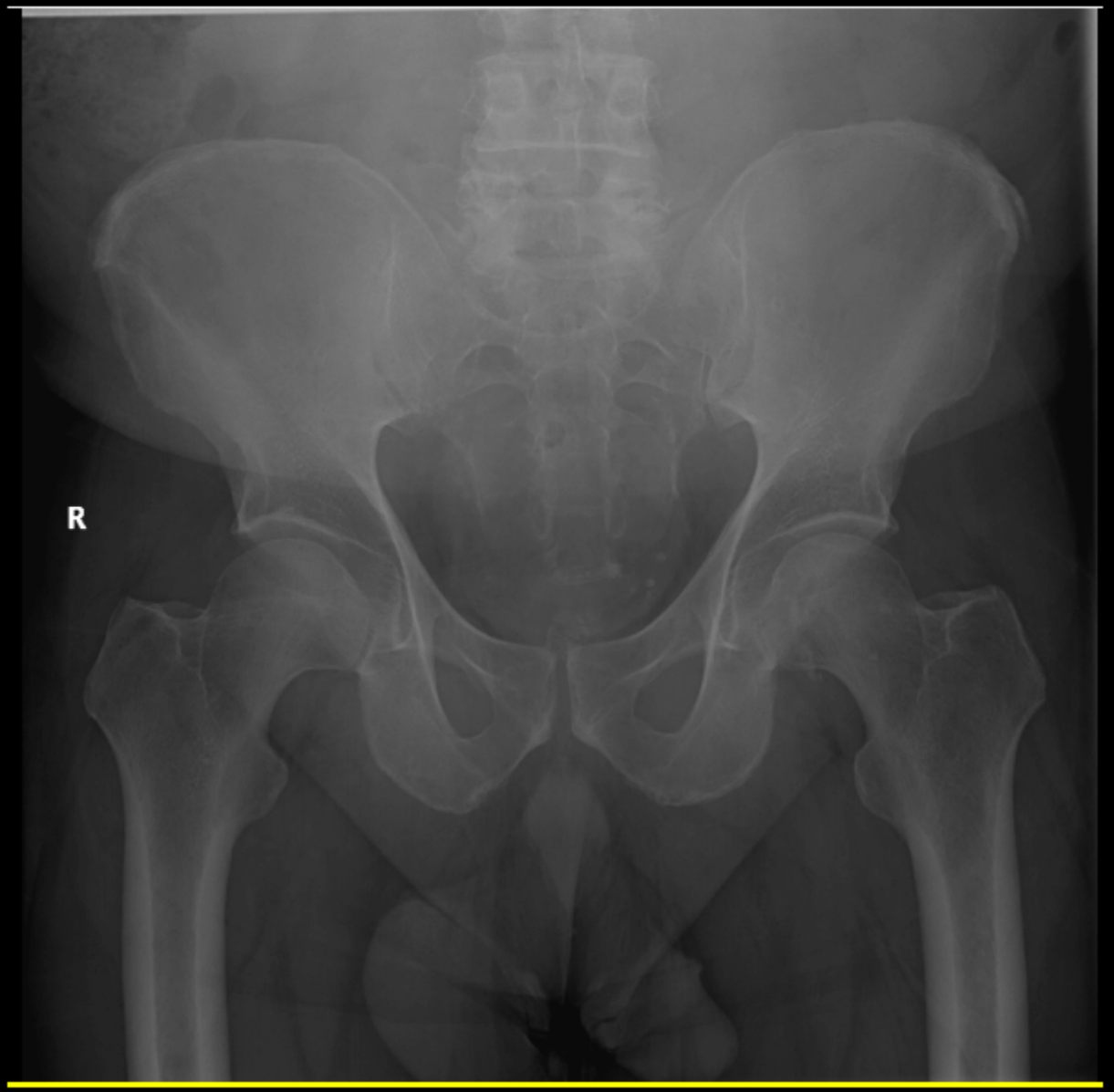
Examples

- 54 year old man with

- M spike 1.8 gm/dL, IgG kappa,
- Bone marrow: 30% κ-restricted plasma cells,

- Hemoglobin 11.6 gm/dL
- Serum creatinine 0.8 mg/dL
- Normal serum Calcium and
- Normal bone survey

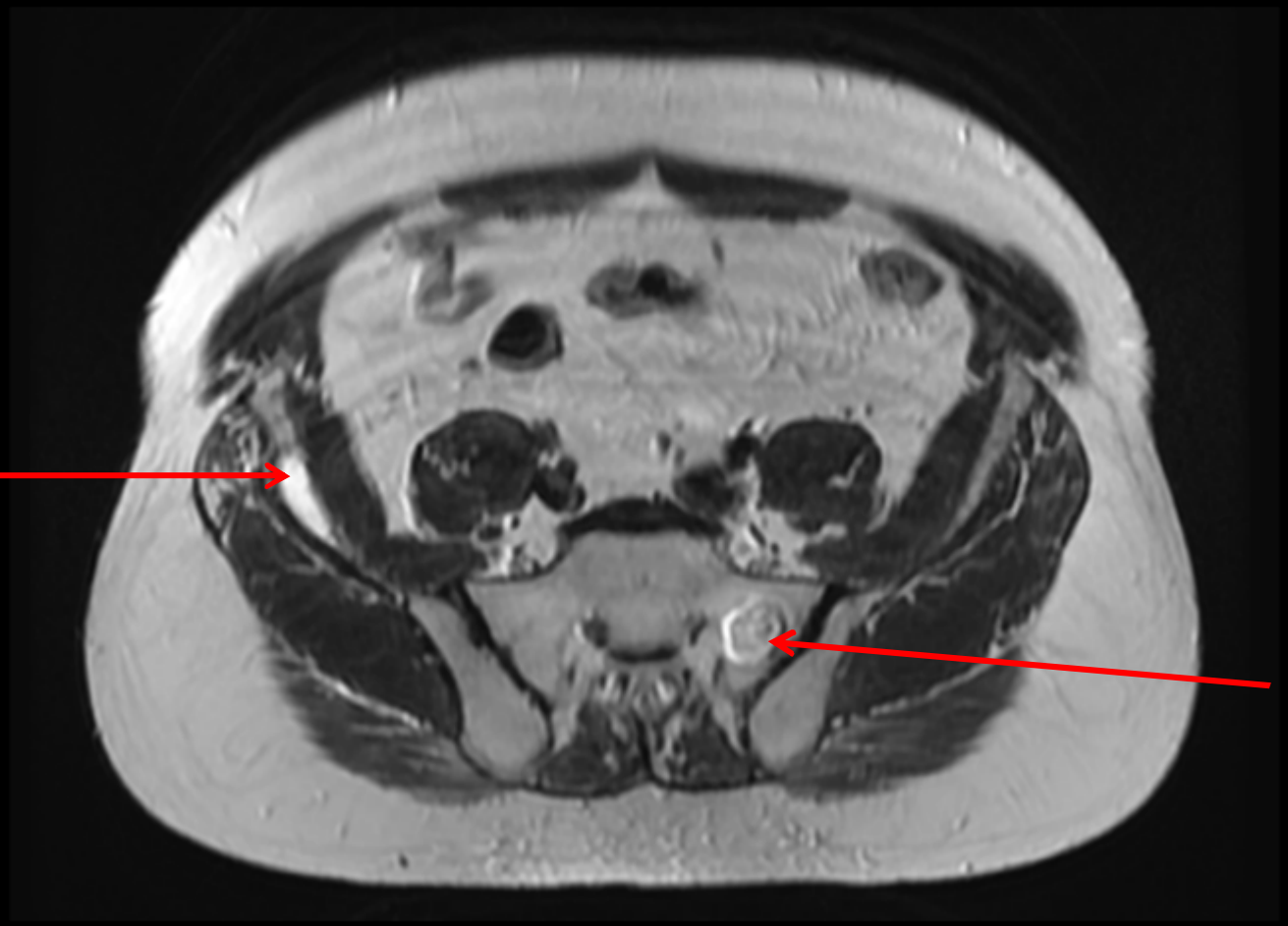
Plain Radiograph



Both iliac wing appear unremarkable

Courtesy of Dr. Suman Kambalpatti

Magnetic Resonance Imaging



Enhancing foci involving
(1) Right ilium 3.3 x 1.2 cm;
(2) Left sacrum 2.2 x 1.8 cm

Courtesy of
Dr. Suman Kambalpatti

Examples

- 79 year old healthy man with IgA Lambda paraprotein. No h/o diabetes, hypertension or cardiac problems. He was detected to have

- M spike 1.2 gm/dL, IgA Lambda,
- Bone marrow: 40% λ-restricted plasma cells,
- 24 Hour Urine Light chain 1.4 gms

- Hemoglobin 11.8 gm/dL;
- Serum creatinine 1.7 mg/dL;
- Normal serum Calcium; and
- Normal bone survey

Renal Function Determination

- Changes in Creatinine clearance based on age and Creatinine 1.7
	eGFR
– Age 52	52
– Age 62	45
– Age 79	40
– Age 85	39

Diagnostic Criteria

- Protein Criteria
  - Serum
  - Urine
  - Light chain
- Bone marrow plasma cells
- Myeloma Defining Events (MDE)

NEEED TO MEET ALL 3 CRITERIA FOR DIAGNOSIS OF MM

Protein Criteria - Serum

- For the diagnosis of myeloma no specific threshold for the size of the M protein is needed
- The absolute level of monoclonal protein, 3 gm/dL, is important to differentiate MGUS from SMM irrespective of type of immunoglobulins, IgG or IgA
- Differential levels of IgG, IgA or IgM predicts for different predisposition to progression to myeloma
- Other lymphoproliferative diseases (CLL, NHL) may have clonal paraprotein, however other required MM diagnostic criteria precludes need for their specific exclusion.

Protein Criteria - Urine

- Similar to serum protein, for the diagnosis of myeloma no specific threshold for the size of the M protein is needed
- A specific level of urine M protein to differentiate MGUS from SMM is needed. This level is under review and will be update.
- Presence of urine monoclonal light chain alone, in absence of serum light chain is adequate for diagnosis of MM
- For diagnosis of light-chain MGUS absence of immunoglobulin heavy chain on serum immunofixation is required.

Protein Criteria – Free Light chain

- To diagnose presence of a clonal plasma cell disorder solely based on presence of SFL, we need
  1. An abnormal free light-chain ratio(<0.26 or >1.65);
  2. An increased concentration of a serum free light chain (increased kappa FLC in patients with ratio > 1.65 and increased lambda FLC in patients with ratio < 0.26);
  3. *Absence of heavy chain expression by immunofixation.

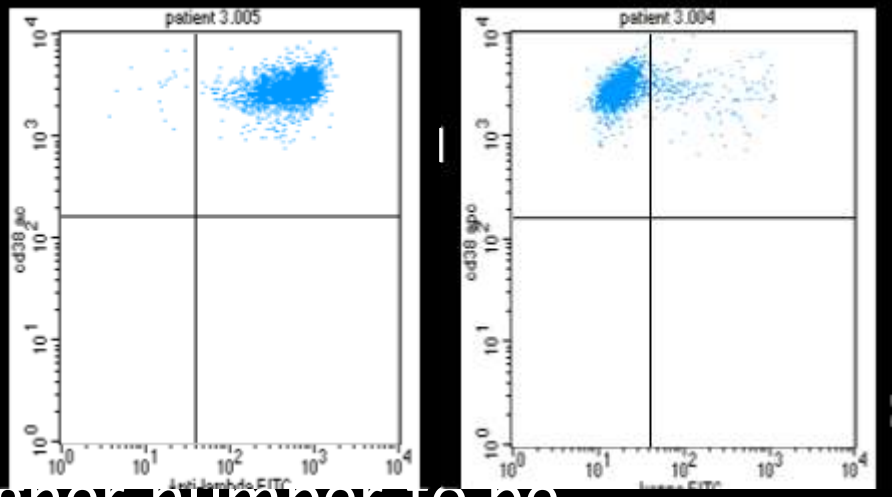
- If patients do not meet end-organ damage criteria for myeloma, they will be considered to have light chain MGUS if bone marrow clonal plasma cells are less than 10%, and SMM if they are 10% or more. (Dispenzieri et al. Lancet 201)

Uninvolved Immunoglobulin Levels

- Suppression of uninvolved occurs in MGUS and SMM. E.g. 25% of MGUS patients (18% with one and 7% with 2 Igs), and 52% of SMM patients (22% with 1 and 30% with 2 Igs). In this study, immunoparesis was associated with a significant impact on PFS in MGUS and SMM patients (P <0 .001). However, suppression of uninvolved immunoglobulins per se without evidence of other end organ damage was not considered to be a “myeloma-defining event (MDE).”

Bone Marrow Criteria

- Presence of clonal plasma cells of ≥10% in the BM aspirate or biopsy (which ever is higher if both done) is required for diagnosis of MM and to differentiate MGUS from SMM
- Confirmation of clonality by immunostaining or flow cytometryis essential for diagnosis.
- At least 200 cell count is re cells in the BM.
- If both aspirate and biopsy flow cytometry done then higher number to be considered.



Bone Marrow Criteria

- A biopsy proven bony or soft-tissue plasmacytoma showing clonal plasma cells is also adequate as confirming tissue involvement in absence of clear BM involvement .

- Although important for prognostication, cytogenetic or FISH identified abnormalities are not required or adequate for diagnosing MM.

Diagnostic Criteria

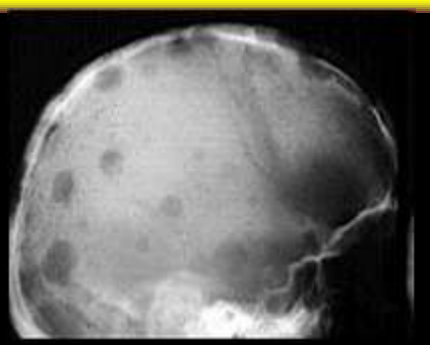
- Protein Criteria
  - Serum
  - Urine
  - Light chain
- Bone marrow plasma cells
- Myeloma Defining Events (MDE)

Anemia

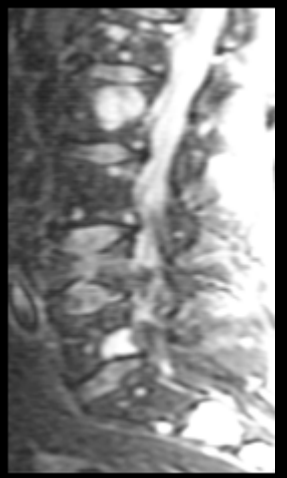
- Level of anemia to be consider as MDE is:
  - Hemoglobin 2 g/dl below the lower limit of normal or
  - their baseline hemoglobin <10 g/dl that is felt related to the underlying clonal plasma cell disorder.
- It is necessary to exclude other causes of anemia if one suspected.

Bone Lesion

- Skeletal survey – First choice. If lytic lesion/s observed then adequate for diagnosis of MM.



- If skeletal survey is negative for lytic lesion but if MRI performed then ≥ 3 hyperintense lesions or one large macrofocal lesion will be considered as MDE.



- If PET/CT performed then CT detected lytic lesion > 1 cm OR ≥ 3 smaller lesions with or without PET positivity should be considered as MDE.

Bone Lesion

- Severe osteopenia by itself is not adequate, and if associated with compression fracture it will require additional investigation to rule out or confirm myeloma-related bone disease.
- Although bone markers suggest bone turnover, change in bone marker is not adequate as MDE.
- Lesions seen on CT/MRI/PET are not necessarily diagnostic for myeloma and if alternative malignancy is suspected then it should be investigated.

Renal Dysfunction

- The use of impaired renal function as a myeloma defining event will be based on the following:
  - 1) In a patient with prior estimated glomerular filtration rate (eGFR), a significant drop of eGFR from baseline (>=35% change over 1 year with no other identifiable cause); OR
  - 2) an eGFR of 50 ml/min or lower with no other identifiable cause; OR
  - 3) evidence of light chain cast nephropathy on renal biopsy.
- The GFR be measured or calculated using the standard MDRD creatinine clearance formula.

Renal Dysfunction

- The It is important to establish the relationship of renal dysfunction to the plasma cell disorder. i.e. BJPshould be present in order to support such relationship. In absence of significant Bence Jones proteinuria a renal biopsy may be necessary for confirmation. When in doubt one should do a renal biopsy for confirmation.

- If indicated, other causes of renal dysfunction should be considered before attributing renal dysfunction to myeloma
- We do not require a renal biopsy for everyone, but if uncertain as to the cause of the renal dysfunction then a biopsy is necessary. A biopsy is not currently required for light-chain cast nephropathy if significant BJP which is the predominant urinary protein.

Hypercalcemia

- Defined as increased: serum calcium >0.25 mmol/l above the upper limit of normal or >2.75 mmol/l, adjusted for serum albumin and ph if available. (11.0 mg/dL).

- Hypercalcemia must be that is felt related to the underlying clonal plasma cell disorder.

Symptomatic Hyperviscosity

- If patient has a symptomatic hyperviscosity that is felt to be related to serum monoclonal protein requiring therapeutic intervention.

What are not MDE

- Presence of amyloidosis* or MIDD, in absence of other MDE, is not diagnostic of MM by itself. AL Amyloidosis or MIDD should be considered distinct entities since the biology of their clones are more indolent than in multiple myeloma.
- However, if BM is >10% clonal plasma cells, then These patients should have access to the same drugs used for myeloma because these diseases are caused by a clonal plasma cell population.
- Recurrent bacterial infections (> 2 episodes in 12 months)
- Presence of neurological symptoms

Special Diagnostic Conditions

Presence of Non secretory MM

- No M protein in serum and/or urine with immunofixation
- Normal FLC ratio.
- Bone marrow clonal plasmacytosis ≥10% or plasmacytoma
- Presence of one or more myeloma defining events
  – May need biopsy confirmation.

Special Diagnostic Conditions

Solitary Plasmacytoma of Bone

- No or small M protein in serum and/or urine
- Single area of bone destruction due to clonal plasma cells
- Bone marrow not consistent with multiple myeloma
- Normal skeletal survey and MRI OR PET/CT.
- No myeloma defining events other than solitary bone lesion.

Special Diagnostic Conditions

Extramedullary plasmacytoma

- No or small M protein in serum and/or urine.
- Extramedullary tumor of clonal plasma cells
- Normal bone marrow
- No myeloma defining events including normal skeletal survey and MRI OR PET/CT.

Special Diagnostic Conditions

Multiple or recurrent plasmacytoma

- No or small M protein in serum and/or urine.
- More than one localized area of bone destruction or extramedullary tumor of clonal plasma cells which may be recurrent
- Normal bone marrow
- Normal skeletal survey and MRI OR PET/CT if done.
- No myeloma defining events other than the localized bone lesions.

Special Diagnostic Conditions

Light chain MGUS

- an abnormal free light-chain ratio(<0.26 or >1.65);
- an increased concentration of a serum free light chain (increased kappa FLC in patients with ratio > 1.65 and increased lambda FLC in patients with ratio < 0.26). The level above the laboratory normal along with appropriate change in the ratio is adequate provided other criteria for diagnosis are met.
- OR clonal light chain in urine
- AND no IgH expression by immunofixation

Special Diagnostic Conditions – POEMS Syndrome

Mandatory	1.	Polyneuropathy
Major criteria	2.	Monoclonal plasma cell disorder
Major criteria	3.	-Sclerotic bone lesions -Castleman's disease -Elevated levels of VEGF-a
Minor criteria	4.	-Organomegaly or lymphadenopathy -Extravascular volume overload (edema, pleural effusion, or ascites) -Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, and pancreatic) -Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomata, plethora, acrocyanosis, flushing, and white nails) -Papilledema -Thrombocytosis/polycythemia

Both mandatory major criteria, 1 of 3 other major criteria, and 1 of 6 minor criteria in the absence of other causes for the abnormalities

Indication for treatment

- When patient has symptomatic myeloma – i.e. Presence of MDEs.

Indication for Retreatment

- Time to next treatment TNT is defined as time from registration on trial to next treatment or death due to any cause, whichever comes first.
- TNT important in future phase III trials.
- To accurately define TNT, next treatment should start uniformly.
- The consensus is that next treatment should start when there is either clinical relapse or a significant paraprotein relapse.

Indication for Retreatment

- **Clinical relapse** defined as requiring one or more of the following direct indicators of increasing disease and/or end organ dysfunction (MDE) that are felt related to the underlying plasma cell proliferative disorder:
- 1. Development of new soft tissue plasmacytomas or bone lesions on imaging.
- 2. Definite increase in existing plasmacytoma or bone lesionsis defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion
- 3. Hypercalcemia
- 4. Decrease in hemoglobin as described for diagnosis
- 5.A recurrent or new renal dysfunction as described
- 6. Hyperviscosity requiring therapeutic intervention.

Indication for Retreatment

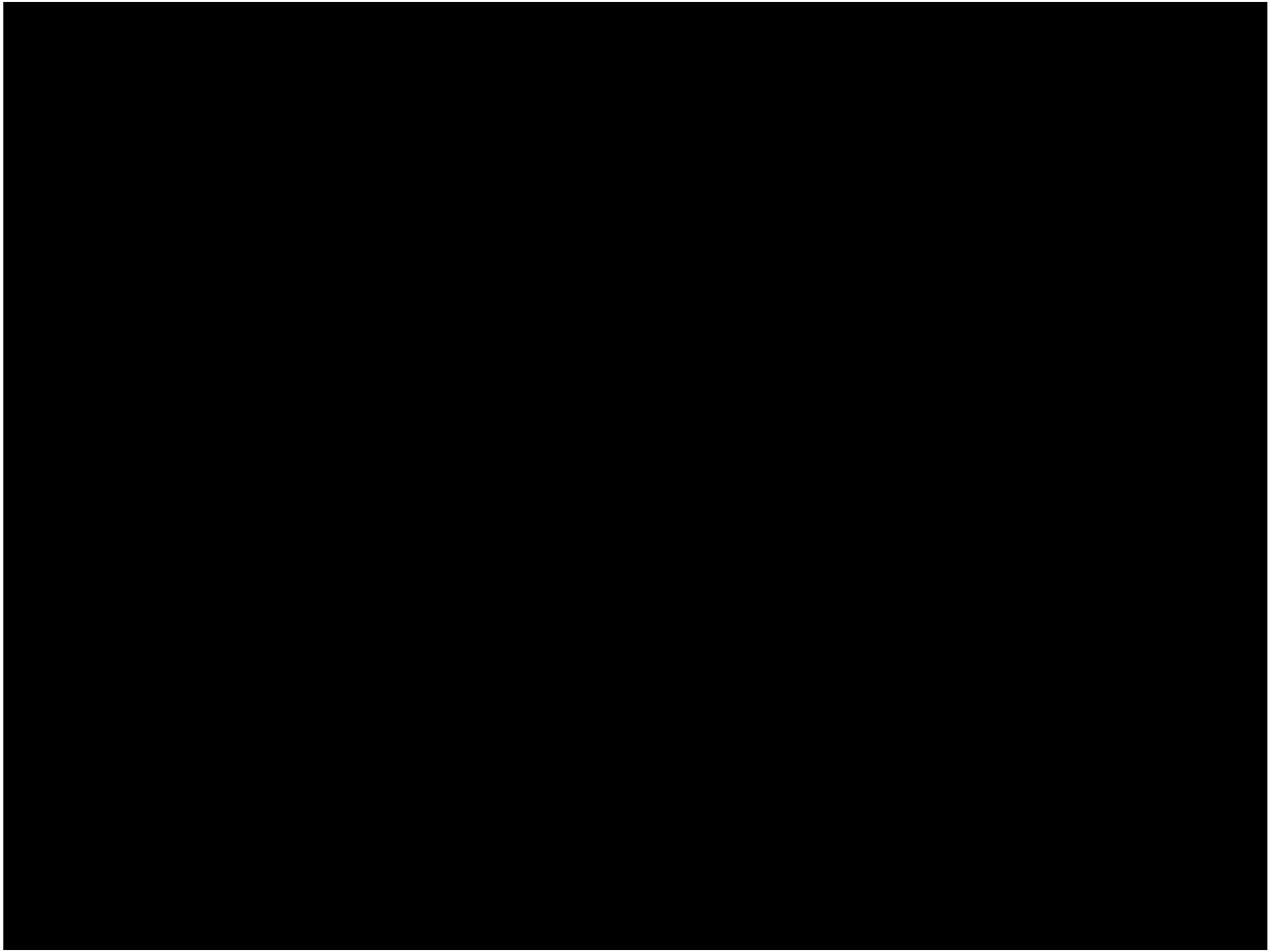
- **Significant paraprotein relapse** defined In patients who do not have clinical relapse:
- 1. Doubling of the M-component in two consecutive measurements separated by < 2 months with the reference value of 0.5 gm/dL; OR
- 2.In two consecutive measurements any of the following increases:
  - the absolute levels of serum M protein by ≥1gm/dl; or
  - an increase of urine M protein by ≥500mg /24h; or
  - an increase of involved FLC level by ≥20mg/dl (plus an abnormal FLC ratio) or 25% increase (whichever is greater).

The "paraprotein relapse" represents the rate of rise or absolute level of increase in M protein at which the panel felt that myeloma therapy should be restarted even if signs and symptoms of new end organ damage are not yet apparent.

Indication for Retreatment

- Patients with oligosecretory disease, we will need to have clinical relapse as defined above.
- For patients with PR with monoclonal protein levels of 0.5 gm/dL either the clinical or significant paraprotein relapse can be utilized.
- While patients relapsing from CR or VGPR either clinical relapse can be utilized or if paraprotein relapse is considered then the paraprotein levels should be above ≥0.5 gm/dL
- Currently presence of high risk features does not change the parameters for treatment or retreatment and are not considered as indicative of early intervention.

- These criteria will not exclude any of the current MM patients
- So patients included in all ongoing and planned studies will not change
- These criteria may only add patients who otherwise are not well defined.



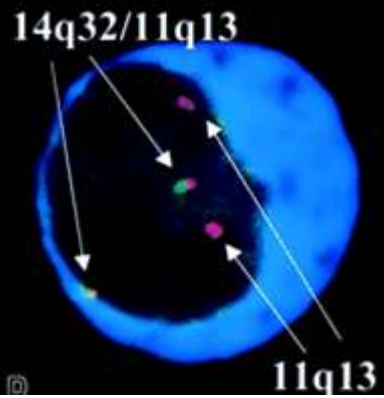
What risk factors?

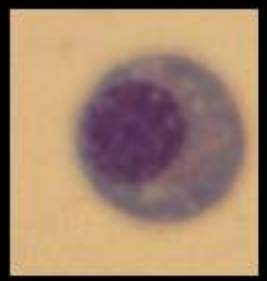
- Serum: β2m, albumin, LDH
- Conventional cytogenetic abnormality
- FISH: <u>on identified plasma cells</u>

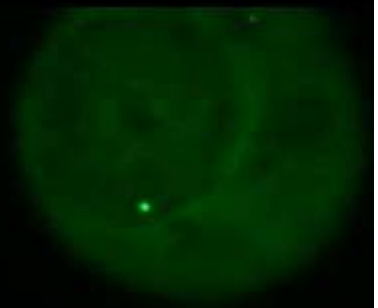
Immuno-FISH

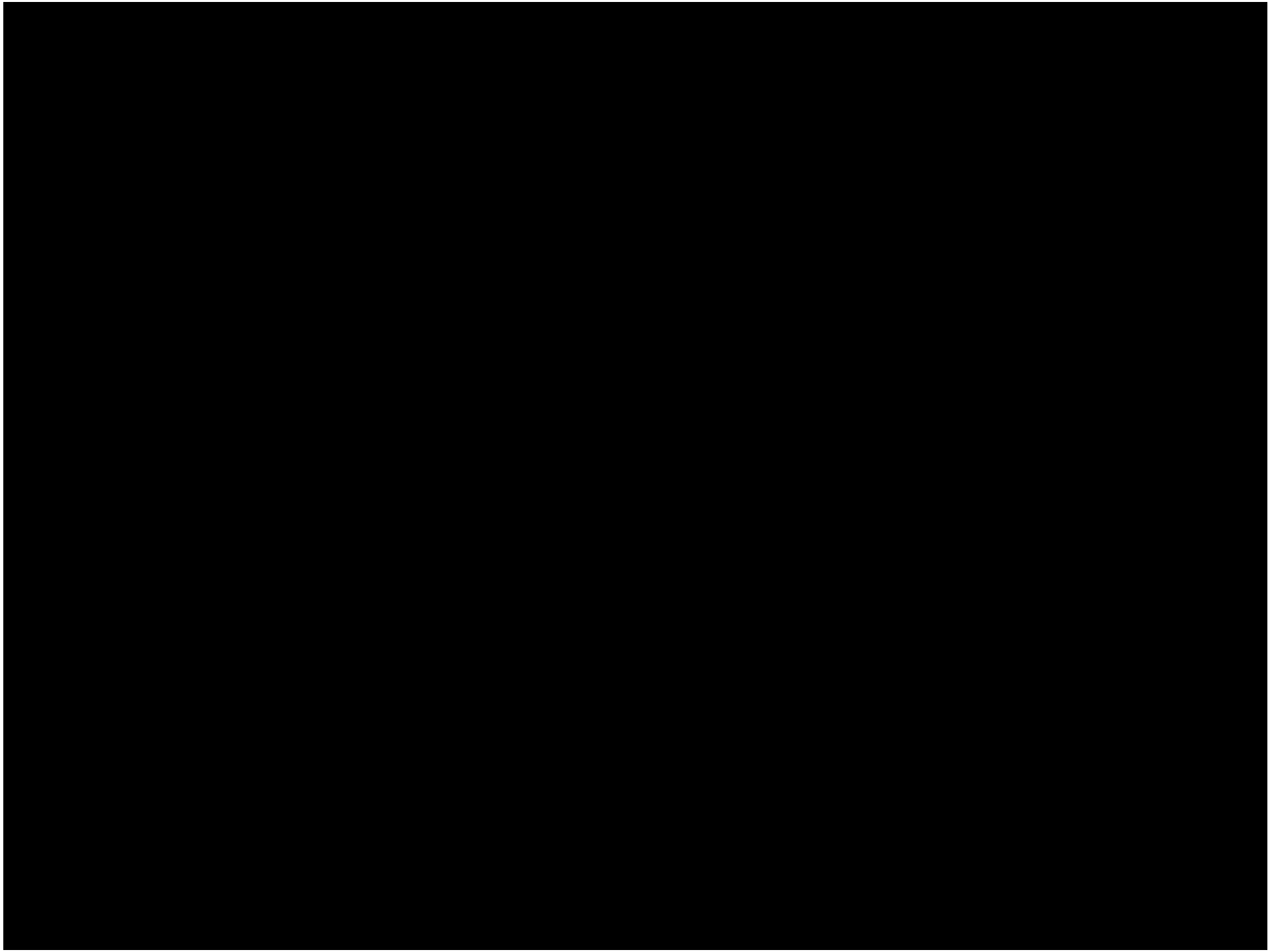
Cell sorting/CD138

GIEMSA + FISH







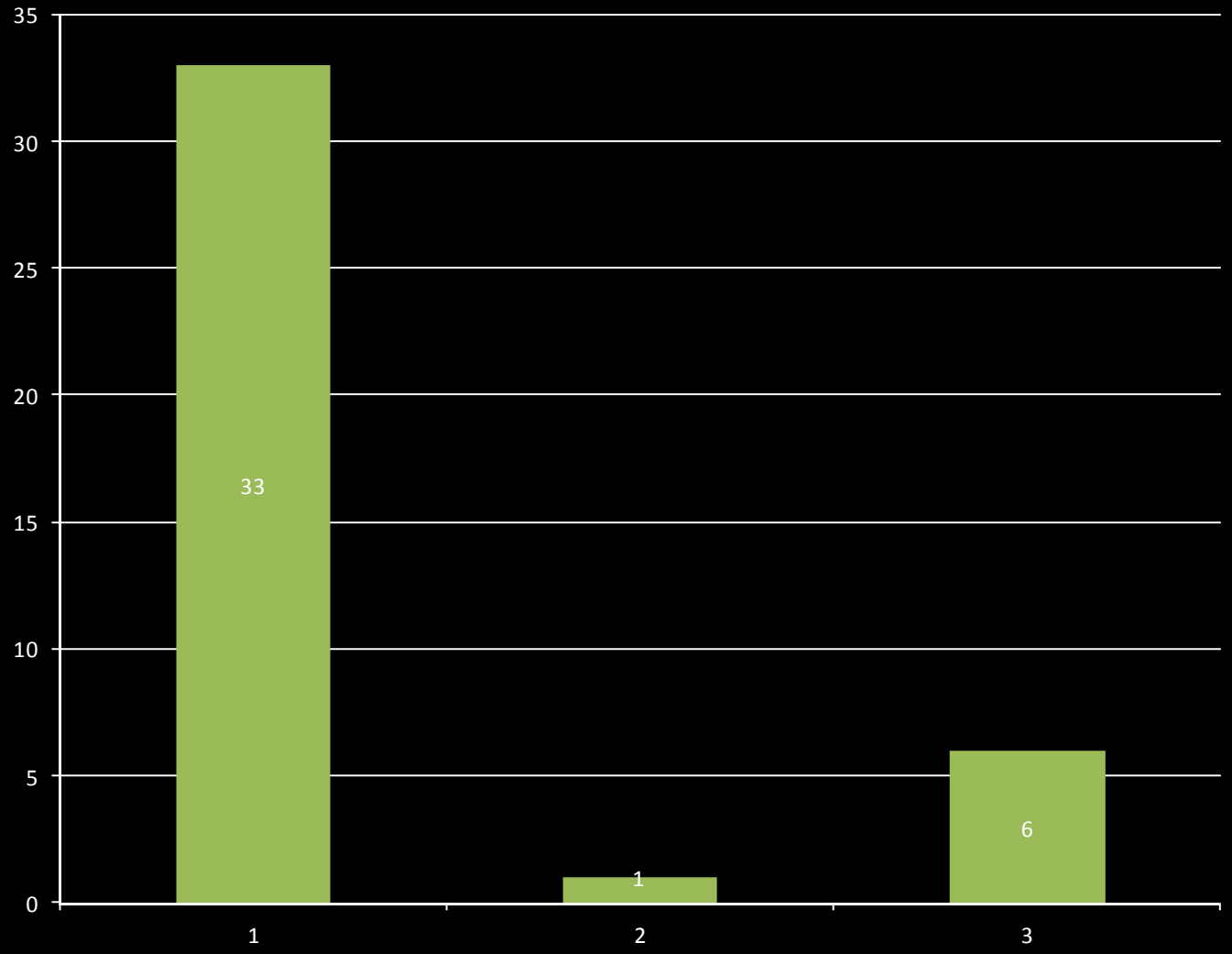


11. In diagnosing symptomatic myeloma current CRAB features need to be further modified.

1.Agree

2.Disagree

3.Unsure



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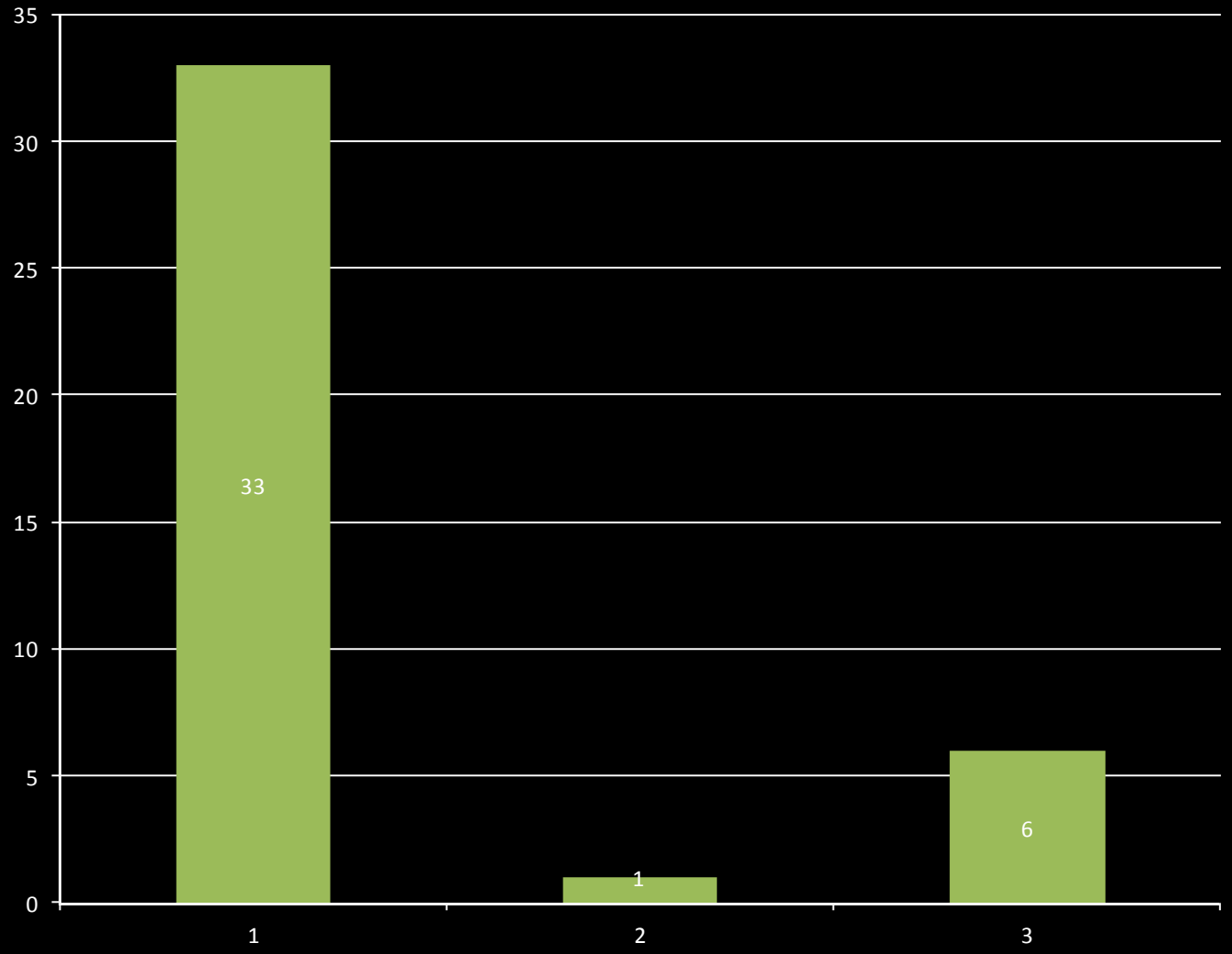

Bone Marrow Criteria

- If 3 or more lytic lesions, and a clonal paraprotein then BM involvement by ≥ 10% clonal plasma cells is not required. However, before diagnosing MM other causes of metastatic bone lesions should be considered and if indicated biopsy of one lytic lesion may be required for diagnosis of MM

Bone Marrow Criteria – Solitary Plasmacytoma

- Presence of solitary plasmacytoma confirmed by biopsy, without excess clonal plasma cells in the bone marrow, is not adequate for the diagnosis of multiple myeloma. e.g. If a patient appears to have a solitary plasmacytoma, confirmed by PET CT or MRI, and the bone marrow has <10% clonal plasma cells, then it is not considered adequate for the diagnosis of myeloma. The patient should be considered as solitary plasmacytoma if the bone marrow has no clonal involvement, or solitary plasmacytoma plus MGUS if there is clonal involvement less than 10%. Note that both entities are treated identically.

Bone Marrow Criteria -Solitary Plasmacytoma

- Presence In suspected myeloma, if clonal PCs in the bone marrow are less than 10%, then one may need to repeat the aspirate or may need to biopsy a bone lesion. If there are clonal plasma cells in the marrow of less than 10%, but the biopsy of a bony lesion lesion proves plasmacytoma a diagnosis of myeloma can be made provided it is not solitary. If a patient with suspected myeloma does not have any plasmacytomas and has less than 10% clonal plasma cells, but has anaemia (per definition below), or renal dysfunction (as defined below), than it is necessary that these myeloma defining events (MDE) are confirmed to be directly related to the clonal plasma cells carefully. E.g. It would be most unusual to have a haemoglobin of < 10 gm/dL due to <10% plasma cell infiltration in the BM. In this case a biopsy proven bone lesion (if >2 lesions), histopathologic evidence of kidney involvement, or a second bone marrow examination and elimination of all other causes of anemia

Renal dysfunction – MIDD and Amyloid

- The presence of monoclonal Ig deposition disease(MIDD) or AL amyloidosis should not be considered a myeloma defining event; these conditions should be considered distinct entities since the biology of the clone in these disorders is more indolent than in multiple myeloma, and the diagnosis and supportive care require dedicated interventions. Patients with these diagnoses, however, should have access to the same drugs used for myeloma because these diseases are caused by a clonal plasma cell population which has proven to be sensitive to the same drugs and regimen used for multiple myeloma

Renal Dysfunction

- If patient has renal biopsy which reflects MM related change, (light chain cast nephropathy) or AL amyloidosis then it will be adequate to consider as active myeloma and consider therapeutic intervention irrespective of serum creatinine or creatinine clearance; however, myeloma patients with amyloidosis requires specialized supportive care. The presence of AL amyloid on kidney biopsy does not necessarily indicate active myeloma. If there are ≥10% clonal plasma cells in the bone marrow with proteinuria and the kidney biopsy is AL amyloid, the patient could be defined as having primary diagnosis of AL amyloid with myeloma as associated disease. Similarly If there are ≥10% clonal plasma cells in the bone marrow with the kidney biopsy is showing MIDD then, the patient could be defined as having primary diagnosis of MIDD with myeloma as associated disease.