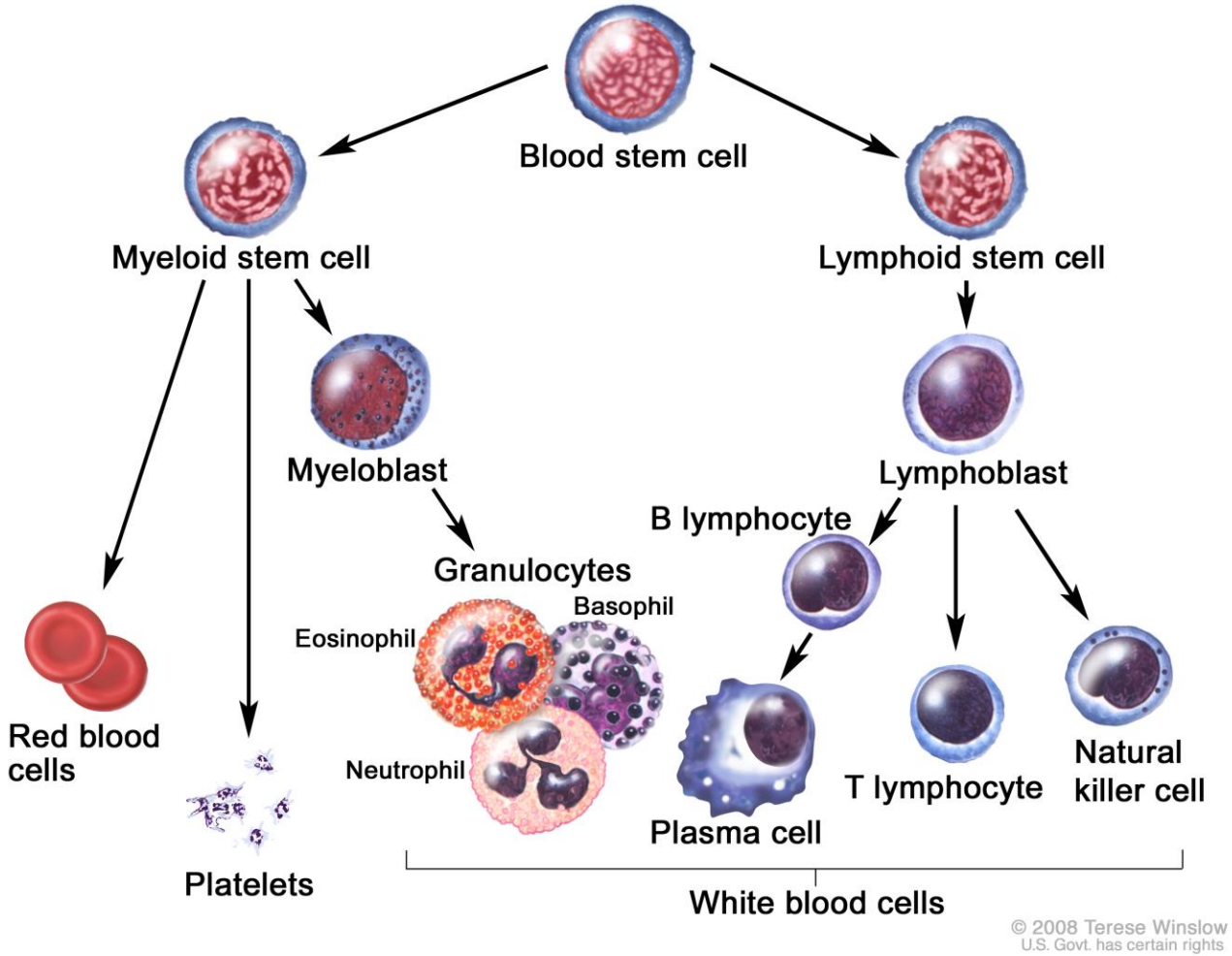
Multiple myeloma
definitions, diagnostics and response criteria

Plasma cell is the final stage of lymphocyte B differentiation



Monoclonal gammapathies

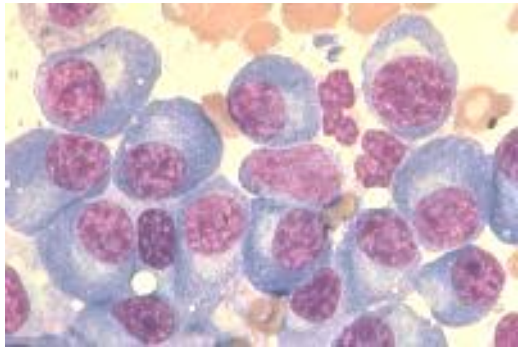
- Group of disorders associated with monoclonal proliferation of plasma cells.

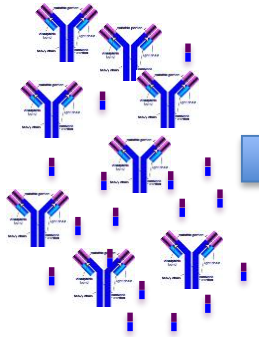
- **MGUS** - monoclonal gammapathy of undetermined significance defined by presence of:
  - M-protein **below 30 g/l** **and**
  - the bone marrow clonal **plasma cells below 10%** **and**
  - **no** related organ or tissue impairment (ROTI/CRAB)
  - treatment: “Watch and Wait”

- Asymptomatic (**smouldering**) myeloma defined by presence of:
  - **M-protein at least 30 g/l** **or**
  - bone marrow clonal **plasma cells** of **at least 10%** **and**
  - **no** ROTI/**CRAB**
  - treatment: “Watch and Wait”

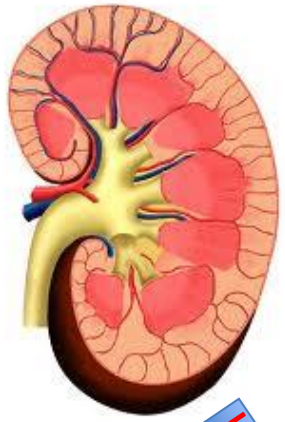
Multiple myeloma (symptomatic)

- Multiple myeloma is a monoclonal gammapathy characterized by clonal proliferation of atypical plasma cells and defined by presence of:
  - **M-protein** in **serum and/or urine** **and**
  - Bone marrow (clonal) **plasma cells** or plasmacytoma **and**
  - **Related organ or tissue impairment**





Kidney destruction



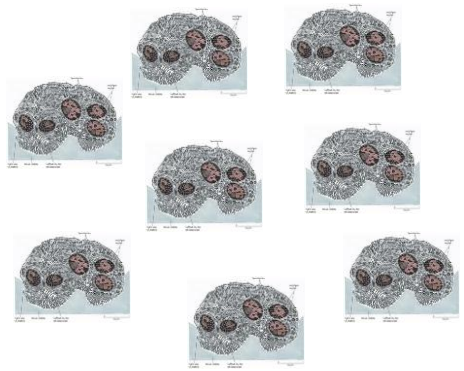
Creatinine ⇧

Low erythropoeitin

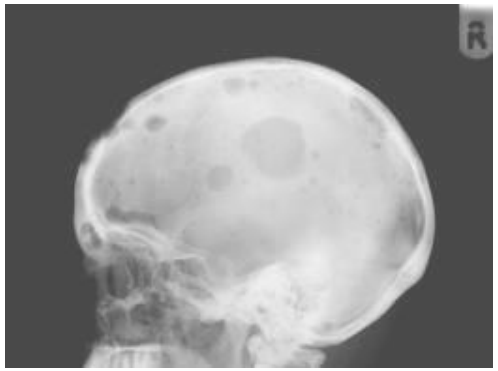
Hematopoesis supression

Anemia

Osteoclasts activation



Bone destruction

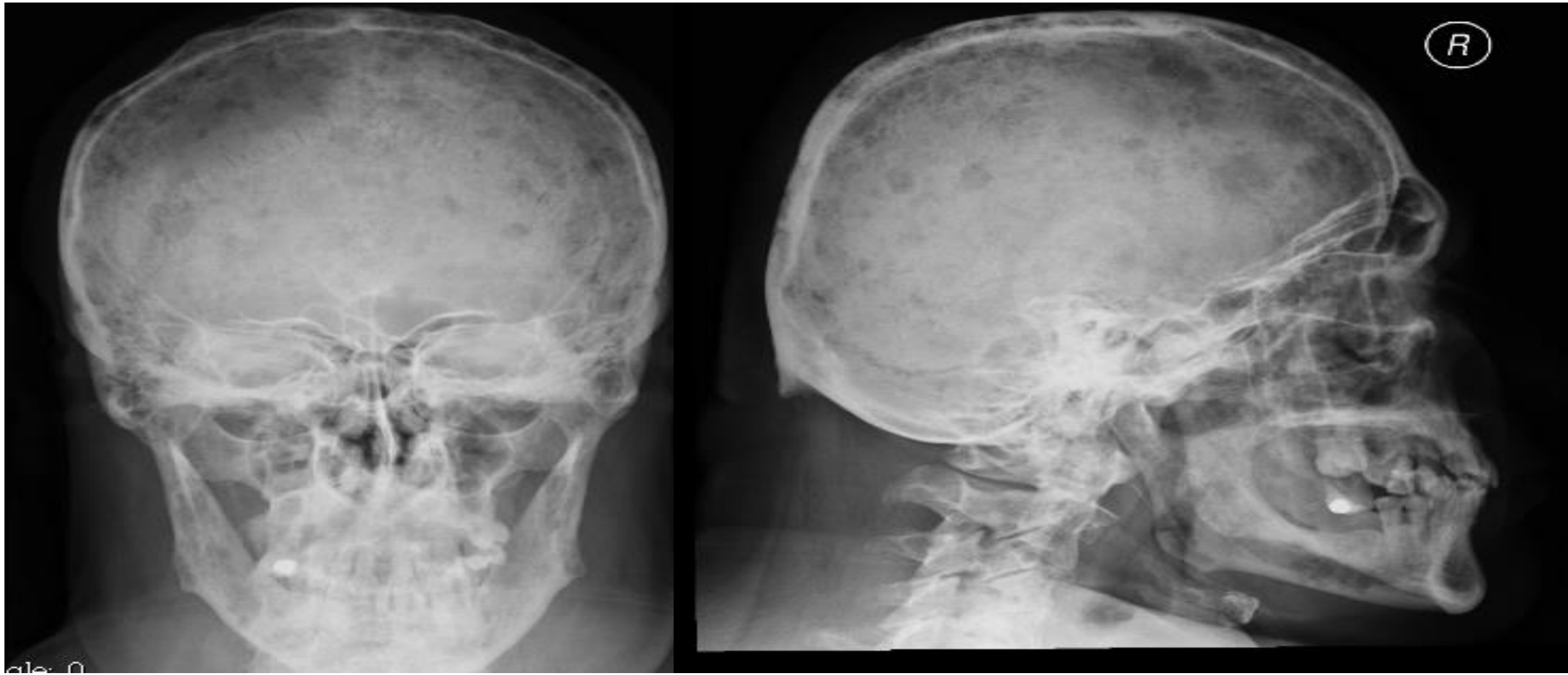


Calcium ⇧

Fractures

Related organ or tissue impairment ROTI/CRAB (now SLIMCRAB)

- **S** ixty percent of plasma cells in bone marrow and/or
- **L**i ight chains
  - the ratio of involved to not involved serum free light chains (measured by FreeLite Binding Site test) at least 100 and concentration of involved free light chains of at least 100 mg/dl and/or
- **M**agnetic resonance
  - presence of at least 2 focal infiltration seen in resonance of the whole body (Whole Body STIR) and/or
- **C** alcium levels increased:
  - serum calcium >0.25 mmol/l above the ULN or > 2.75 mmol/l and/or
- **R** enal insufficiency:
  - creatinine >173 mmol/l and/or
- **A** naemia:
  - haemoglobin 2 g/dl below the LLN or haemoglobin <10 g/dl and/or
- **B** one lesions: lytic lesions (CT/X-Ray) or osteoporosis with compression fractures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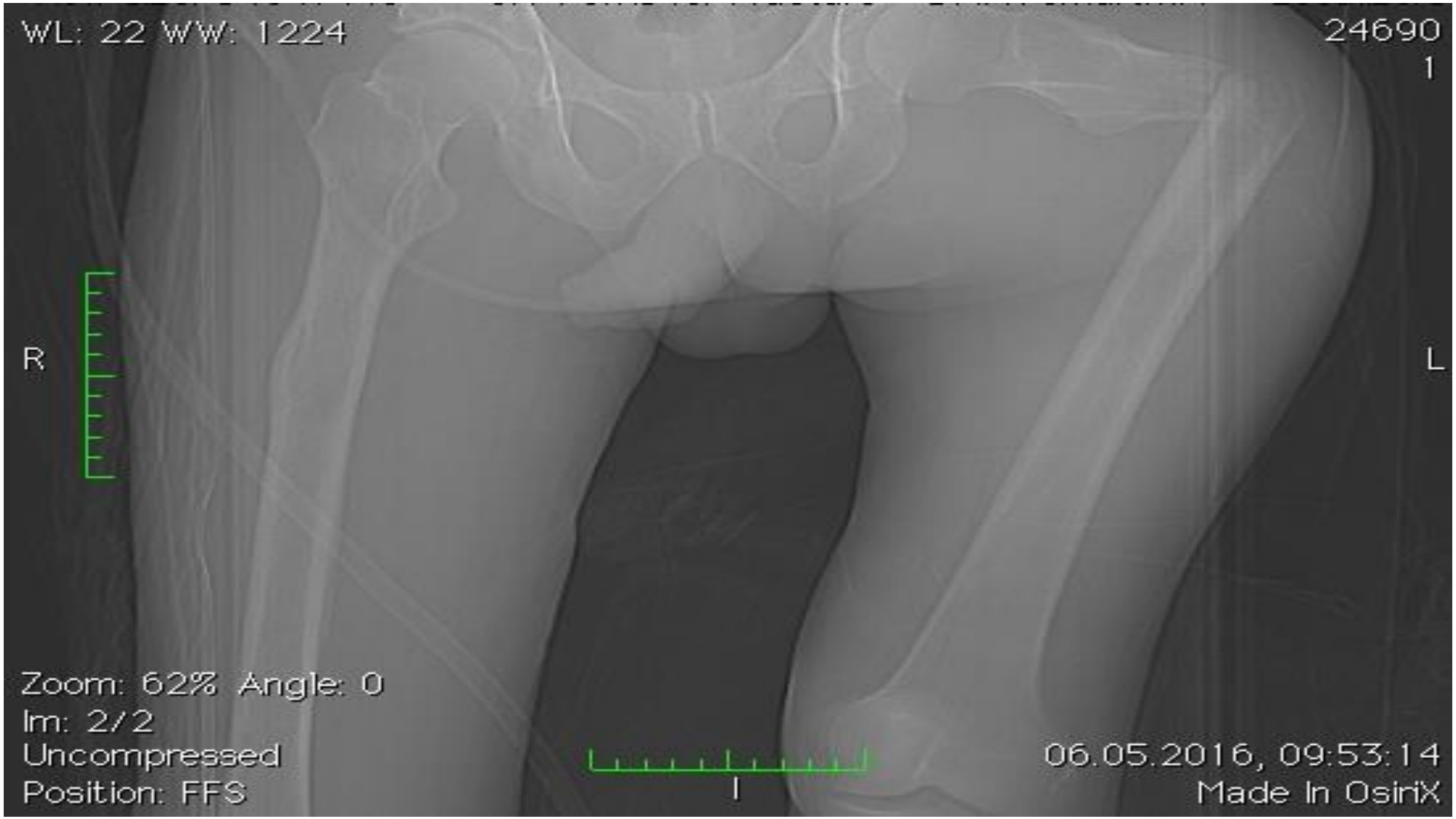
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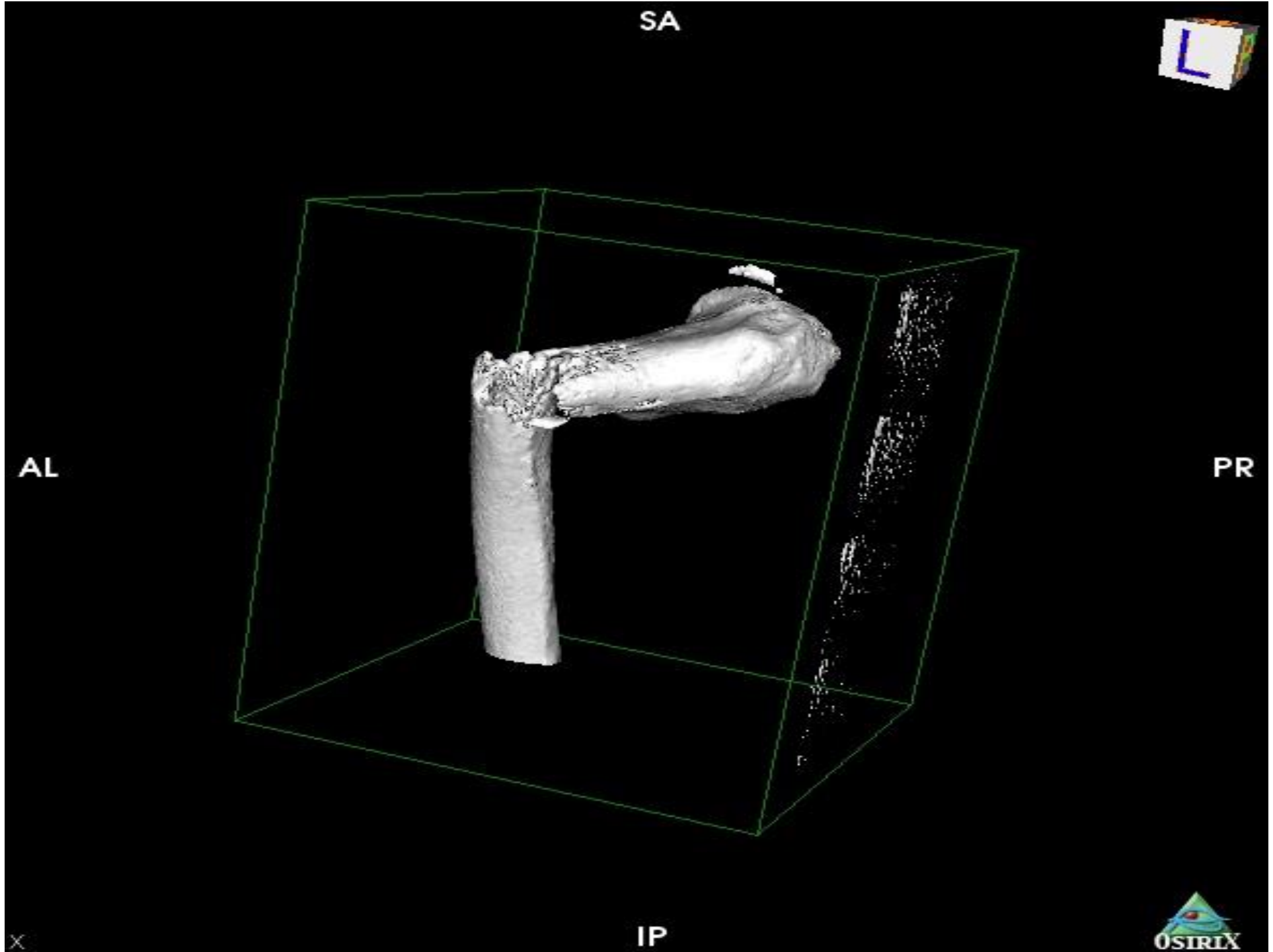
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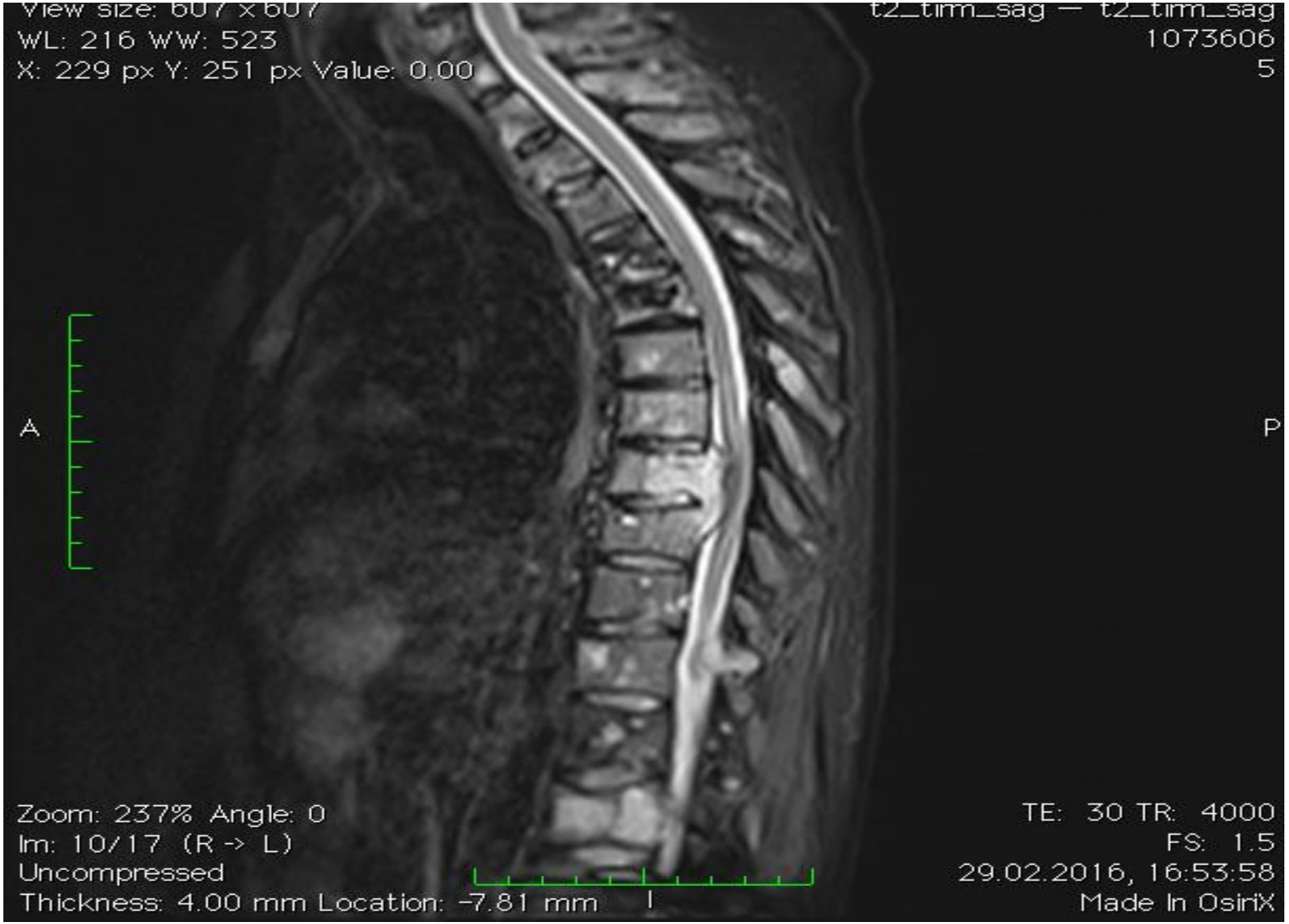
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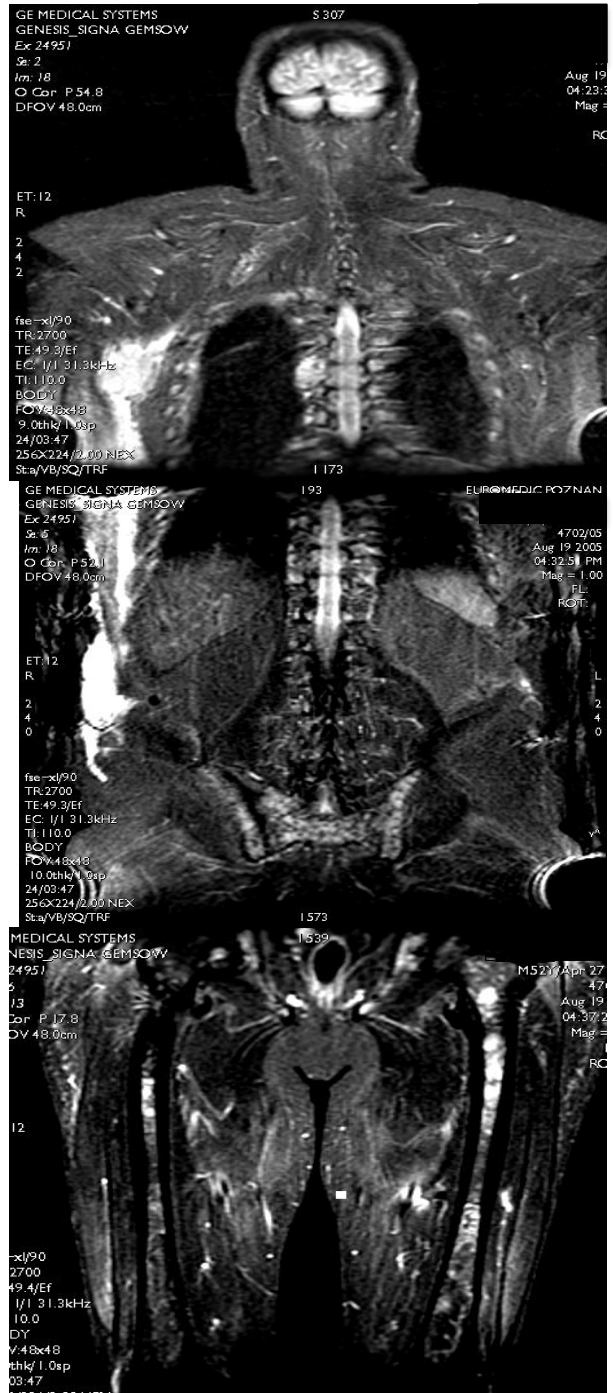
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O Cor P 54.8
DFOV 48.0cm
S 307
ET: 12
R
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fse-xl/90
TR:2700
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EC: 1/1 31.3kHz
TI: 110.0
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Se:6
Im: 18
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Sta/VB/SQ/TRF
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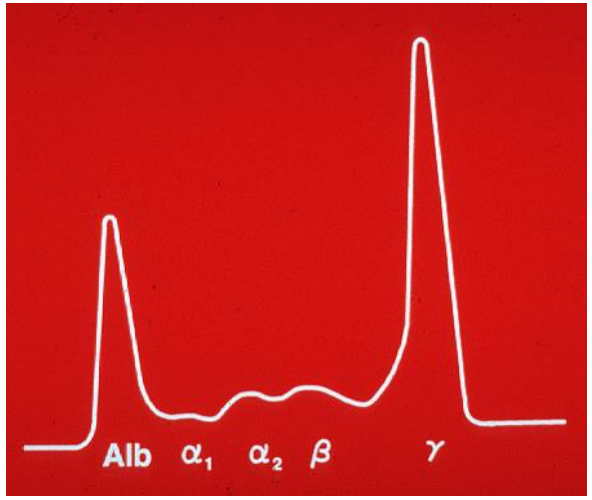
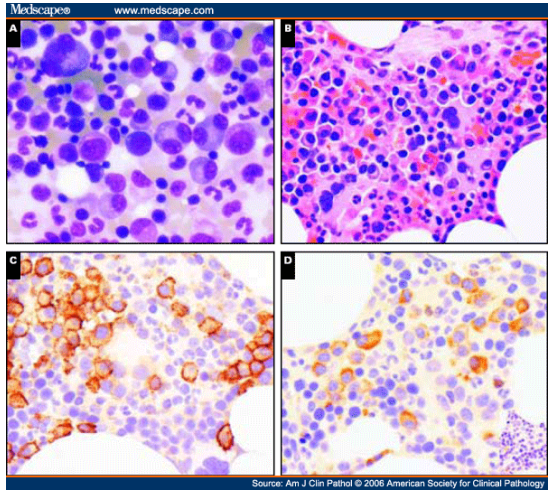
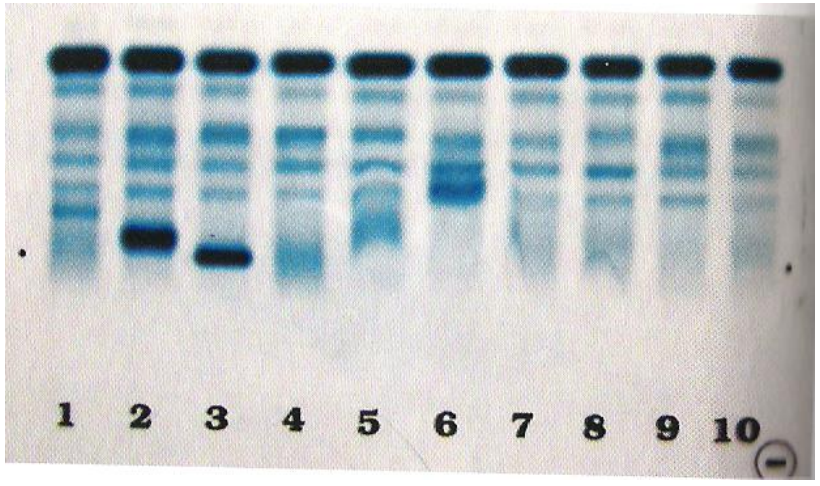
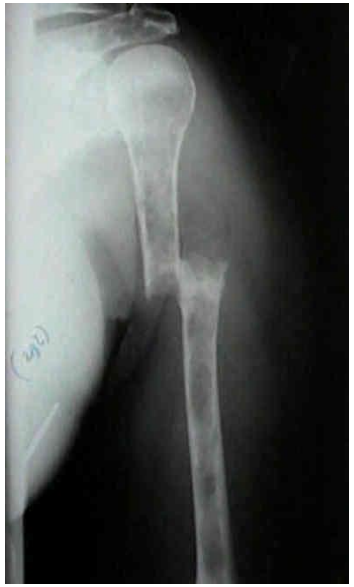
Methods of tumor burden assessment



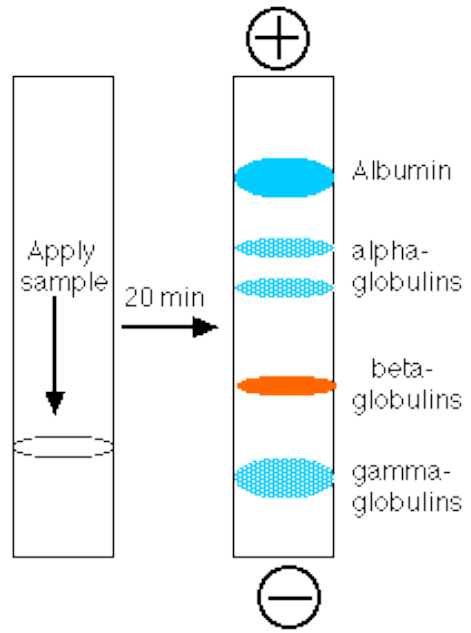




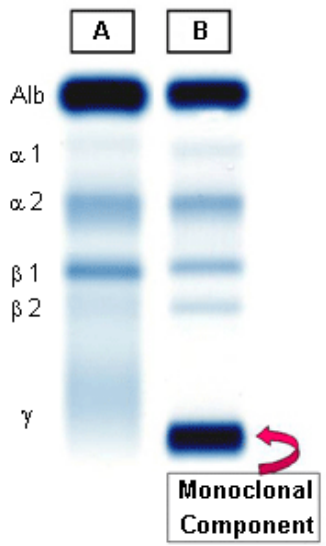


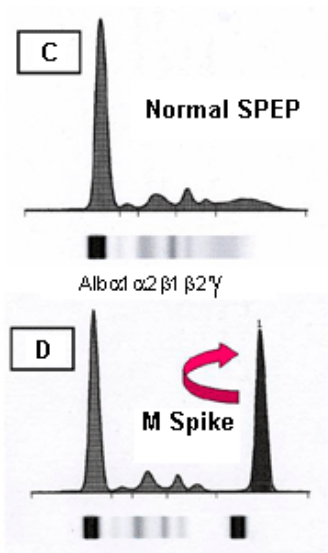
M-protein (serum and urine)

- Immunoelectrophoresis (TPE)
  - Distribution of proteins on the gel based on charge and size
  - Sensitivity: 0.5 g/l
  - Recommended for screening and treatment monitoring



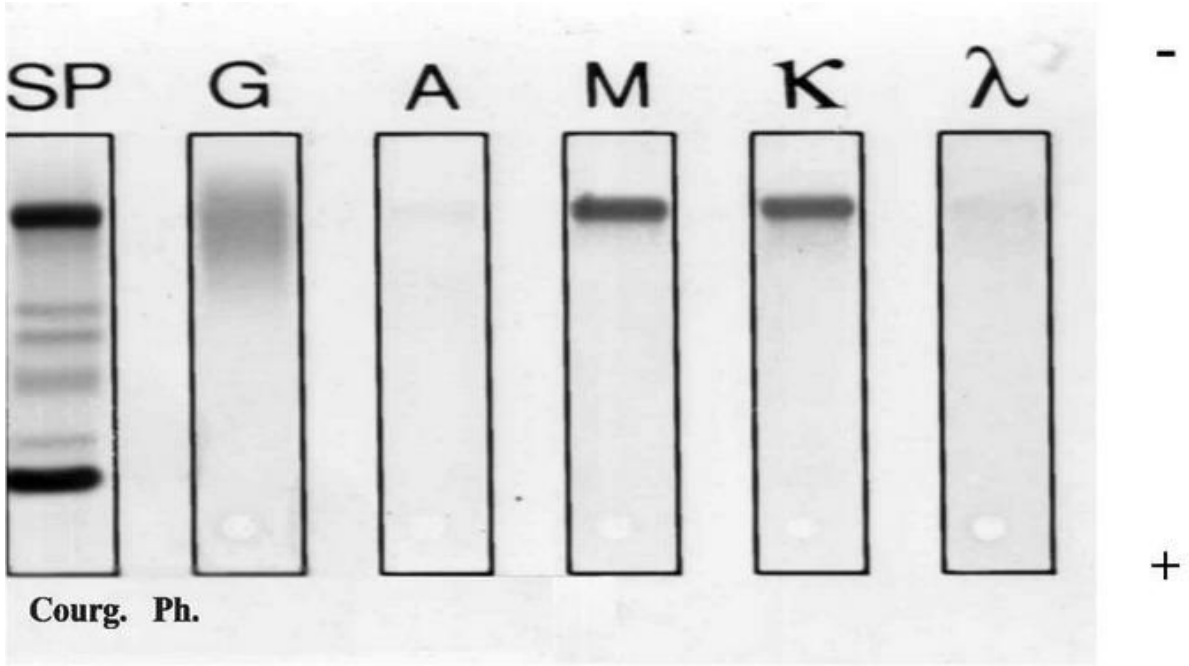
Separating serum proteins by electrophoresis





M-protein (serum and urine)

- Immunofixation (IFIX)
  - Detects and types of monoclonal antibodies
  - Sensitivity: 0.15 g/l
  - Recommended for screening and CR confirmation



Serum free light chains measurement

- In physiology
  - kappa and lambda FLC are present in serum in the same concentration
  - FLC ratio (FLCr) = kappa/lambda ≈1 (N: 0.26-1.65)

- In monoclonal gammapathies one of FLC is produced more than the other:
  - FLCr is usually disturbed (higher than 1.65 or lower than 0.26)

- FLC (FLCr) is recommended during:
  - screening
  - treatment monitoring in patient with oligosecretory MM (solitary plasmacytoma, non-secretory MM) and light chain disease (?)
  - to confirm sCR

Tests not recommended for treatment efficacy assessment

- Bone marrow
  - Recommended for screening (including trepan biopsy, cytogenetics and FISH) to confirm the diagnosis and to assess the risk
  - Recommended to confirm CR

- Skeletal survey (X-ray, MRI, PET-CT)
  - Recommended for screening,
  - Recommended when clinically indicated and as “good clinical practice” once a year

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group

Antonio Palumbo, Hervé Avet-Loiseau, Stefania Oliva, Henk M. Lokhorst, Hartmut Goldschmidt, Laura Rosinol, Paul Richardson, Simona Caltagirone, Juan José Lahuerta, Thierry Facon, Sara Bringhen, Francesca Gay, Michel Attal, Roberto Passera, Andrew Spencer, Massimo Offidani, Shaji Kumar, Pellegrino Musto, Sagar Lonial, Maria T. Petrucci, Robert Z. Orlowski, Elena Zamagni, Gareth Morgan, Meletios A. Dimopoulos, Brian G.M. Durie, Kenneth C. Anderson, Pieter Sonneveld, Jésus San Miguel, Michele Cavo, S. Vincent Rajkumar, and Philippe Moreau

Table 1. Standard Risk Factors for MM and the R-ISS

Prognostic Factor	Criteria
ISS stage	
I	Serum β_2-microglobulin < 3.5 mg/L, serum albumin ≥ 3.5 g/dL
II	Not ISS stage I or III
III	Serum β_2-microglobulin ≥ 5.5 mg/L
CA by iFISH	
High risk	Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)
Standard risk	No high-risk CA
LDH	
Normal	Serum LDH < the upper limit of normal
High	Serum LDH > the upper limit of normal
A new model for risk stratification for MM	
R-ISS stage	
I	ISS stage I and standard-risk CA by iFISH and normal LDH
II	Not R-ISS stage I or III
III	ISS stage III and either high-risk CA by iFISH or high LDH

Abbreviations: CA, chromosomal abnormalities; iFISH, interphase fluorescent in situ hybridization; ISS, International Staging System; LDH, lactate dehydrogenase; MM, multiple myeloma; R-ISS, revised International Staging System.

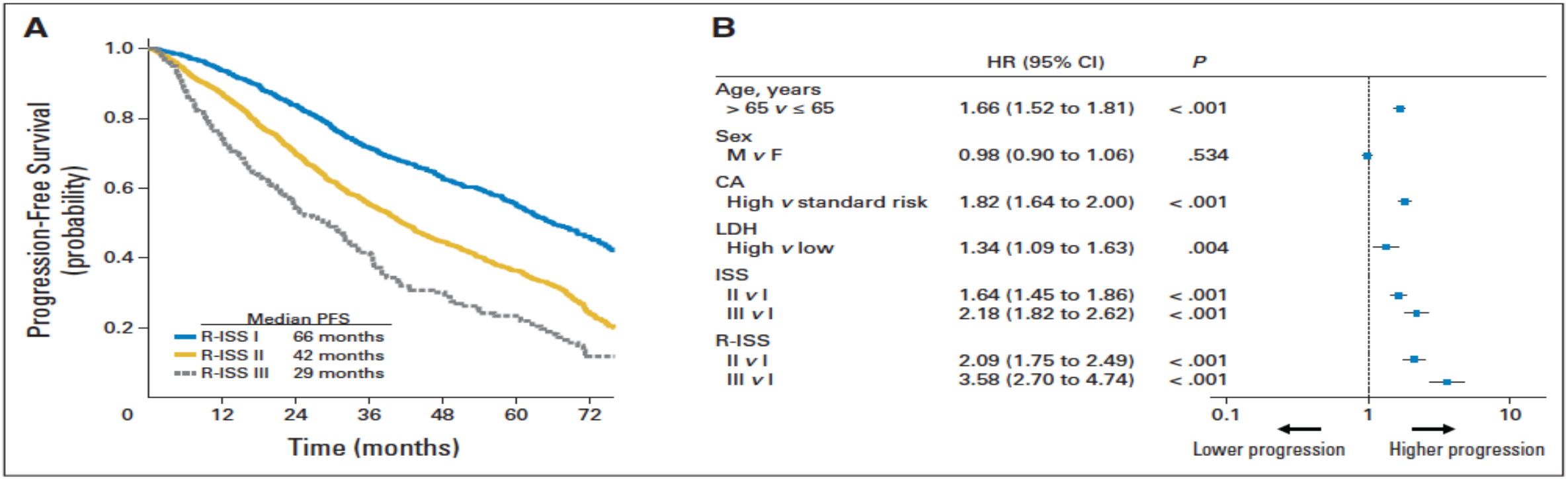
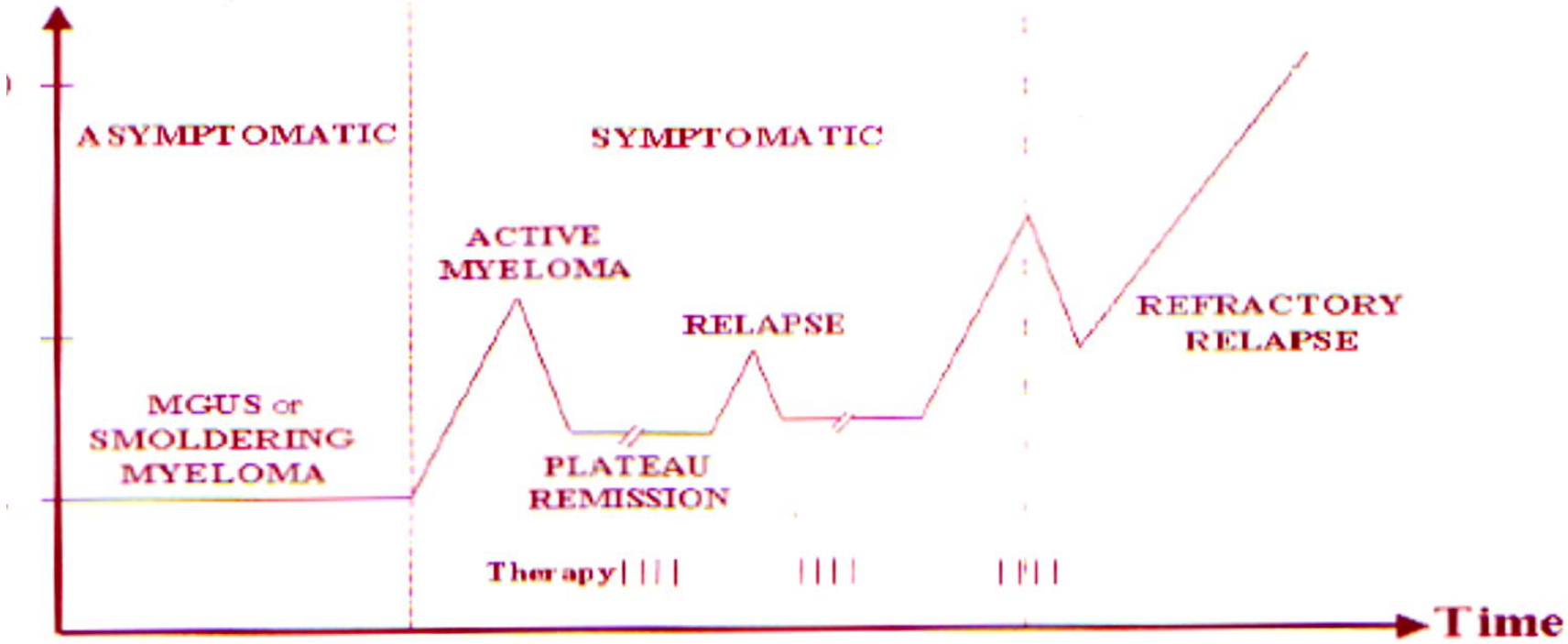


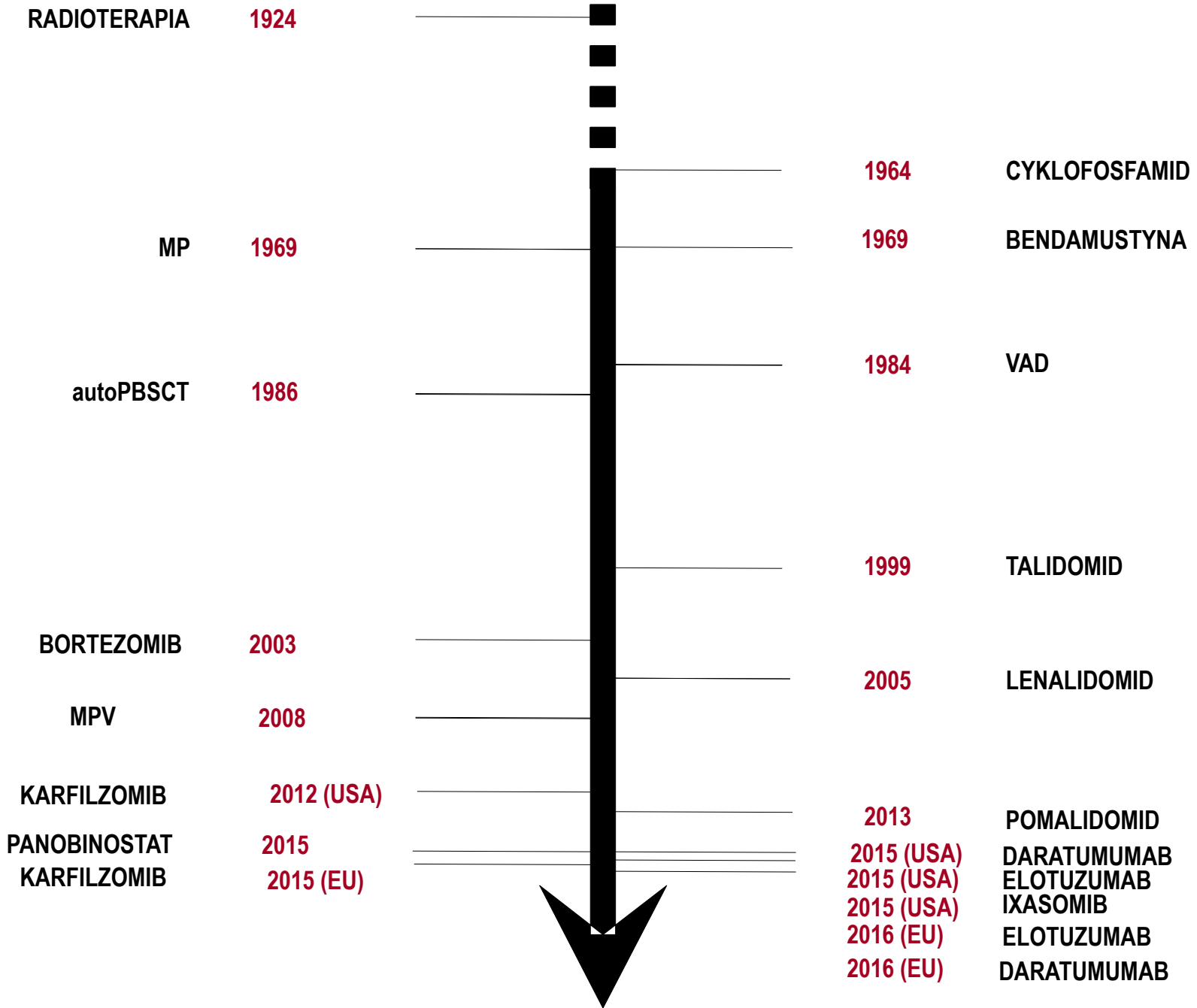
Fig 2. (A) Progression-free survival (PFS) in patients with multiple myeloma stratified by revised International Staging System (R-ISS) algorithm. Median PFS was 66 months for patients with R-ISS stage I, 42 months for patients with R-ISS stage II, and 29 months for patients with R-ISS stage III. (B) Univariable analysis of PFS. CA, chromosomal abnormalities; F, female; HR, hazard ratio; LDH, lactate dehydrogenase; M, male; NR, not reached.

Natural history of MM?



Treatment of MM

- Multiple myeloma remains mostly (?) uncurable
- “Watch and Wait” in smouldering myeloma
- There is no gold standard method of treatment
- Patients should be treated in clinical studies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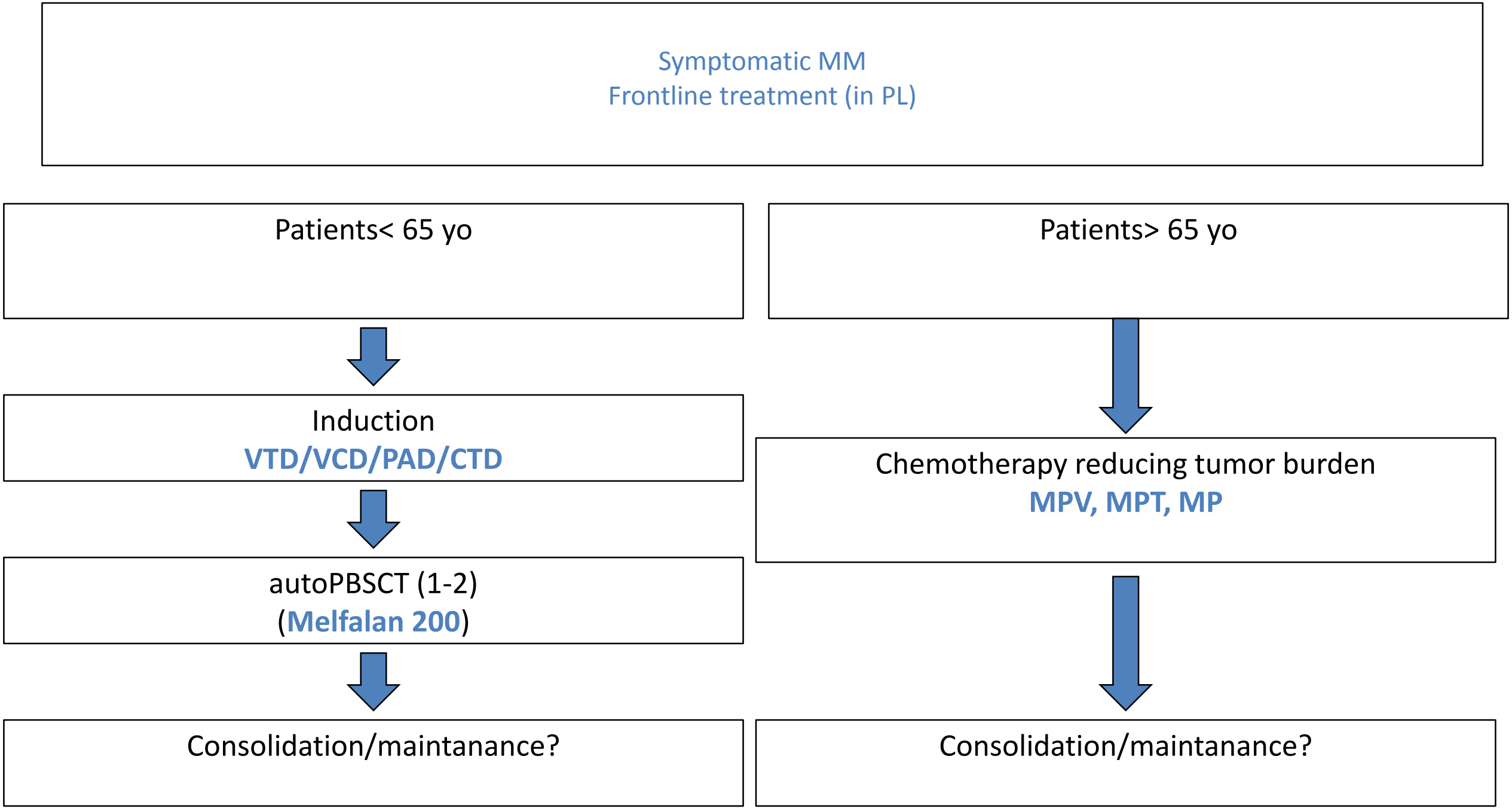
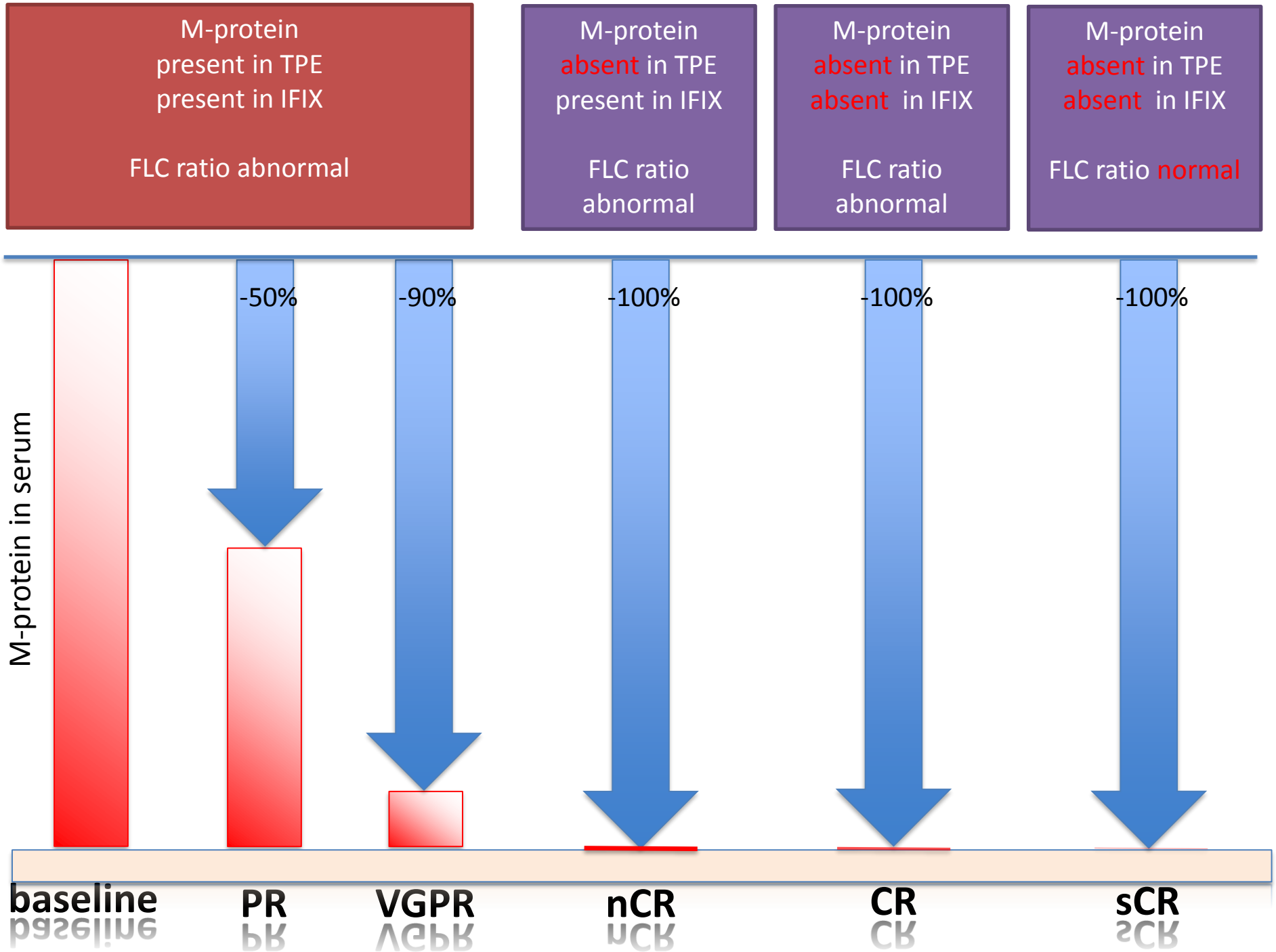
MP 1969
autoPBSCT 1986
BORTEZOMIB 2003
MPV 2008
KARFILZOMIB 2012 (USA)
PANOBINOSTAT 2015
KARFILZOMIB 2015 (EU)
1964 CYKLOFOSFAMID
1969 BENDAMUSTYNA
1984 VAD
1999 TALIDOMID
2005 LENALIDOMID
2013 POMALIDOMID
2015 (USA) DARATUMUMAB
2015 (USA) ELOTUZUMAB
2015 (USA) IXASOMIB
2016 (EU) ELOTUZUMAB
2016 (EU) DARATUMUMAB


Symptomatic MM
Frontline treatment (in PL)
Patients< 65 yo
Induction
VTD/VCD/PAD/CTD
autoPBSCT (1-2)
(Melfalan 200)
Consolidation/maintanance?
Patients> 65 yo
Chemotherapy reducing tumor burden
MPV, MPT, MP
Consolidation/maintanance?


M-protein present in TPE present in IFIX
FLC ratio abnormal
M-protein absent in TPE present in IFIX
FLC ratio abnormal
M-protein absent in TPE absent in IFIX
FLC ratio abnormal
M-protein absent in TPE absent in IFIX
FLC ratio normal
M-protein in serum
-50%
-90%
-100%
-100%
-100%
baseline
PR
VGPR
nCR
CR
sCR

IMWG Criteria for MRD in Multiple Myeloma

	Response subcategory	Response criteria
IMWG MRD negativity criteria (Requires CR as defined below)	Sustained MRD negative	MRD negative in the marrow (Next-generation flow or Next-generation sequencing) and by imaging as defined below, confirmed one year apart. Subsequent evaluations can be used to further specify the duration of negativity (e.g., MRD negative @ 5 years etc)
	Imaging MRD-negative	MRD negative as defined below (Next-generation flow or Next-generation sequencing) PLUS Disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT[3]
	Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by next-generation flow cytometry[4] on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in MM (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 next generation sequencing on bone marrow aspirates in which presence of a clone is defined as less than 2 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[5] or higher

Kumar et al, Lancet Oncology 2016

Progressive disease[a] To be used for calculation of time to progression and progression-free survival end points for all patients including those in CR (includes primary progressive disease and disease progression on or off therapy)	Progressive Disease: requires any one or more of the following: Increase of ⩾25% from baseline in Serum M-component and/or (the absolute increase must be ⩾0.5 g/dl)[b] Urine M-component and/or (the absolute increase must be ⩾200 mg/24 h Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels. The absolute increase must be >10 mg/dl. Bone marrow plasma cell percentage: the absolute % must be ⩾10%[c] Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas Development of hypercalcemia (corrected serum calcium >11.5 mg/dl or 2.65 mmol/l) that can be attributed solely to the plasma cell proliferative disorder
Clinical relapse[a]	Clinical relapse requires one or more of: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features)[b] It is not used in calculation of time to progression or progression-free survival but is listed here as as something that can be reported optionally or for use in clinical practice 1. Development of new soft tissue plasmacytomas or bone lesions 2. Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is 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 (> 11.5 mg/dl) [2.65 mmol/l] 4. Decrease in hemoglobin of ⩾2 g/dl [1.25 mmol/l] (see Table 3 for further details) 5. Rise in serum creatinine by 2 mg/dl or more [177 μmol/l or more]
SD (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 CR, VGPR, PR or progressive disease

New generations of MM drugs

- Proteaosome inhibitors (PIs):
  - Carfilzomib:
    - IV
    - No neuropathy
    - Higher risk of cardiac toxicity
  - Iksazomib:
    - PO
    - Works in high cytogenetics
- Immunomodulatory drugs (IMMIDs):
  - Pomalidomide (3rd generation of IMIDs)
    - Stronger than thalidomide and lenalidomide
    - No neuropathy
    - Higher risk of myelosuppression
- Monoclonal antibodies:
  - Daratumumab:
    - antyCD38
    - Effective and approved on every level of disease (naïve anf refractory MM) in combinations with PI and IMMIDS
  - Elotuzumab
    - antySC1(SLAMF7)
    - Effective in combination with lenalidomide and pomalidomide