Multiple Myeloma

Multiple Myeloma

- **Definition:**

  B-cell malignancy characterised by abnormal proliferation of plasma cells able to produce a monoclonal immunoglobulin (M protein)

- **Incidence:**

  3 - 9 cases per 100000 population / year

  more frequent in elderly

  modest male predominance

Multiple Myeloma = M-CRAB

- **Monoclonal protein**
- **Calcium**
- **Renal failure**
- **Anemia**
- **Bone pain with lytic lesions**

Disorders Associated with M- Protein

- **Neoplastic cell proliferation**
  - **multiple myeloma**
  - **solitary plasmacytoma**
  - **Waldenstrom macroglobulinemia, CLL**
  - **heavy chain disease**
  - **primary amyloidosis AL**
- **Undetermined significance**
  - **monoclonal gammopathy of undetermined significance (MGUS)**
- **Transient M protein**
  - **viral infection**
  - **post-valve replacement**
- **Solid Malignacy**
  - **bowel cancer, breast cancer**
- **Immune dysregulation**
  - **AIDS, old age**
- **Chronic inflamation**

Multiple Myeloma

- **Clinical forms:**
  multiple myeloma
  solitary plasmacytoma
  plasma cell leukaemia
- **M protein:**
  - is seen in 99% of cases in serum and/or urine
  IgG > 50%, IgA 20-25%, IgE or IgD 1-3%
  light chain 20%
  - 1% of cases are nonsecretory

Multiple Myeloma

Clinical manifestations are related to malignant behaviour of plasma cells and abnormalities produced by M protein

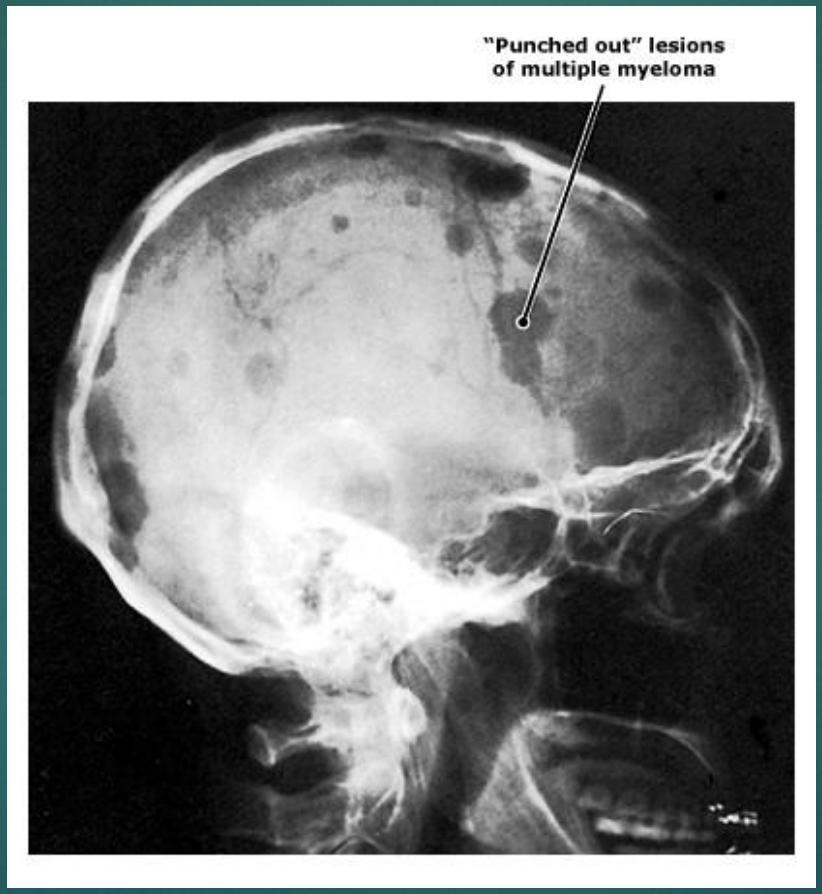
- **plasma cell proliferation:**
  - **multiple osteolytic bone lesions**
  - **hypercalcemia**
  - **bone marrow suppression (pancytopenia)**
- **monoclonal M protein**
  - **decreased level of normal immunoglobulins**
  - **hyper viscosity, RENAL FAILURE, amyloidosis**

Multiple Myeloma

Clinical symptoms:

- **bone pain, pathologic fractures**
- **weakness and fatigue**
- **serious infection**
- **renal failure**
- **bleeding diathesis (hyper viscosity)**

Lytic Bone Lesion



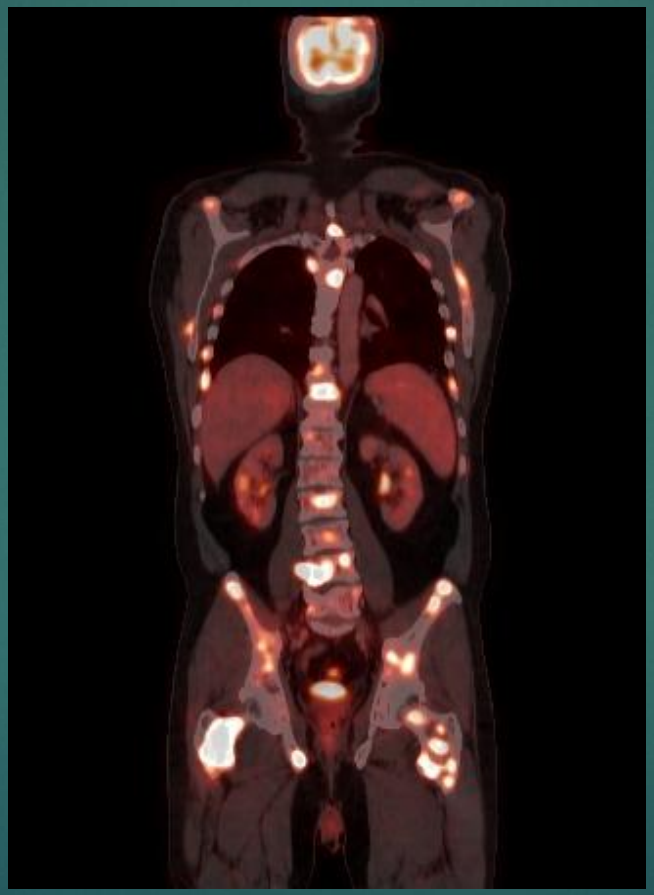
MM & Skeletal Complications

~ 80% of patients with multiple myeloma will have evidence of skeletal involvement on skeletal survey

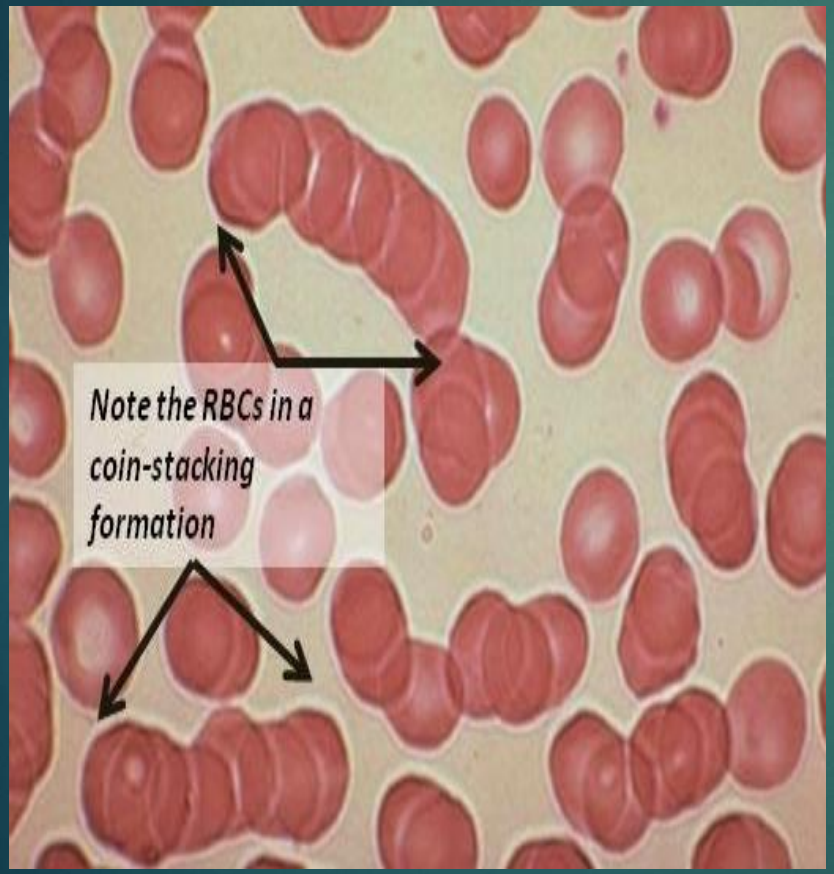
- Vertebrae: 65%
- Ribs: 45%
- Skull: 40%
- Shoulders: 40%
- Pelvis: 30%
- Long bones: 25%

Dimopoulos M, et al. Leukemia. 2009:1-12.

MM: PET Scan

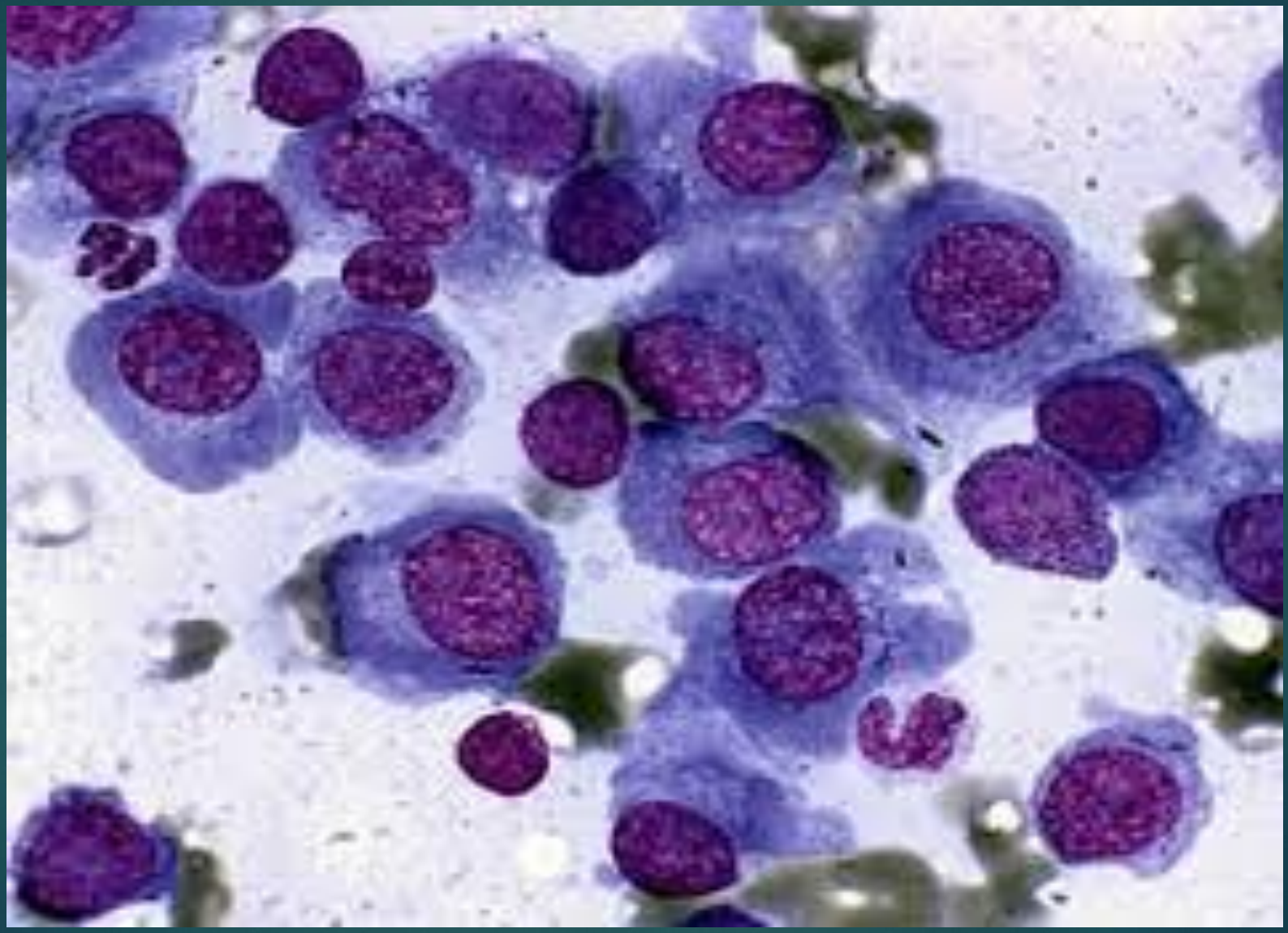


Multiple Myeloma



Laboratory tests:

- ESR > 100
- anaemia, thrombocytopenia
- Rouleau in peripheral blood smears
- marrow plasmacytosis > 10 -15%
- hyperproteinaemia
- hypercalcemia
- proteinuria
- renal failure



Diagnostic Criteria for Multiple Myeloma

Major criteria

I. Plasmacytoma on tissue biopsy

II. Bone marrow plasma cell > 30%

III. Monoclonal M spike on electrophoresis IgG > 3,5g/dl,

IgA > 2g/dl, light chain > 1g/dl in 24h urine sample

Minor criteria

a. Bone marrow plasma cells 10-30%

b. M spike but less than above

c. Lytic bone lesions

d. Normal IgM < 50mg, IgA < 100mg, IgG < 600mg/dl

- I + b; I + c; I + d
- II + b; II + c; II + d
- III + a; III + c; III + d
- a + b +c
- a + b+ d

Multiple Myeloma

All 3 criteria must be met (except unsecretory):

1. Presence of a serum or urinary monoclonal protein
2. Presence of clonal plasma cells in the bone marrow or a plasmacytoma
3. Presence of end organ damage felt related to the plasma cell dyscrasia, such as:
   - Increased calcium concentration
   - Lytic bone lesions
   - Anemia
   - Renal failure

Smoldering Multiple Myeloma SMM, Asymptomatic

Both criteria must be met:

- Serum monoclonal protein ≥3 g/dL and/or bone marrow plasma cells ≥10 percent
- No end organ damage related to plasma cell dyscrasia

Monoclonal Gammopathy of Undetermined Significance (MGUS)

All 3 criteria must be met:

- Serum monoclonal protein <3 g/dL
- Bone marrow plasma cells <10 percent
- No end organ damage related to plasma cell dyscrasia or a related B cell lymphoproliferative disorder

Monoclonal gammopathy of undetermined significance (MGUS)

- **M protein**
  - **3% of people > 70 years**
  - **15% of people > 90 years**
  - **MGUS is diagnosed in 67% of patients with an M protein**
  - **10% of patients with MGUS develop multiple myeloma, 1% per year**

POEMS Syndrome

- Osteosclerotic myeloma
  - Polyneuropathy
  - Organomegaly
  - Endocrinopathy
  - Monoclonal protein
  - Skin changes

MM: Evaluation

- CBC and differential,peripheral blood smear
- Chemistry: serum calcium, creatinine, albumin, LDH , beta-2 microglobulin, and C-reactive protein
- Serum protein electrophoresis (SPEP) + IF
- Quantification of immunoglobulins
- Urinalysis and a 24-hour urine collection for electrophoresis (UPEP) + IF
- Serum free monoclonal light chain (FLC)

MM Evaluation

- Serum viscosity should be measured if the M-protein concentration is high
- Bone marrow aspiration and biopsy with immunophenotyping, conventional cytogenetics, and fluorescence in situ hybridization (FISH)
- Metastatic bone survey with plain radiographs including the humeri and femoral bones should be performed in all patients.
- MRI, CT, or PET/CT

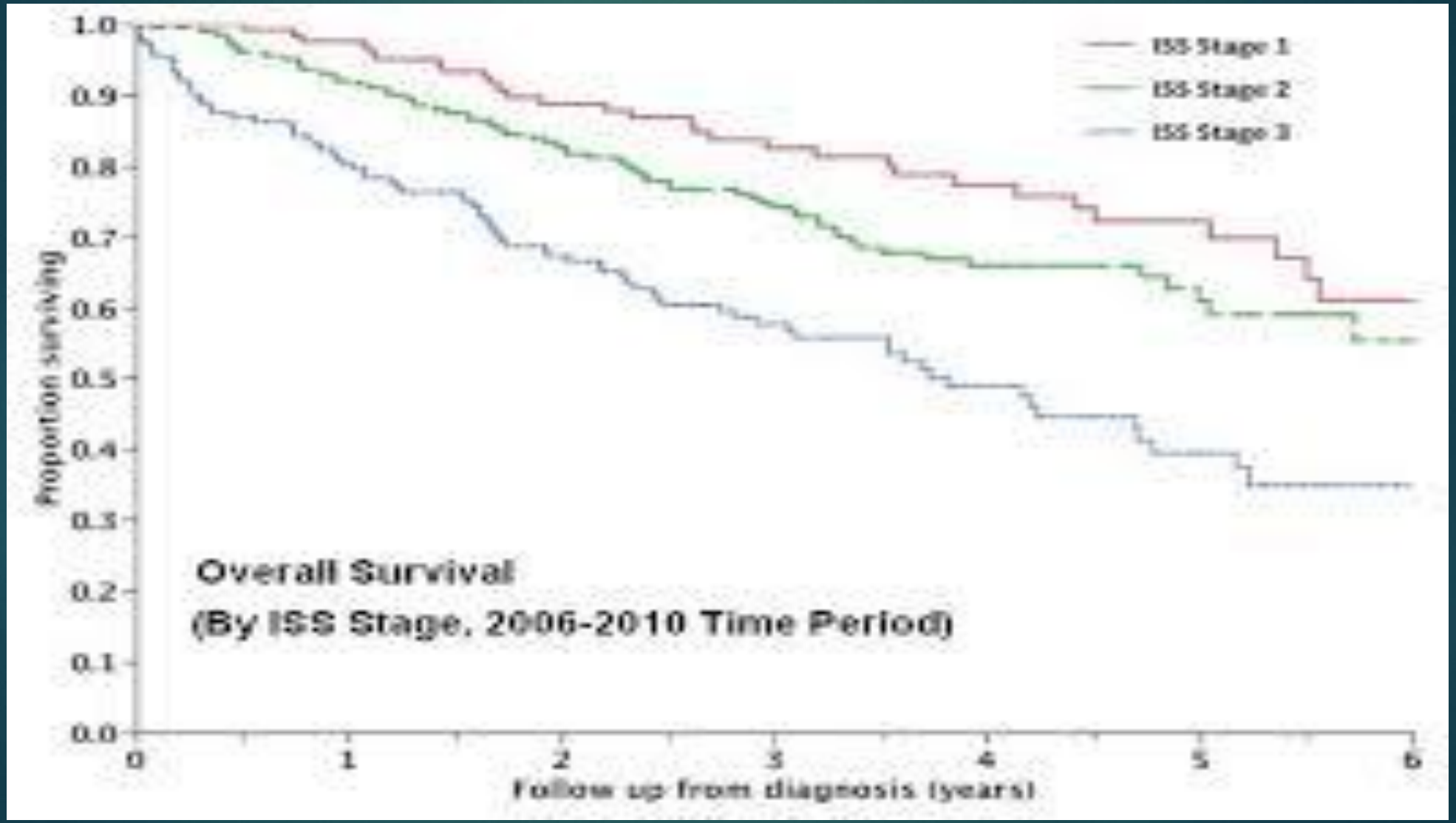
Staging for MM

International staging system (ISS)

- **Stage I — B2M <3.5 mg/L and serum albumin ≥3.5 g/dL**
- **Stage II — neither stage I nor stage III**
- **Stage III — B2M ≥5.5 mg/L**

Median overall survival for patients with ISS stages I, II, and III are 62, 44, and 29 months

MM Survival by ISS

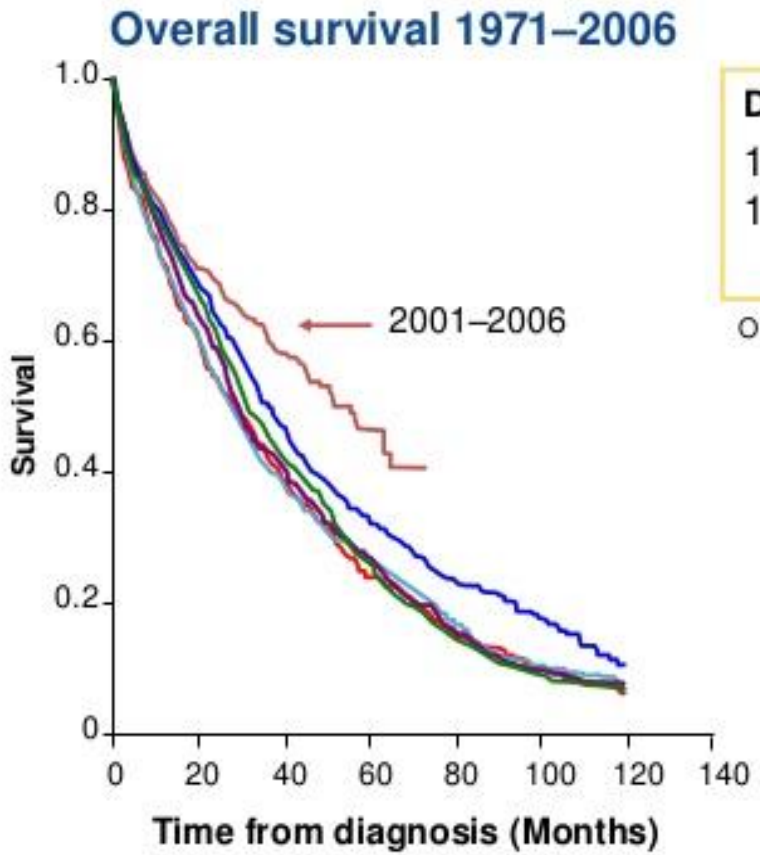


Cytogenenetics, Interphase FISH

- Poor prognosis (median survival 25 months): t(4;14)(p16;q32), t(14;16)(q32;q23), and

  -17p13
- Intermediate prognosis (median survival 42 months): -13q14
- Good prognosis (median survival 50 months): all others

Trends in Overall Survival of MM

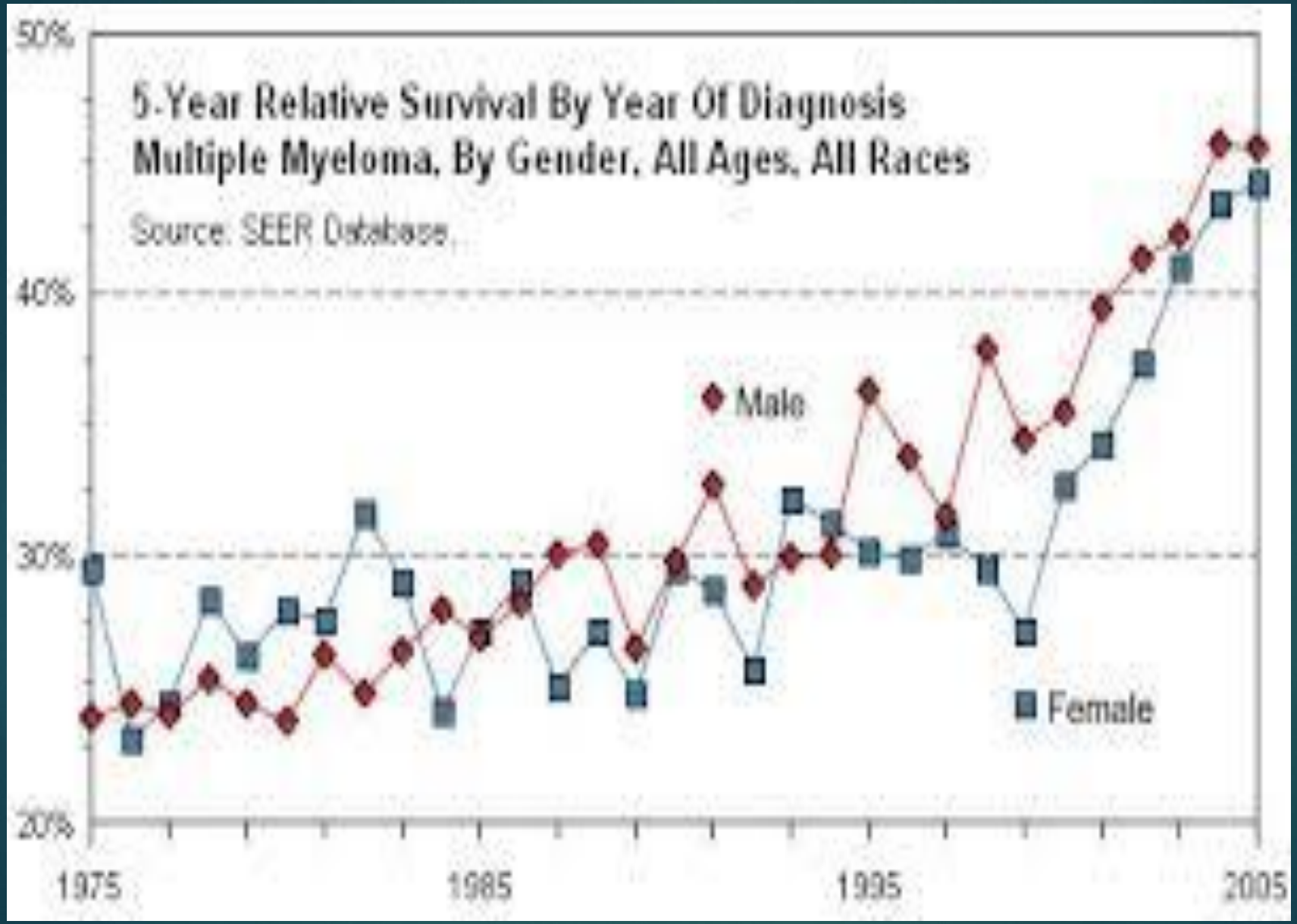


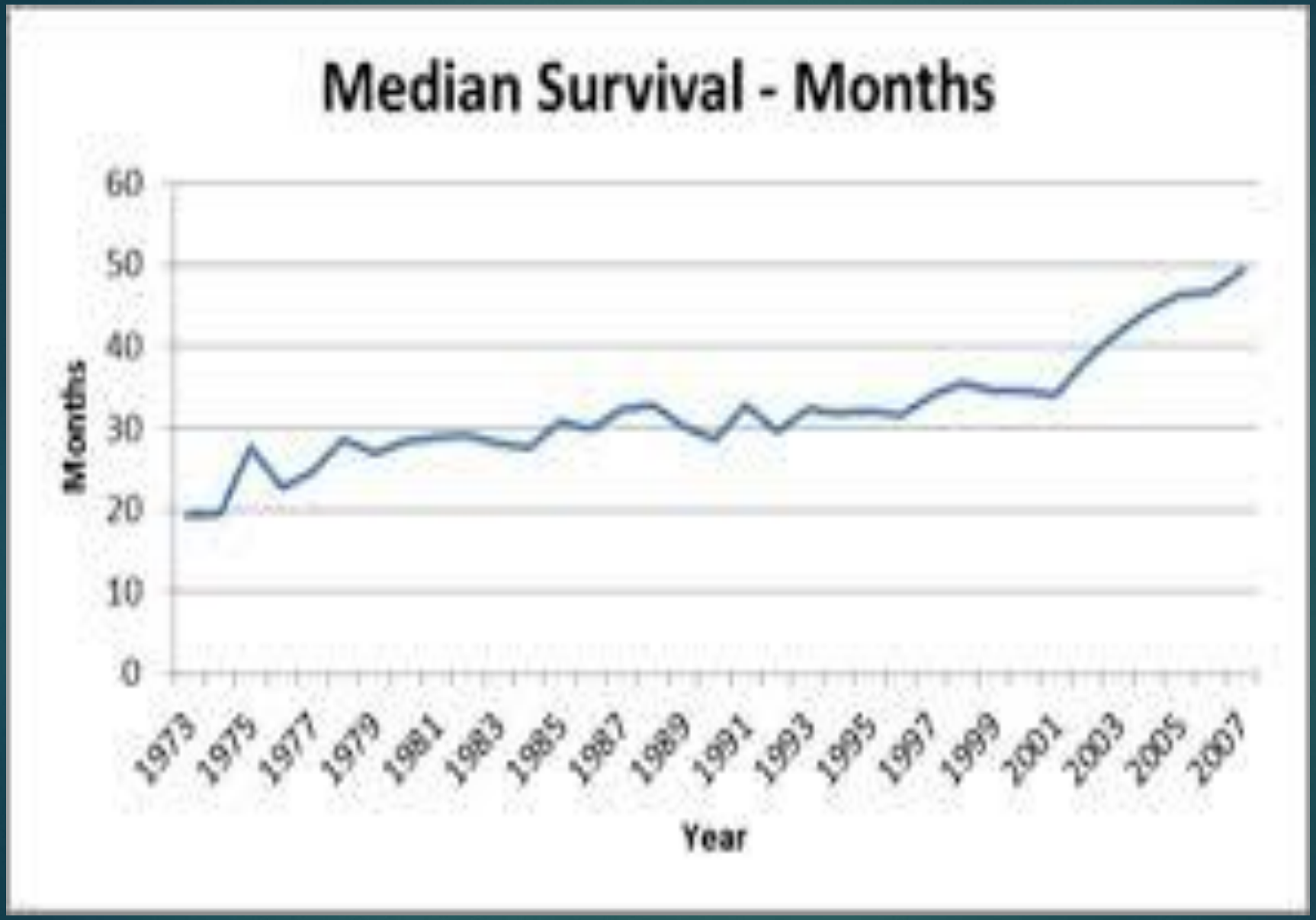
Diagnosis period	Median OS
1996–2006	45 months
1971–1996	30 months (P<0.001)

OS, overall survival.

1971–1976
1977–1982
1983–1988
1989–1994
1995–2000
2001–2006

Kumar SK, et al. *Blood*. 2008;111:2516-2520.


5-Year Relative Survival By Year Of Diagnosis
Multiple Myeloma, By Gender, All Ages, All Races
Source: SEER Database
50%
40%
30%
20%
1975
1985
1995
2005
Male
Female


Median Survival - Months
Months
60
50
40
30
20
10
0
1973
1975
1977
1979
1981
1983
1985
1987
1989
1991
1993
1995
1997
1999
2001
2003
2005
2007
Year

MM: RISK STRATIFICATION

- FISH for detection of t(4;14), t(14;16), and del17p13
- Conventional cytogenetics (karyotyping) for detection of del 13 or hypodiploidy
- The presence of any of the above markers defines high risk myeloma, which encompasses the 25 percent of MM patients who have a median survival of approximately two years or less despite standard treatment

Multiple Myeloma

Poor prognosis factors

- **cytogenetic abnormalities**
- **High β-2 microglobulin**
- **Advanced stage**
- **Hypercalcemia**
- **Renal failure**
- **Plasma cell leukaemia**

MM: Indications for Treatment

- Anemia (hemoglobin <10 g/dL or 2 g/dL below normal)
- Hypercalcemia (serum calcium >11.5 mg/dL)
- Renal insufficiency (serum creatinine>2 mg/dL)
- Lytic bone lesions or severe osteopenia
- Extramedullary plasmacytoma

Treatment of Multiple Myeloma

- **Patients fit< 65 years**
  - **induction with combination of IMIDS, cyclophosphamide, dexamethasone and velcade**
  - **High dose chemo with autologous stem cell transplantation**
- **Patients > 65 years**
  - **conventional chemotherapy, new drugs**

Treatment of Multiple Myeloma

- **Conventional chemotherapy**
  - **Melphlan + Prednisone**
  - **M2 (Vincristine, Melphalan, Cyclophosphamid, BCNU, Prednisone)**
  - **VAD (Vincristin, Adriamycin, Dexamethasone)**
- **Response rate 50-60% patients (CR very low)**
- **Long term survival 5-10% patients**

Treatment of Multiple Myeloma

- Autologous transplantation
  - Fit patients < 65
  - treatment related mortality 5-10%
  - response rate 80%
  - long term survival 40-50%

- allogeneic stem cell transplantation
  - patients < 45-50 years with HLA-identical donor
  - Poor prognostic factors
  - treatment related mortality 40-50%
  - long term survival 20-30%

Treatment of Multiple Myeloma

- **New methods**
  - **Reduced intensity allogeneic transplantation**
  - **Thalidomide, Revlimid, Pomalidomide**
  - **Proteasome inhibitors – bortezomib, carfilsomibe**
  - **New drugs – anti IL-6, HDAC inhibitors, anti CD38 (DARATUMOMAB)**

Treatment of Multiple Myeloma

- **Supportive treatment**
  - **biphosphonates, calcitonin**
  - **recombinant erythropoietin**
  - **immunoglobulins**
  - **plasmapheresis**
  - **radiation therapy**

Monoclonal gammopathy of undetermined significance (MGUS)

- **M protein presence, stable**
- **levels of M protein: IgG < 3,5g IgA < 2g LC<1g/day**
- **normal immunoglobulins - normal levels**
- **marrow plasmacytosis < 5%**
- **complete blood count - normal**
- **no lytic bone lesions**
- **no signs of disease**

The end