

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 Malignancy
 - bowel cancer, breast cancer
- ◎ Immune dysregulation
 - AIDS, old age
- ◎ Chronic inflammation

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

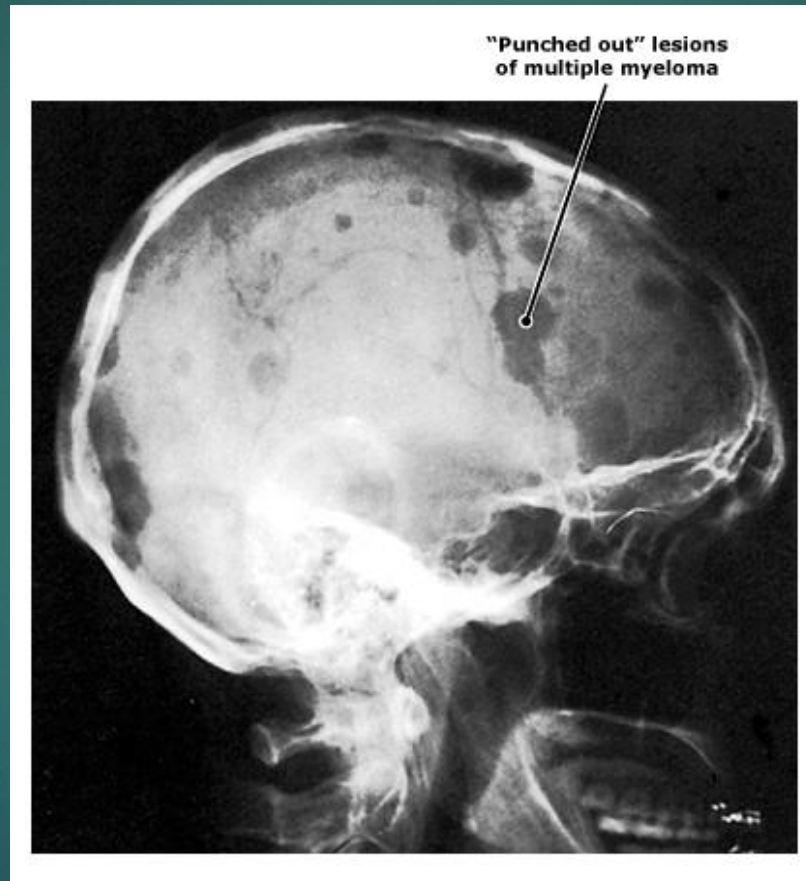
- ◎ **plasma cell proliferation:**
 - multiple osteolytic bone lesions
 - hypercalcemia
 - bone marrow suppression (pancytopenia)
- ◎ **monoclonal M protein**
 - decreased level of normal immunoglobulins
 - hyper viscosity, RENAL FAILURE, amyloidosis

Multiple Myeloma

Clinical symptoms:

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

Lytic Bone Lesion



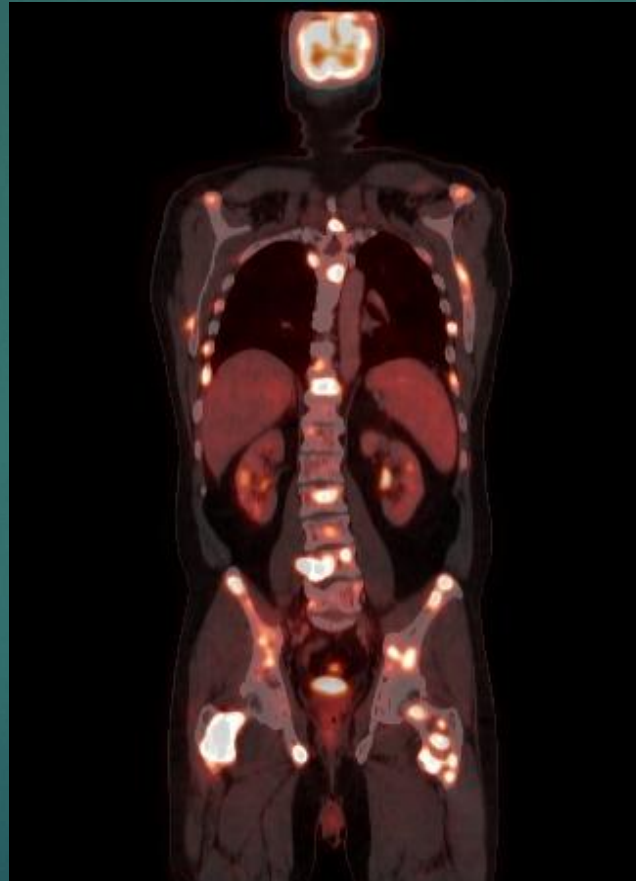
MM & Skeletal Complications

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

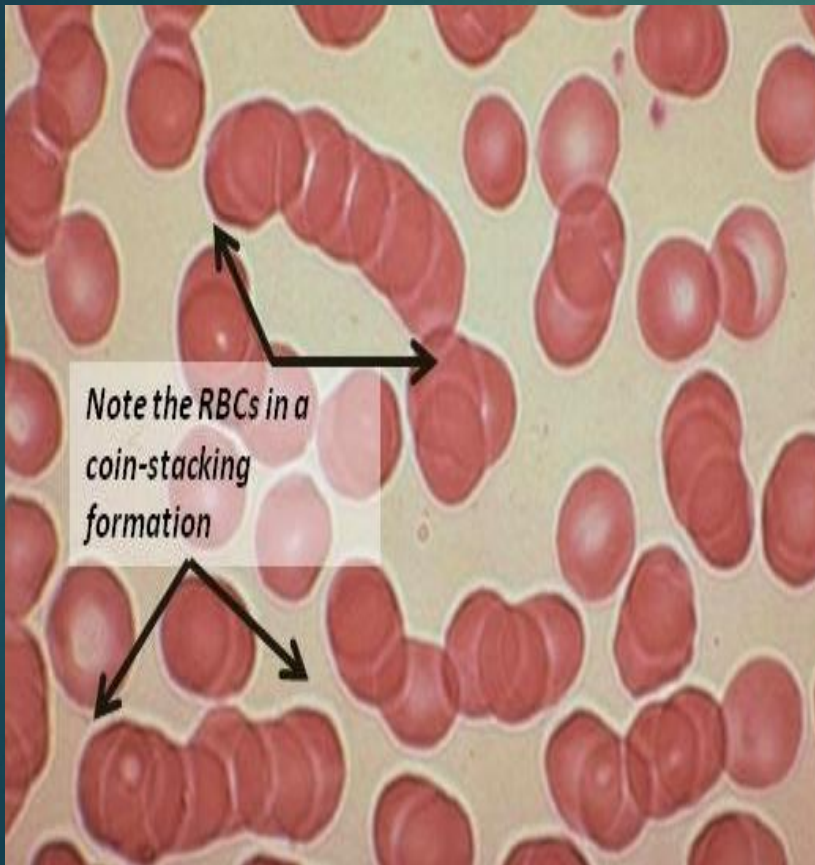
- Vertebrae: 65%
- Ribs: 45%
- Skull: 40%
- Shoulders: 40%
- Pelvis: 30%
- Long bones: 25%



MM: PET Scan

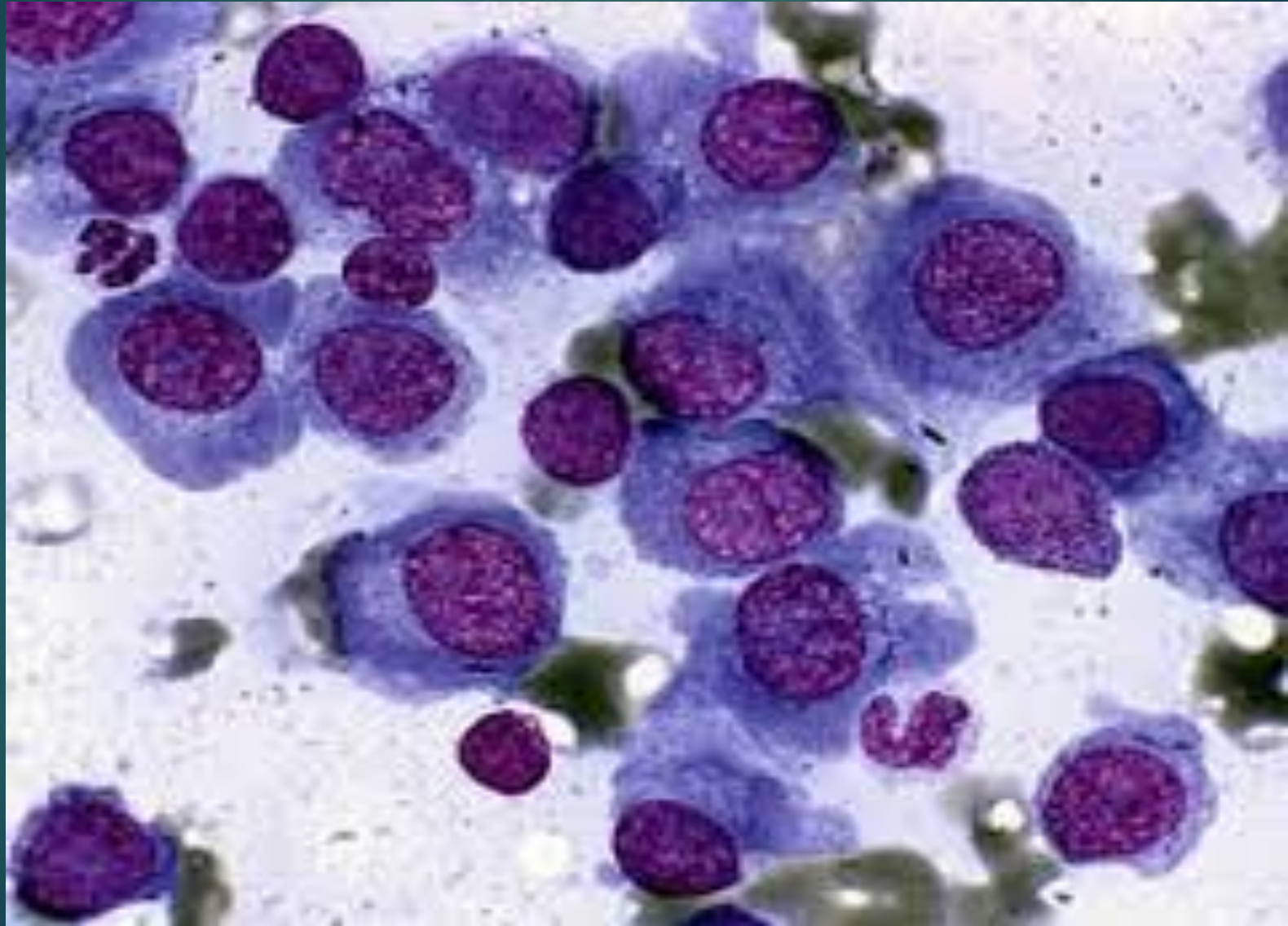


Multiple Myeloma



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

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

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)

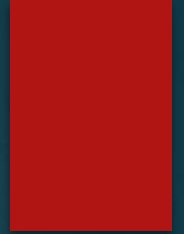
All 3 criteria must be met:

- ▶ 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

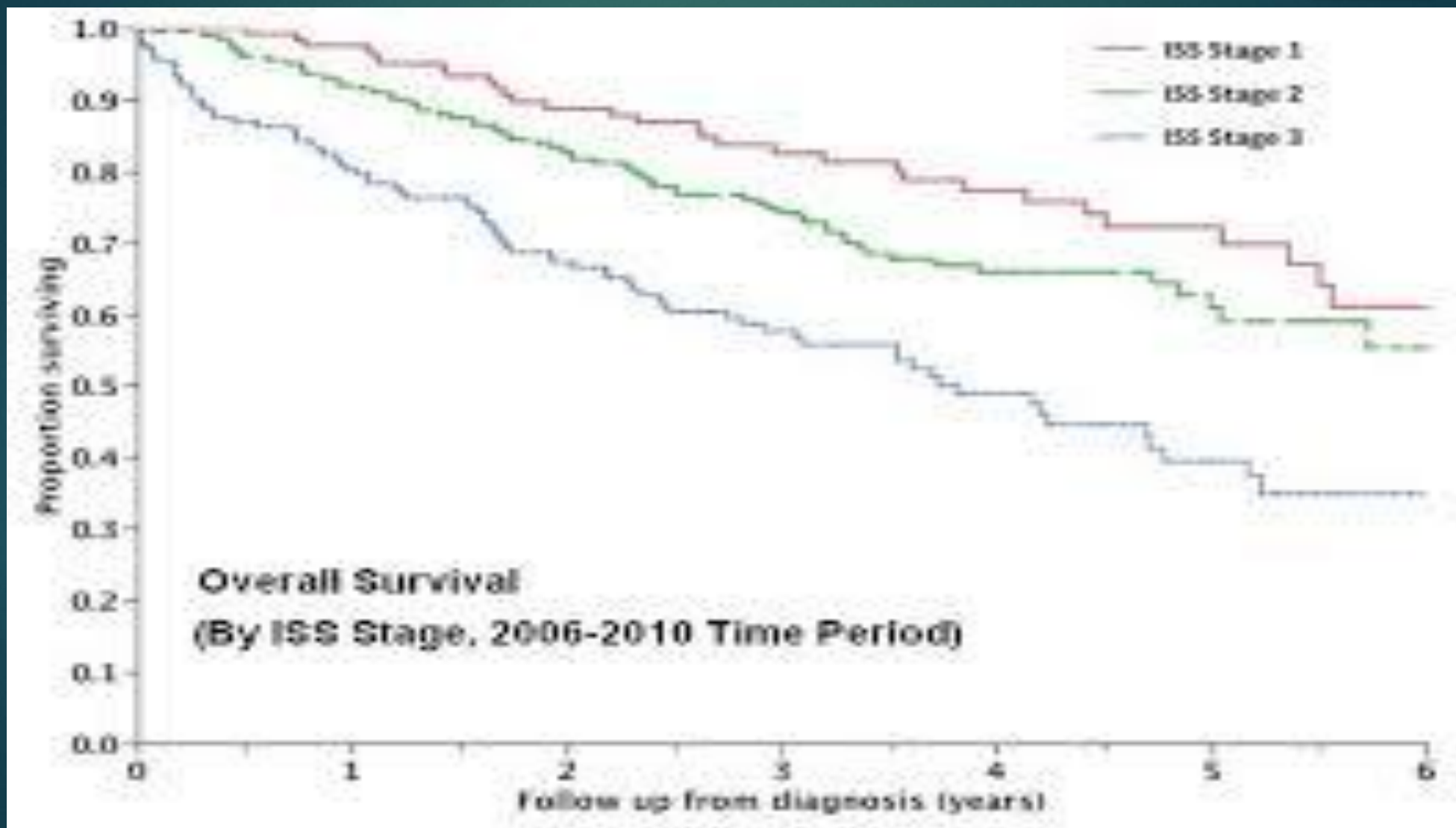
Staging for MM

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

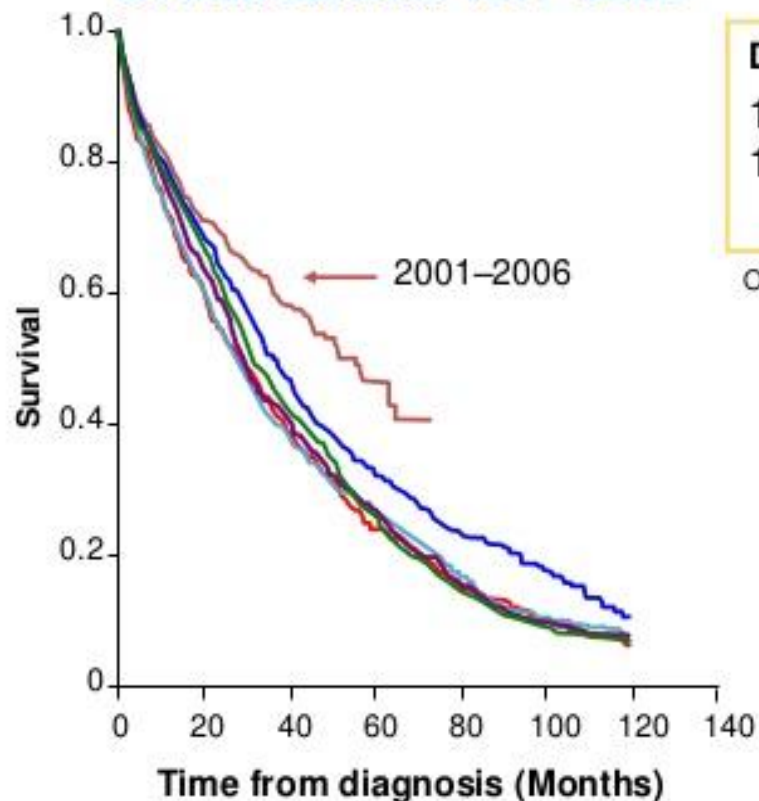


Cytogenetics, Interphase FISH

- ▶ 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^M

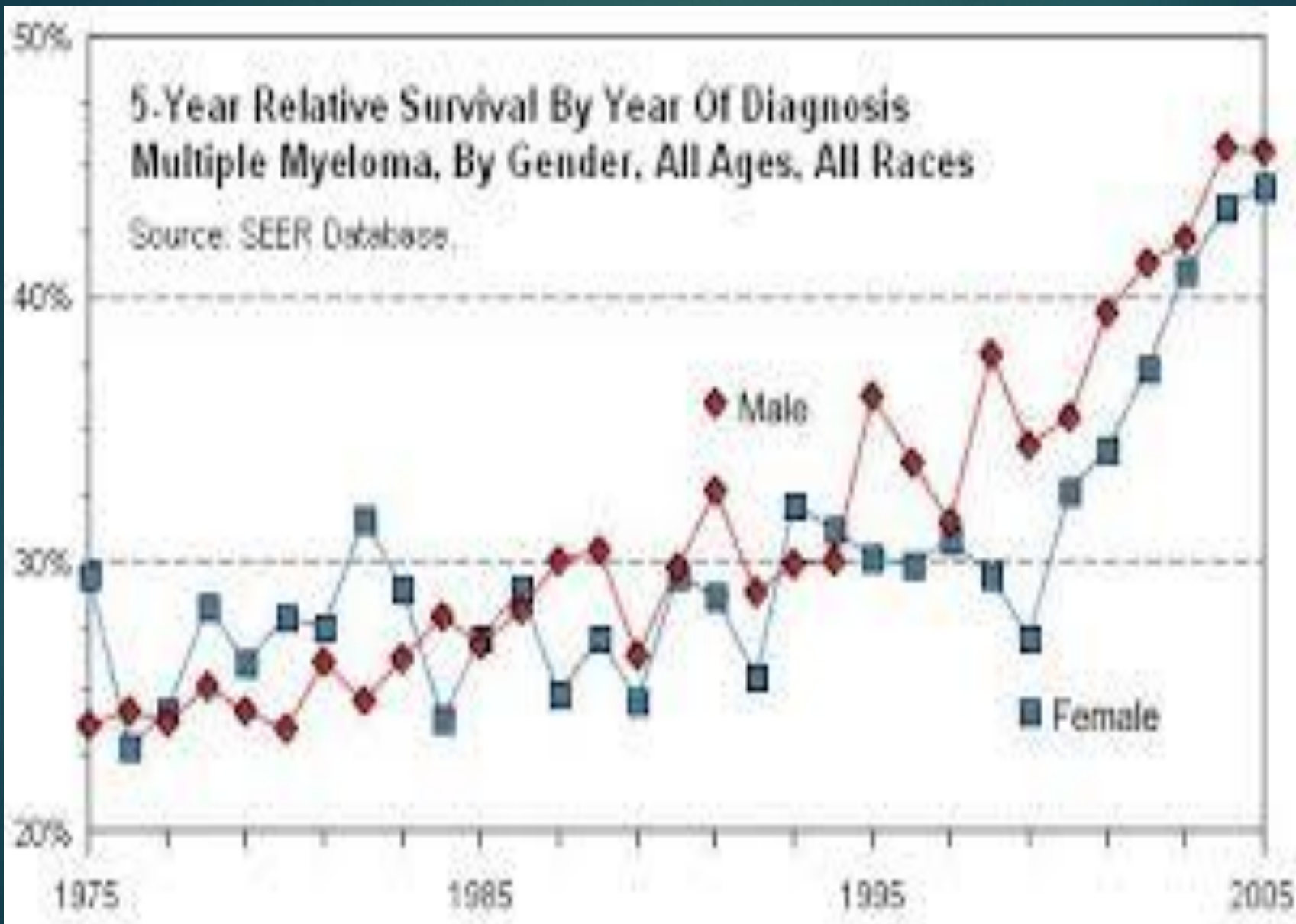
Overall survival 1971–2006



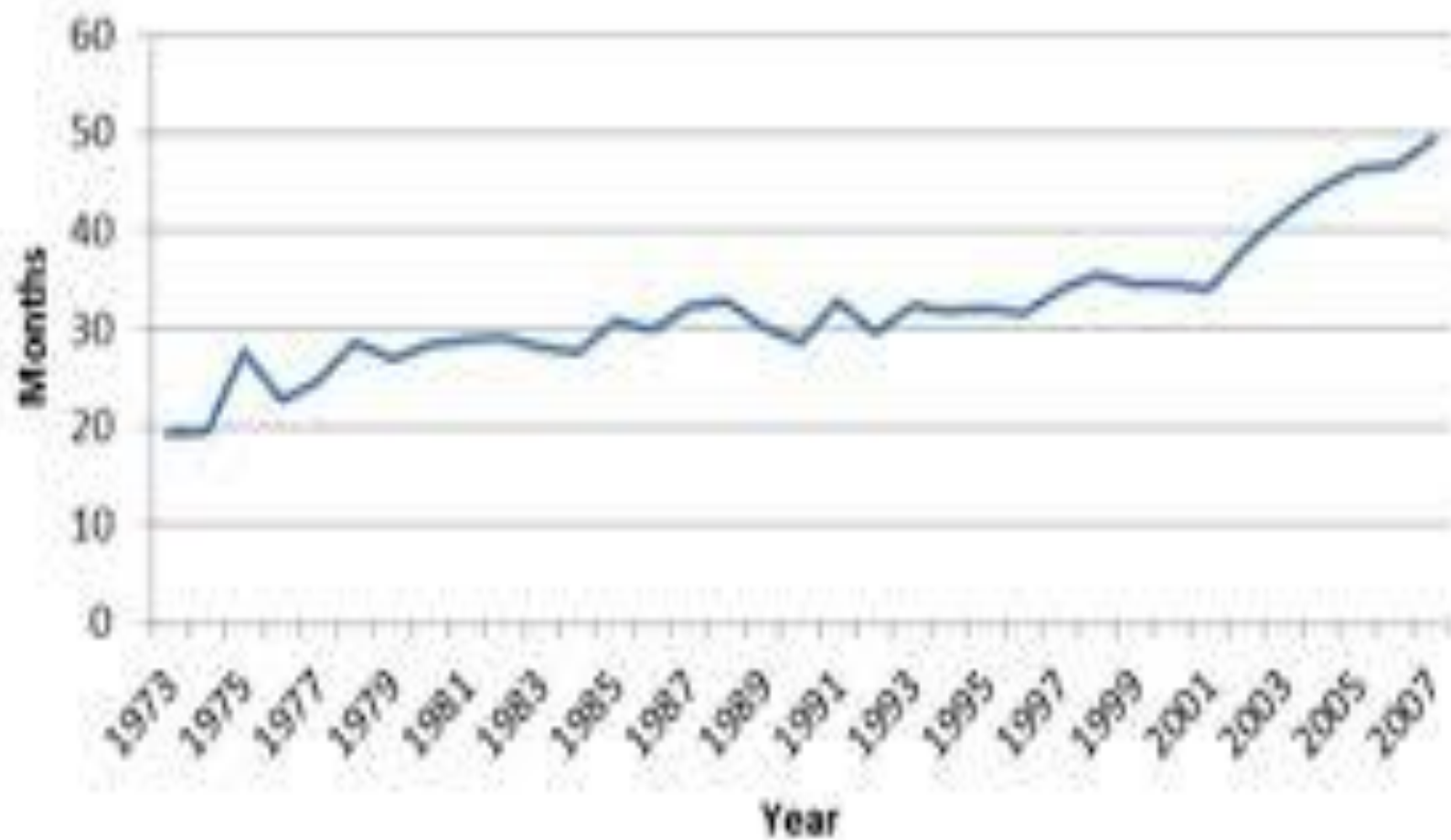
Diagnosis period	Median OS
1996–2006	45 months
1971–1996	30 months ($P < 0.001$)

OS, overall survival.

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



Median Survival - Months



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

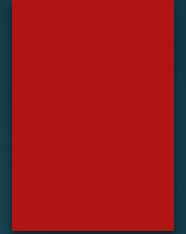
Poor prognosis factors

- ▶ 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**

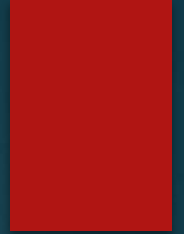
Treatment of Multiple Myeloma

- ▶ **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, carfilzomib**
 - ▶ **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

