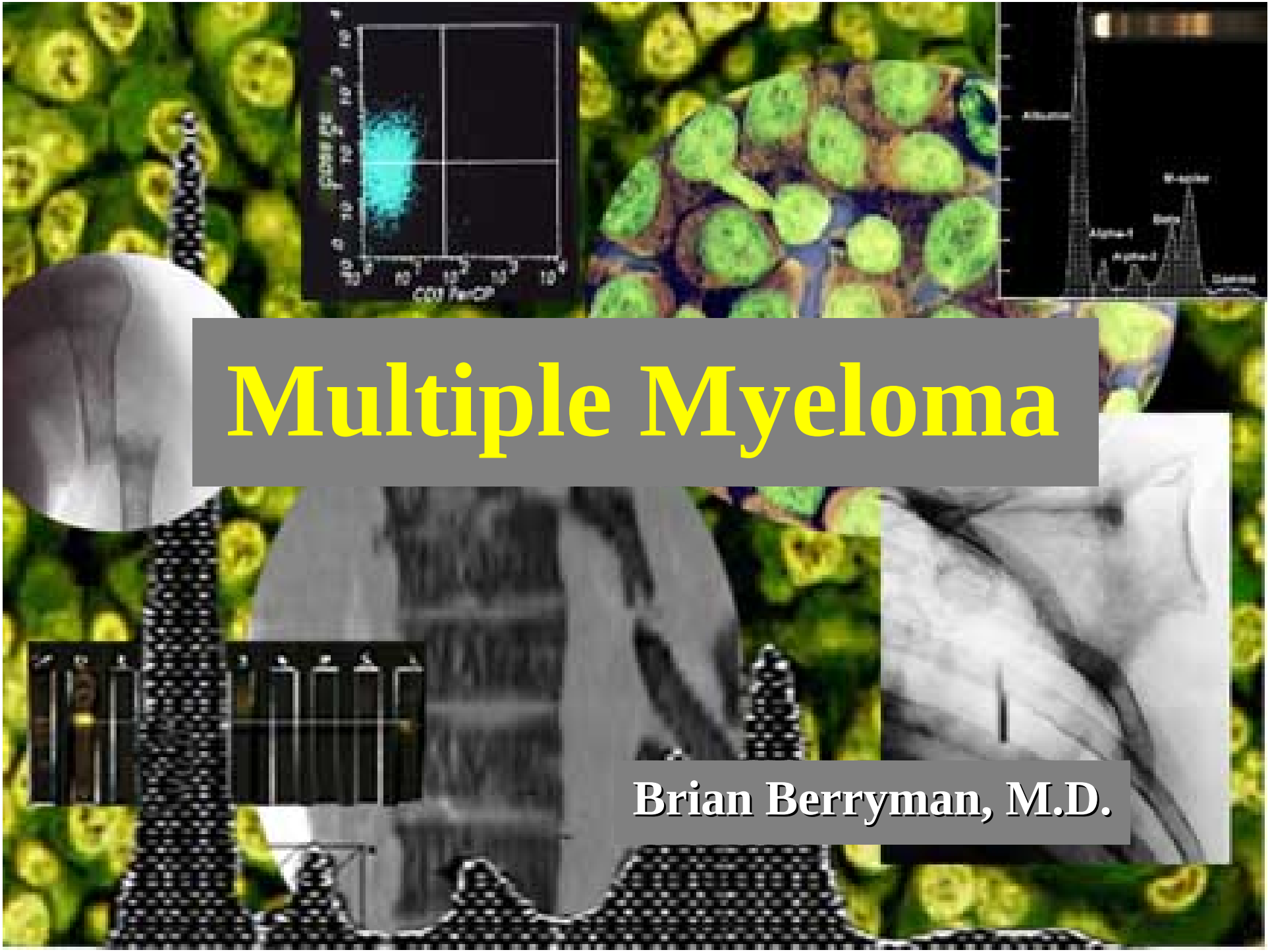


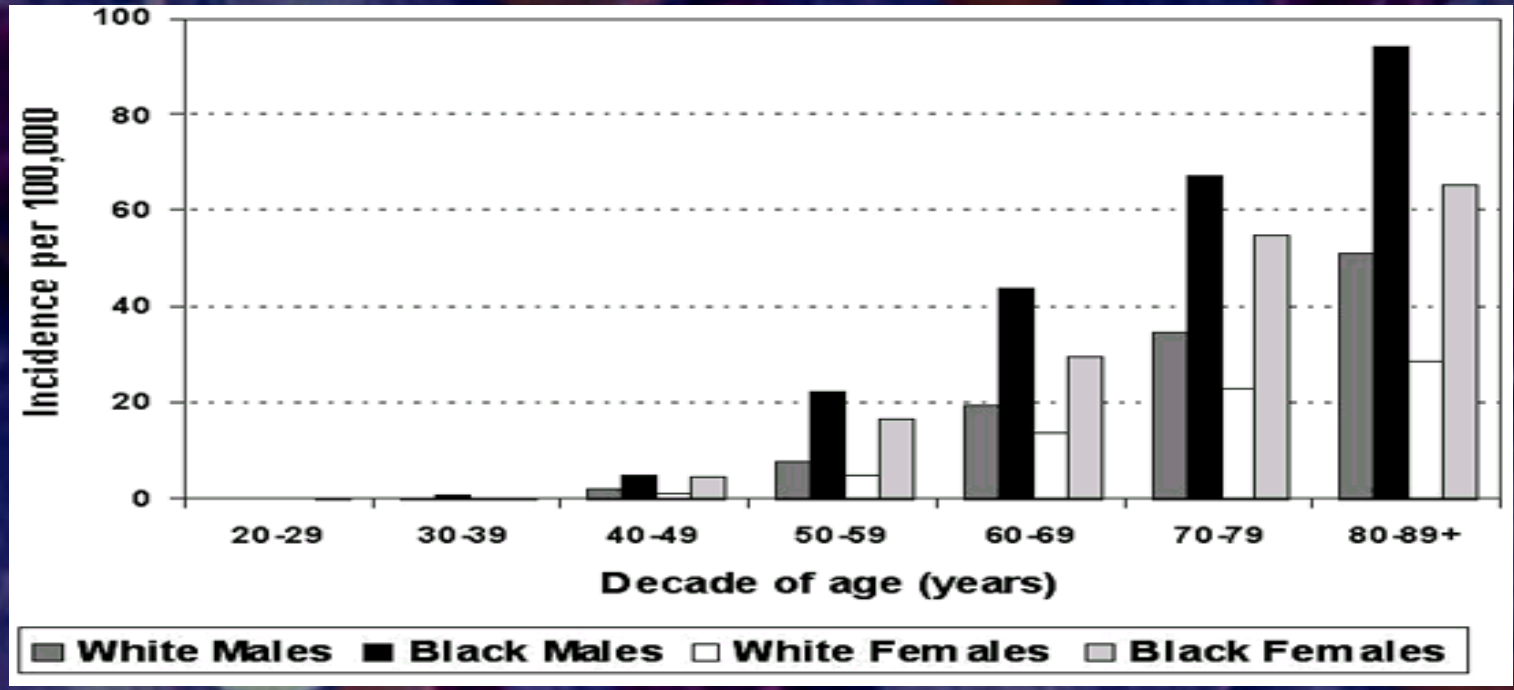
Multiple Myeloma

Brian Berryman, M.D.

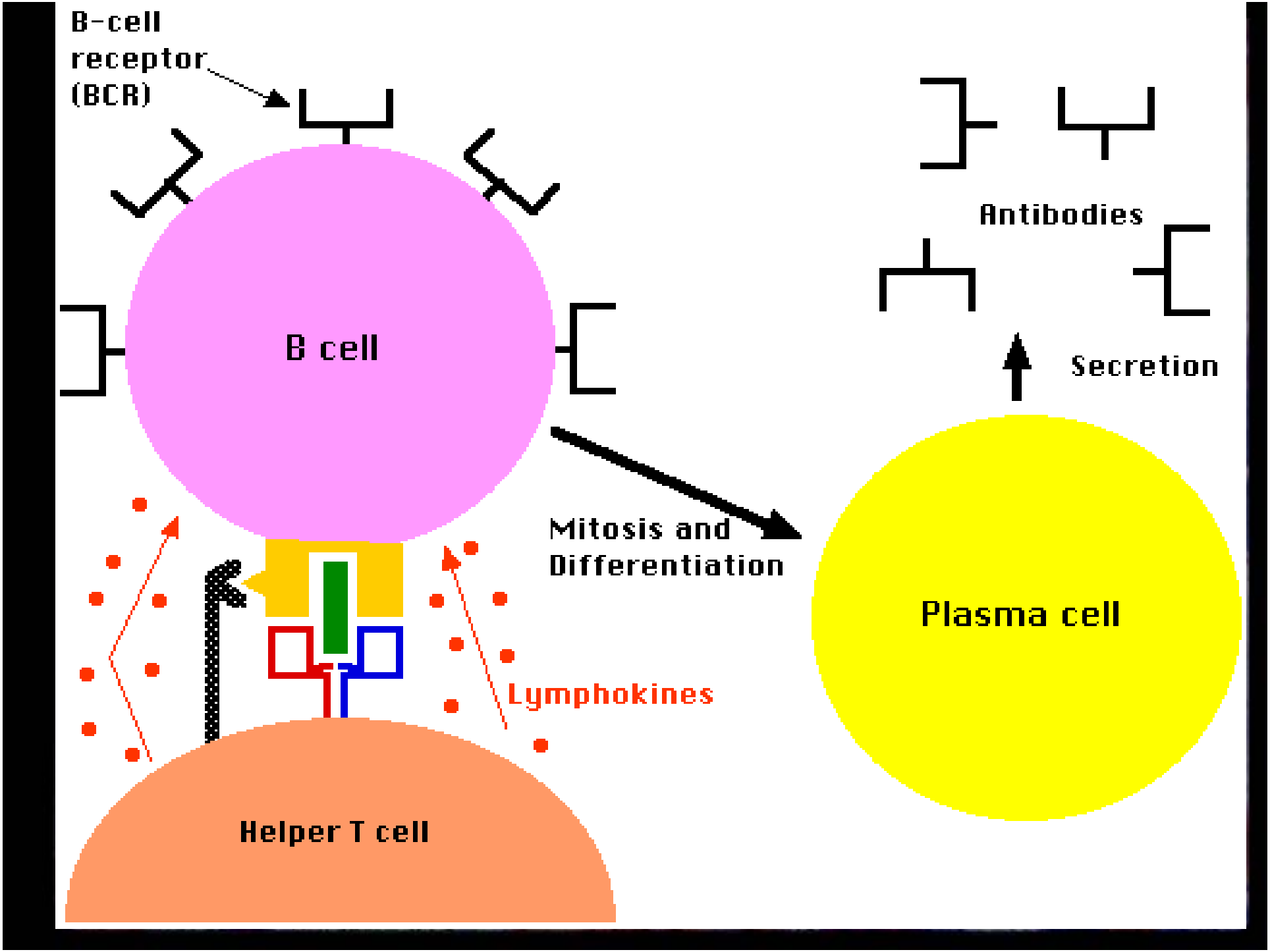
Myeloma- Introduction

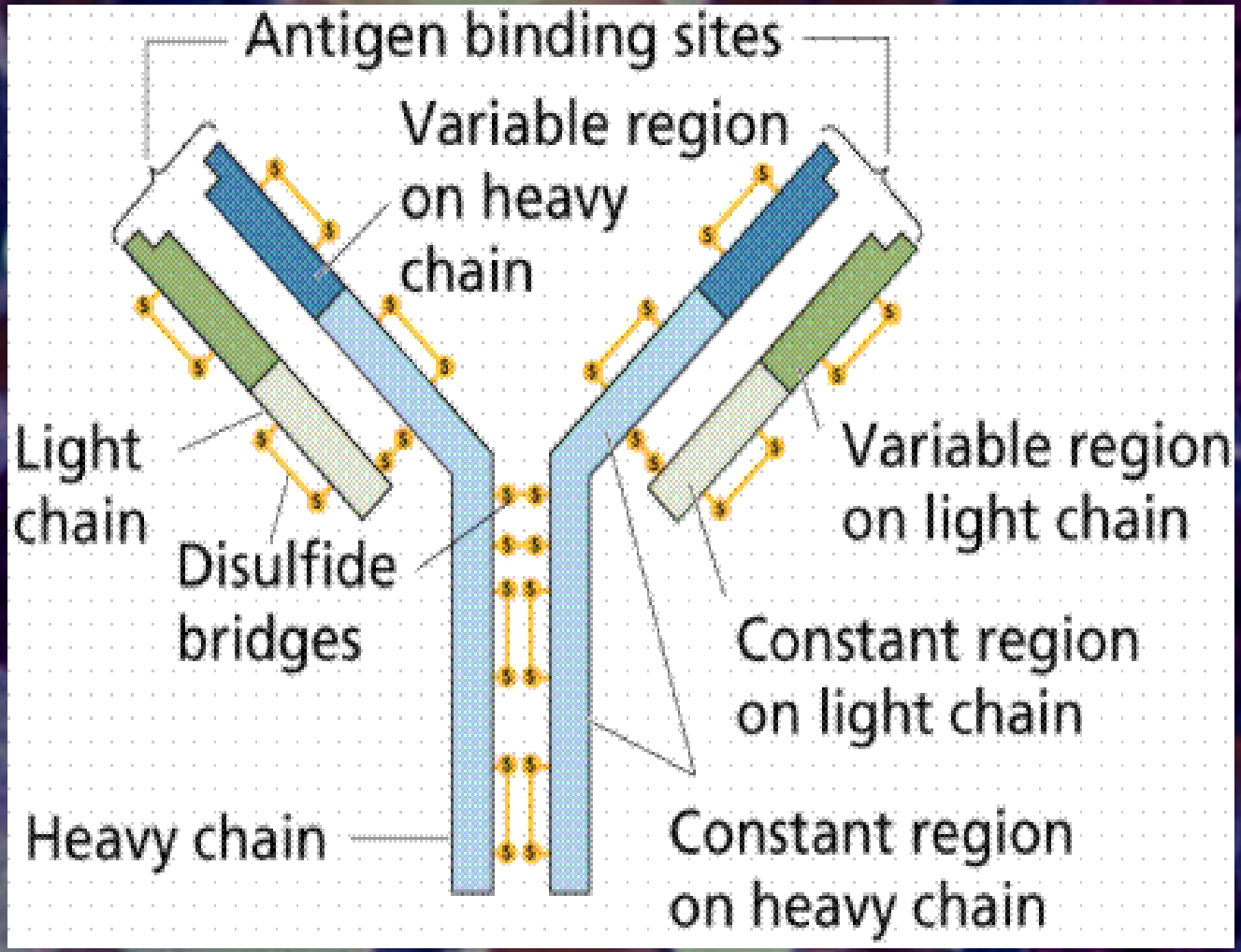
- A clonal disorder of plasma cells (B-cells).
- Affects 1 in 300,000.
  - 1% of all new malignancies (16,000 per year)
  - 10% of all new hematologic malignancies
  - 2% of all cancer deaths (11,300 per year)
- Median age of onset: 66
- Most common hematologic malignancy in African Americans.

Myeloma- Introduction



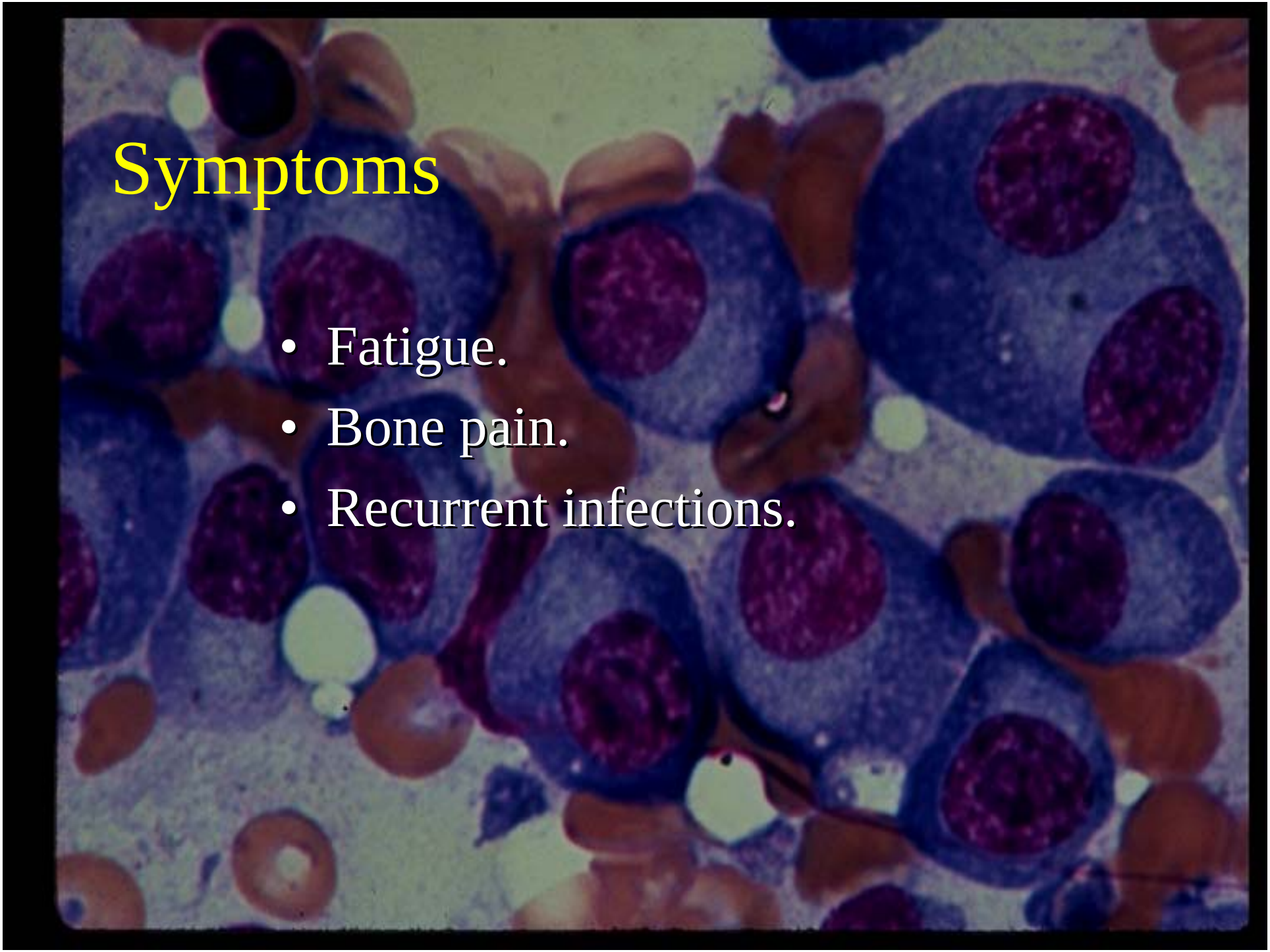
- Survival:
  - Pre-chemotherapy: 7 months
  - Current: 24-30 months +


B-cell
receptor
(BCR)
B cell
Antibodies
Secretion
Mitosis and
Differentiation
Plasma cell
Lymphokines
Helper T cell


Antigen binding sites
Variable region on heavy chain
Light chain
Disulfide bridges
Variable region on light chain
Constant region on light chain
Heavy chain
Constant region on heavy chain

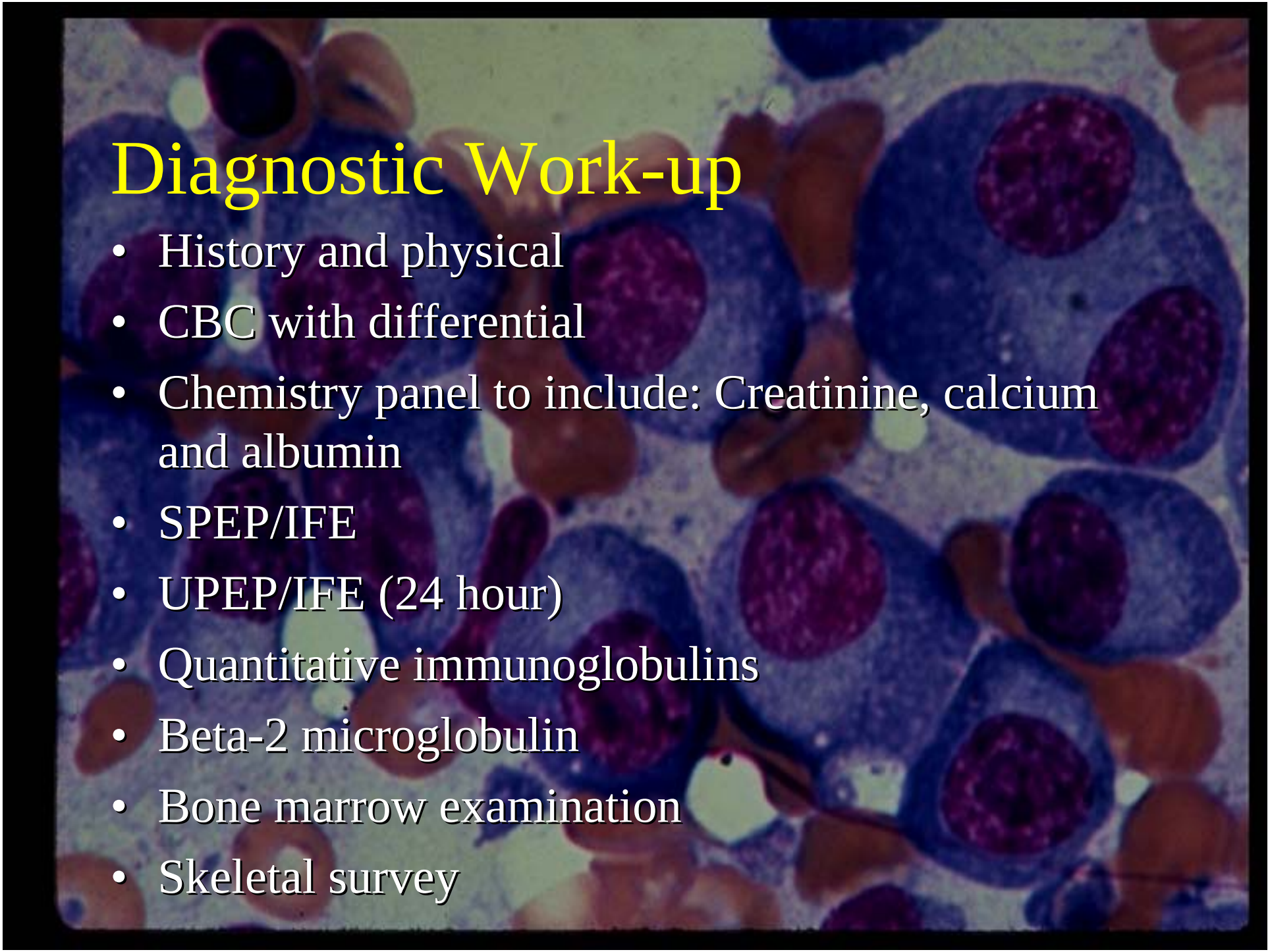
Myeloma- Risk Factors

- No specific etiologic agent
- Risk factors include:
  - Ionizing radiation.
  - Chronic Antigenic Stimulation.
  - Environmental.
    - Benzene
    - Hair dyes



Symptoms

- Fatigue.
- Bone pain.
- Recurrent infections.



Diagnostic Work-up

- History and physical
- CBC with differential
- Chemistry panel to include: Creatinine, calcium and albumin
- SPEP/IFE
- UPEP/IFE (24 hour)
- Quantitative immunoglobulins
- Beta-2 microglobulin
- Bone marrow examination
- Skeletal survey

Diagnostic Work-up

- Serum free light chain measurement (especially in light chain, oligo-secretory and non-secretory disease)
- LDH
- CRP
- Myeloma FISH panel on bone marrow
- MRI
- PET

Hypercalcemia

- Occur in a third of patients.
- Symptoms: bony pain, polydipsia/ polyuria, confusion, and constipation
- May be precipitated by dehydration or intravenous contrast
- Treat with vigorous hydration, diuresis, bisphosphonates, and steroids

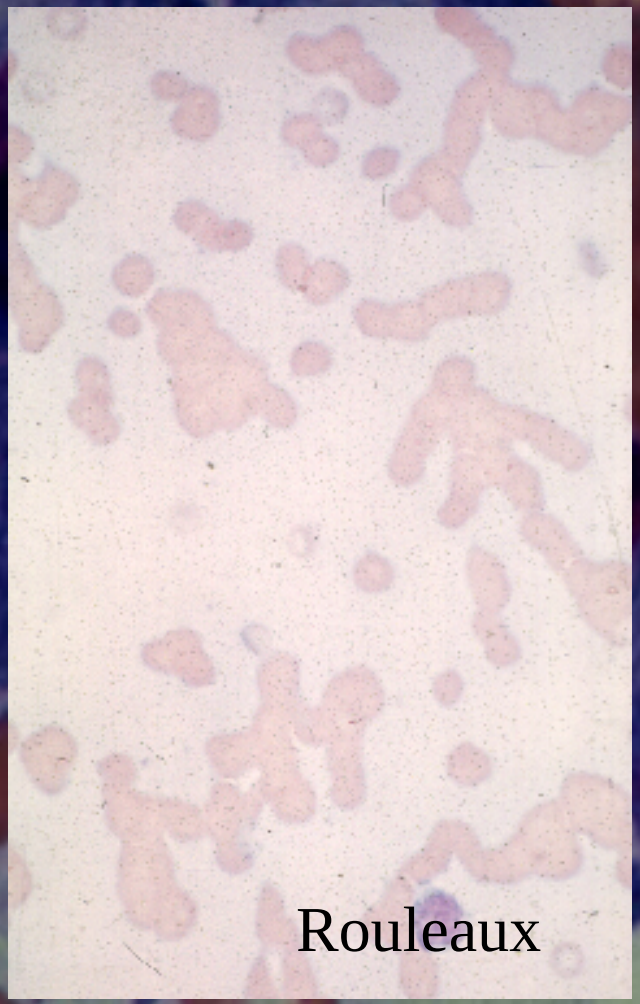
Skeletal Manifestations

- Occur in >70% patients
  - Multiple 70%
  - Isolated lesion or diffuse osteopenia 15%
  - Normal 15%
- Blastic lesions in <2%.

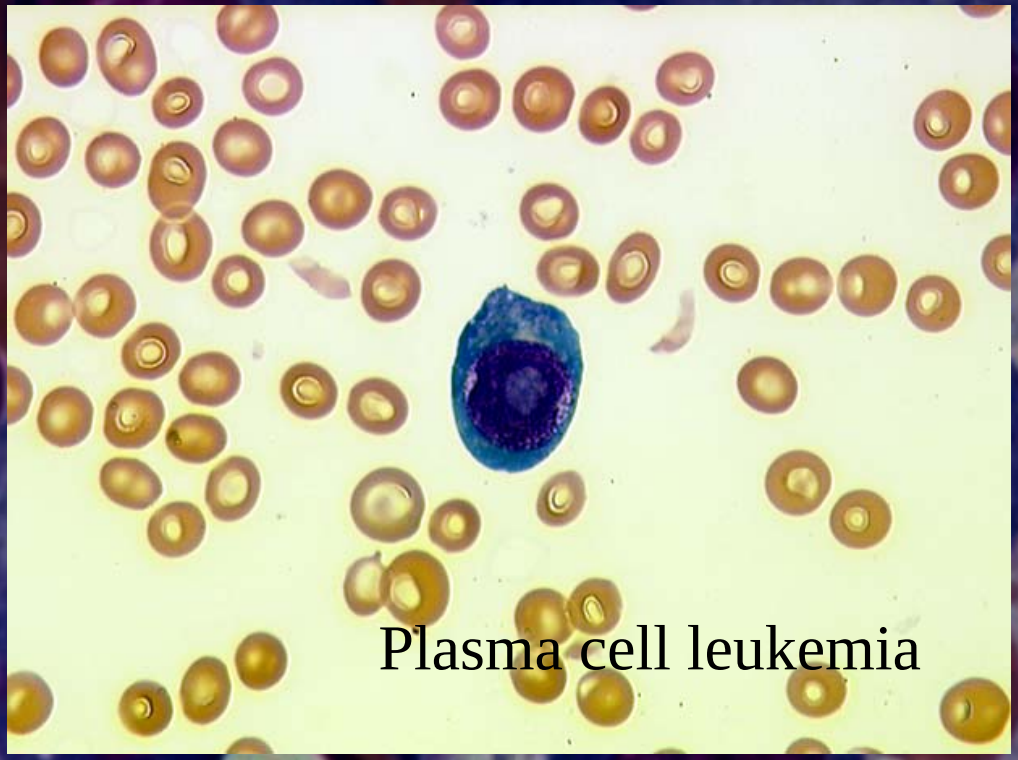
Renal Manifestations

- Elevated creatinine in 50%
- Myeloma kidney- usually LC disease
- Amyloid with nonspecific proteinuria.
- Caution with NSAIDs and IV contrast
- HYDRATION!

Blood Smear

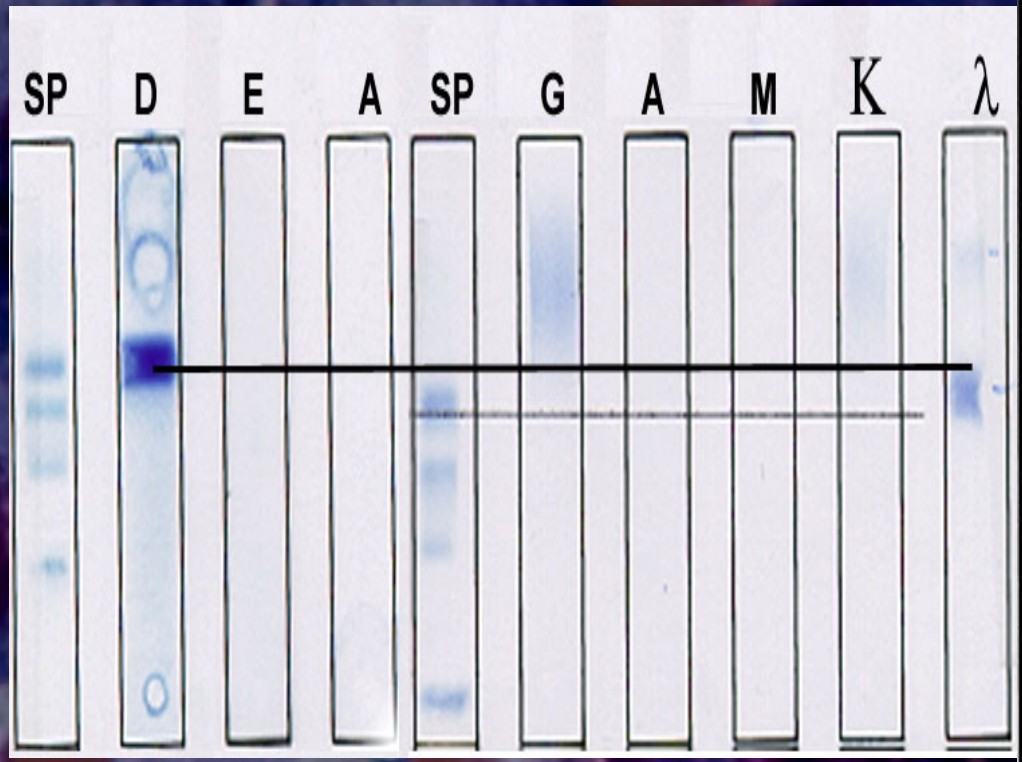


Rouleaux

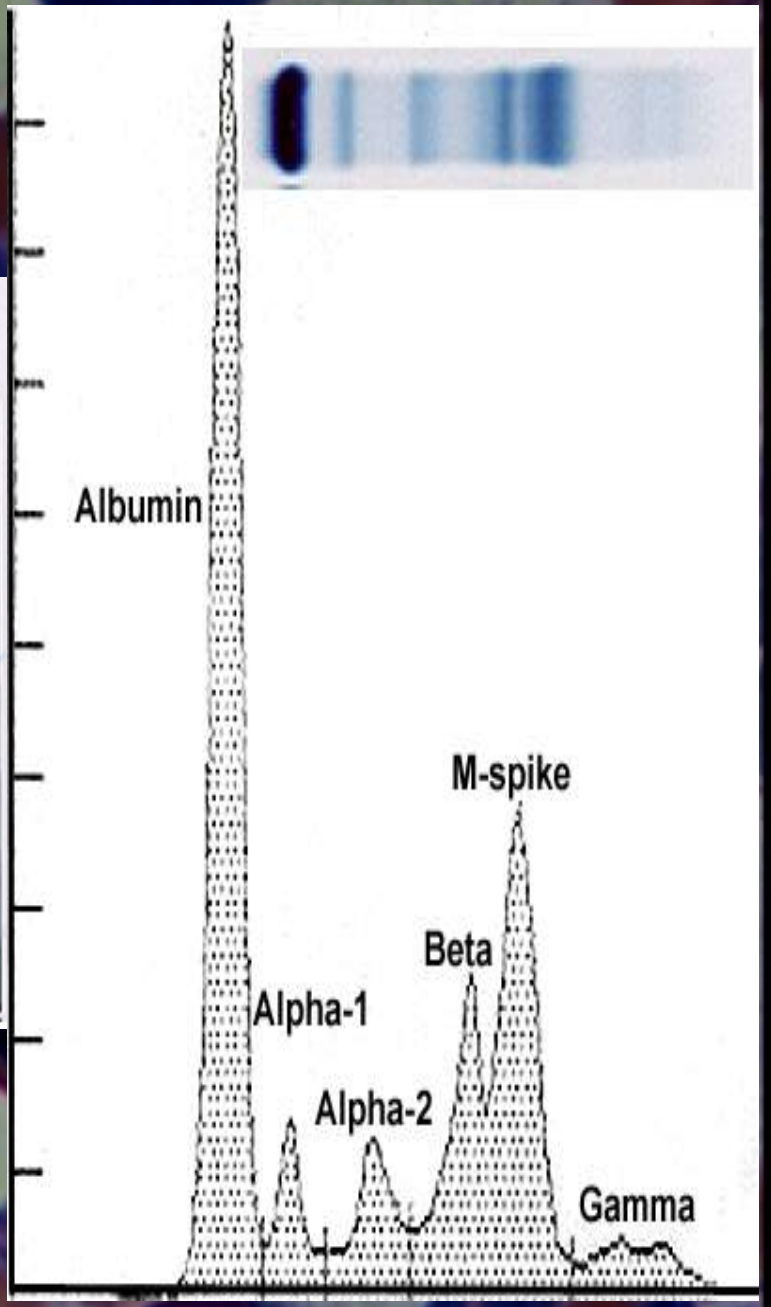


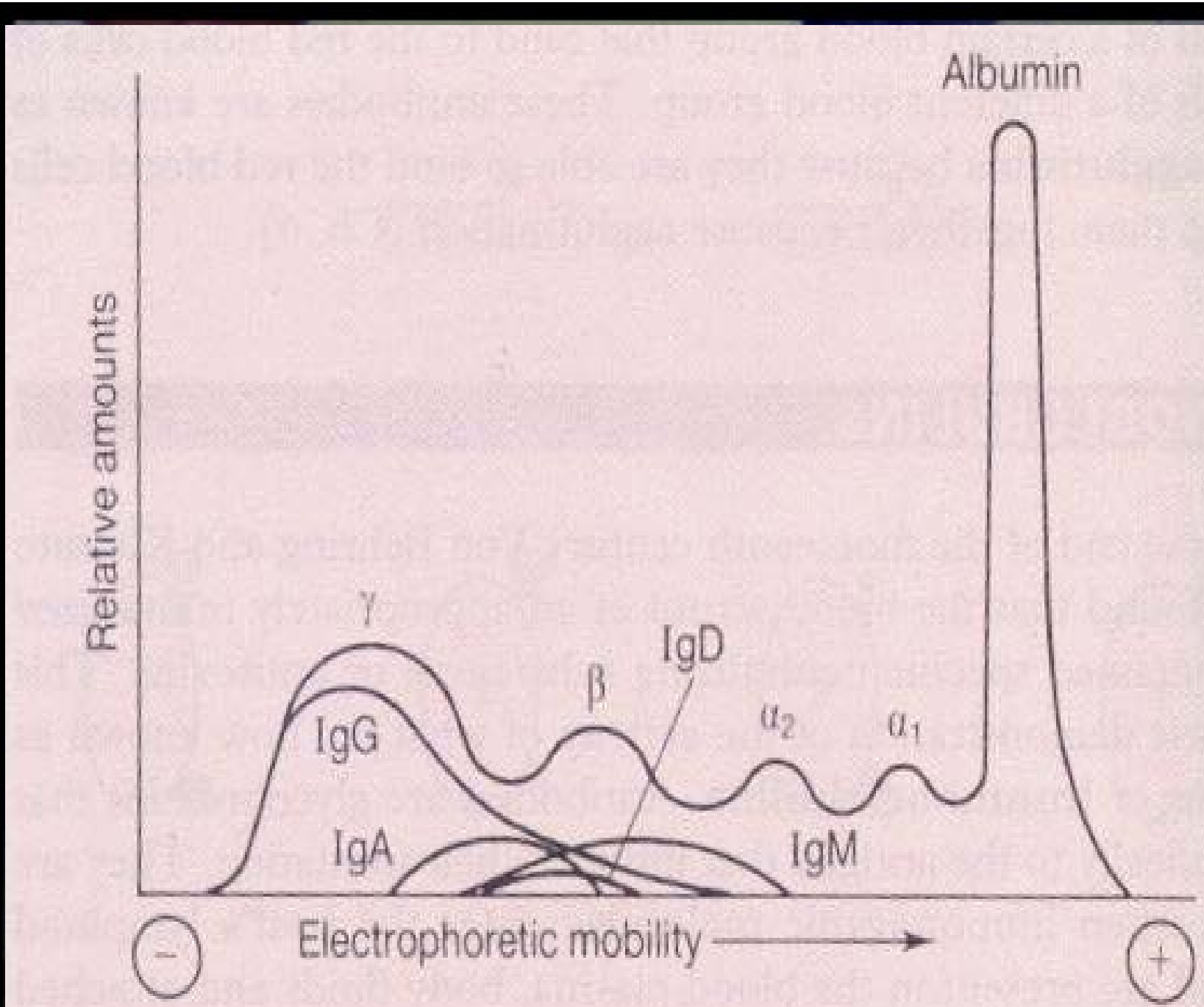
Plasma cell leukemia

SPEP/IFE

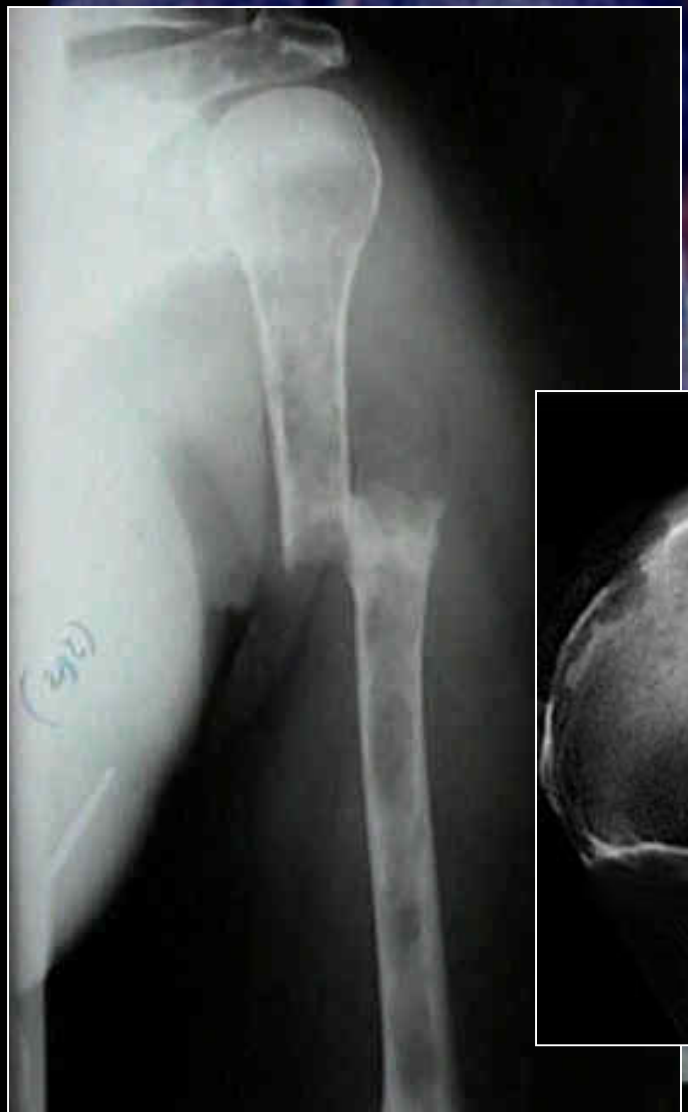


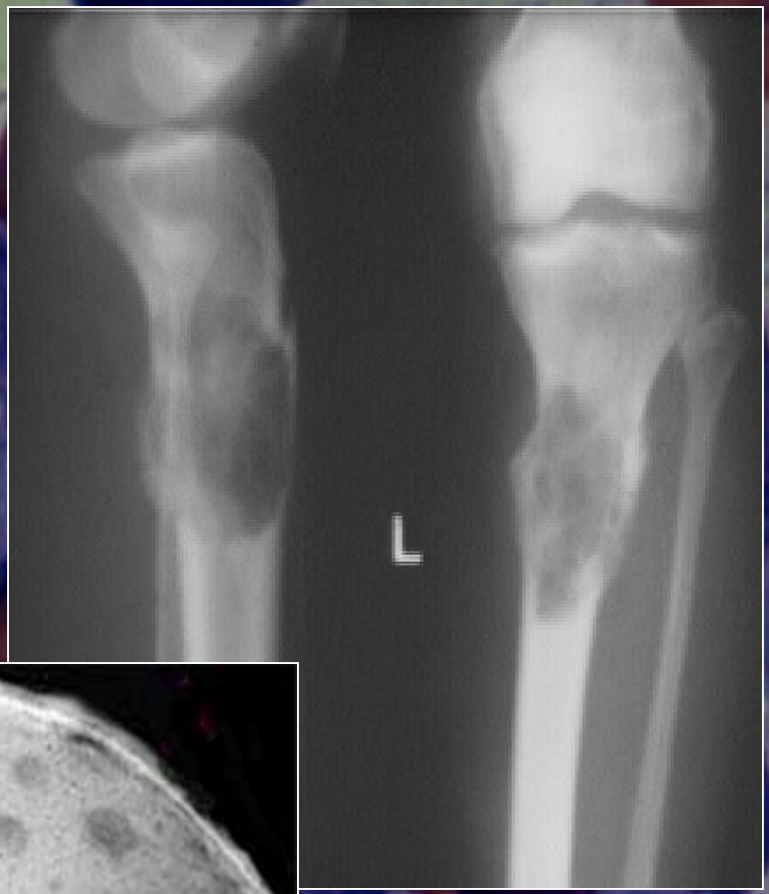
IgD λ myeloma

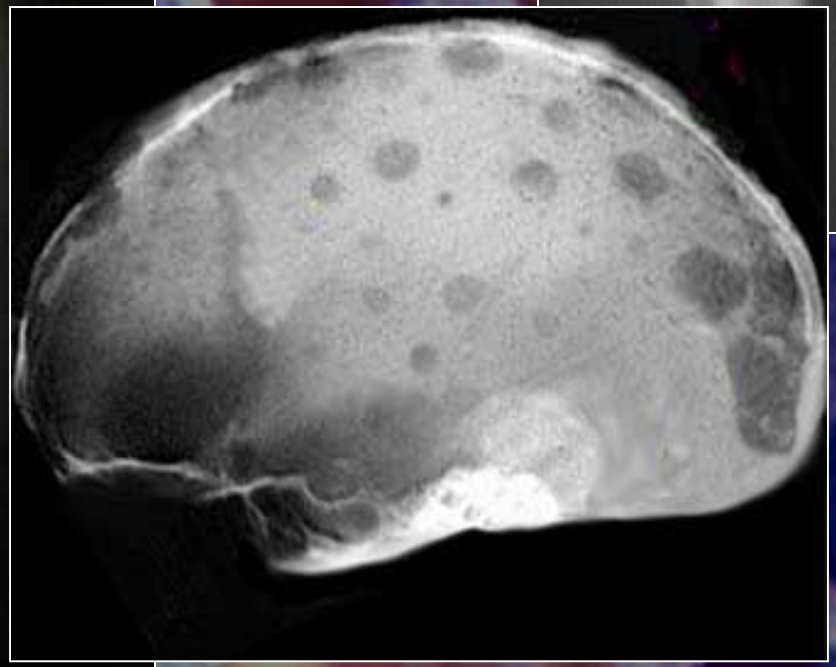



Albumin
Relative amounts
γ
IgD
β
IgG
α2
α1
IgA
IgM
Electrophoretic mobility
−
+

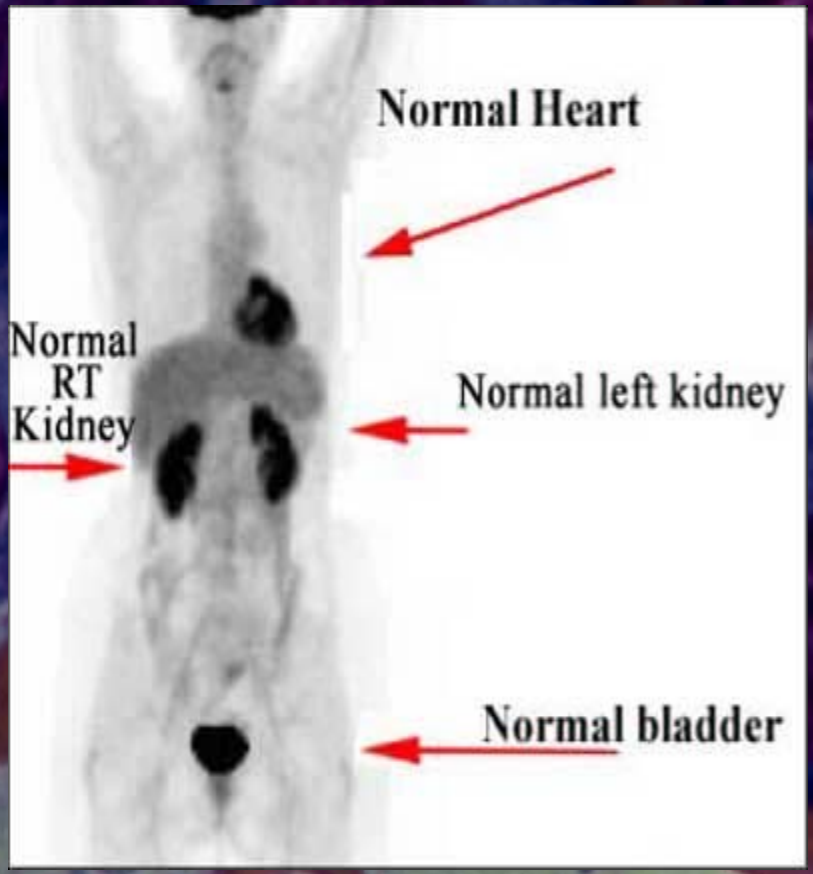
Bone Survey

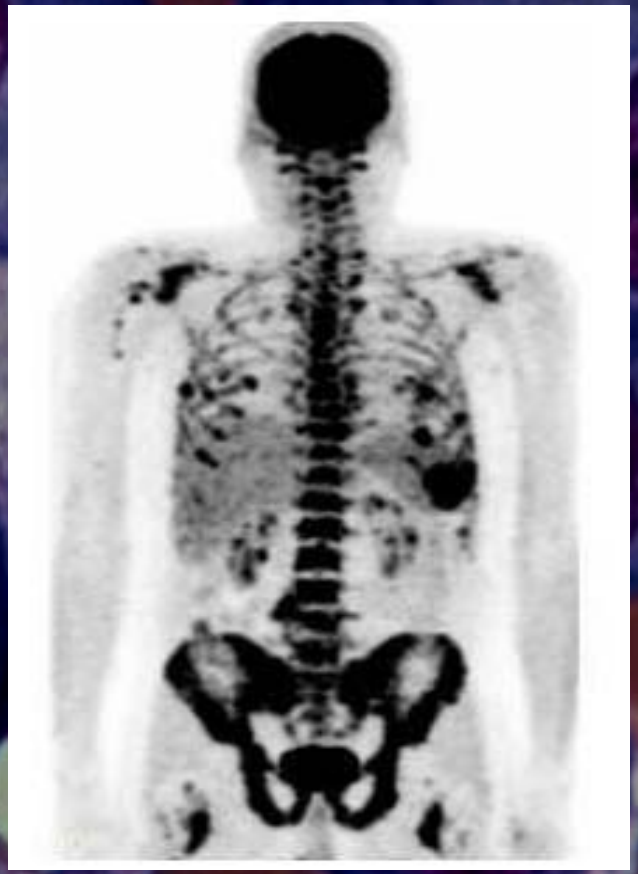


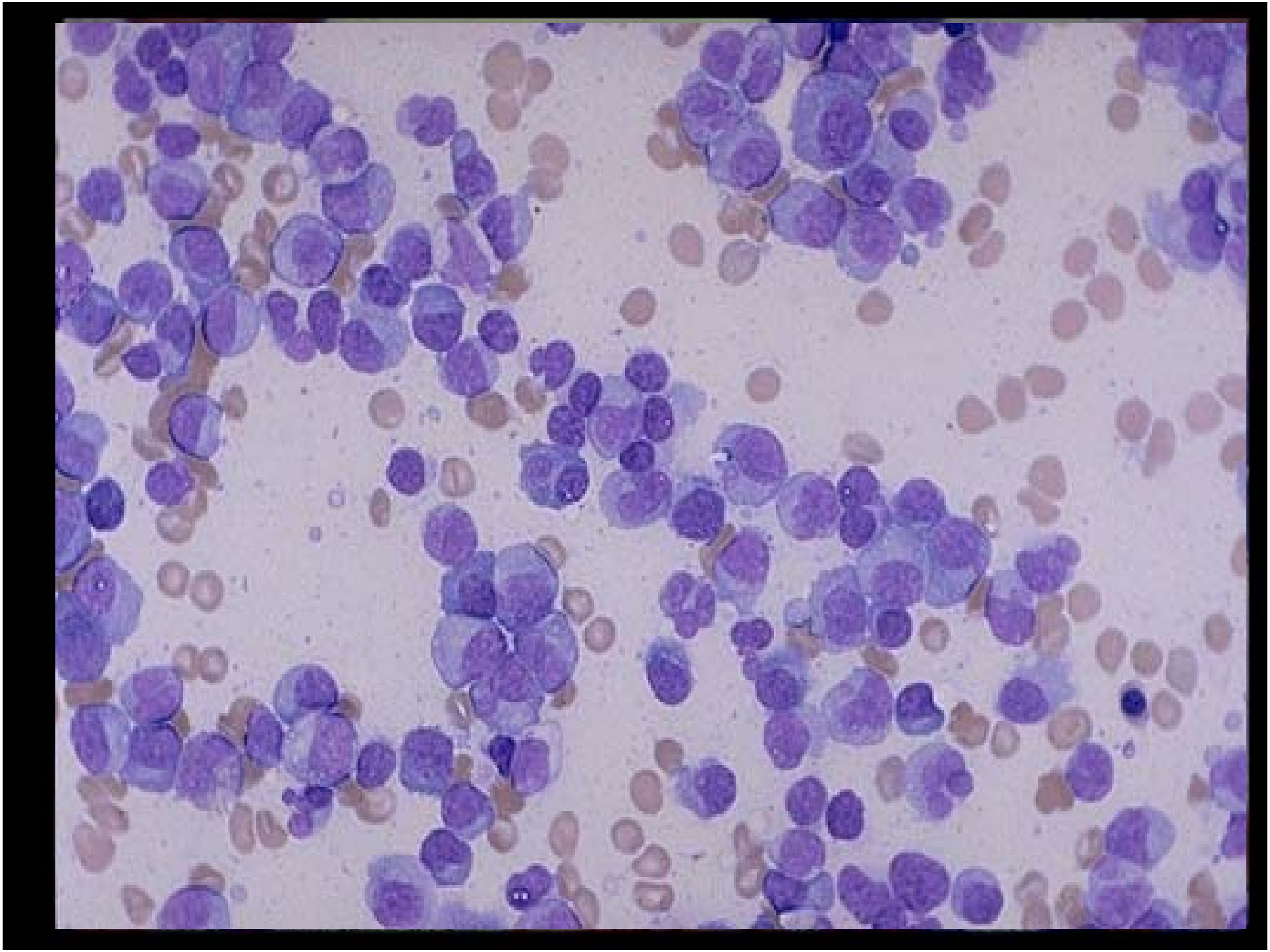




PET Scan

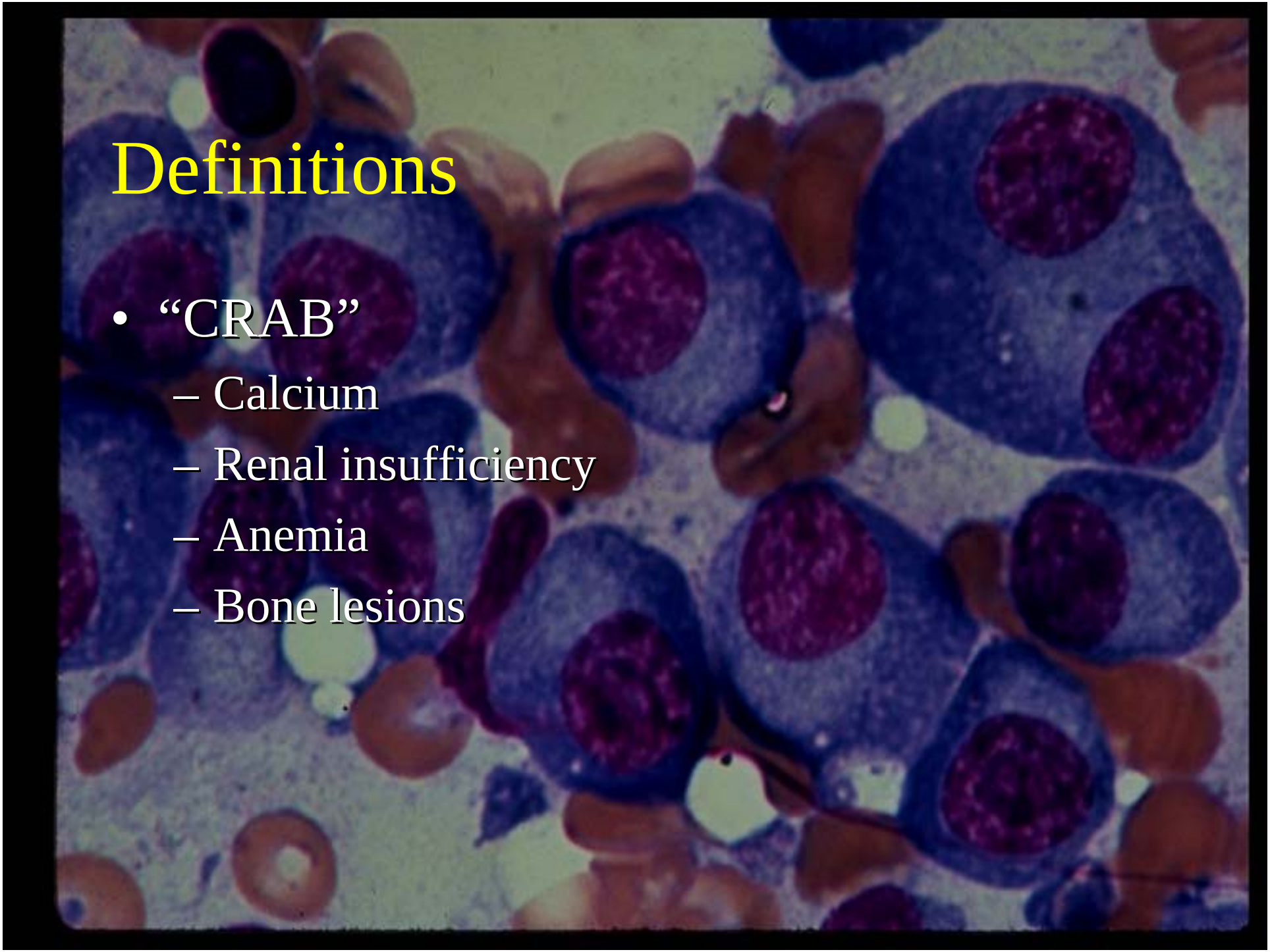

Normal Heart
Normal RT Kidney
Normal left kidney
Normal bladder





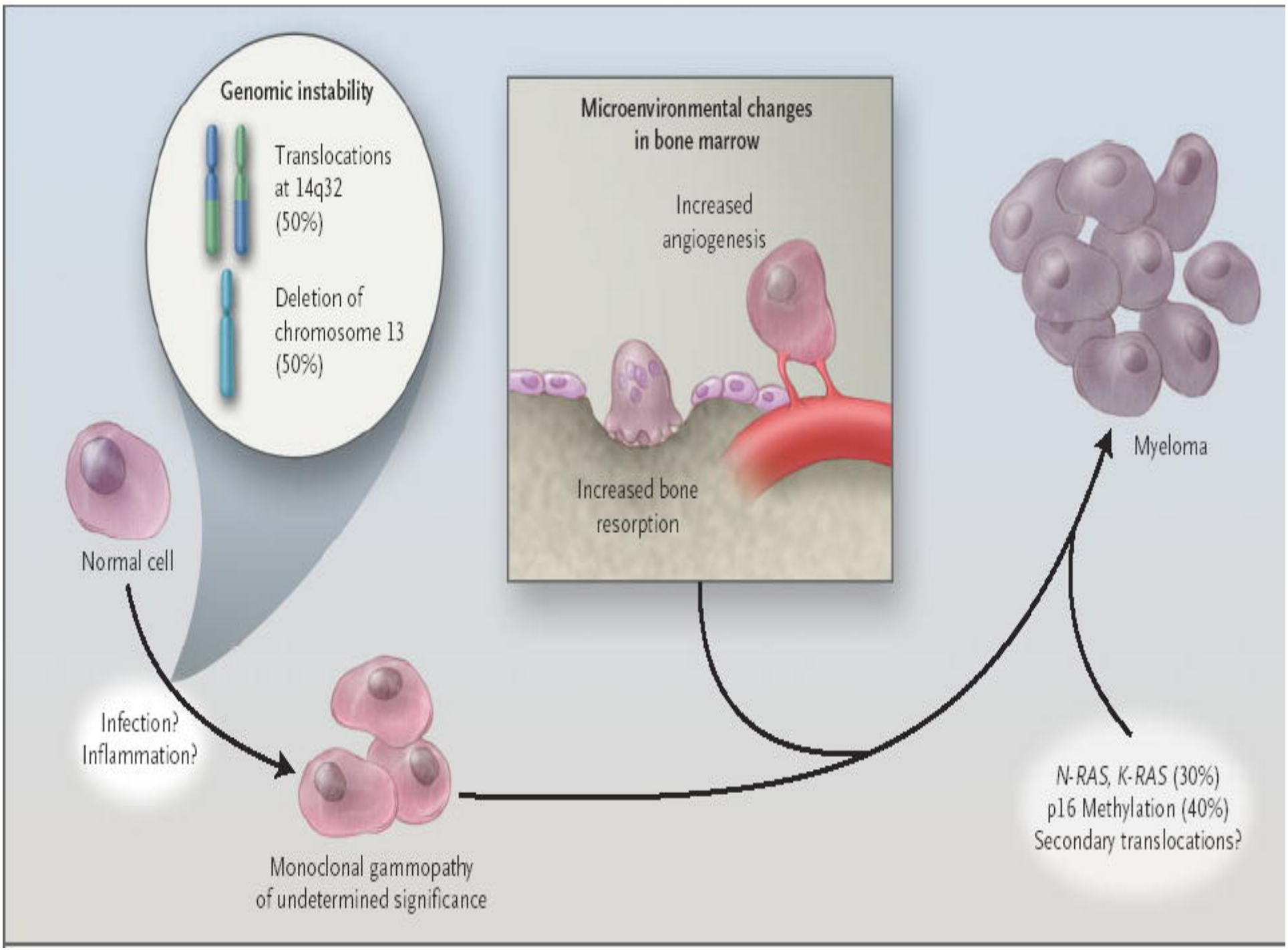
Definitions

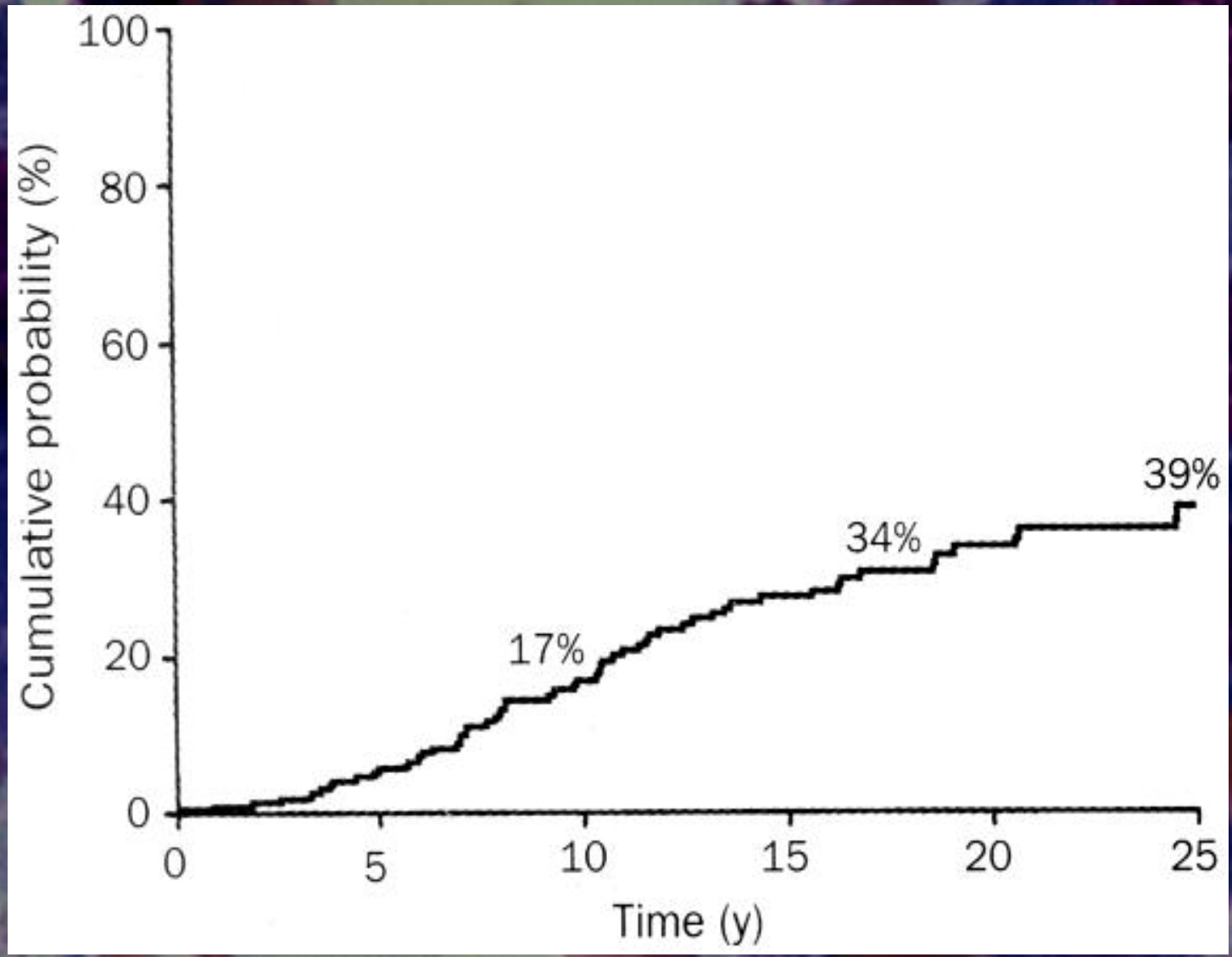
- MGUS- Monoclonal gammopathy of unclear significance
  - M-protein < 3 g/dL
  - Plasma cells in bone marrow <10%
  - No related organ or tissue impairment (CRAB)
  - May evolve to Multiple Myeloma (20% in 8-10 years)



Definitions

- "CRAB"
  - Calcium
  - Renal insufficiency
  - Anemia
  - Bone lesions


Genomic instability
Translocations at 14q32 (50%)
Deletion of chromosome 13 (50%)
Microenvironmental changes in bone marrow
Increased angiogenesis
Increased bone resorption
Myeloma
Normal cell
Infection? Inflammation?
Monoclonal gammopathy of undetermined significance
N-RAS, K-RAS (30%)
p16 Methylation (40%)
Secondary translocations?


Cumulative probability (%)
100
80
60
40
20
0
17%
34%
39%
0
5
10
15
20
25
Time (y)

Definitions

- Smoldering or Indolent Multiple Myeloma
  - M-protein ≥ 3 g/dL
  - Plasma cells in bone marrow ≥ 10%
  - M-protein in urine
  - No related organ or tissue impairment (CRAB)

Definitions

- Symptomatic Multiple Myeloma
  - M-protein in blood and/or urine
  - Bone marrow clonal plasma cells or plasmacytoma
  - Related organ or tissue impairment or symptoms

Staging

Stage I

Low burden (<0.6 x 10^{12})- All below:

- HB > 10 g/dl
- IgG < 5g/dl
- UPEP M < 4 g/24 hrs
- Normal Xrays or solitary plasmacytoma
- Ca<12 mg/dl
- IgA < 3 g/dl

Stage II

Intermediate (0.6-1.2 x 10^{12})

- Neither I nor III

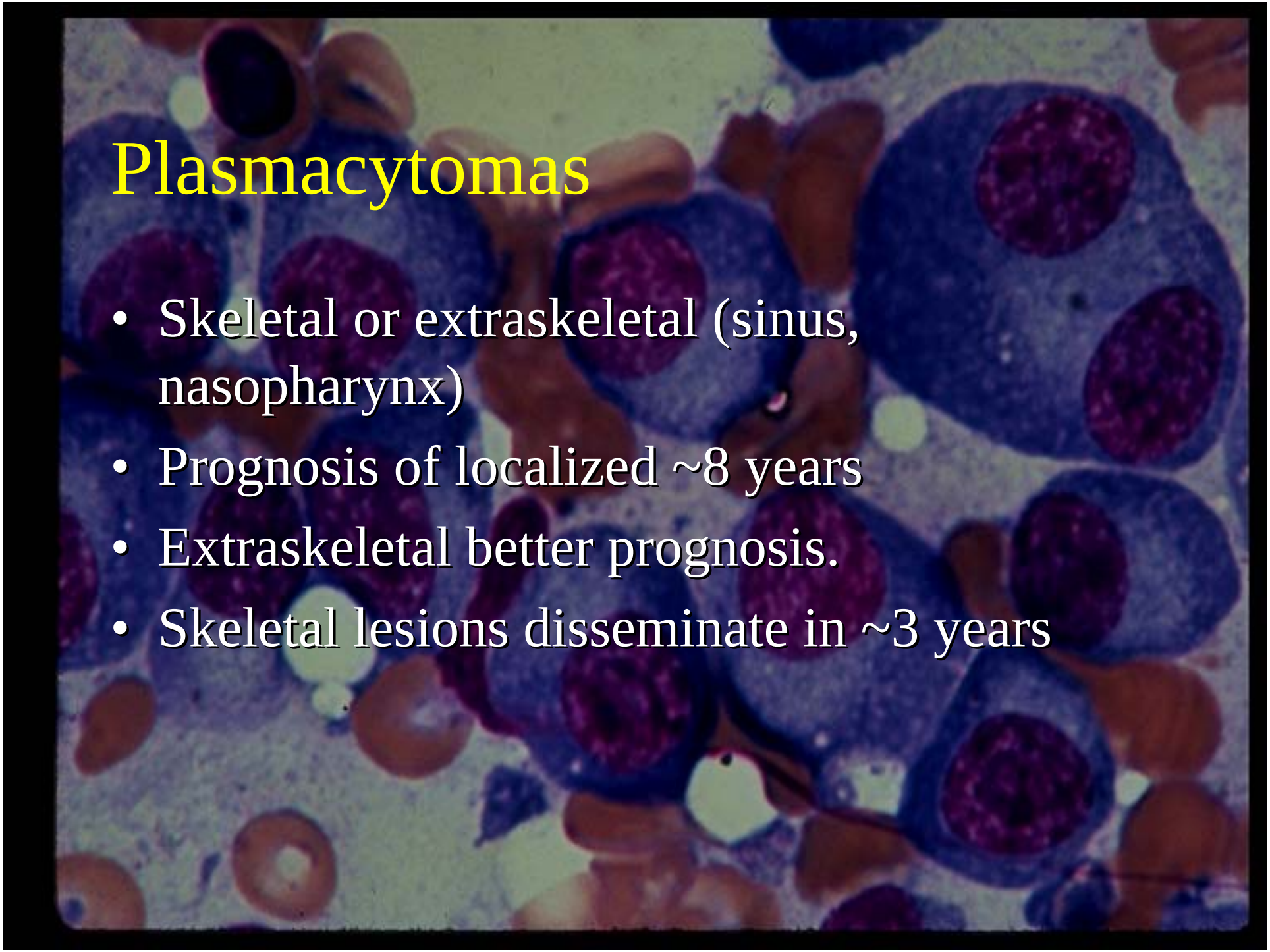
Stage III

High Tumor burden (>1.2)- ANY of:

- HB < 8.5
- IgG >7 g/dl
- UPEP M > 12 g/24
- Extensive bony disease
- Ca >12
- IgA > 5 gm/dl

Myeloma- Natural History

- 90% cases are disseminated and progressive, 3% indolent and 7% localized
- Clinical course and symptoms relate to:
  - Occurrence and locations plasmacytomas
  - Impairment hematopoeisis
  - Skeletal disease (bony, Ca++)
  - Protein abnormalities (viscosity, low nl Ig, amyloid, renal, neuropathy)

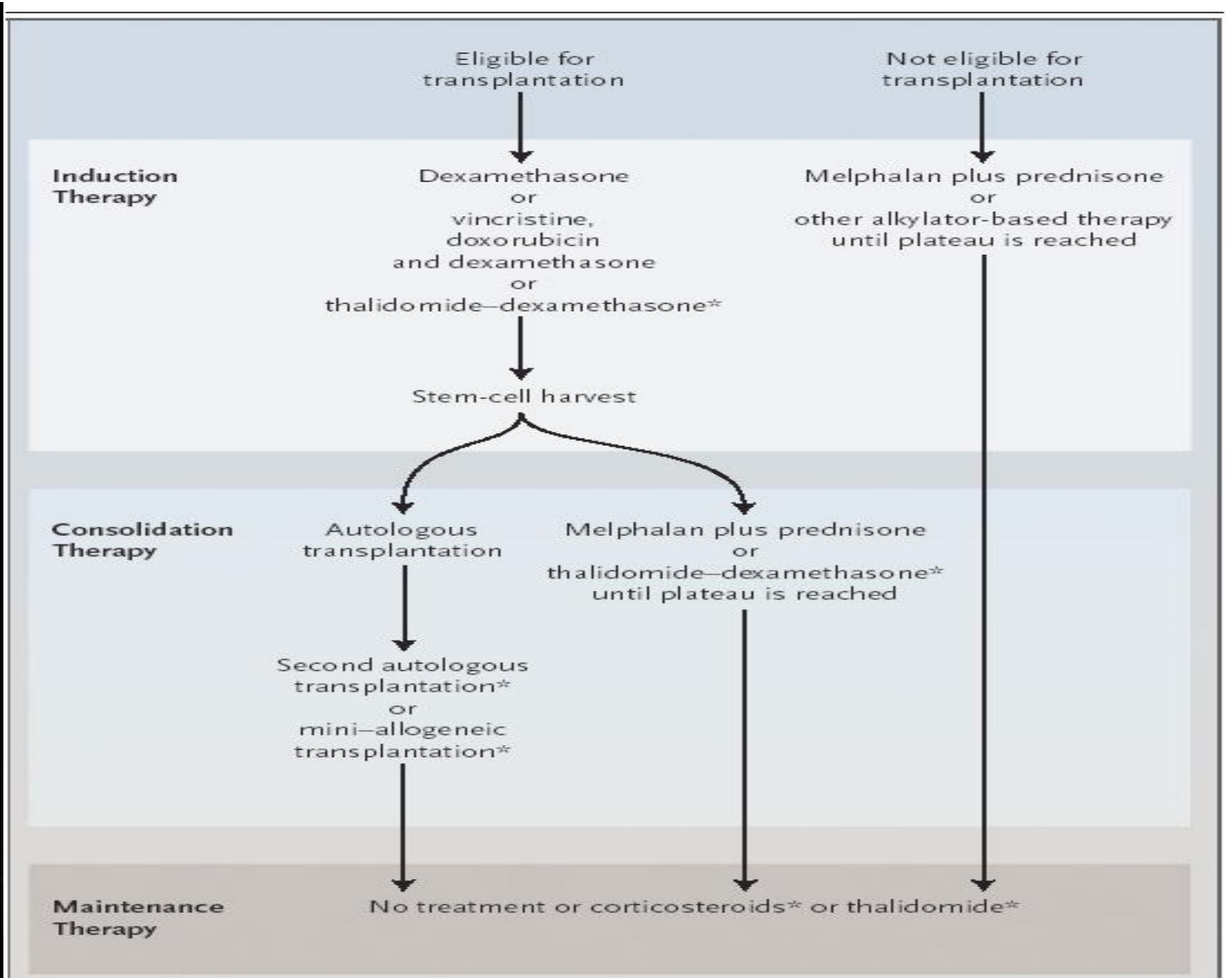


Plasmacytomas

- Skeletal or extraskeletal (sinus, nasopharynx)
- Prognosis of localized ~8 years
- Extraskeletal better prognosis.
- Skeletal lesions disseminate in ~3 years

Prognostic Factors

- Performance status
- Stage
- Cytogenetics
- LDH
- Plasmablastic variants/Plasma cell leukemia


Eligible for transplantation
Not eligible for transplantation
Induction Therapy
Dexamethasone or vincristine, doxorubicin and dexamethasone or thalidomide–dexamethasone*
Melphalan plus prednisone or other alkylator-based therapy until plateau is reached
Stem-cell harvest
Consolidation Therapy
Autologous transplantation
Melphalan plus prednisone or thalidomide–dexamethasone* until plateau is reached
Second autologous transplantation* or mini–allogeneic transplantation*
Maintenance Therapy
No treatment or corticosteroids* or thalidomide*

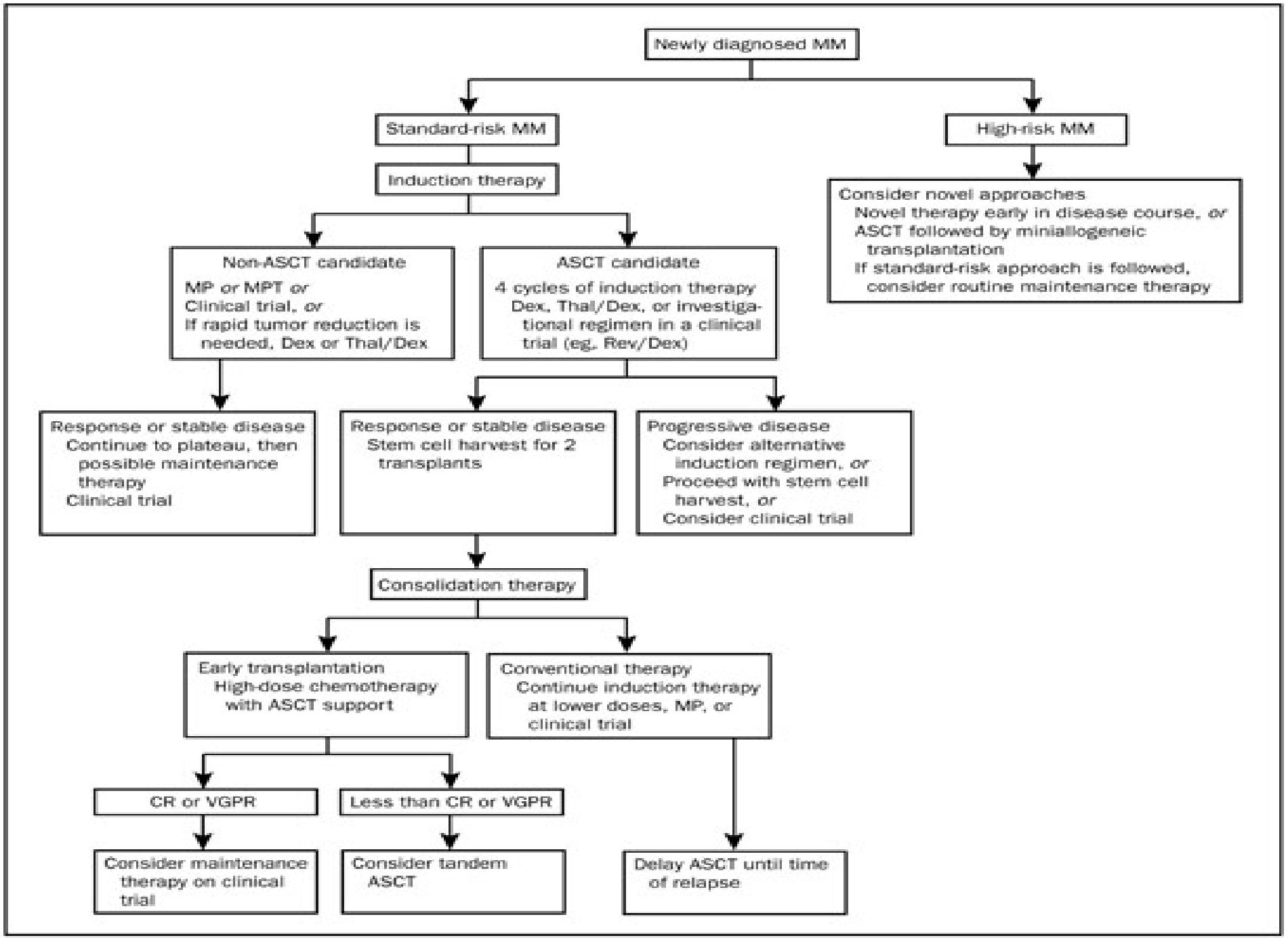

Newly diagnosed MM
Standard-risk MM
High-risk MM
Induction therapy
Consider novel approaches
Novel therapy early in disease course, or
ASCT followed by miniallogeneic transplantation
If standard-risk approach is followed, consider routine maintenance therapy
Non-ASCT candidate
MP or MPT or
Clinical trial, or
If rapid tumor reduction is needed, Dex or Thal/Dex
ASCT candidate
4 cycles of induction therapy
Dex, Thal/Dex, or investigational regimen in a clinical trial (eg, Rev/Dex)
Response or stable disease
Continue to plateau, then possible maintenance therapy
Clinical trial
Response or stable disease
Stem cell harvest for 2 transplants
Progressive disease
Consider alternative induction regimen, or
Proceed with stem cell harvest, or
Consider clinical trial
Consolidation therapy
Early transplantation
High-dose chemotherapy with ASCT support
Conventional therapy
Continue induction therapy at lower doses, MP, or clinical trial
CR or VGPR
Less than CR or VGPR
Consider maintenance therapy on clinical trial
Consider tandem ASCT
Delay ASCT until time of relapse

Table 1. Major Classes of Drugs Used in the Treatment of Myeloma.*

Drug	Regimen and Usual Starting Dose	Response Rate		Trial
		Newly Diagnosed Disease	Relapsed Disease	
		percentage†		
Alkylating agents				
Melphalan and prednisone‡	Repeated every 6 wk Melphalan, 8–10 mg PO on days 1–7 Prednisone, 60 mg per day PO on days 1–7	50–55	—	Myeloma Trialists' Collaborative Group[20]
Combinations, e.g., VBMCP§	Repeated every 5 wk Vincristine, 0.03 mg/kg (maximum 2 mg) IV on day 1 Carmustine, 0.5 mg/kg IV on day 1 Melphalan, 0.25 mg/kg PO on days 1–7 Cyclophosphamide, 10 mg/kg IV on day 1 Prednisone, 1 mg/kg PO on days 1–7	60	15¶	Myeloma Trialists' Collaborative Group,[20] Cavo et al.[21]
Corticosteroids				
Pulsed dexamethasone	Repeated every 4–5 wk Dexamethasone, 40 mg PO on days 1–4, 9–12, and 17–20	45	25–35	Alexanian et al.,[22] Alexanian et al.[23]
VAD	Repeated every 4 wk Vincristine, 0.4 mg per day IV continuous infusion on days 1–4 Doxorubicin, 9 mg/m² IV continuous infusion on days 1–4 Dexamethasone, 40 mg PO on days 1–4, 9–12, and 17–20	55–65	25–50	Alexanian et al.,[19] Alexanian et al.,[22] Alexanian et al.[24]
Thalidomide and its analogues				
Thalidomide	Repeated every 4 wk 200–400 mg PO on days 1–28	35	25–45	Rajkumar et al.,[16] Weber et al.,[17] Singhal et al.,[25] Kumar et al.,[26] Juliusson et al.[27]
Thalidomide–dexamethasone	Repeated every 4 wk Thalidomide, 200 mg PO on days 1–28 Dexamethasone, 40 mg PO on days 1–4, 9–12, and 17–20‖	65–70	50	Weber et al.,[17] Rajkumar et al.,[28] Dimopoulos et al.[29]
Melphalan–prednisone–thalidomide	Repeated every 4 wk Melphalan, 4 mg/m² PO on days 1–7 Prednisone, 40 mg/m² PO on days 1–7 Thalidomide, 100 mg PO on days 1–28	80	—	Palumbo et al.[30]
Cyclophosphamide–thalidomide–dexamethasone	Repeated every 3 wk Cyclophosphamide, 50 mg PO on days 1–21 Thalidomide, 200–800 mg PO on days 1–21 Dexamethasone, 40 mg PO on days 1–4	—	75	Garcia-Sanz et al.[31]
CC-5013**	25–30 mg PO on days 1–21 every 28 days	—	25	Richardson et al.[32]
Bortezomib	1.3 mg/m² on days 1, 4, 8, and 11 every 21 days	—	25	Richardson et al.[33]

* PO denotes orally; VBMCP vincristine, carmustine, melphalan, cyclophosphamide, and prednisone; VAD vincristine, doxorubicin, and dexamethasone; IV intravenous; mg/kg milligrams per kilogram of body weight; and mg/m² milligrams per square meter of body-surface area

† Percentages are estimates based on the results of all studies in which the given regimen was used.

‡ Appropriate trials of melphalan–prednisone in patients with relapsed or refractory disease who have not received alkylator therapy have not been conducted.

§ Several drug combinations have been studied; VBMCP is the combination most commonly studied and used.

¶ The response rate reflects effectiveness in patients with relapsed or refractory disease and previous alkylator therapy.

‖ In one study, dexamethasone was administered on days 1–4, 9–12, and 17–20 in odd cycles and on days 1–4 in even cycles.

** CC-5013 is not commercially available.

Table 2. Results of Major Randomized Trials with Autologous Stem-Cell Transplantation in Myeloma.

Trial	Comparison	No. of Patients	Outcome	Comments	Study
Intergroupe Francophone du Myélome 90	Conventional-dose chemotherapy vs. autologous bone marrow transplantation	200	Superior event-free survival and overall survival with transplantation; 5-yr survival, 52 percent with transplantation vs. 12 percent with chemotherapy (P=0.03)	All patients <65 yr of age, all received interferon maintenance therapy, and survival with chemotherapy was shorter than expected	Attal et al.[37]
Medical Research Council Myeloma VII	Conventional-dose chemotherapy vs. autologous stem-cell transplantation	401	Superior progression-free survival and overall survival with transplantation; median survival, 54 mo with transplantation vs. 42 mo with chemotherapy (P=0.04)	All patients <65 yr of age	Child et al.[38]
PETHEMA*	Conventional-dose chemotherapy vs. autologous stem-cell transplantation	216	No difference in progression-free survival or overall survival; median survival, 65 mo with transplantation vs. 67 mo with chemotherapy	Median age, 56 yr; only 164 patients responding to induction chemotherapy underwent randomization	Bladé et al.[39]
Myélome Autogreffe 91	Conventional-dose chemotherapy vs. autologous stem-cell transplantation	190	No significant difference in event-free survival or overall survival; median survival, 55 mo with transplantation vs. 50 mo with chemotherapy	All patients 55–65 yr of age	Fermand et al.[40]
Intergroup S9321	Conventional-dose chemotherapy vs. autologous stem-cell transplantation vs. allogeneic transplantation	549	Median progression-free survival, 25 mo with autologous transplantation vs. 21 mo with chemotherapy (P=0.05); no significant difference in overall survival	After 39 patients were enrolled, allogeneic transplantation group closed; 52 percent of patients assigned to chemotherapy received salvage transplantation at relapse	Barlogie et al.[41]
Myélome Autogreffe	Early vs. delayed autologous stem-cell transplantation	185	Median event-free survival, 39 mo with autologous transplantation vs. 13 mo with chemotherapy; no significant difference in overall survival	All patients <56 yr of age; early transplantation associated with shorter duration of chemotherapy and symptoms	Fermand et al.[42]
Intergroupe Francophone du Myélome 94	Single vs. double autologous stem-cell transplantation	399	Superior event-free survival and overall survival with double transplantation; 7-yr survival, 42 percent with double transplantation vs. 21 percent with single transplantation (P=0.01)	All patients <60 yr of age; benefit of second transplantation restricted to those with less than very good partial response to first	Attal et al.[43]
Bologna 96	Single vs. double autologous stem-cell transplantation	220	Superior event-free survival with double transplantation; no significant difference in overall survival; median survival, 60 mo with double transplantation vs. 56 mo with single transplantation	Interim analysis of first 220 patients	Cavo et al.[44]
Myélome Autogreffe 95	Single vs. double autologous stem-cell transplantation	230	No difference in progression-free or overall survival	All patients <56 yr of age	Fermand et al.[45]

* PETHEMA denotes Programa para el Estudio y Tratamiento de las Hemopatías Malignas.

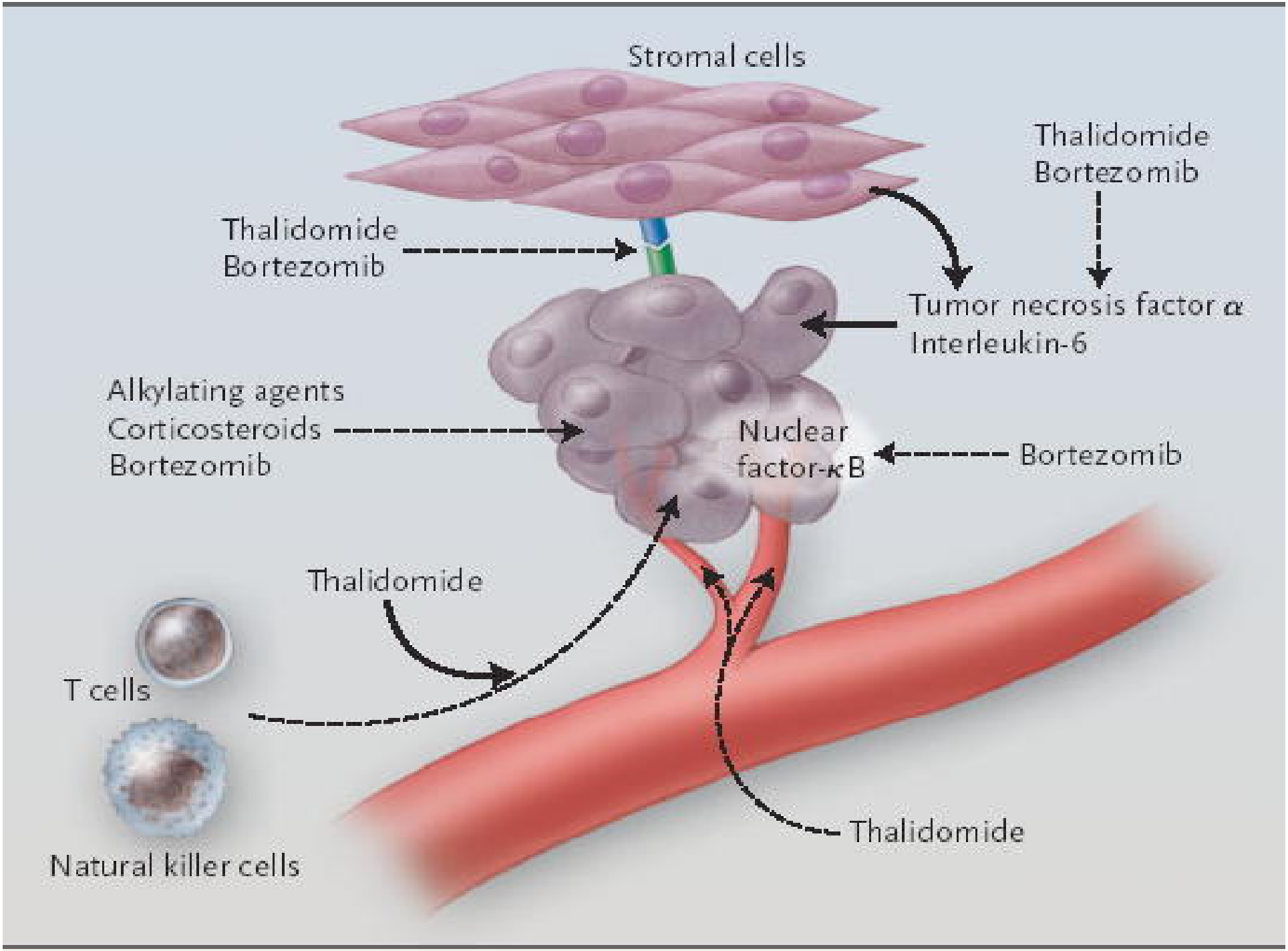

Stromal cells
Thalidomide
Bortezomib
Thalidomide
Bortezomib
Tumor necrosis factor α
Interleukin-6
Alkylating agents
Corticosteroids
Bortezomib
Nuclear
factor-κB
Bortezomib
Thalidomide
T cells
Natural killer cells
Thalidomide

Table 3. Treatment of Complications in Multiple Myeloma.

Complication	Therapeutic Options
Myeloma bone disease	Pamidronate or zoledronic acid in patients with documented bone disease Encouragement of activity to prevent osteopenia and deep-vein thrombosis Pain control with narcotic analgesics, if needed; avoidance of nonsteroidal antiinflammatory agents Radiation to treat painful bony lesions refractory to pain medication or cord compression Surgical intervention to prevent or treat pathologic fractures Vertebroplasty or kyphoplasty for selected vertebral lesions, to reduce pain and improve height
Anemia	Treatment of reversible causes such as deficiencies of iron, B_{12}, or folate Erythropoietin for symptomatic anemia during chemotherapy Transfusions as needed
Infections	Vaccination against *Streptococcus pneumoniae*, *Haemophilus influenzae*, and influenza Consideration of prophylactic broad-spectrum antibiotic therapy when corticosteroids are used Intravenous immune globulin for recurrent serious infections associated with hypogammaglobulinemia Consideration of prophylaxis against *Pneumocystis carinii* when prolonged corticosteroid therapy is used; avoidance of trimethoprim–sulfamethoxazole when thalidomide is used
Hypercalcemia	Intravenous fluids and corticosteroids Bisphosphonates when hypercalcemia is severe or unresponsive to hydration and corticosteroids
Renal failure	Correction of reversible causes such as dehydration, hypercalcemia, and hyperuricemia Chemotherapy (e.g., vincristine, doxorubicin, and dexamethasone; dexamethasone alone; or thalidomide–dexamethasone) for rapid control of disease Alkaline diuresis for acute renal failure due to cast nephropathy; avoid alkalinization in patients with hypercalcemia Trial of plasma exchange in acute evolving renal failure
Hyperviscosity syndrome	Plasma exchange for symptomatic patients (serum viscosity does not correlate well with symptoms)