Multiple Myeloma
Klinik, laboratuvar, tanı, prognoz

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İç Hastalıkları ve Hematoloji Uzmanı

Tanım

- Multiple myeloma (MM) monoklonal immunoglobulin salgılayan bir plazma hücresi klonunun neoplastik proliferasyonu ile karakterize bir hastalıktır.
- Bu plazma hücresi klonu kemik iliğinde prolifere olurken çoğu kez kemikte de osteolitik lezyonlar, osteopeni, ve/veya patolojik kırıklara neden olurlar

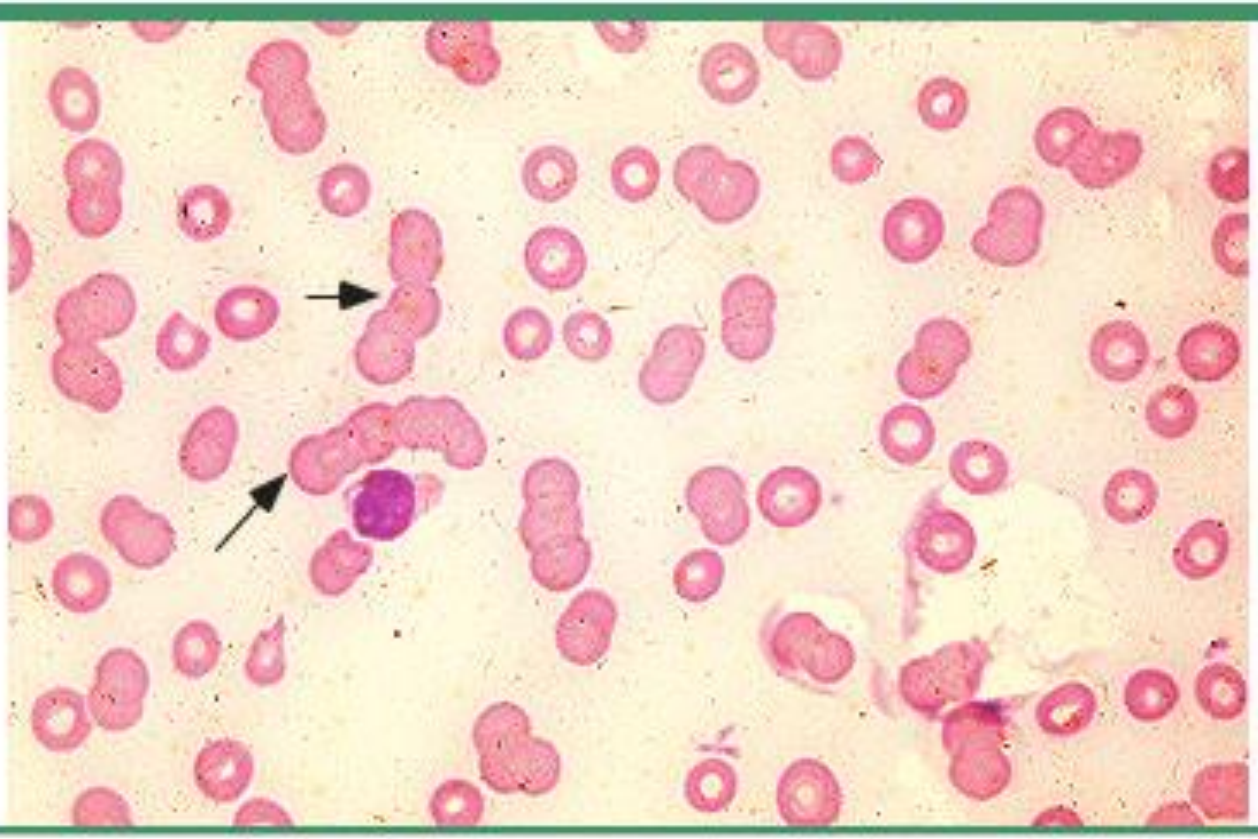
Nasıl tanı konulur I

- Açıklanamayan anemi (%73), halsizlik (%32), kilo kaybı (%24) gibi malignite ile ilişkilendirilebilecek şikayetler
- Bel, sırt, kosta ağrıları (%58) ve beraberinde x-ray ile saptanan litik kemik lezyonları
- Semptomatik veya tesadüfen saptanan hiperkalsemi (%28)
- Akut böbrek yetmezliği (kreatinin yükselmesi %48) gelişmesi
- Sık geçirilen enfeksiyonlar

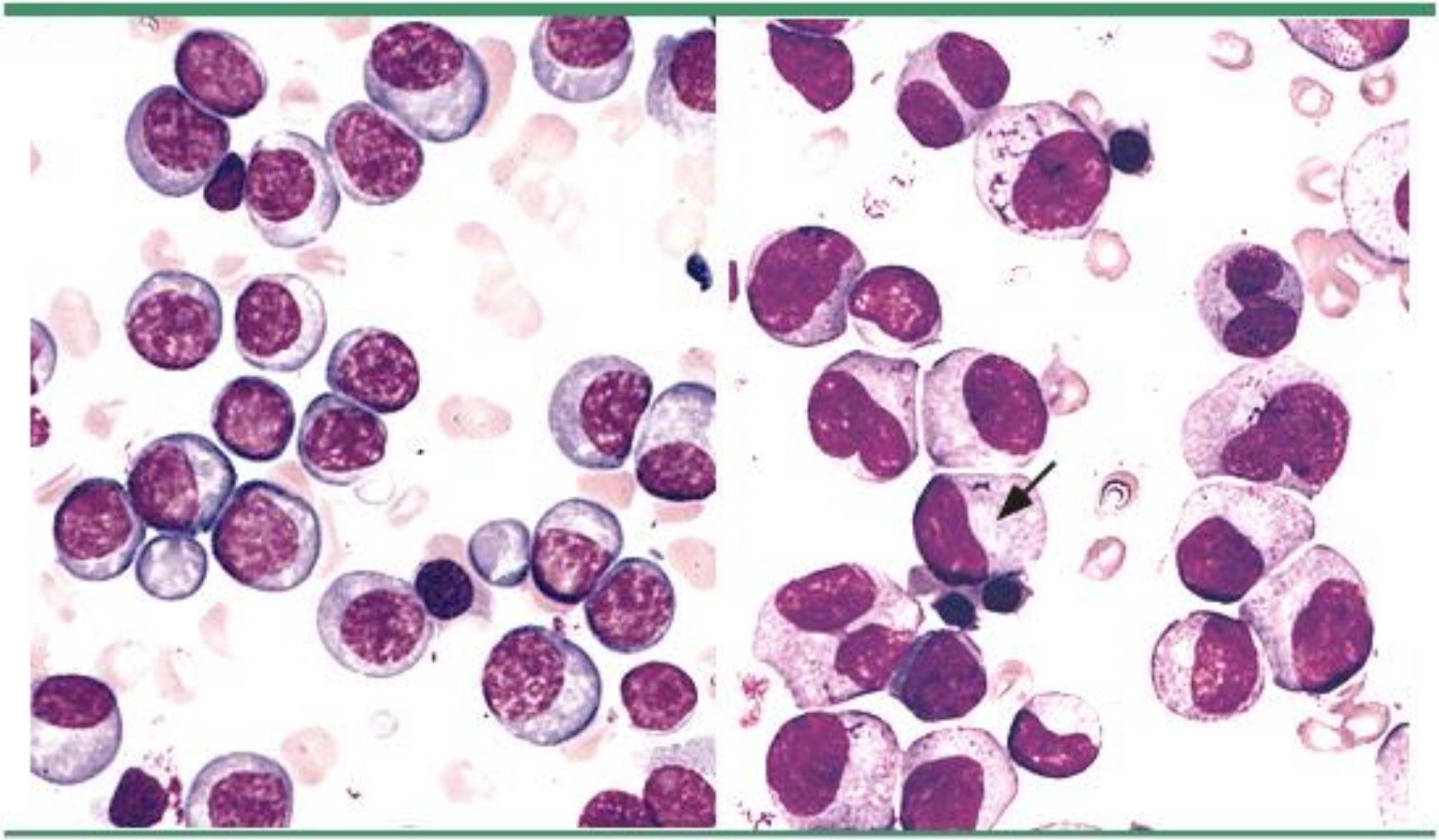
Nasıl tanı konulur II

- Sedimantasyon hızı, CRP, beta 2 mikroglobulin değerlerinde yükselme
- Serumda protein değerinde (globulin fraksiyonunda) artma
- SPEP ile gama fraksiyonunda monoklonal protein
- Kan ve/veya idrarda immün elektroforezde monoklonal bant saptanması (IgG %52, IgA %21, κ veya λ %16) %3 nonsekretuar
- Periferik yaymada rouleaux formasyonu
- Kemik iliğinde myeloma (neoplastik plazma) hücresi infiltrasyonu

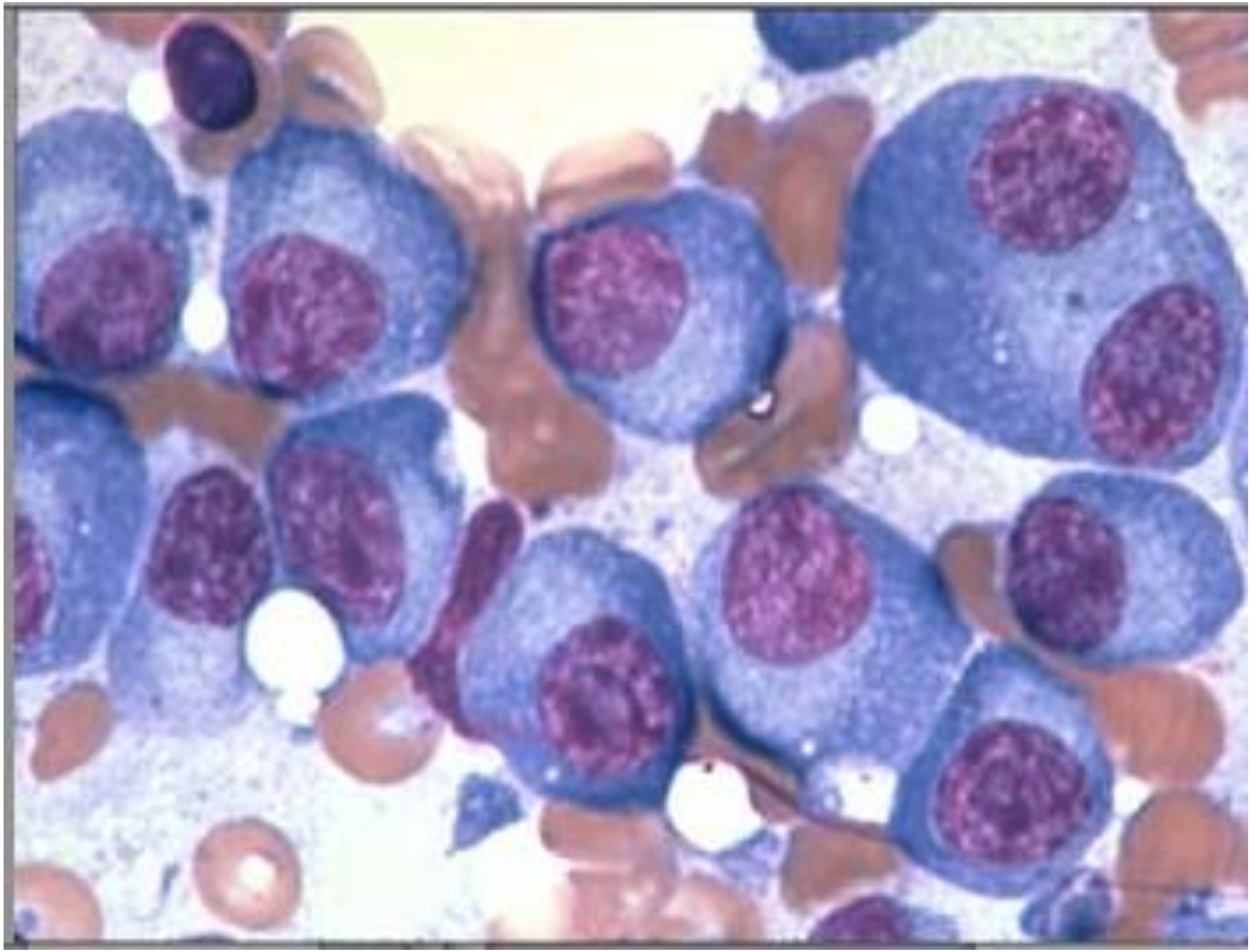
Rouleaux formation in multiple myeloma



Multiple myeloma



Bone marrow aspirate smears from two different patients with multiple myeloma, illustrating a preponderance of mostly mature-appearing plasma cells with eccentrically placed nuclei and prominent Golgi zones (arrow) (Wright Giemsa stain).



Monoklonal gamopati yapan diğer hastalıklar

- Waldenström Makroglobulinemisi
- Primer sistemik (AL) amiloidozis
- KLL ve Non-Hodgkin Lenfoma gibi lenfoproliferatif hastalıklar
- Ağır zincir hastalıkları (α , γ , μ gibi)
- Soliter ekstramedüller plazmositoma
- Osteosklerotik myeloma (POEMS sendromu = polinöropati, organomegali, endokrinopati, monoklonal protein, deri (skin) değişiklikleri)

İstenecek tetkikler

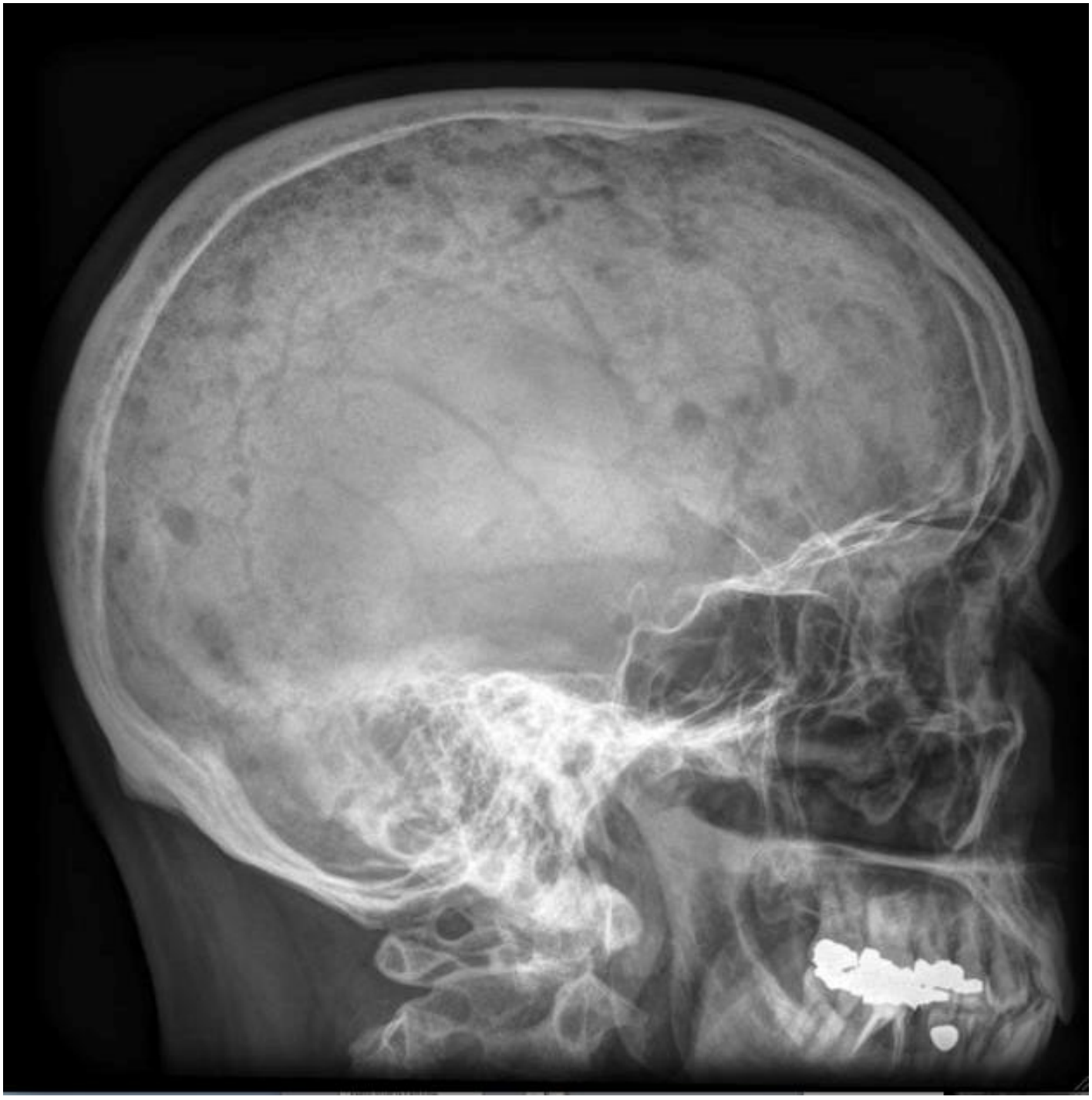
- Hemogram, periferik yayma
- Kreatinin, SH, CRP, Ca, P, LDH, $\beta_2$mcg,
- SPEP
- Serum ve 24 st'lik idrarda İmmün Elektroforez (IEP),
- Serumda free (monoklonal) light chain (FLC) analizi
- Kemik survey'i (iskelet MR'ı, gerekirse PET-BT)
- Kemik iliği aspirasyon ve biyopsisi (yayma, immünofenotipleme, FISH (del 13, del 17p13, t(4;14), t(11;14),t(14;16), 1q21 amplification) ve karyotipleme

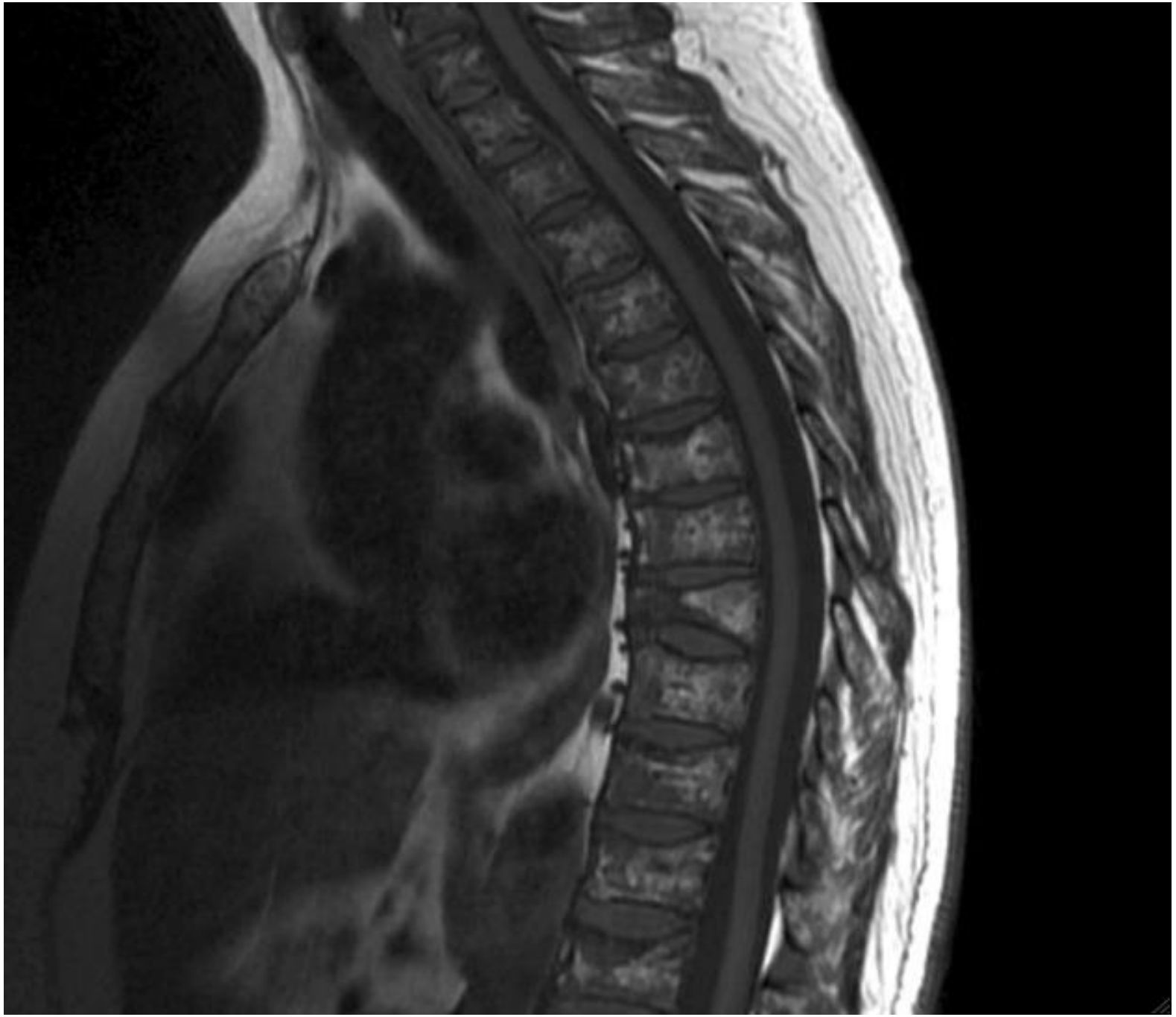
Prognostik kriterler

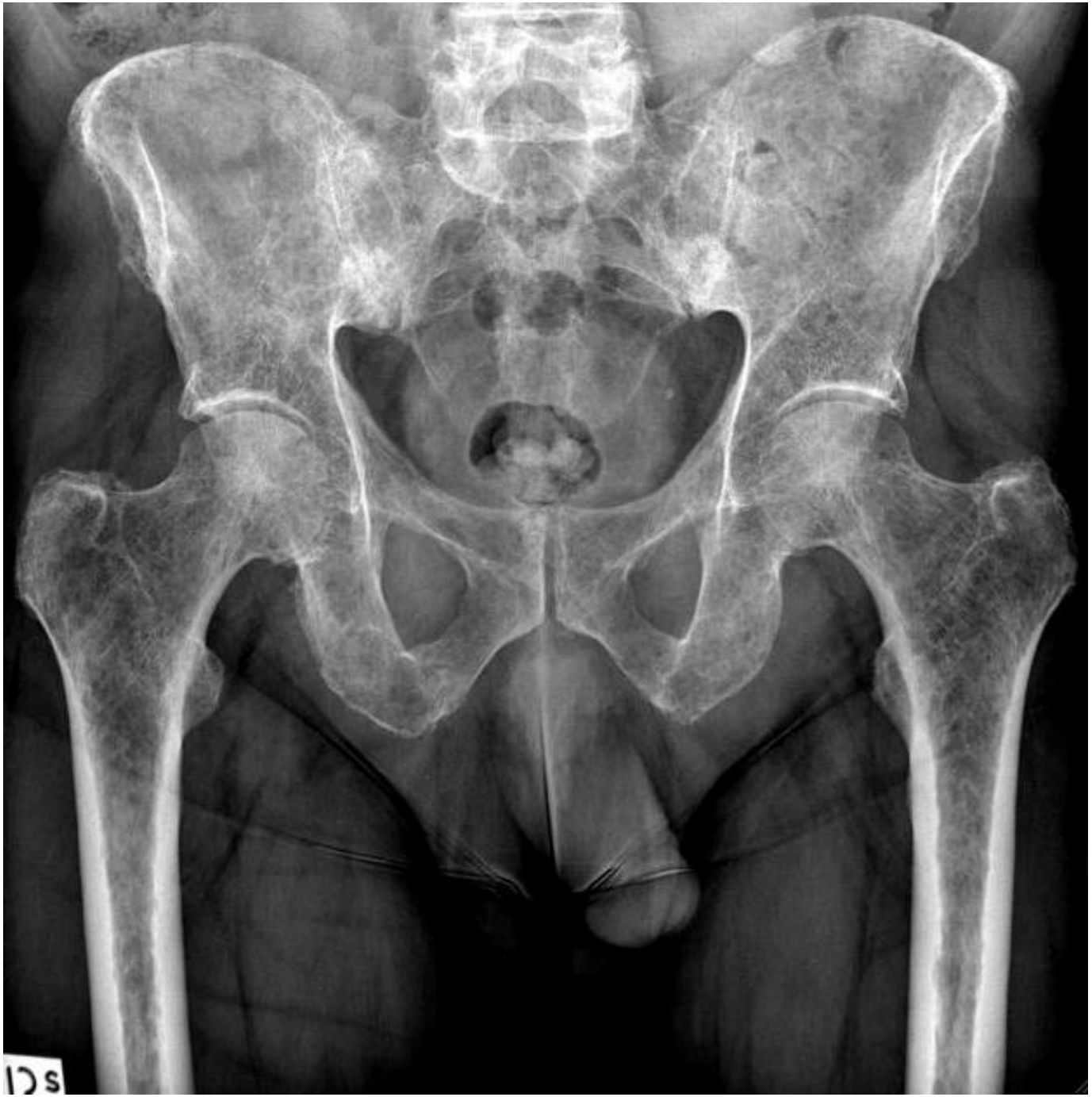
- Standart risk (%75)
  - FISH t (11;14), t (6;14)
  - Hiperdiploidi
- Yüksek risk %25
  - FISH del 17p13, t (4;14), t (14;16)
  - Sitogenetik delesyon 13
  - Sitogenetik hipodiploidi
  - PCLI $\geq$ %3
- İntermediate risk
  - t (4;14), $\beta_2$mcg < 4 , Hemoglobin $\geq$ 10 g/dL

Hastaya ait prognostik faktörler

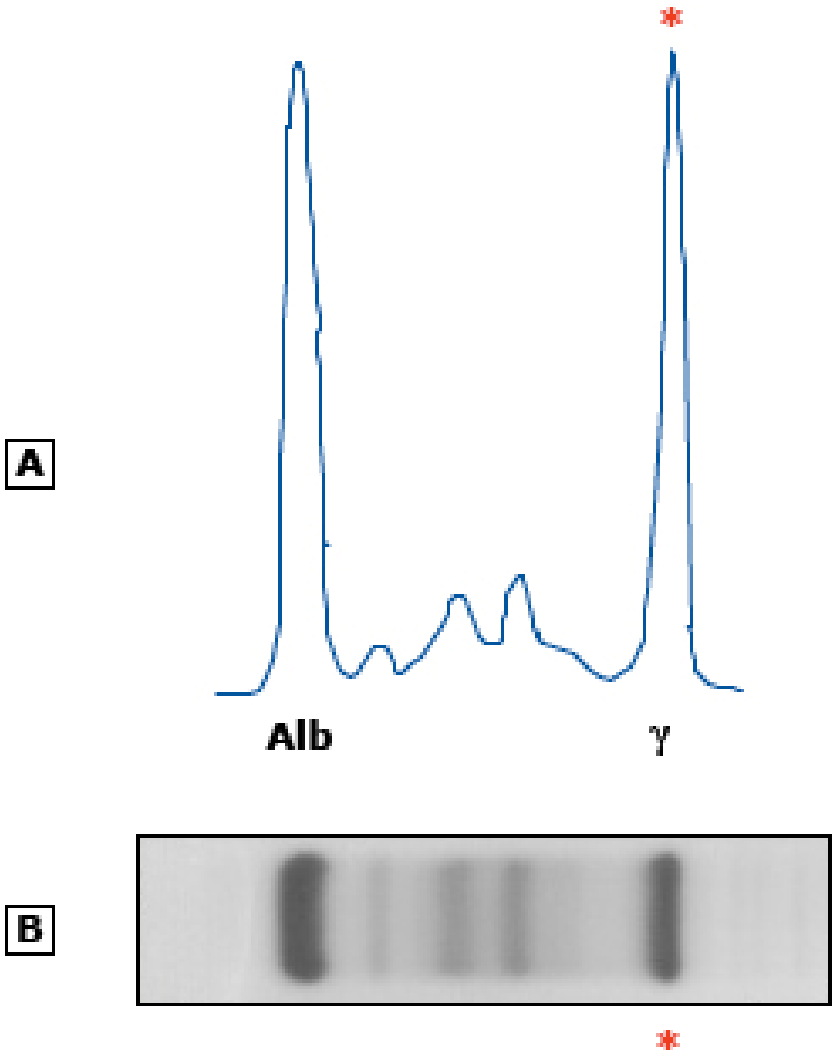
- ECOG Performans durumu 3 veya 4 (1,9)
- Serum albümin $<$ 3 g/dL (1,7)
- Yaş $\geq$ 70 (1,5)
- Serum kreatinin $\geq$ 2 mg/dL (1,5)
- Trombosit $<$ 150000/mikroL (1,5)
- $\beta_2$mcg $>$ 4 mg/L (1,5)
- Plasma cell labeling index $\geq$ %1 (1,5)
- Serum Kalsiyumu $\geq$ 11 mg/dL (1,3)
- Hemoglobin $<$ 10 g/dL (1,3)
- Kemik iliğinde plasma hücresi % si $\geq$ %50 (1,2)



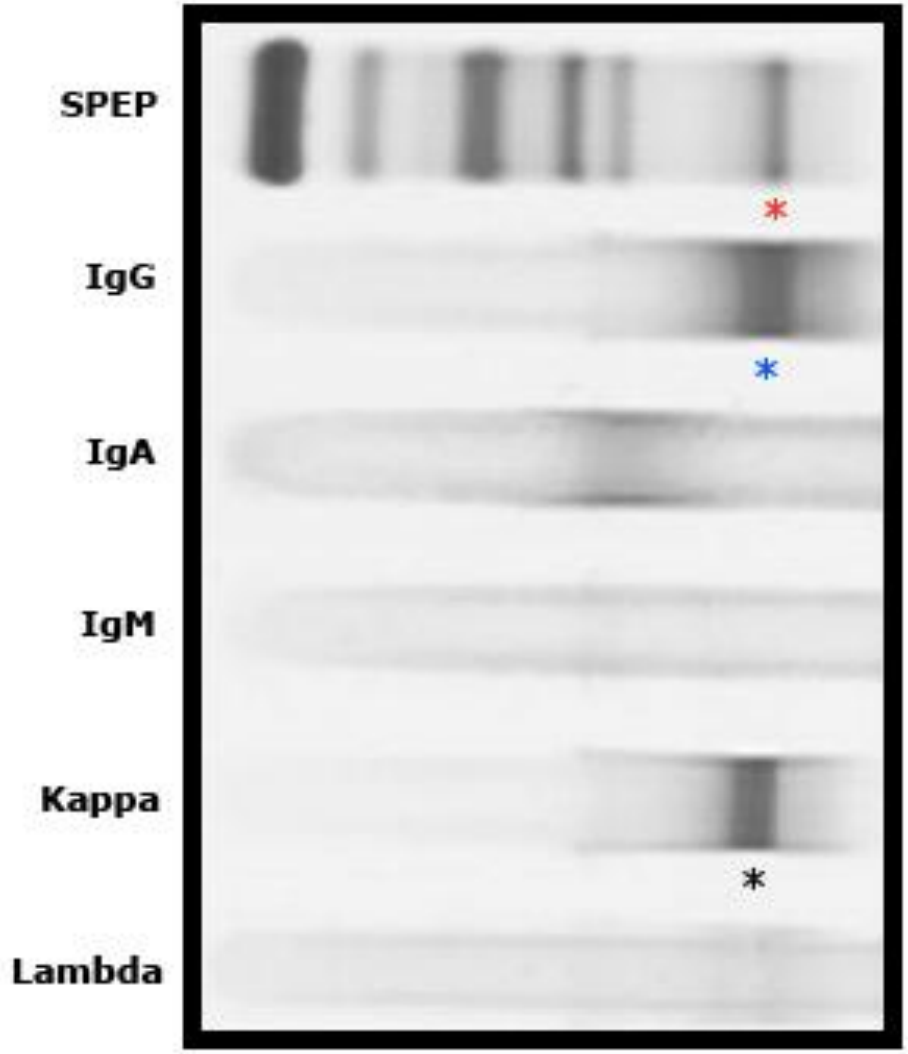




Monoclonal pattern on serum protein electrophoresis (SPEP)



Monoclonal gammopathy on immunofixation



IgG kappa

Diagnostic criteria for multiple myeloma and related disorders

Multiple myeloma (all 3 criteria must be met)
Presence of a serum or urinary monoclonal protein
Presence of clonal plasma cells in the bone marrow or a plasmacytoma
Presence of end organ damage felt related to the plasma cell dyscrasia, such as:
- Increased calcium concentration
- Lytic bone lesions
- Anemia, or
- Renal failure
Smoldering (asymptomatic) multiple myeloma (SMM, both criteria must be met)*
Serum monoclonal protein ≥3 g/dL and/or ≥10 percent to <60 percent bone marrow clonal plasma cells
No end organ damage related to plasma cell dyscrasia (see list above)
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 (see list above)

* Patients with serum involved/uninvolved free light chain ratio of 100 or more, and those with >1 focal lesion on MRI should be considered to have multiple myeloma rather than SMM.

Adapted from: Br J Haematol 2003; 121:749 and Leukemia 2001; 15:1274 and N Engl J Med. 2011;365:474 and Blood 2013;122:4172

Durie-Salmon staging system for multiple myeloma

Stage I
Low cell mass: <0.6 x 10^{12} cells/m^2 **PLUS** all of the following:
Hgb >10 g/dL
Serum IgG <5 g/dL
Serum IgA <3 g/dL
Normal serum calcium
Urine monoclonal protein excretion <4 g/day
No generalized lytic bone lesions
Stage II
Intermediate cell mass: neither stage I nor stage III
Stage III
High cell mass: >1.2 x 10^{12} cells/m^2 **PLUS** one of more of the following:
Hgb <8.5 g/dL
Serum IgG >7 g/dL
Serum IgA >5 g/dL
Serum calcium >12 mg/dL (3 µmol/L)
Urine monoclonal protein excretion >12 g/day
Advanced lytic bone lesions
Stage III is subclassified as IIIA or IIIB based on serum creatinine
A. Serum creatinine <2 mg/dL (177 µmol/L)
B. Serum creatinine ≥2 mg/dL

International Staging System (ISS)

- Stage I: $\beta_2$mcg $<$ 3,5 mg/L ve serum albümin $\geq$ 3,5 g/dL
- Stage II: Stage I veya Stage II grubuna girmeyenler
- Stage III: $\beta_2$mcg $\geq$ 5,5 mg/L

Median overall survival

- Stage I: 62 ay
- Stage II: 44 ay
- Stage III: 29 ay

MM’da tedavi

CRAB (organ hasarı)

- Anemi (hemoglobin <10 g/dL veya normale göre 2 g/dL daha düşük)
- Hiperkalsemi (serum kalsiyum >11.5 mg/dL)
- Renal yetmezlik (serum creatinine >2 mg/dL)
- Litik kemik lezyonları veya ağır osteopeni
- Ekstrameduller plasmasitoma (soliter plasmasitoma hariç)

Otolog transplantasyona uygunluk

- Avrupa'da < 65 yaş ve komorbid engel yoksa MM hastaları otolog HCT adayı. Amerikada yaş kriteri yok. Kişiye özel değerlendiriliyor.
- ABD'de otolog HCT yapılamayacaklar:
  - Yaş >77
  - Direkt bilirubin >2.0 mg/dL
  - Serum kreatinin >2.5 mg/dL
  - ECOG performans sınıfı 3 veya 4
  - New York Heart Association fonksiyon durumu Class III veya IV

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2014
Multiple Myeloma

NCCN Guidelines Index
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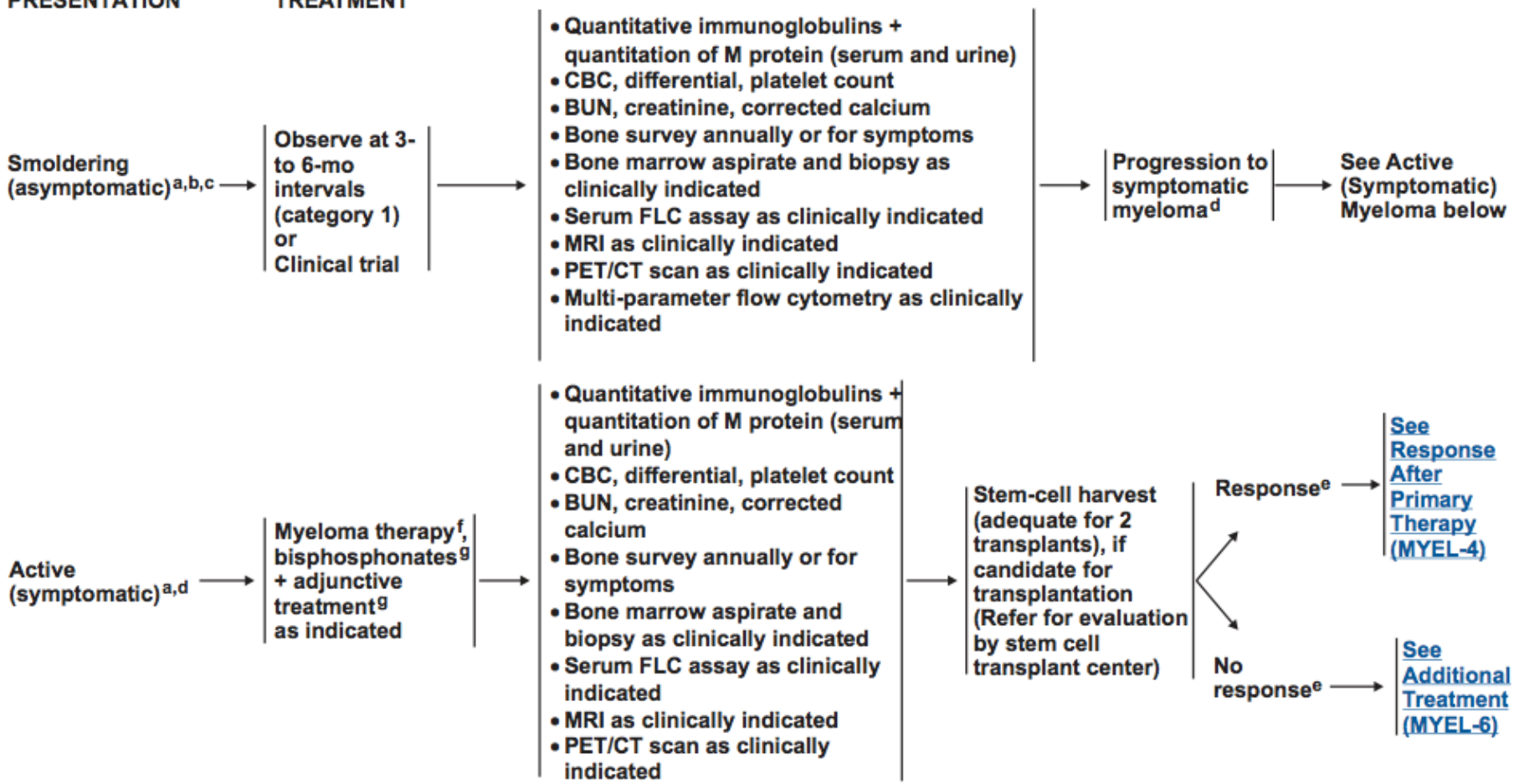
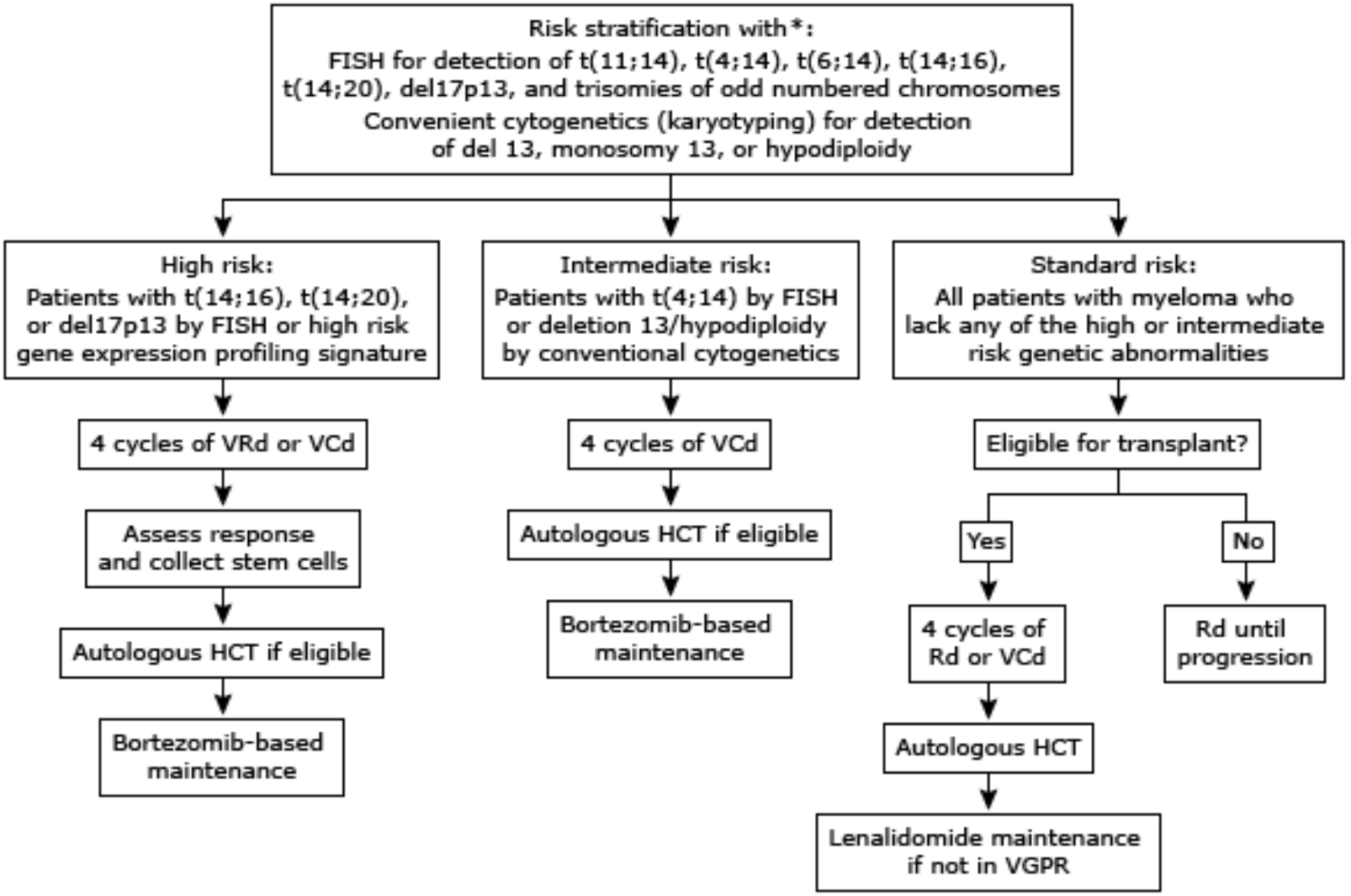


Initial treatment of multiple myeloma by risk stratification



Tedaviye yanıt kriterleri

Complete response (CR)
No M protein in serum and urine by immunofixation
AND
No current evidence of soft tissue plasmacytoma
AND
Bone marrow aspirate and biopsy demonstrate less than 5 percent plasma cells
In patients who lack measurable M proteins in the serum and urine being monitored using the FLC levels, the definition of CR requires a normalization of the FLC ratio in addition to the above criteria.
Very good partial response (VGPR)
Serum and urine M protein detectable by immunofixation but not on electrophoresis or at least a 90 percent reduction in serum M-protein with a urine M protein <100 mg/24 hrs
In patients who lack measurable M proteins in the serum and urine being monitored using the FLC levels, the definition of VGPR requires >90 percent decrease in the difference between involved and uninvolved free light chain levels.
Partial response (PR)
At least 50 percent reduction in serum M-protein
AND
Reduction of 24-hour urinary M protein by 90 percent or to <200 mg/24 hrs
AND
At least 50 percent reduction in size of any soft tissue plasmacytomas, if present at baseline
In patients who lack measurable M proteins in the serum and urine being monitored using the FLC levels, the definition of PR requires ≥50 percent decrease in the difference between involved and uninvolved free light chain levels FLC levels. If the FLC levels were also unmeasurable at baseline, a 50 percent reduction in bone marrow plasma cells is acceptable as long as the original bone marrow contained at least 30 percent plasma cells.

Tedaviye yanıt kriterleri

Stable disease (SD)
Does not meet criteria for CR, VGPR, PR, or PD
Progressive disease (PD)
At least 25 percent increase from lowest response value in any of the following:
- Serum M protein (absolute increase must be ≥0.5 g/dL)
- Urine M protein (absolute increase must be ≥200 mg/24 hrs)
- Bone marrow plasma cell percentage (absolute increase must be ≥10 percent)
- Difference in the kappa and lambda FLC (absolute increase must be >10 mg/dL)
OR
Increase in the size or development of new bone lesions or soft tissue plasmacytomas
OR
Development of a serum calcium >11.5 mg/dL without other cause
The FLC criteria should only be used for patients with unmeasurable M protein in the serum and urine.

Multiple Myeloma’nın komplikasyonları

- Hiperkalsemi
- Böbrek yetmezliği
- Enfeksiyon
- İskelet lezyonları (ağrı, kırıklar, kord basısı)
- Hiperviskozite
- Anemi
- Tromboz
- Nöropati