NCCN 10th Annual Congress:
Hematologic Malignancies™

Patient Case Studies & Panel Discussion

Amyloidosis, POEMS Syndrome, Plasmacytoma

Panelists: Damian J. Green, MD, *Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance;* Amrita Y. Krishnan, MD, *City of Hope Comprehensive Cancer Center*

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CASE 1

Damian J. Green, MD

Fred Hutchinson Cancer Research Center/

Seattle Cancer Care Alliance

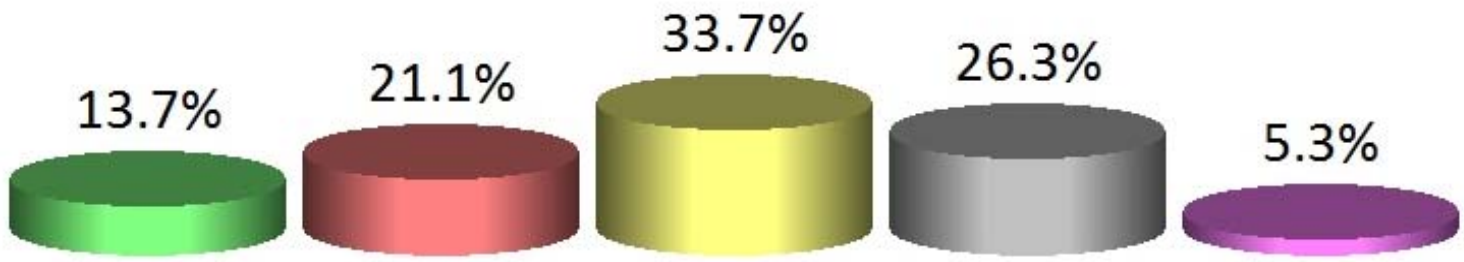
Case 1: Plasma Cell Disorders

- A 64 y.o. woman diagnosed with λ light chain multiple myeloma and arrives to the stem cell transplant service for pre-transplant evaluation. She had no lytic bone lesions. She had 20% clonal plasma cells in the bone marrow at diagnosis (marrow not available for review).
- Her serum λ light chain dropped >90% after 4 cycles of bortezomib, lenalidomide and dexamethasone induction therapy.
- She reports persistent chronic nausea and diminished appetite (predated initiation of therapy) mild dyspnea on exertion and lower extremity edema.

ARS Question

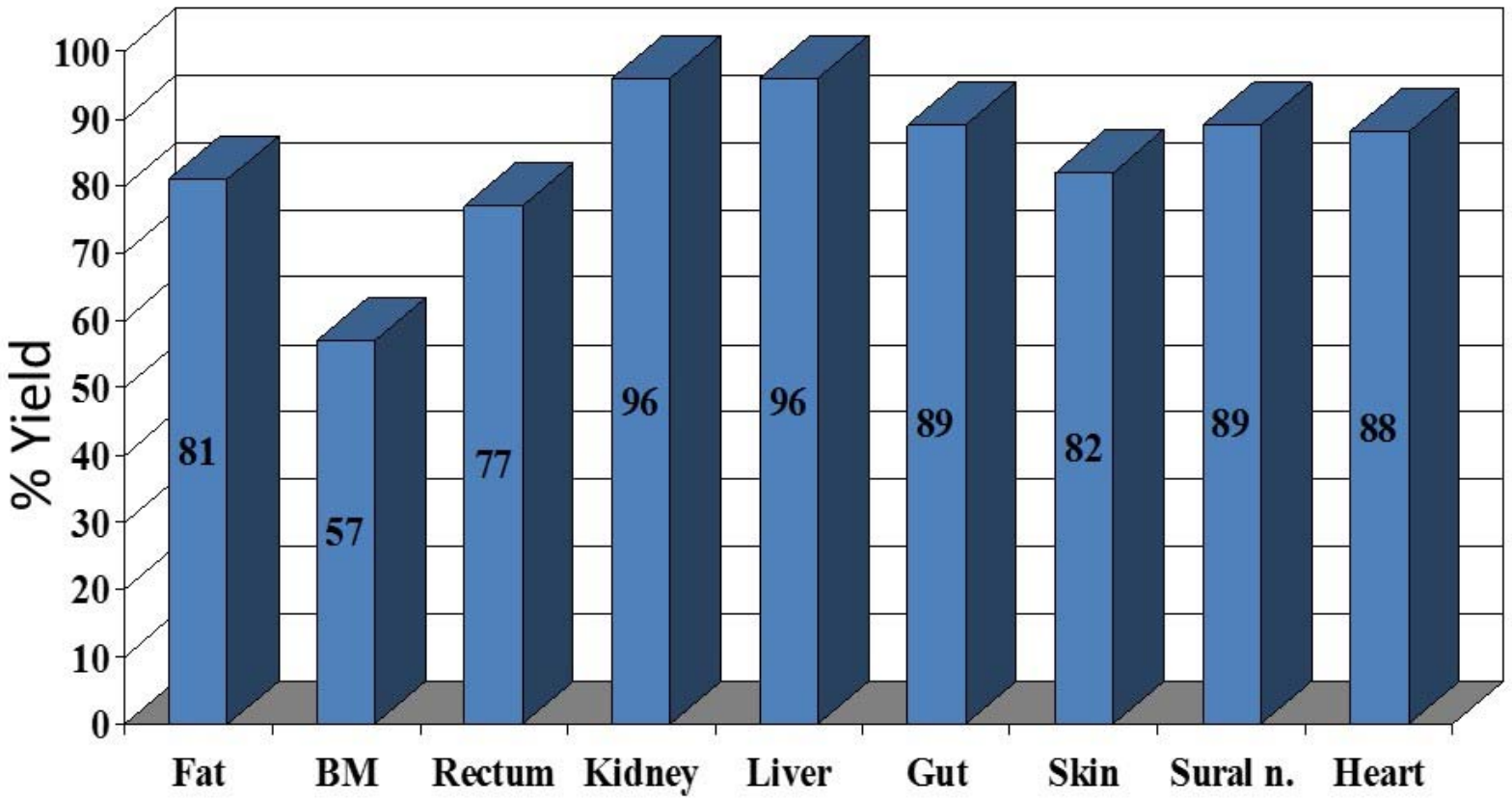
What would be the best "next step" in the management of this patient?

1. Proceed with chemotherapy based mobilization and stem cell collection
2. EGD with biopsies
3. Abdominal fat pad biopsy
4. Repeat bone marrow biopsy with Congo Red staining
5. Rectal biopsy



Total: 95

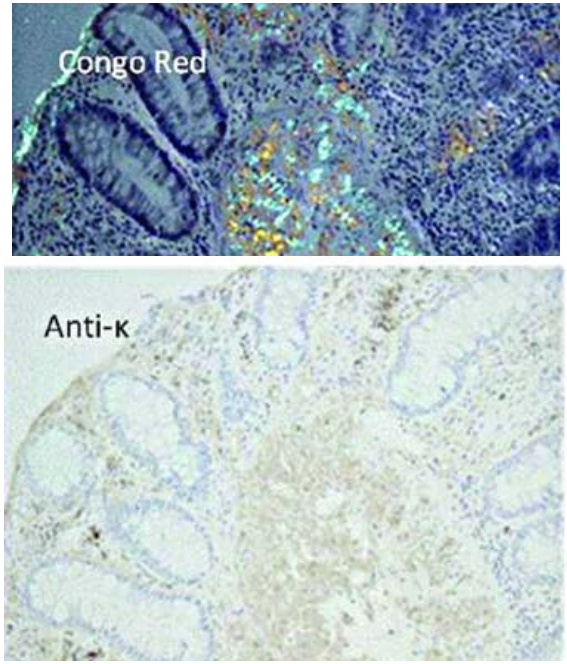
Primary AL Amyloidosis: Biopsy Yield



Kyle and Gertz, Mayo Clinic

ARS Question

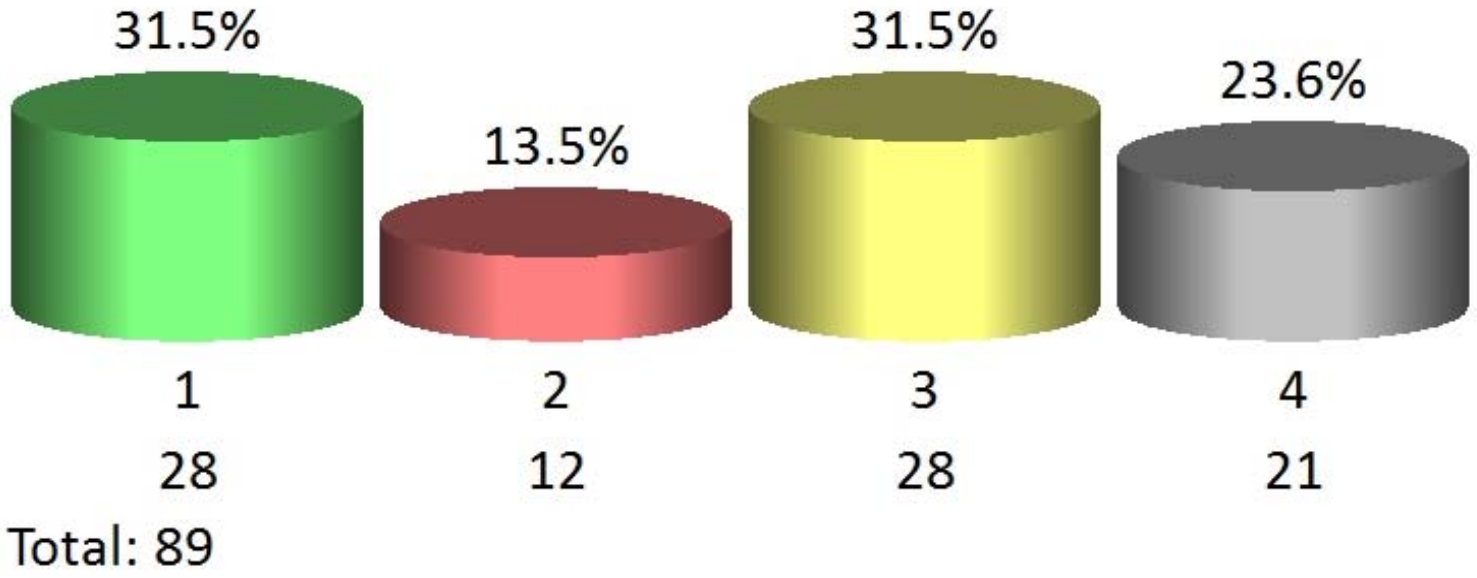
You obtain the EGD.



Images: Shameem Mahmood et al. Haematologica 2014;99:209-221

The most sensitive method for evaluating amyloid subtype is:

1. Congo Red staining
2. IHC
3. Immunoflorescence microscopy
4. Mass spectrometry by laser capture



Most common sites of AL amyloid deposition:

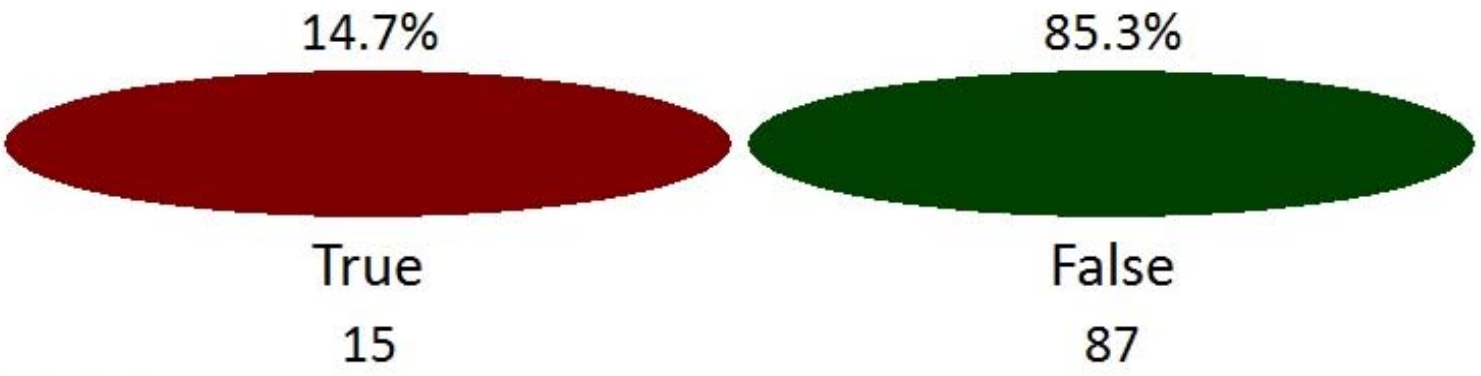
- Cardiac ~70%
- Renal 65%
- Liver 17%
- GI tract 8%
- Soft tissue 17%
- Autonomic nervous system 14%
- Peripheral nervous system 15%

ARS Questions

The biopsy reveals the presence of amyloidosis (AL subtype). The patient reports two episodes of blood streaked emesis several days after the procedure. Her platelets are 120, PTT is not prolonged, INR is not elevated, Factor X activity is not diminished.

At this juncture, it is reasonable to inform the patient that the bleeding is not related to her amyloidosis.

1. True
2. False

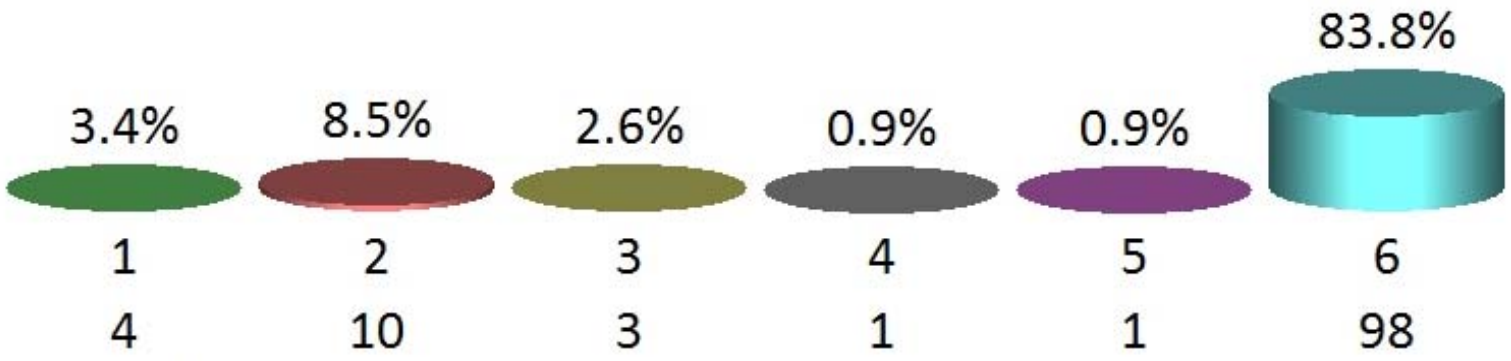


Total: 102

The patient reports dyspnea with moderate exertion and on exam has trace pedal edema.

You order:

1. Chest CT angiogram– to evaluate for emboli
2. Cardiac Echo
3. Serum N-terminal pro-BNP
4. Serum Troponin – T
5. 24-hour halter monitor
6. 2, 3, and 4



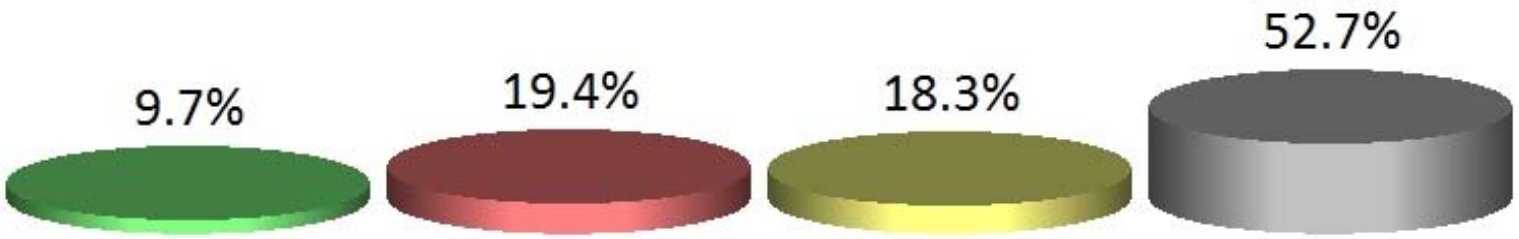
Total: 117

The pro-BNP is 3,000 pg/mL, troponin-T is 0.4 ng/mL.

You recommend:

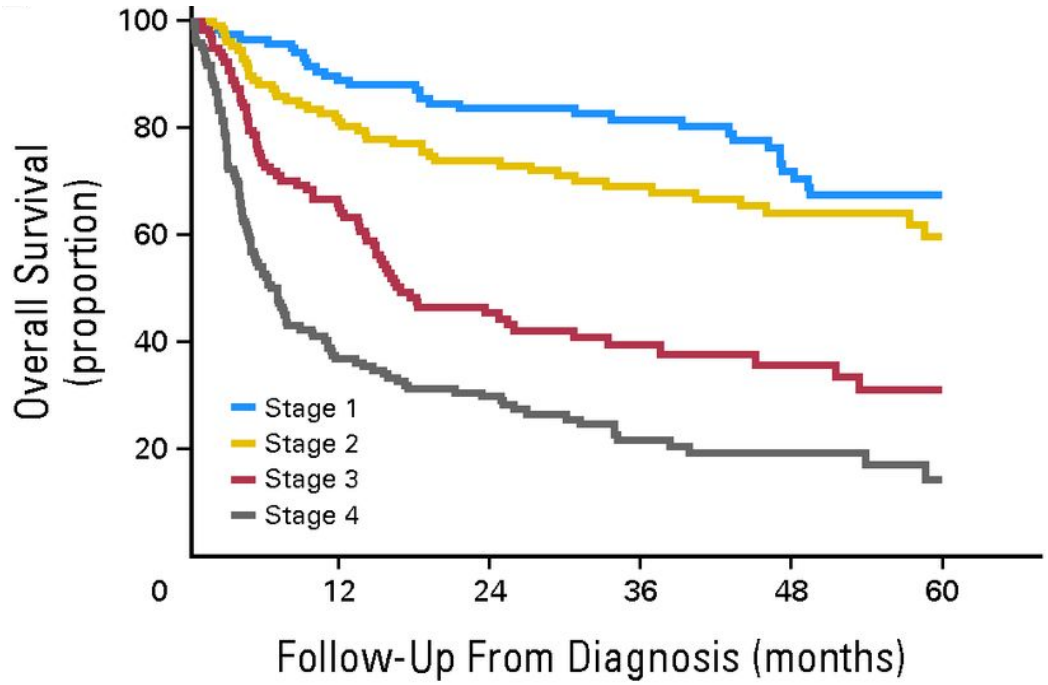
1. Proceed to ASCT with melphalan 200 mg/m^2 conditioning
2. Proceed to ASCT with melphalan 140 mg/m^2 conditioning
3. Inform the patient that she is not an ASCT candidate
4. Recommend that the patient receive additional cycles of bortezomib*/cyclophosphamide/dex with close monitoring of cardiac parameters

*iv



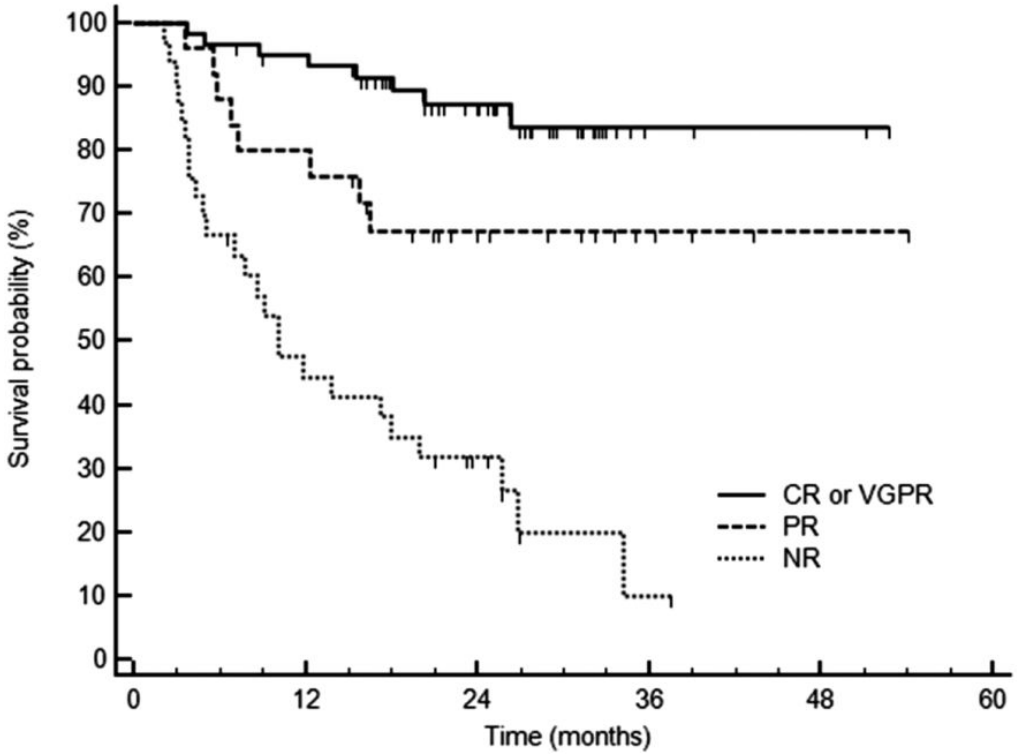
Total: 93

Staging system based on 758 patients



Shajl Kumar et al. JCO 2012;30:989-995

Survival of 118 patients with cardiac AL amyloidosis treated with CyBorD based on response



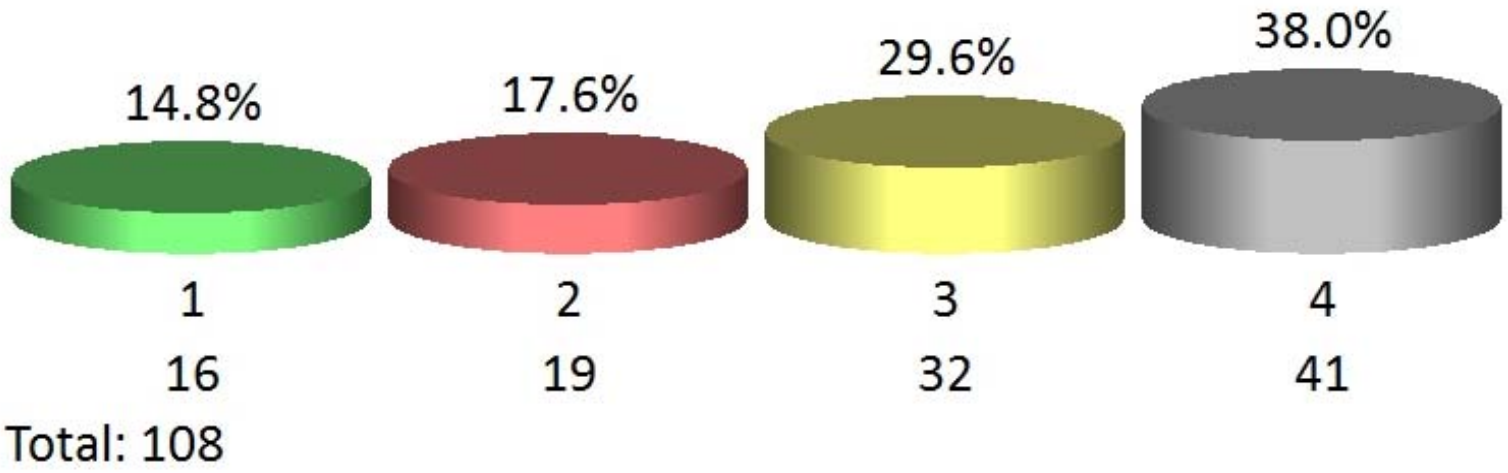
Giovanni Palladini et al. Blood 2015;126:612-615

ARS Question

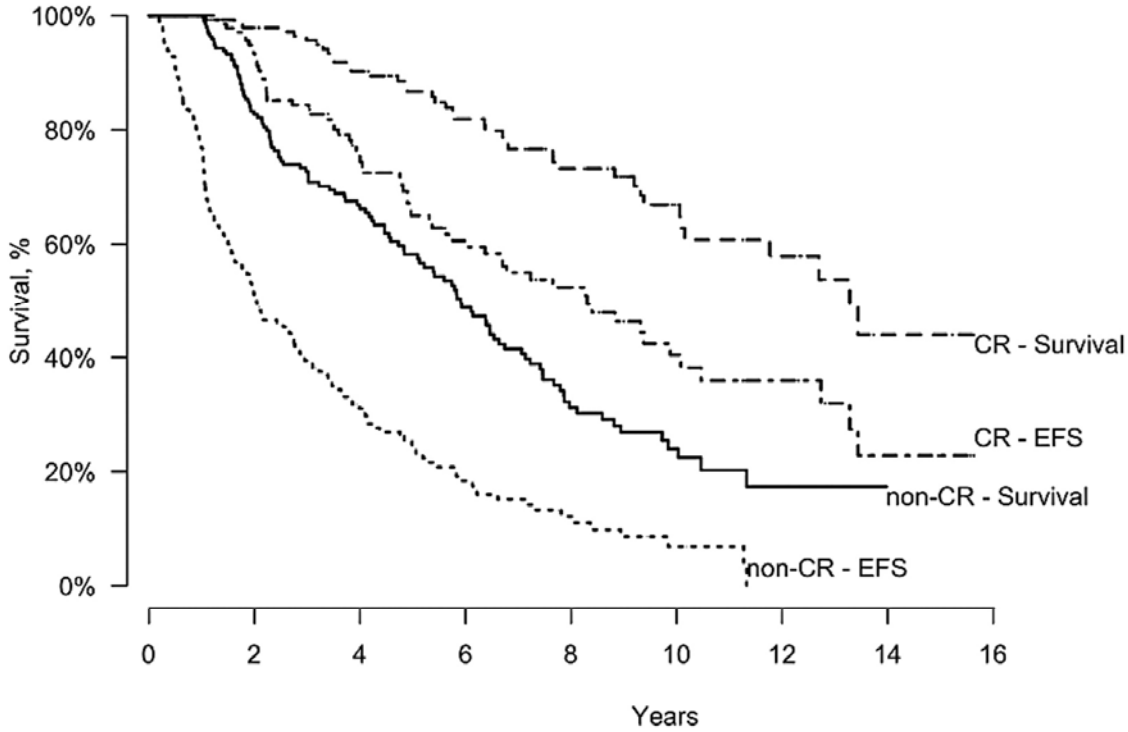
The patient returns home and receives 8 cycles of cyclophosphamide, bortezomib & dexamethasone. Her dyspnea on exertion resolves and her cardiac markers normalize.

At this point she should:

1. Remain on bortezomib maintenance
2. Mobilize stem cells with chemotherapy and transplant with melphalan 200 mg/m^2
3. Mobilize stem cells with GSCF and transplant with melphalan 200 mg/m^2
4. Mobilize stem cells with GSCF and transplant with melphalan 140 mg/m^2



EFS and OS of patients who achieved a hematologic CR (n = 145) after HDM/SCT compared with those who did not (non-CR, n = 195).



Patients, n

CR - Survival :	145	138	113	81	62	33	19	6	0
CR - EFS :	145	143	104	61	48	19	11	3	0
non-CR - Survival :	195	153	97	62	31	16	3	0	0
non-CR - EFS :	195	148	63	33	17	4	0	0	0

Maria Teresa Cibeira et al. Blood 2011;118:4346-4352

Take Home Points:

- Average age at diagnosis is 64 (younger than myeloma)
- Male predominance (65-70%)
- λ light chain in 70% κ in 25% and bi-clonal in 5%
- Localized (single site) amyloidosis have a much better prognosis
- In multivariate analysis studies, cardiac troponin T is a better predictor of survival than troponin I.

Take Home Points:

- There are currently no FDA approved agents for the treatment of AL amyloidosis
- A global phase 3 trial is currently accruing patients studying NEOD001 monoclonal antibody against amyloid protein.

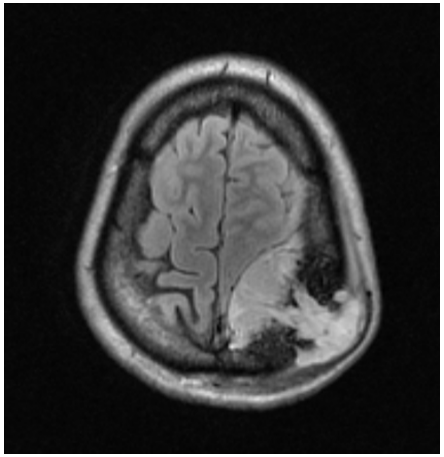
CASE 2

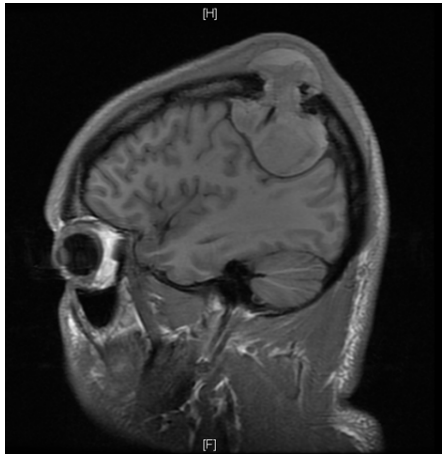
Damian J. Green, MD

Fred Hutchinson Cancer Research Center/

Seattle Cancer Care Alliance

A 47 YO male presents to the ER with a seizure. Brain imaging:





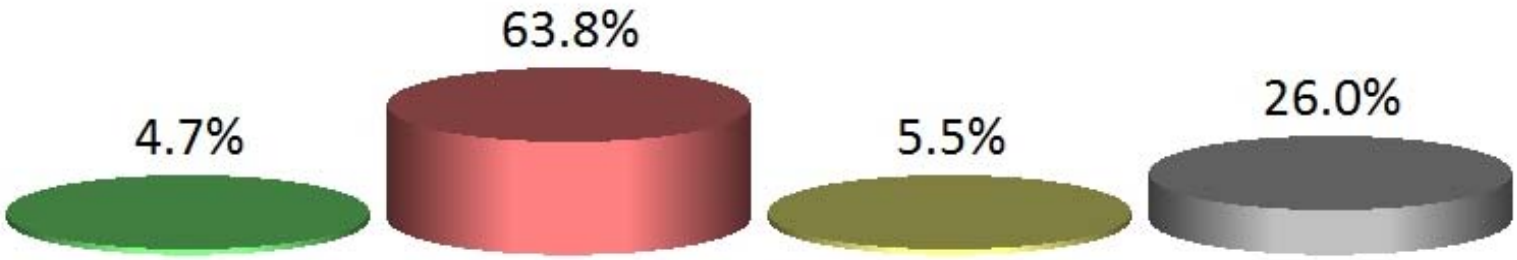
- Surgical resection and pathology demonstrates sheets of clonal λ restricted plasma cells. Surgical margins are negative. Serum protein electrophoresis demonstrates a monoclonal protein spike measured at 0.4 grams/dL IgG λ.

ARS Question

Bone marrow biopsy demonstrates 2% abnormal plasma cells. Labs: no anemia, renal insufficiency or hypercalcemia. LP: no plasma cells, total protein elevated (94 mg/dL).

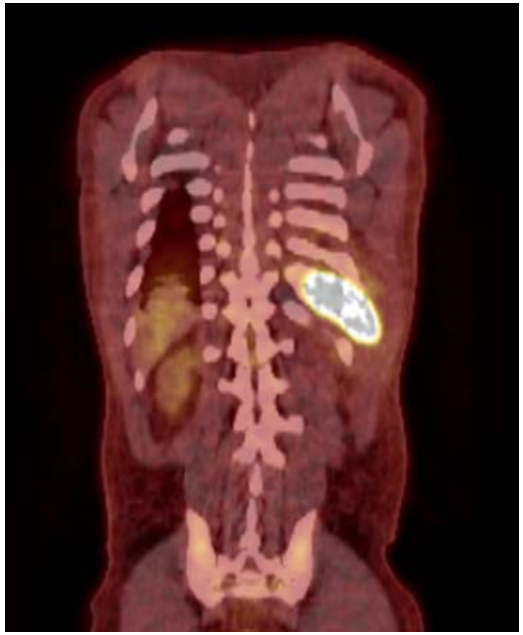
What is the next reasonable step for this patient?

1. Monitor closely
2. Obtain imaging studies (skeletal survey, PET)
3. Administer prophylactic intrathecal methotrexate
4. Irradiate the calvarial site and follow



Total: 127

The skeletal survey reveals sclerotic bone lesions in multiple ribs.
PET imaging demonstrates:



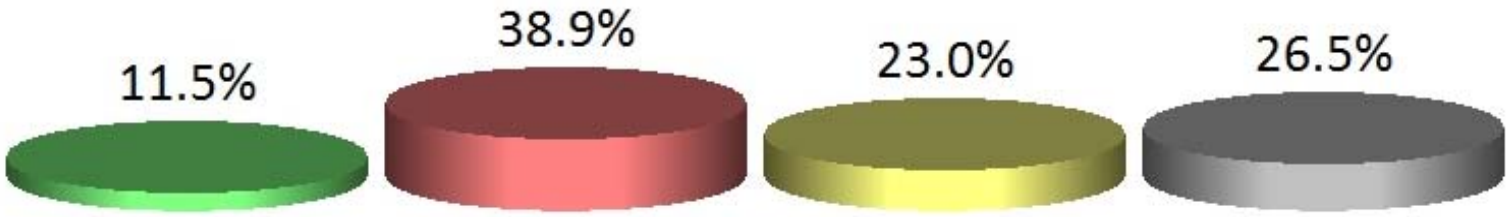
CT guided rib biopsy confirms λ restricted plasma cells

ARS Question

The patient reports fatigue over the past six months, legs which "tire easily" on stairs and symptoms consistent with grade 2 distal sensory neuropathy of the feet.

To make a *diagnosis* of POEMS syndrome, you should obtain:

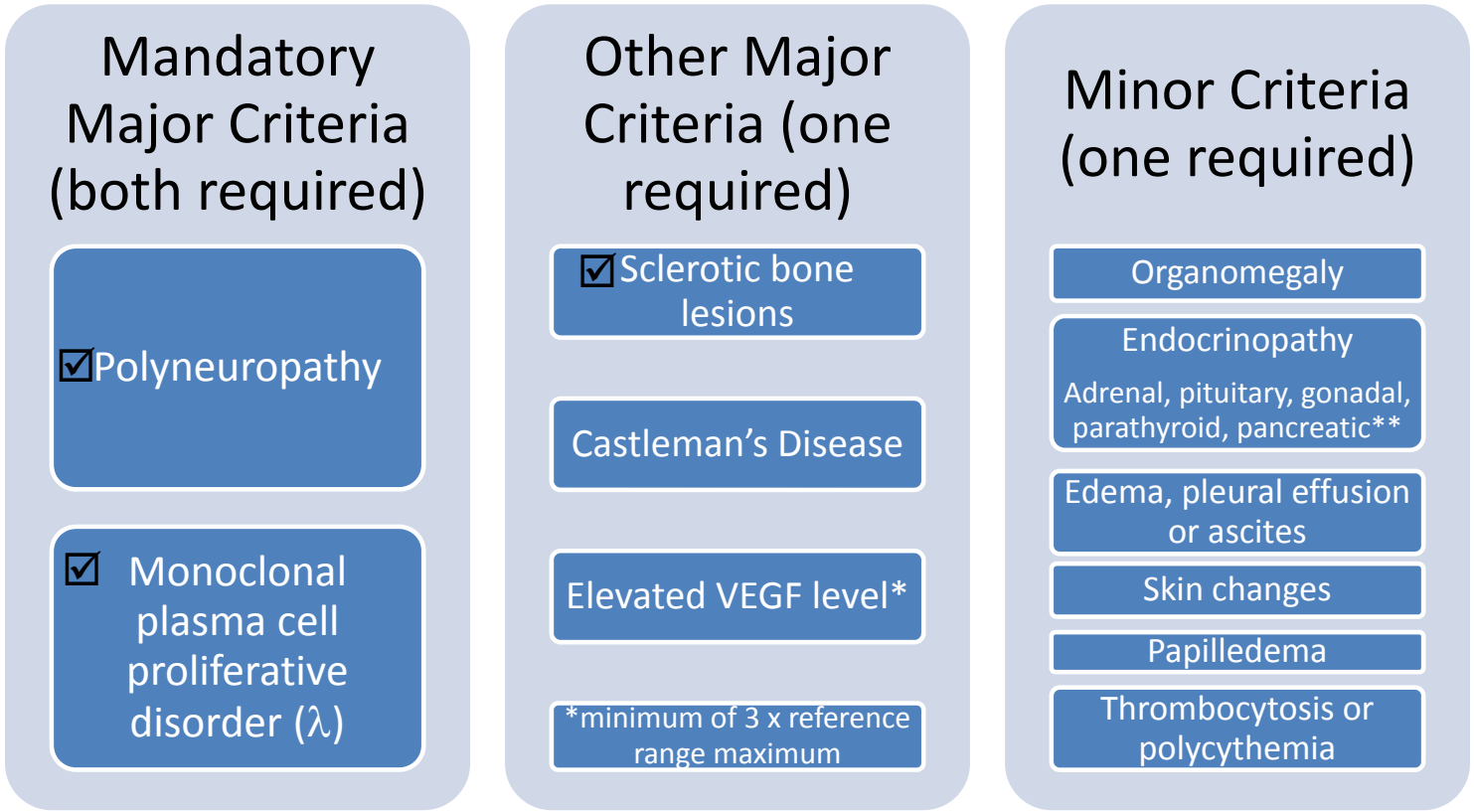
1. Gonadal function studies
2. Vascular endothelial growth factor (VEGF) level
3. Serum IL-6 level
4. Thyroid function studies



1	2	3	4
13	44	26	30

Total: 113

Diagnostic Criteria for POEMS Syndrome:



** Diabetes and hypothyroidism Do not fulfill this criteria

Dispenzieri , A. (2015) Am J Hematology 90:10 (951-962).

Most Common Findings on Presentation:

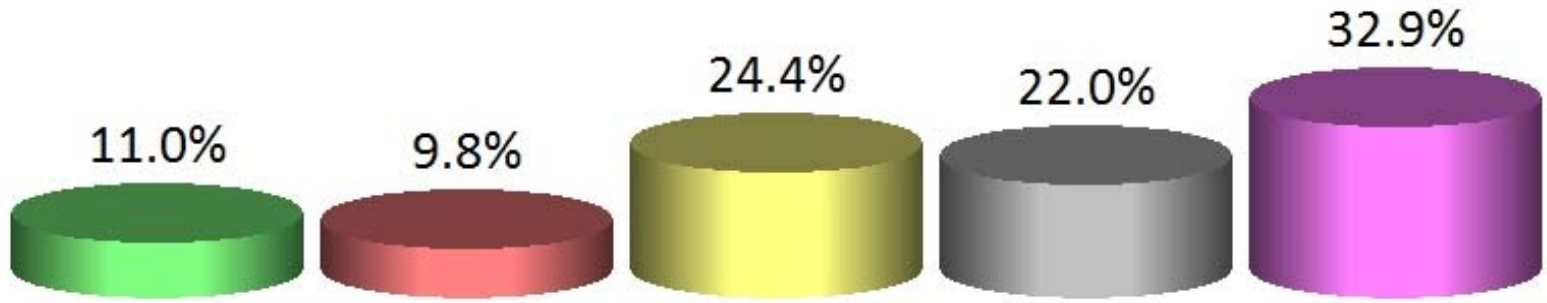
- **Polyneuropathy**- 100%
- **Monoclonal plasma cells**- 100%
- **Osteosclerotic bone lesions**- 97%
- Skin changes- 68%
- **Endocrinopathy** - 67%
- Organomegaly- 50%
- **Increased Protein in CSF**- 100% (>50 mg/dl)
- Thrombocytosis 54%
- Weight loss (>10 LBS)- 37%
- Fatigue- 31%

Dispenzieri , A., et al. (2003) Blood 101(7):2496
Dispenzieri , A. (2015) Am J Hematology 90:10 (951-962)

ARS Question

At this juncture all of the following tests would be reasonable for this patient EXCEPT:

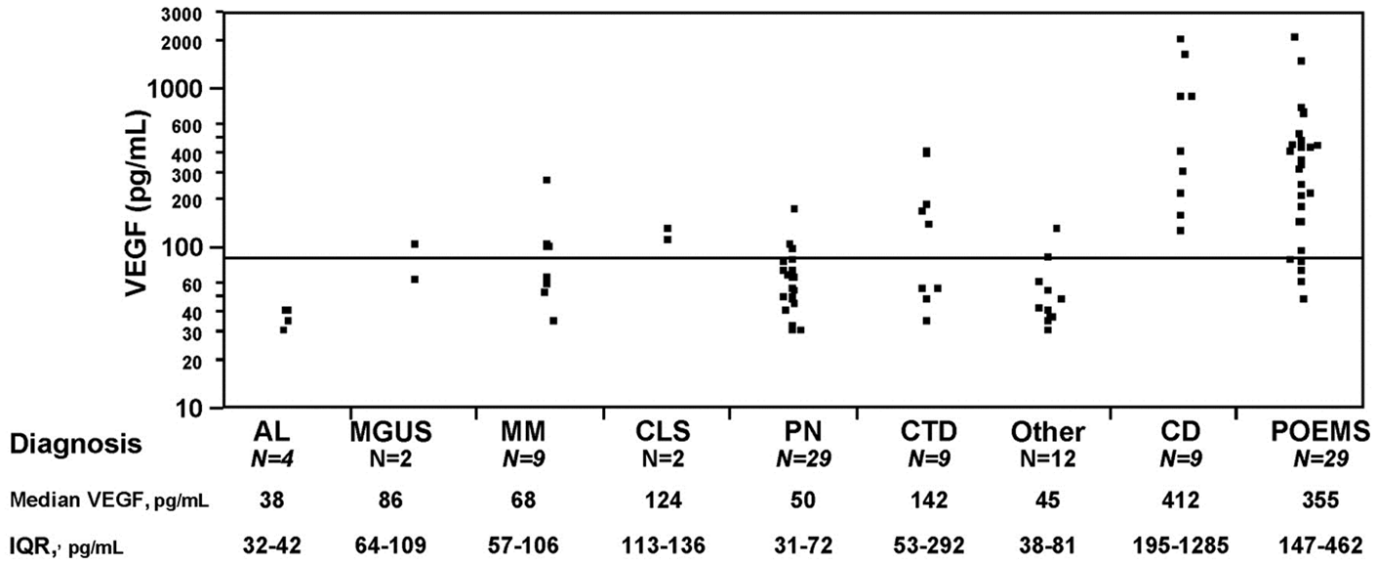
1. Serum VEGF level
2. Plasma VEGF level
3. CSF VEGF level
4. Serum IL-6 level
5. Urine VEGF level



1	2	3	4	5
9	8	20	18	27

Total: 82

VEGF :



Diagnosis	AL	MGUS	MM	CLS	PN	CTD	Other	CD	POEMS
	N=4	N=2	*N=9*	N=2	*N=29*	*N=9*	N=12	*N=9*	*N=29*
Median VEGF, pg/mL	38	86	68	124	50	142	45	412	355
IQR, pg/mL	32-42	64-109	57-106	113-136	31-72	53-292	38-81	195-1285	147-462

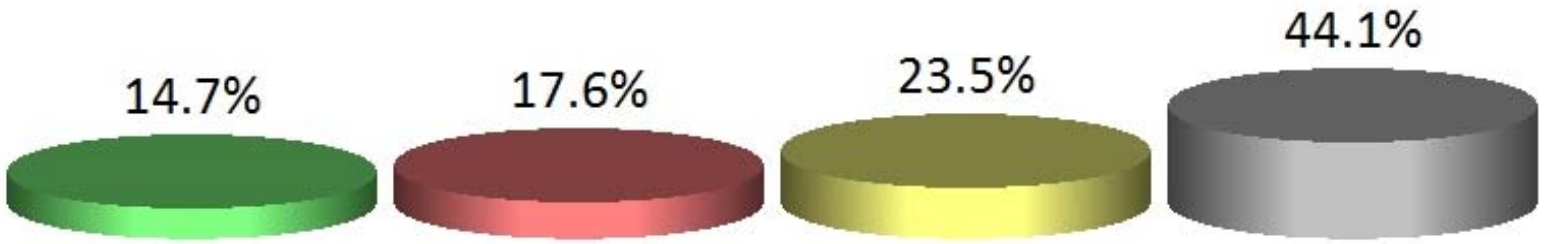
- VEGF of 200 pg/mL (specificity 95%, sensitivity 68%)
- VEGF of 1920 pg/mL (specificity 98%; sensitivity 73%)

Anita D'Souza et al. Blood 2011;118:4663-4665

ARS Question

Reasonable options for management of this patient include all EXCEPT:

1. External beam radiation to the rib and calvarial sites with close follow up
2. Initiation of lenalidomide/dexamethasone followed by radiation
3. Radiation followed by stem cell mobilization, high dose melphalan and transplant
4. Initiation of systemic anti-VEGF therapy with bevacizumab followed by radiation to involved sites



Total: 68

Case Wrap Up:

- The patient received 2 cycles of lenalidomide/dexamethasone
- Then XRT to the calvarial site
- Proceeded to stem cell mobilization, melphalan 200 mg/m^2 and ASCT
- XRT to the rib site was deferred until post ASCT due to a diminished DLCO on pulmonary function studies

Take Home Points:

- POEMS syndrome is rare
  - 0.3/100,000 (Japan)
- Distinguishing from MGUS and Smoldering myeloma is essential
- Isolated disease can be treated with external beam radiation therapy alone
- Survival appears superior to multiple myeloma (~14 years in one study)

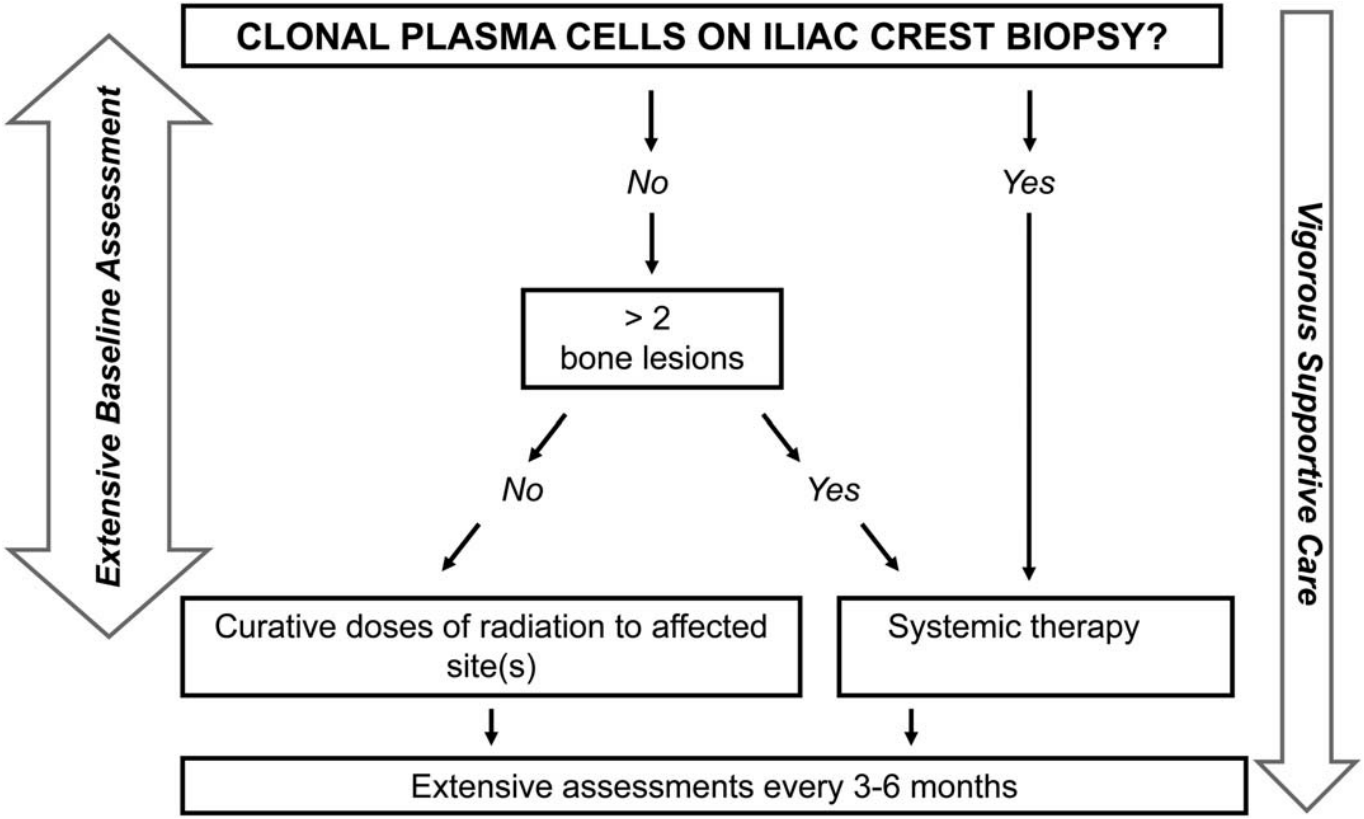
Take Home Points:

- A Phase 2 study French study with lenalidomide/dexamethasone (n=27) demonstrated raid neurological response in some patients (one progression, no deaths)
- Bortezomib also has known anti-VEGF effects. Isolated case reports have demonstrated efficacy (single agent and with cyclophosphamide +/- dex).
  - Caution is warranted in light of risk for proteasome inhibitor related neuropathy

Take Home Points:

- Cochrane review (2012) no randomized controlled trials to evaluate autologous stem cell transplant
  - Six small series (n=57)
  - Two year survival was 94-100%
- Case series have suggested 100% of patients achieve some improvement in neurological symptoms
- 59 patients treated with ASCT at Mayo Clinic
  - PFS 98, 94 and 75% at 1, 2 and 5 years

Proposed POEMS Algorithm:



Dispenzieri , A. (2015) Am J Hematology 90:10 (951-962).

CASE 3

Amrita Y. Krishnan, MD

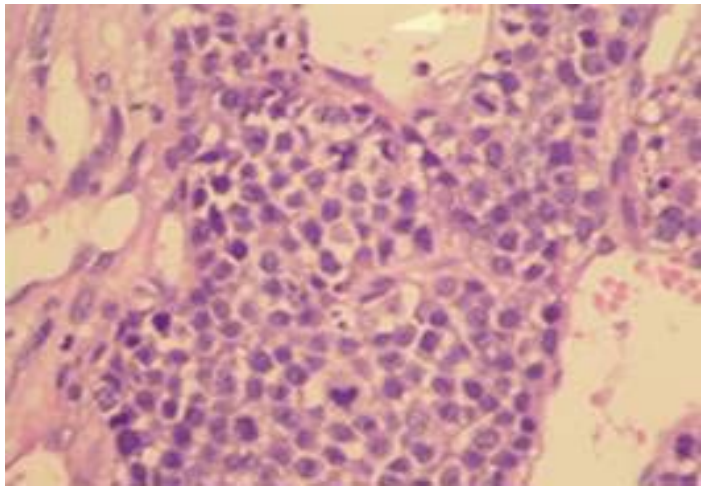
City of Hope Comprehensive Cancer Center

Case

- 65 year old no PMH presented to his MD with two month history of “ pulled muscle in his back”
- MRI Scan showed T 11 expansile lesion
- CT guided biopsy was performed

Biopsy T 11 mass

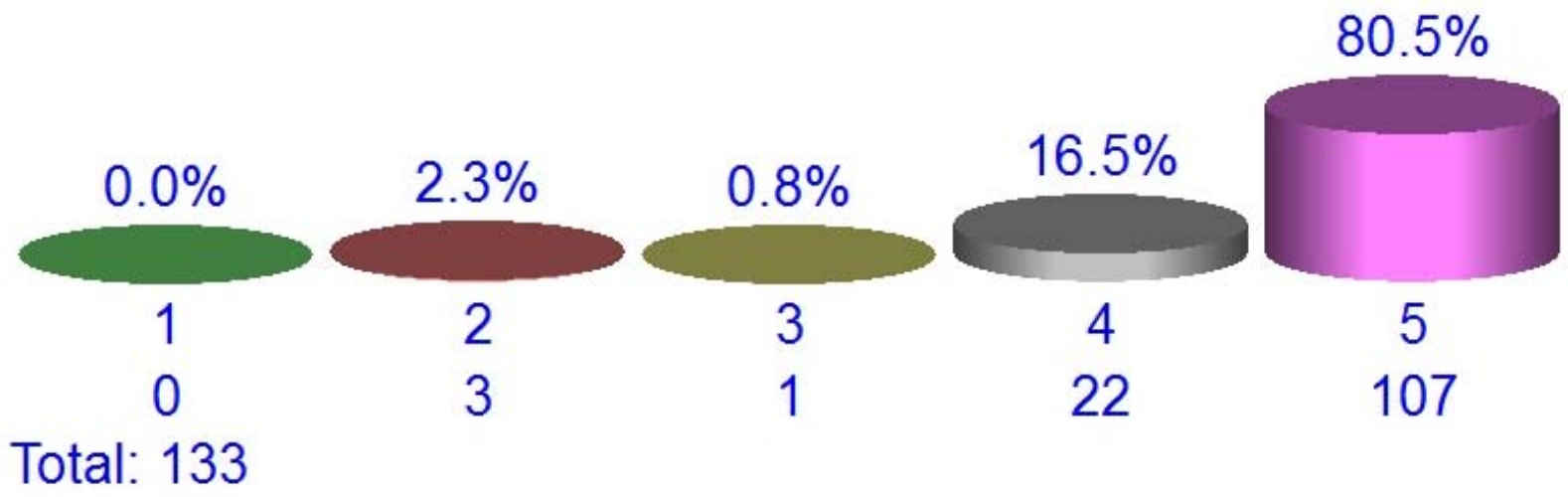
- **Solid mass consisting of homogenous collection of clonal plasma cells**

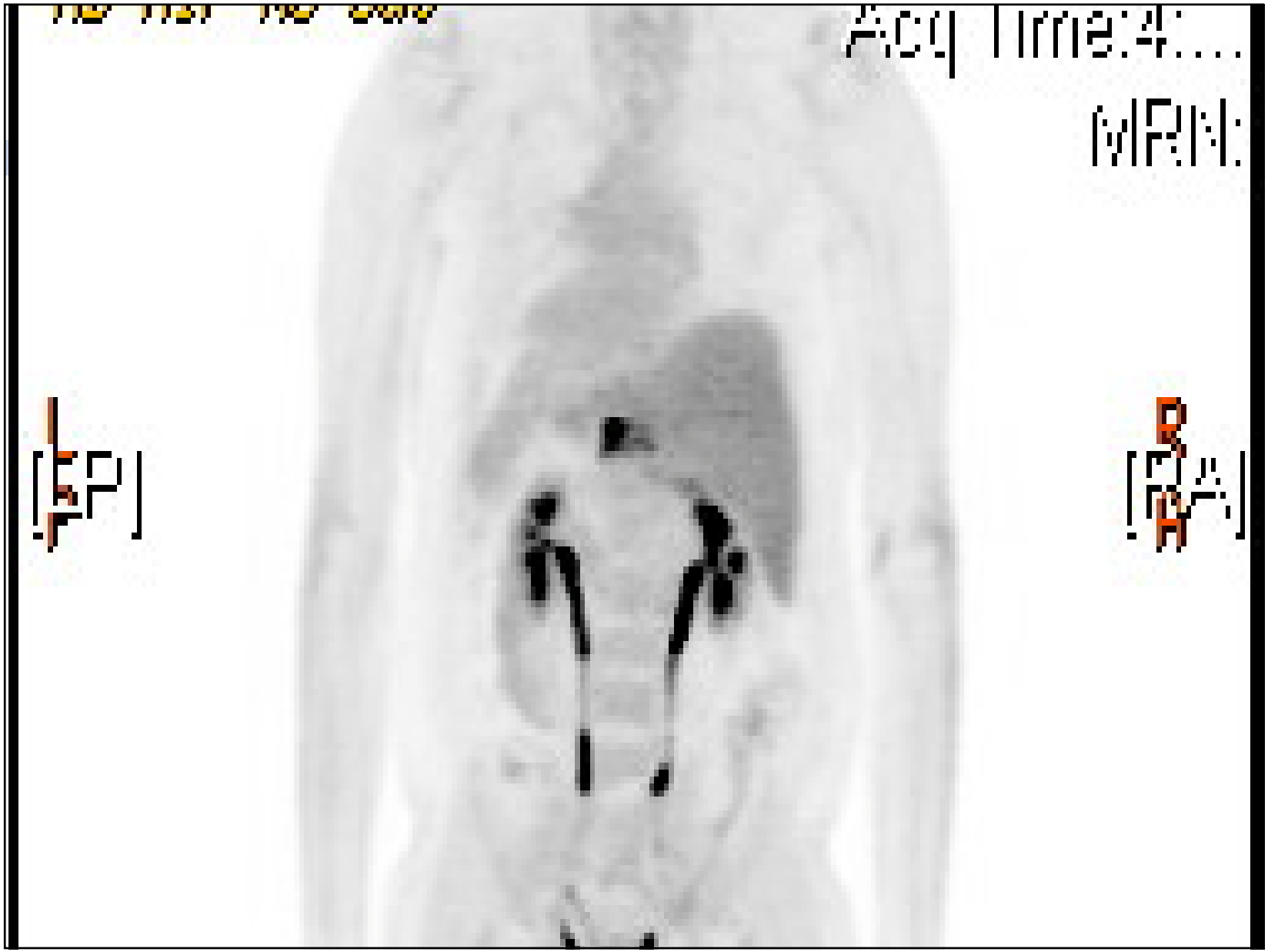


ARS Question

What other tests would you order?

1. Bone Marrow Biopsy/cytogenetics
2. PET CT
3. SPEP/UPEP/ Light Chains
4. 1 and 3
5. **All of the above**





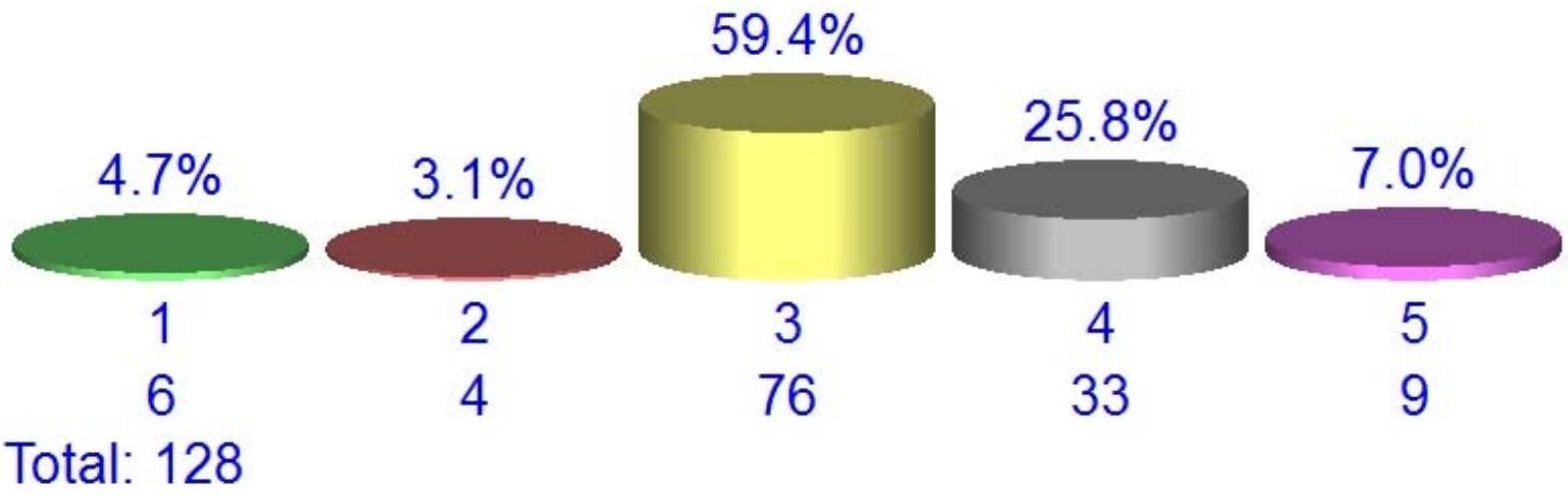
Laboratory Data

- Hb16.5 CA9.4 Cr normal
- SPEP negative
- Kappa 1.51mg/dl Lambda 2.89 mg/dl ratio nl
- Bone Marrow BX no evidence of plasma cell dyscrasia

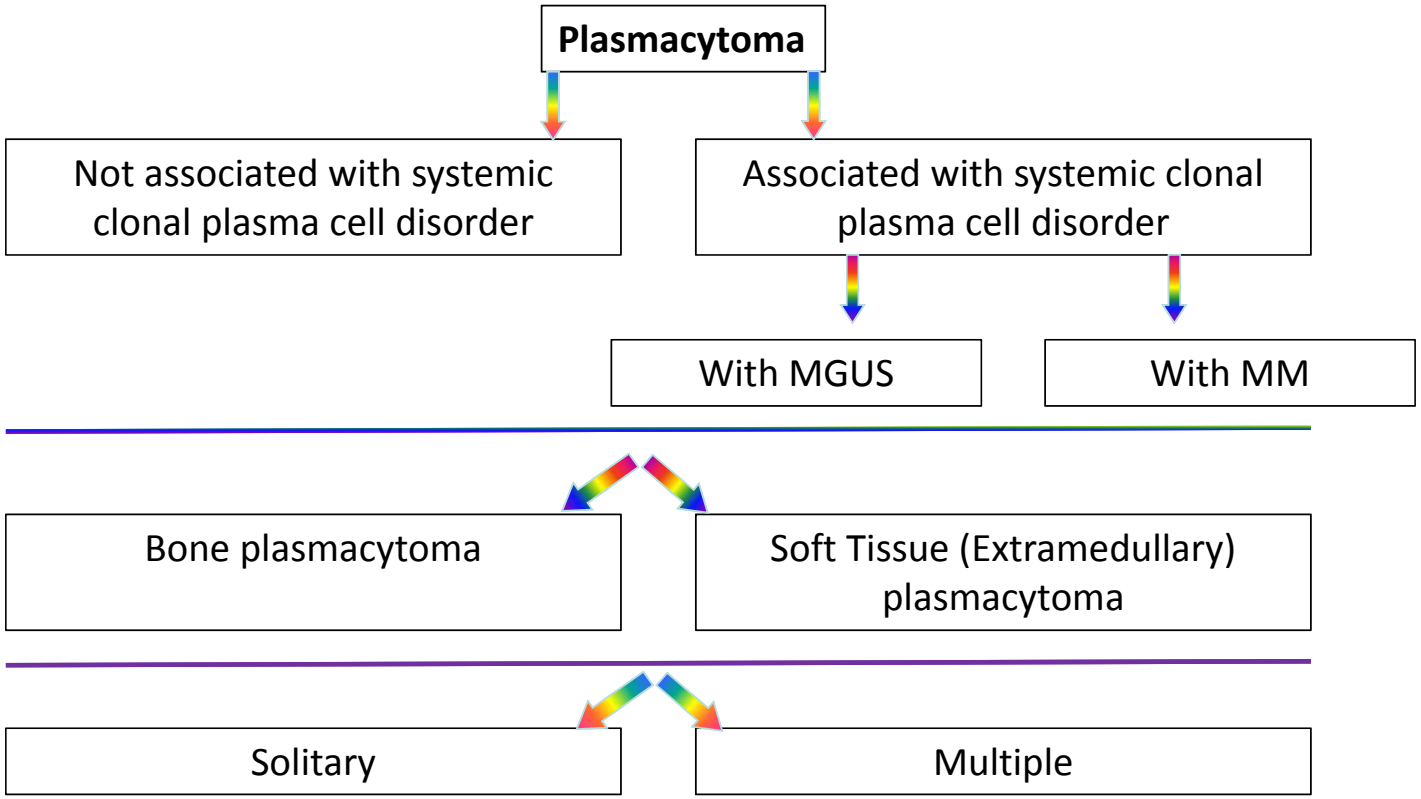
ARS Question

How would you treat?

1. Surgery
2. Chemotherapy
3. **Radiation**
4. Radiation plus Chemotherapy
5. Surgery plus Chemotherapy



Classification



Solitary bone plasmacytoma (SBP)

- **Single bone lesion**
- **Bone marrow plasmacytosis < 10%**
  - no clonal PCs?
- **None or small M Protein in serum or urine (24-72%)**
- **No other lesions on PET Scan (Other than the single lesion)**
- **No CRAB features**

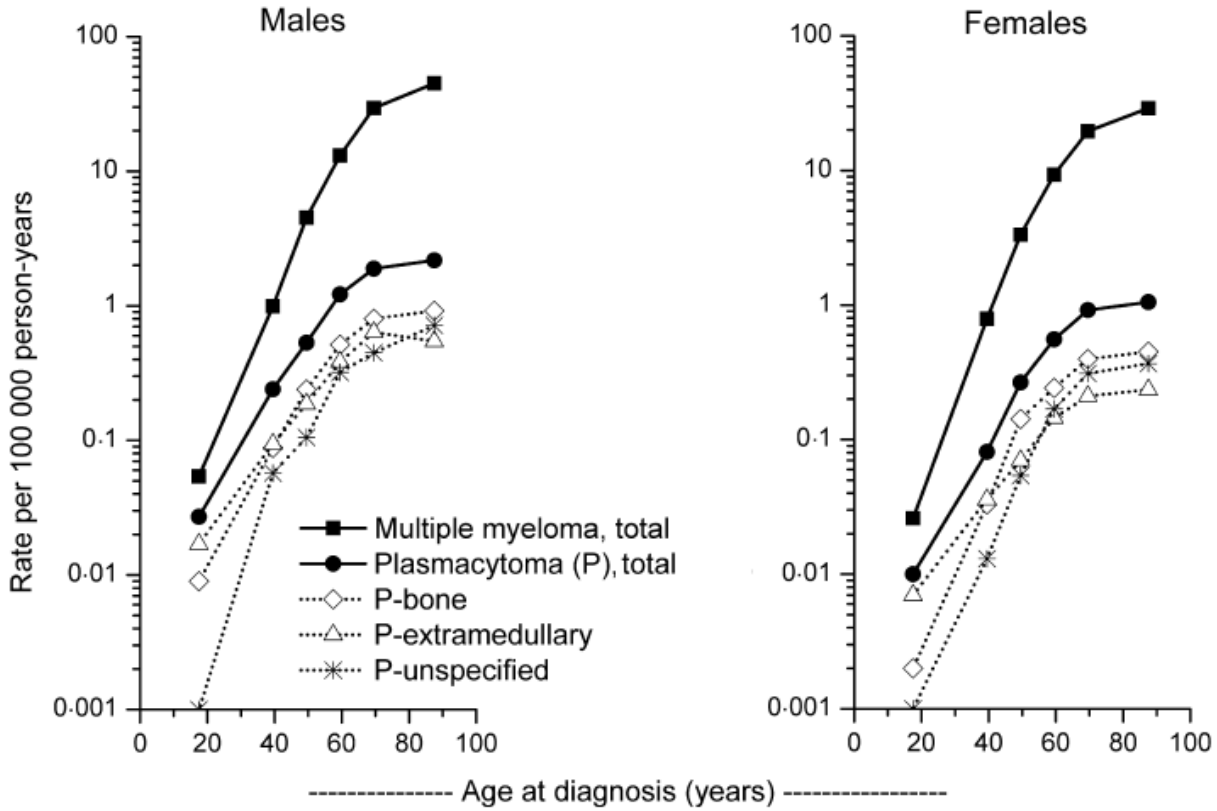
Kyle et al, BJH 2003; 121: 749-757

Extramedullary plasmacytoma (EMP)

- **Single soft tissue lesion with clonal PCs**
- **Bone marrow plasmacytosis < 10%**
  - Some suggest no clonal PCs
- **None or small M Protein in serum or urine (~ 25%)**
- **Normal PET Scan (Other than the single lesion)**
- **No CRAB features**

Kyle et al, BJH 2003; 121: 749-757

SEER study (1992-2004)



Dores, G. M., et al. (2009). Br J Haematol 144(1): 86-94.

Presentation

- Median age 10 years lower than MM (~55 yrs)
- Male predominance (2:1)
- Incidence Increases with age
- African Americans higher incidence
- Axial skeleton affected more commonly than long bones; Spine affected nearly 50%
- EMP most commonly head and neck region, then GI

Suggested Initial Evaluation

- CBC, metabolic panel
- SPEP/ UPEP with IF
- Serum free light chains
- Bone marrow examination with flowcytometry
- (Skeletal survey)/ Whole body low dose CT
- Whole body MRI/ PET scan

Treatment approaches

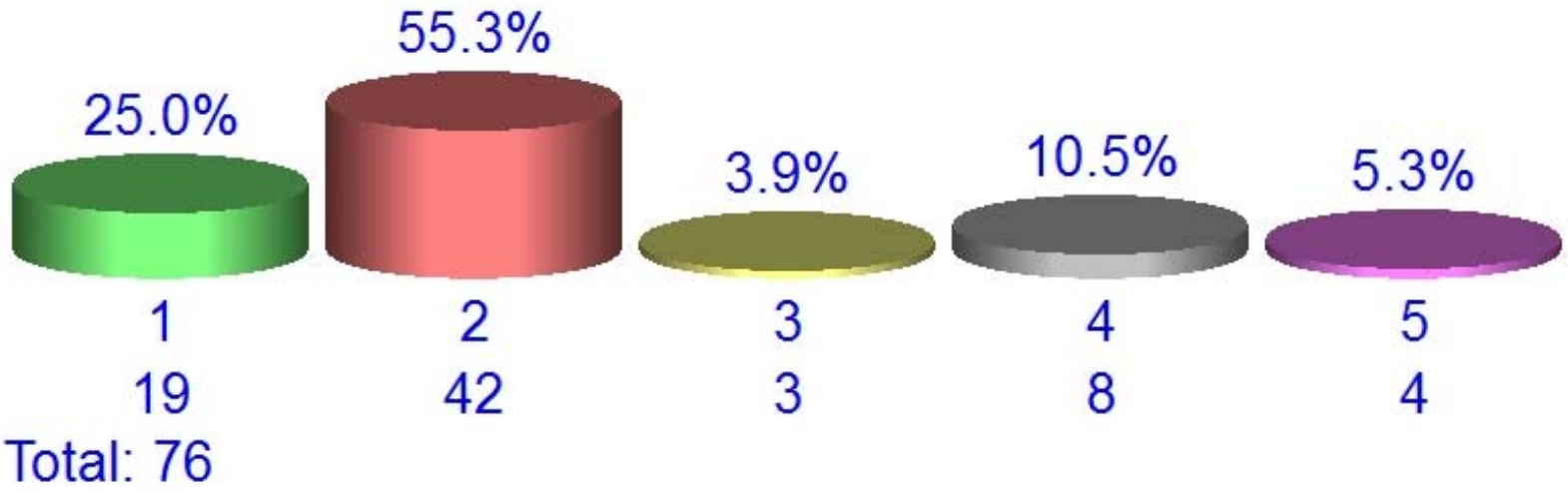
- **Modalities**
  - Radiation therapy
  - Surgery with or without radiation
  - Chemotherapy +/- radiation

- **Outcome measures**
  - Incidence of Local recurrence
  - Progression to MM
  - Overall survival

ARS Question

What factors are important in radiation for SBP or EMP ?

1. Dose should be above 30 GY
2. **Limited field to spare vertebrae or adjacent bone**
3. Limited dose to allow for adjuvant chemo
4. Dose above 45 GY
5. None of the above



Solitary Bone Plasmacytoma

- **Radiation is treatment of choice Recommended >30Gy Local control poorer for lesions > 5 cm**
- **Radiation with a margin of 1-2 cm,**
  - one vertebral body above, one below for spinal lesions
- **Surgery alone insufficient**
  - Limited to fixation and neurological compromise

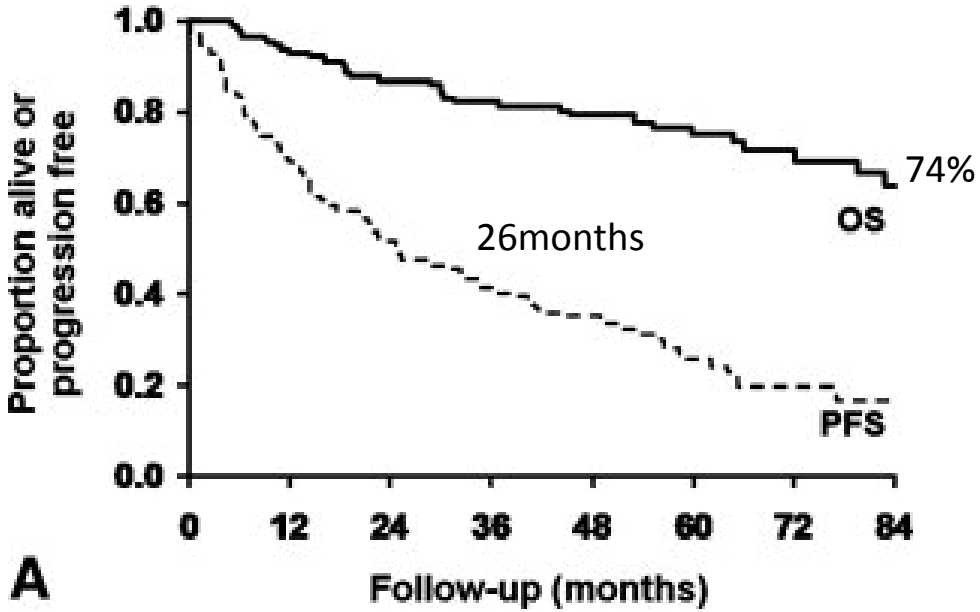
EMP: soft tissue or non-osseus

- **Radiation >30Gy to involved field and/or**
- **surgery (controversial)**
  - Some studies show excellent local control for margin free resections
  - One study suggested better outcome for surgery + RT
- **Role of regional nodal radiation controversial**
  - May have a role in lesions involving Waldeyer's ring

Chemotherapy

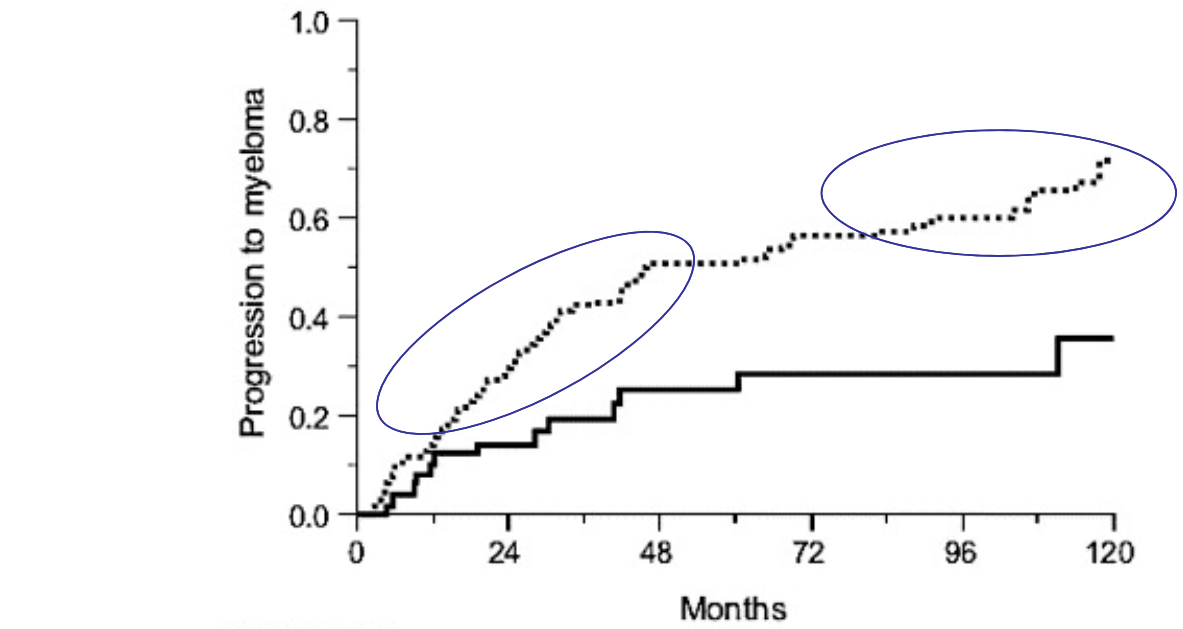
- **No proven role for adjuvant chemotherapy**
  - One study looked at MP, questionable benefit
- **HDM and ASCT has been studied**
  - Role unclear
  - ? For multiple EMP

Long term outcomes



Warsame et al; American Journal of Hematology, Volume 87, Issue 7, 647-651

Bone vs. EMP



Ozsahin et al, International Journal of Radiation Oncology*Biology*Physics Volume 64, Issue 1 2006 210 - 217

Prognostic factors: Progression to MM

- Bone vs. EMP
- Age
- Axial vs. appendicular skeletal involvement
- Plasmacytosis
- Serum free light chain level
- Immunoglobulin suppression
- Tumor angiogenesis; anaplastic/ high grade
- Lesion size
- RT dose
- Residual M-protein at one year post RT

Conclusion: Management of SBP/EMP

- Complete work up for MM including PET scan should be performed in all patients
- Solitary lesions in the absence of myeloma should be treated with RT; >30Gy
- Surgery for neurological emergency, fracture fixations and possibly large EMP (> 5 cm lesions)
- Monitor for progression to MM

NCCN Member Institutions