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P.O.E.M.S. Syndrome

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Disclosures

Company	Disclosure
Celgene	Research dollars
Millenium	Advisory board (Unpaid)
Onyx	Advisory board (Unpaid)
Binding site	Travel award dollars

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POEMS Syndrome

- **Diagnosis / Pathogenesis**
- **Treatment / Outcomes**
- **Future Directions**

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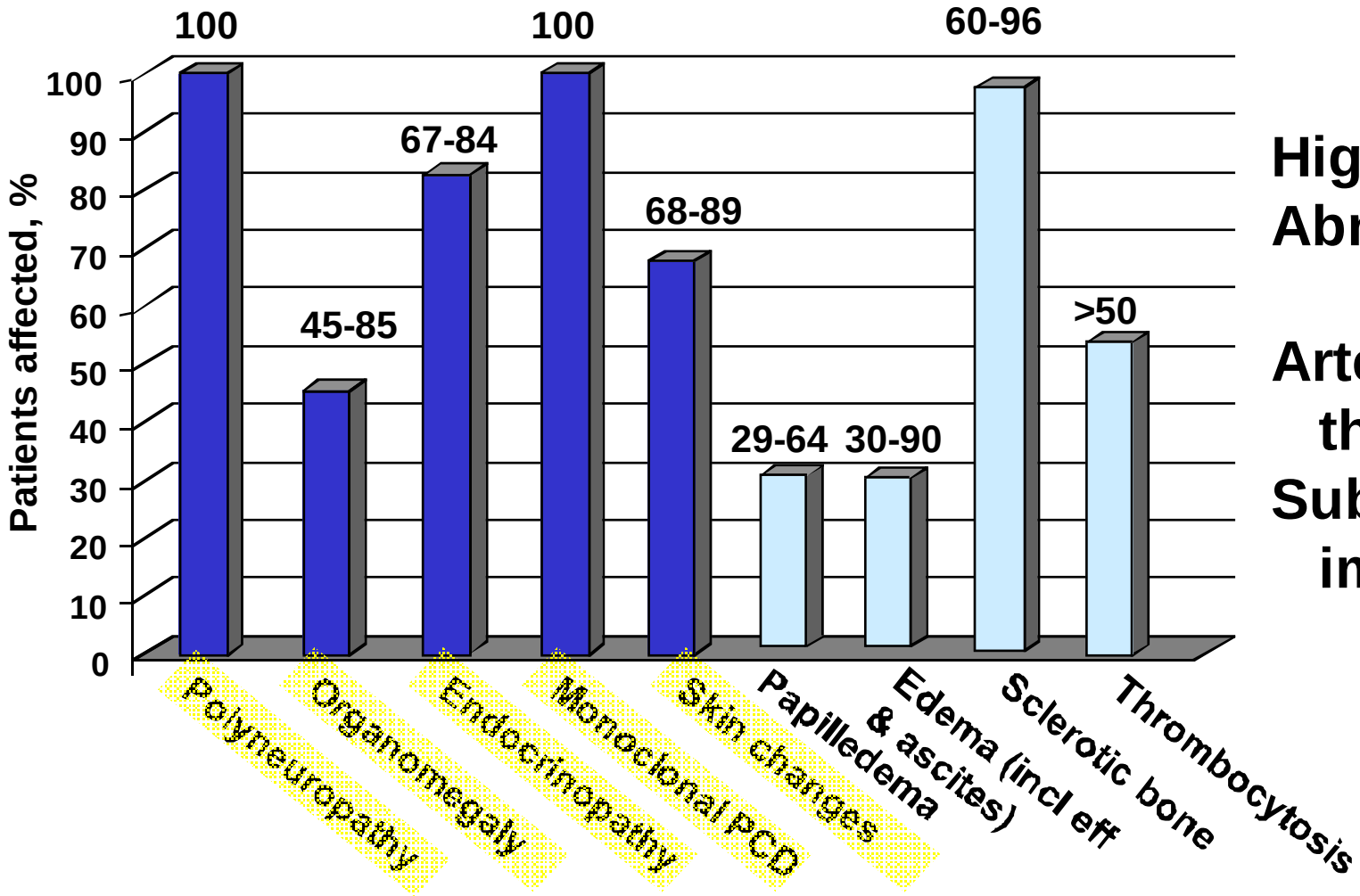
POEMS (PEST) And



High VEGF
Abn. PFTs

Arterial thrombosis
Subtle renal impairment

Dispenzieri A (2003) *Blood*. 101:2496. Nakanishi T (1984) *Neurology*. 34:712. Takatsuki K (1983) Jpn J Clin Oncol. 13:543. Soubrier MJ (1994) *Am J Med* 1994; 97, 543. Li (2011) Annals of hematology. Ghandi (2007) Mayo Clin Proc 2007;82:836-842

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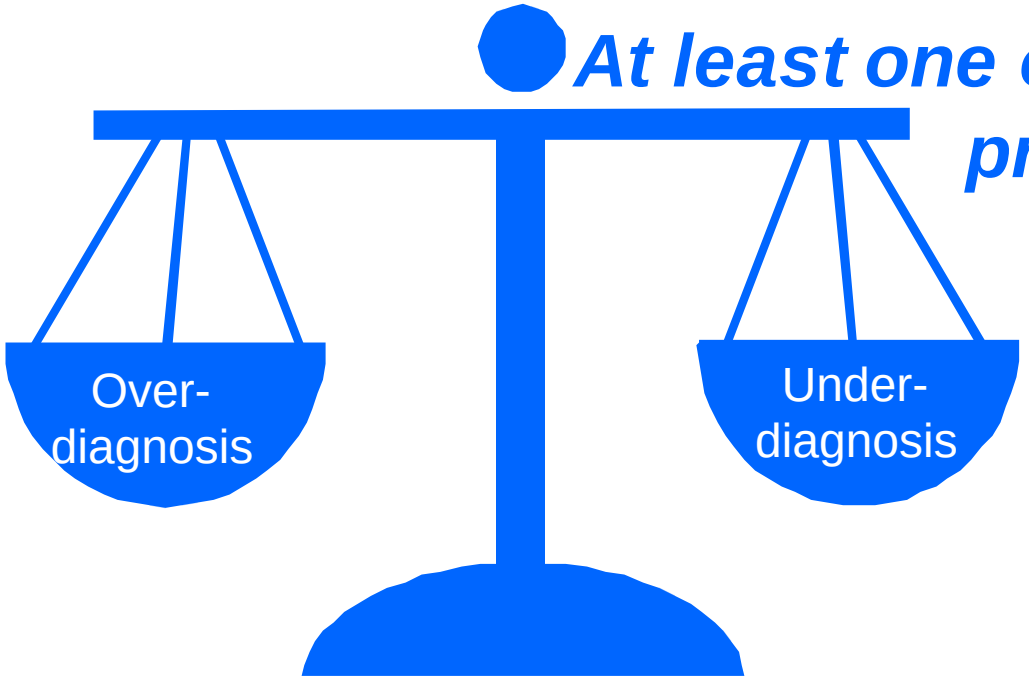
Both 1 and 2 present

MAJOR CRITERIA	***1. Polyneuropathy***
	2. Monoclonal plasma cell dyscrasia (almost always λ)
	3. Sc
	4. Ca
	5. Va
MINOR CRITERIA	6. Or
	7. Ex
	8. En
	9. Sk hema
	10. P apilledema
	11. Thrombocytosis / polycythemia‡

At least one of 3-5 present



At least 1 of 6-11 present

*** Polyneuropathy and monoclonal plasma cell disorder present in all patients; to make diagnosis *at least* one other major criterion and 1 minor criterion is required to make diagnosis**

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Clues to Pathogenesis

- Bone sclerosis
- Unique blood cytokine profile
- Nearly all patients λ light chain restricted
- Overlap with Castleman Disease (aka angiofollicular lymph node hyperplasia)
- How and when patients die

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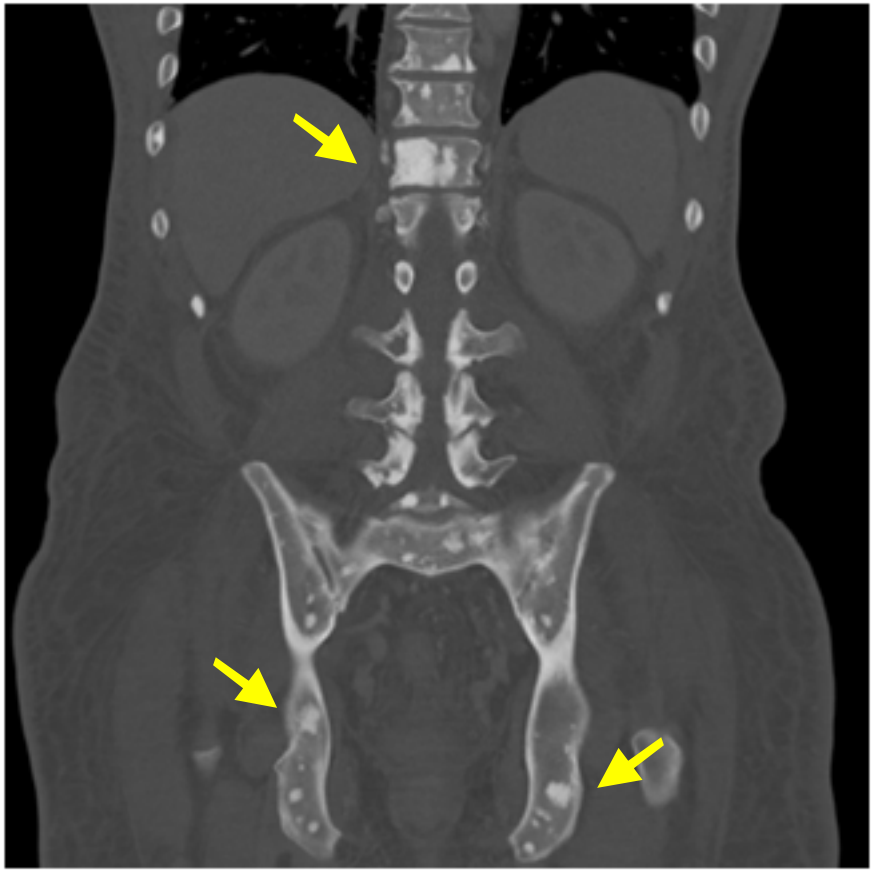
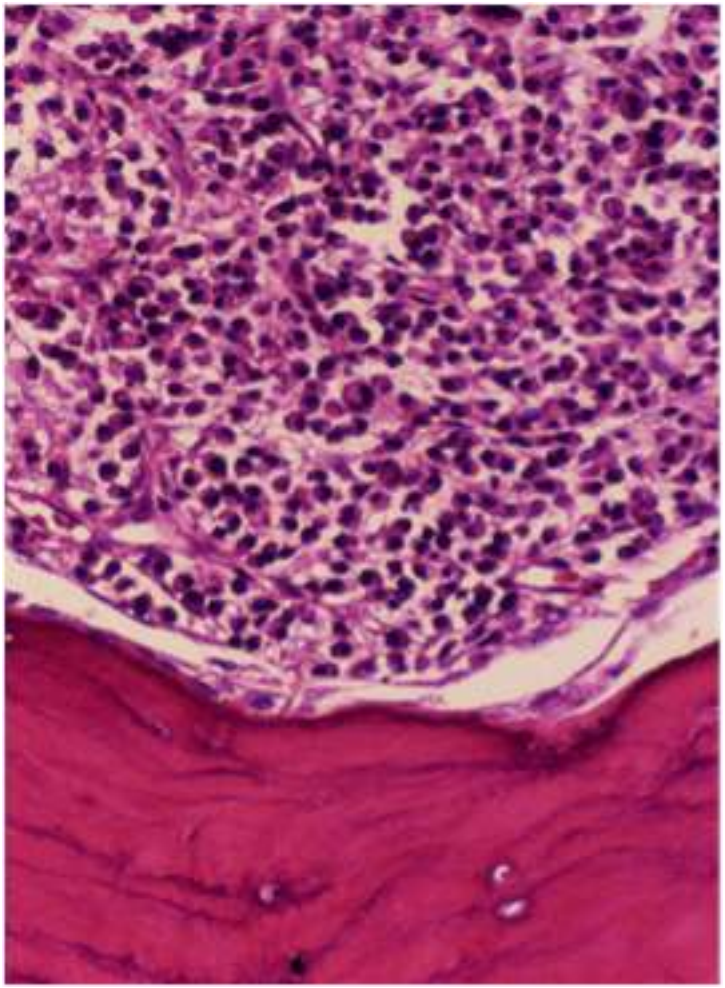


Sclerotic bone lesions



BMPC concentrated near trabeculae or around lymphoid nodules

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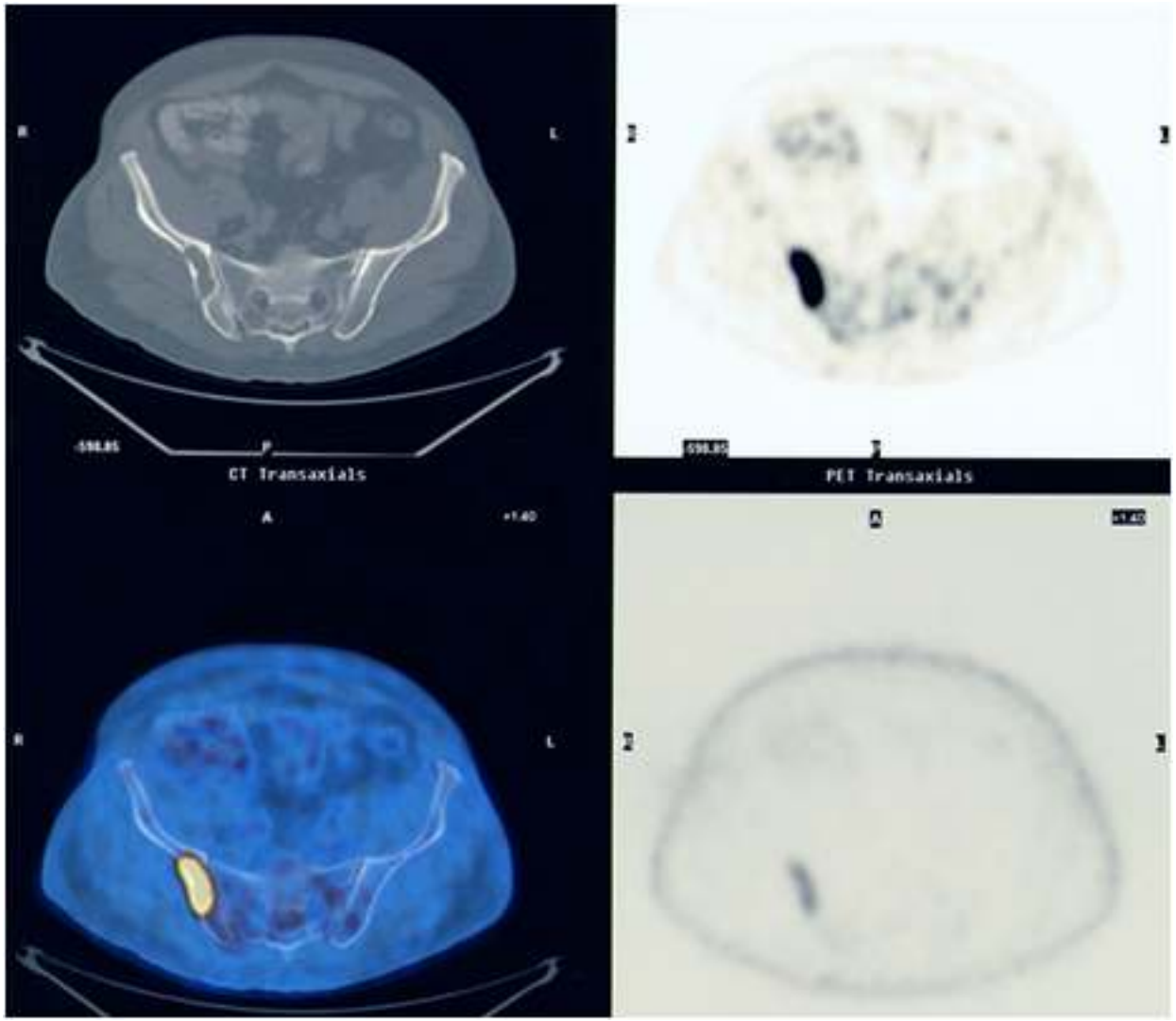
PET Avid Sclerotic Bone Lesion



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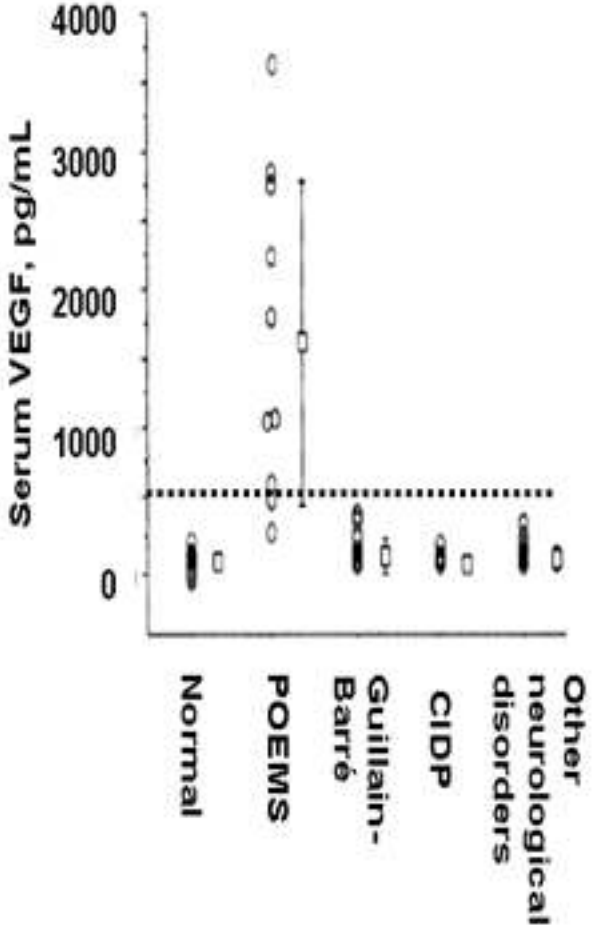
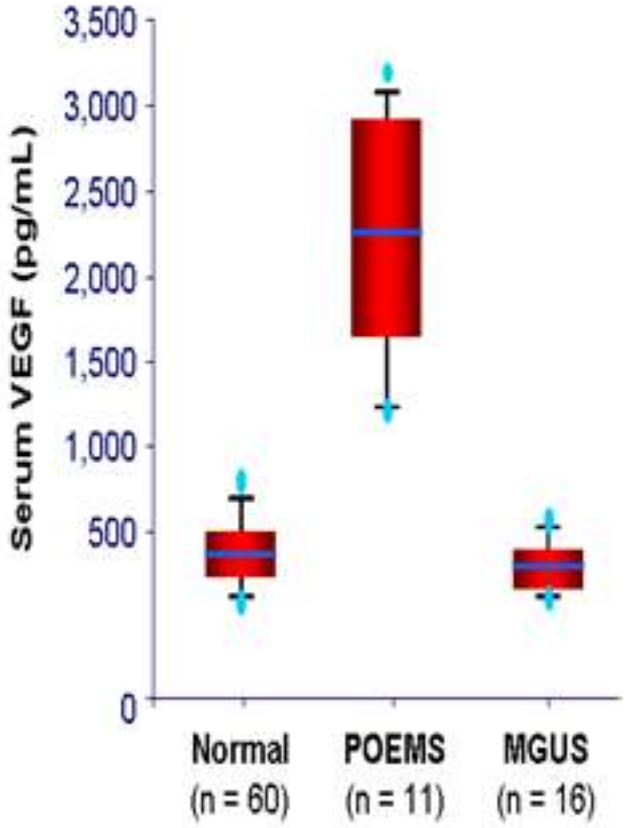
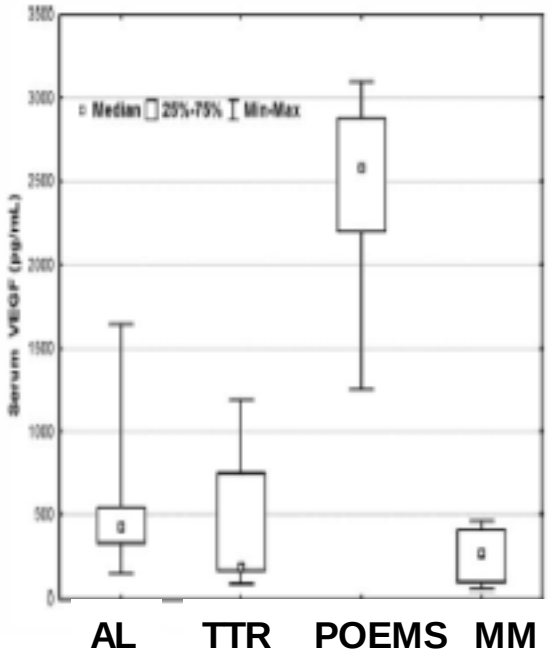
Serum VEGF Differentiating POEMS from other Disorders







Watanabe et al *Muscle Nerve* 21:1390-7, 1998

Scarlato M, et al. Brain. 2005;128:1911-20

Briani et al Muscle Nerve 43: 164-7, 2011

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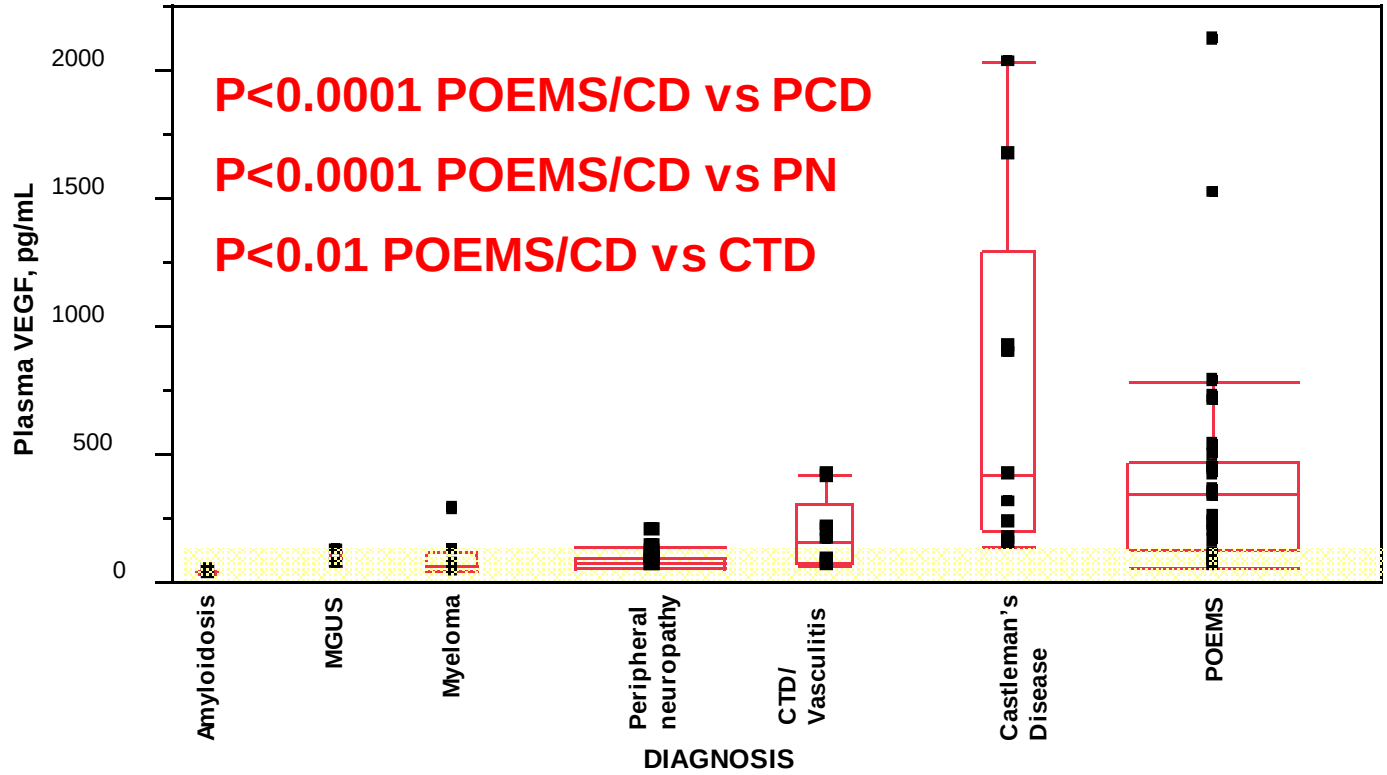
Plasma VEGF in POEMS Syndrome



	AL *N=4*	MM *N=9*	PN *N=29*	CTD *N=9*	CD *N=9*	POEMS *N=29*
Median VEGF[a]	38	68	50	142	412	342
Range	31-42	35-271	31-180	35-403	132-2030	48-2112

D'Souza et al IMW Paris 2011

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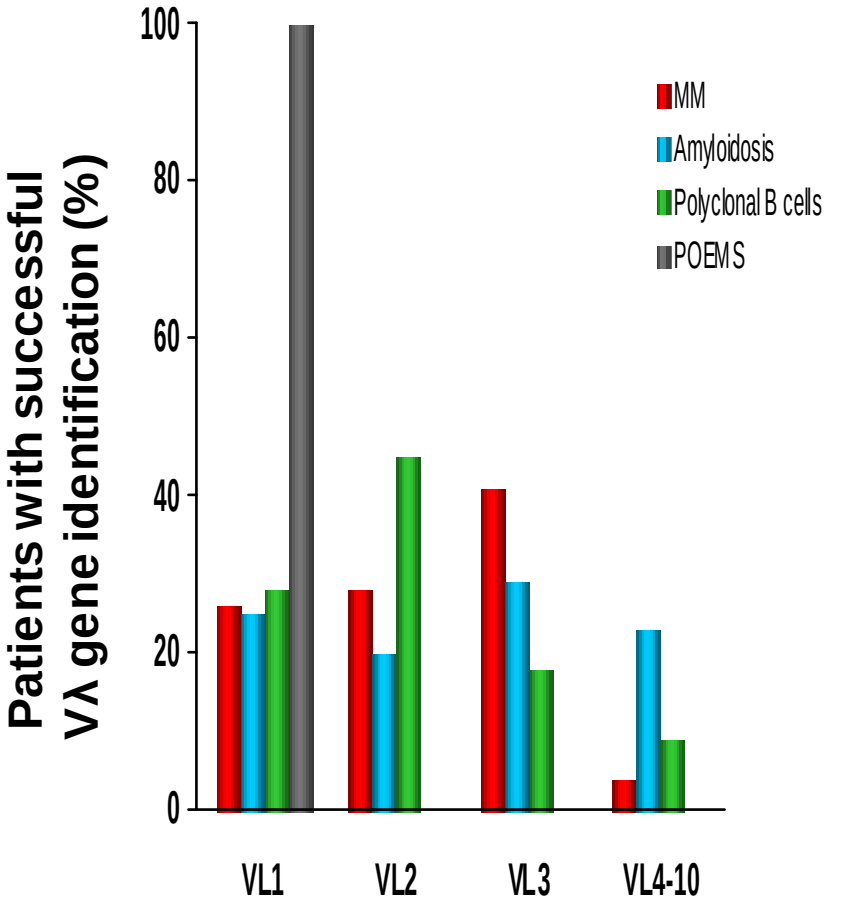
Lambda variable gene usage



B-cell *(No. seq. evaluated)*	IGLV 1-40 or 1-44, %
POEMS¥ (29)	100
ALλ Amyloid (354)	16
Multiple myeloma (92)	12
CLL (182)	13
Autoantibody (287)	14
Burkitt's	2

Abe D, et al. Blood. 2008;112:836-9. Aravamudan B, et al. Blood. 2008;112:[abstract 2744].
Soubrier M, et al. 2004. Haematologica. 89(1):e4-e5.

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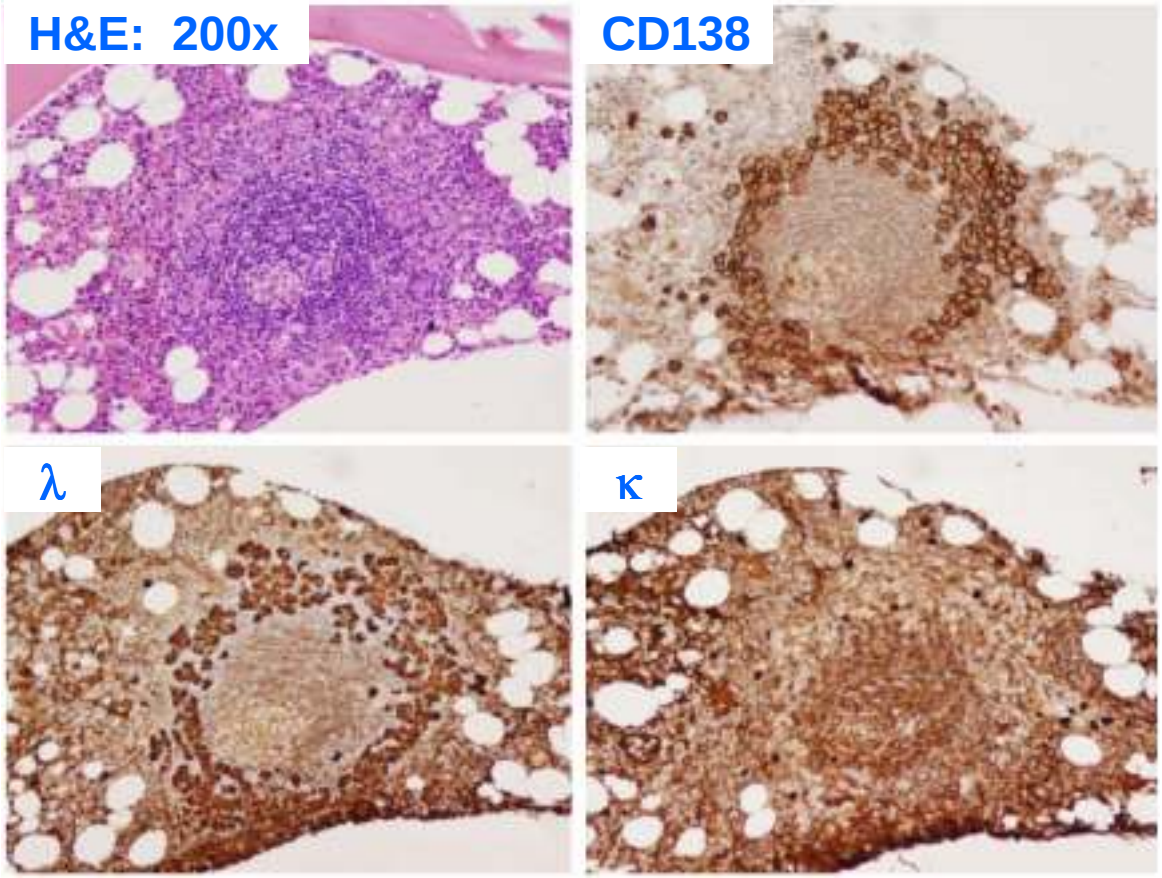
Lymphoid aggregates rimmed by PC in BM biopsy in POEMS



- 33 of 67 cases had lymphoid aggregates
- 32 of these had clonal PC

Dao et al Blood prepub.

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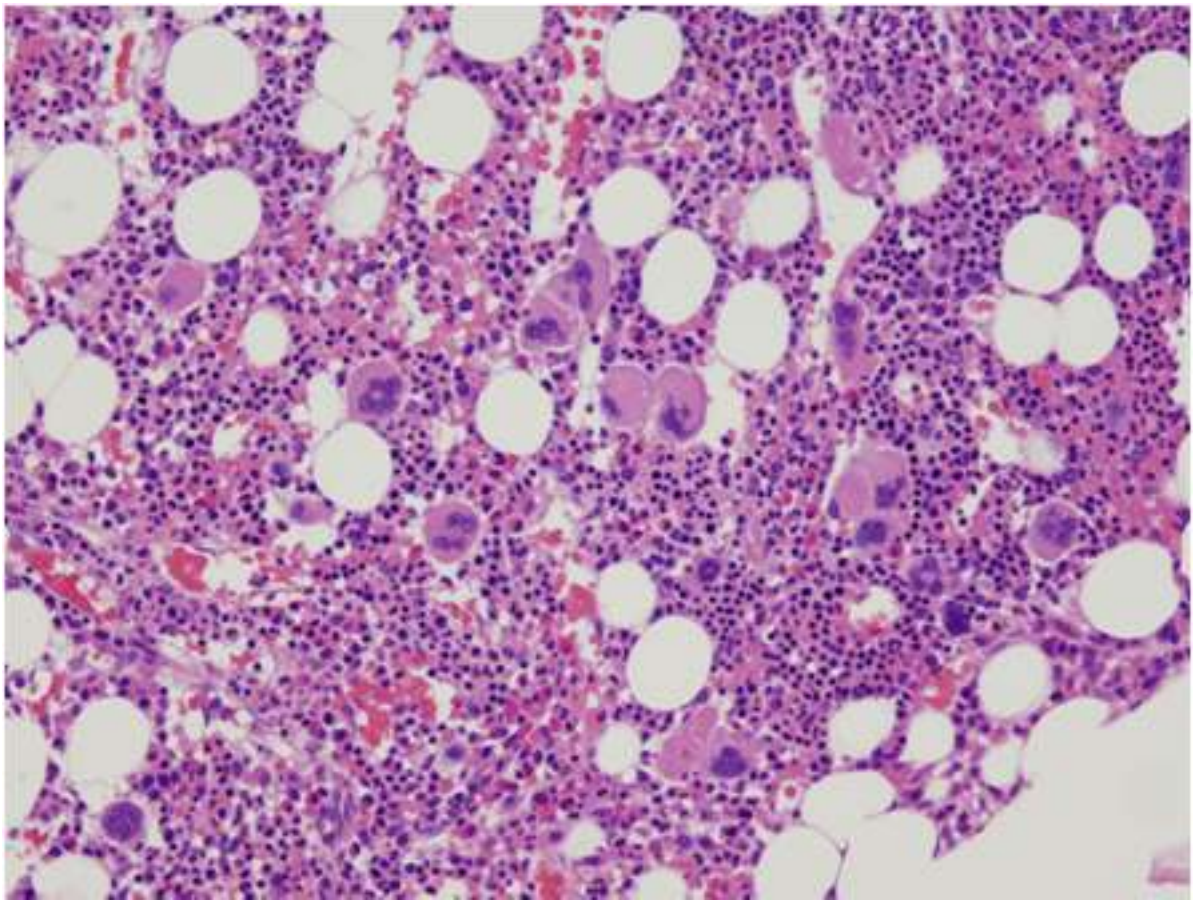
Megakaryocyte clusters and atypia in POEMS Syndrome



- 36 of 67 cases had megakaryocyte hyperplasia

- In toto, only 8/67 with neither mega, lymph rimming, or clonal PC

Dao et al Blood prepub.

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POEMS Syndrome

- Diagnosis / Pathogenesis
- **Treatment / Outcomes**
- Future Directions

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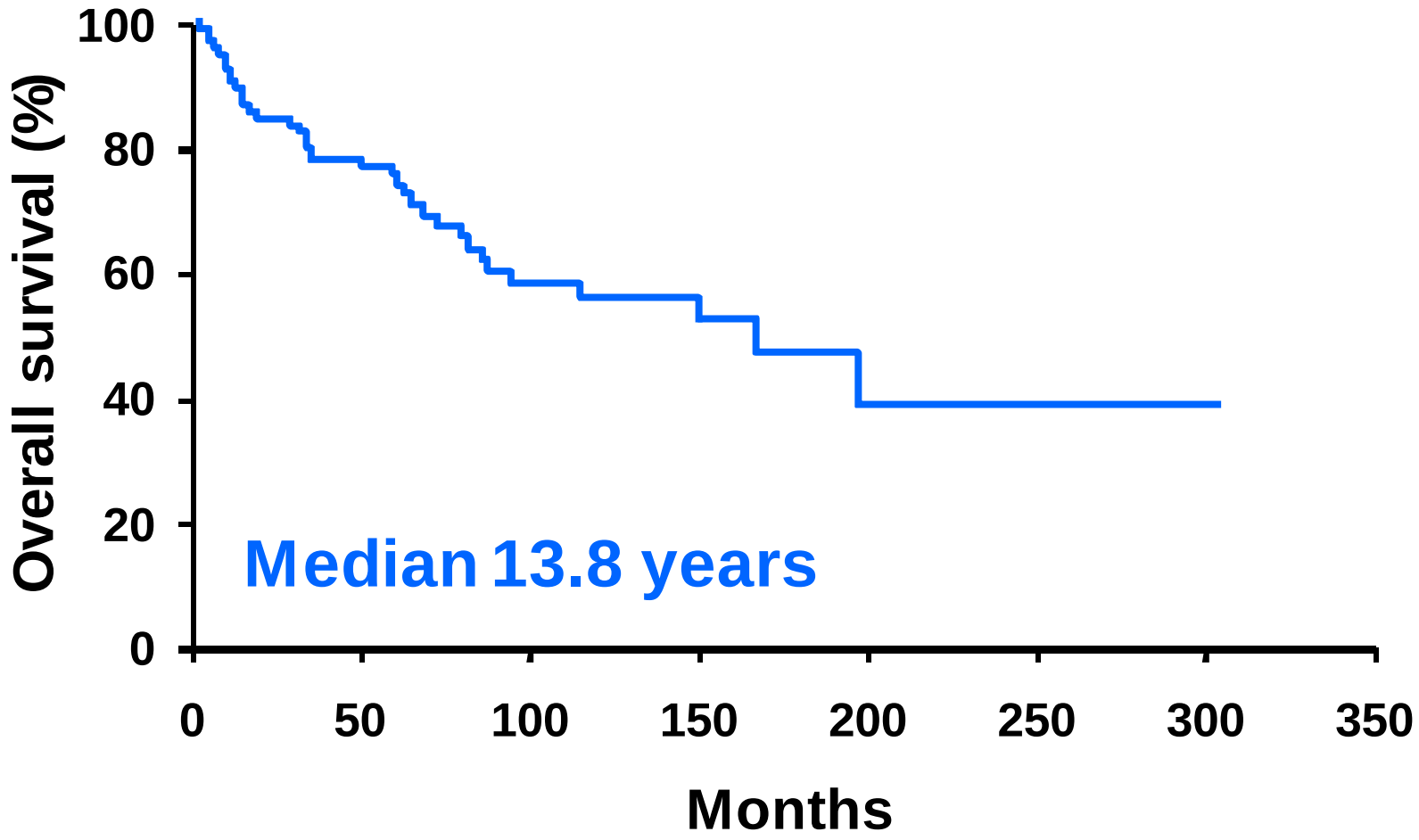
POEMS Syndrome

Overall Survival (99 Mayo Patients)



Dispenzieri A, et al. Blood 2003;101(7):2496-506.

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Prognostic Factors

NEGATIVE

- Clubbing
- Extravascular volume overload
- Respiratory symptoms
- Co-existing CD
- Thrombocytosis (CVA)

FAVORABLE

- Disease amenable to radiation therapy

NEUTRAL

- Number of features

Dispenzieri et al. Blood 2003;101:2496-2506.
Allam et al. Chest 2008;133:969-974

Soubrier et al. AJM 1994;97:543-553.
Li et al. Annals of hematology 2011.

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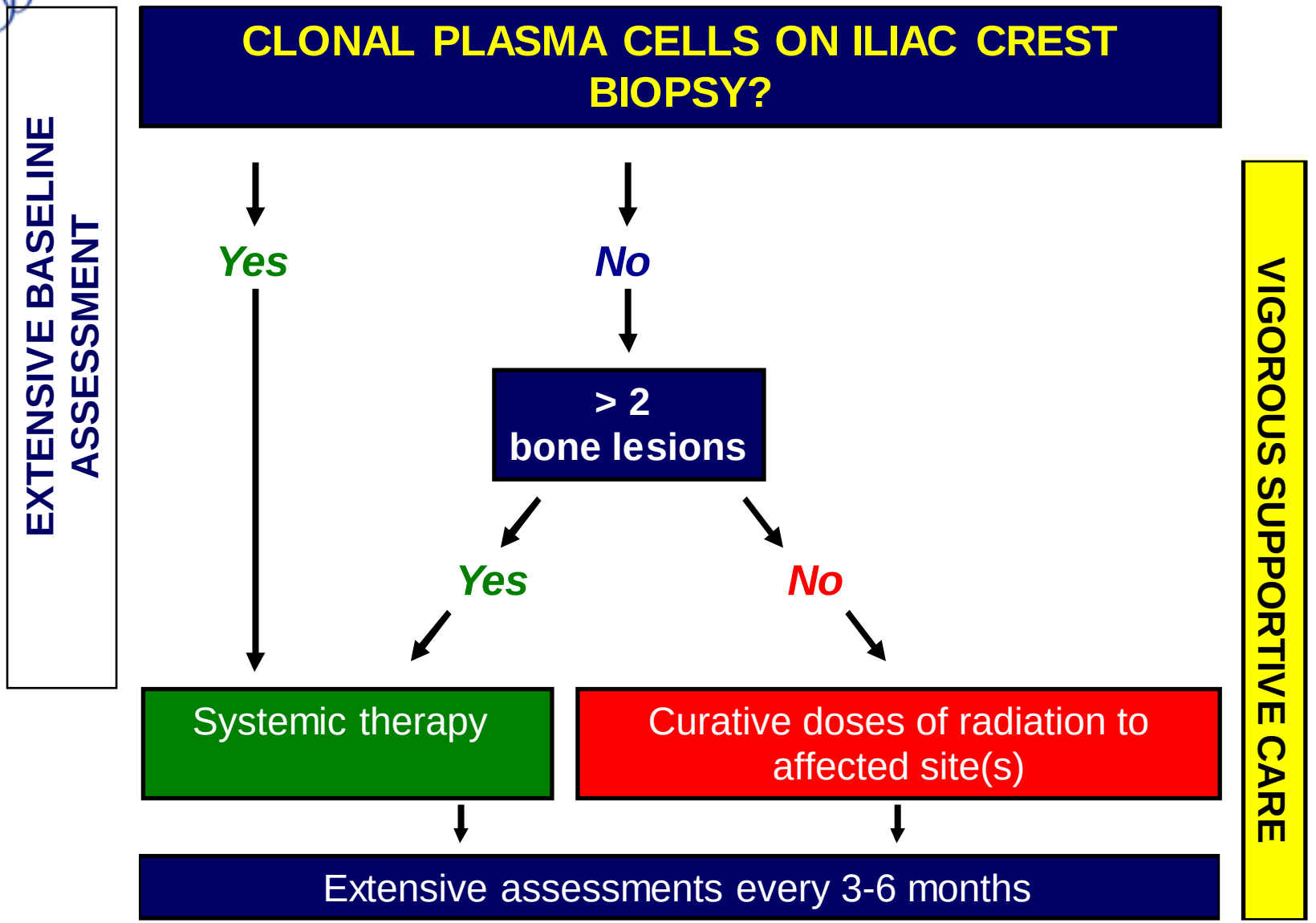
EXTENSIVE BASELINE ASSESSMENT
CLONAL PLASMA CELLS ON ILIAC CREST BIOPSY?
Yes
No
> 2 bone lesions
Yes
No
Systemic therapy
Curative doses of radiation to affected site(s)
Extensive assessments every 3-6 months
VIGOROUS SUPPORTIVE CARE

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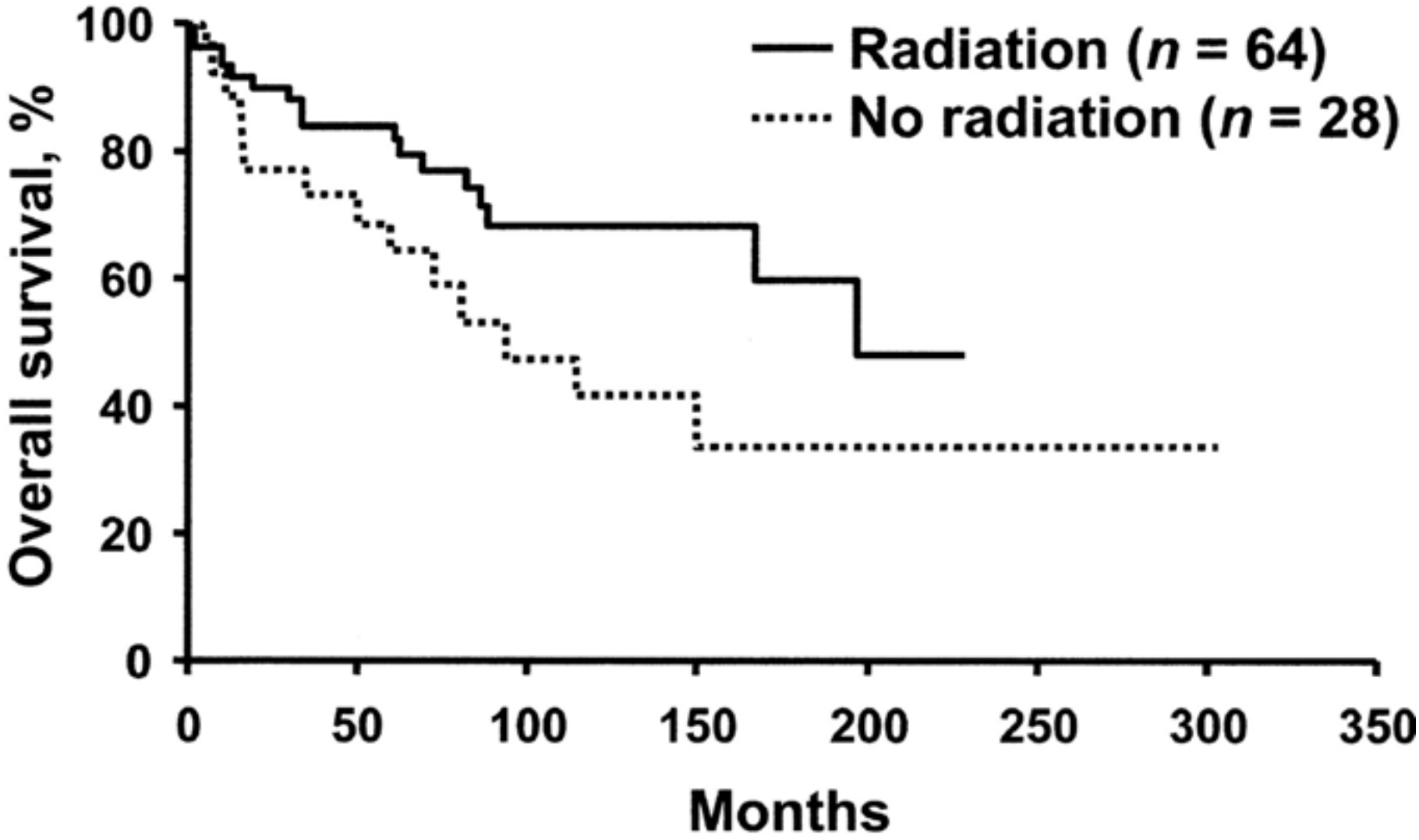


Dispenzieri A, et al. Blood 2003;101(7):2496-506.

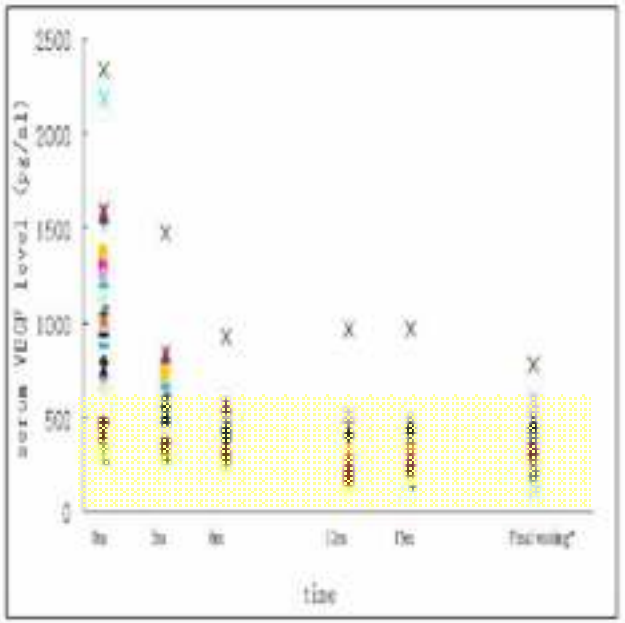
blood

Prepublished online March 10, 2011;
doi:10.1182/blood-2010-12-328112

Combination of melphalan and dexamethasone for patients with newly diagnosed POEMS syndrome

Jian Li, Wei Zhang, Li Jiao, Ming-Hui Duan, Hong-Zhi Guan, Wei-Guo Zhu, Zhuang Tian and Dao-Bin Zhou

- **31 enrolled**
- **12 cycles MDex**
- **Median age 44**



Response type	*N*	% responding
VEGF	*24*	96
Hematologic	*31*	81
Neuro (ONLS)	*31*	100
Organ	*28*	64
Volume	*28*	71
Pulm HTN	*15*	93

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Changes in serum VEGF with different therapies

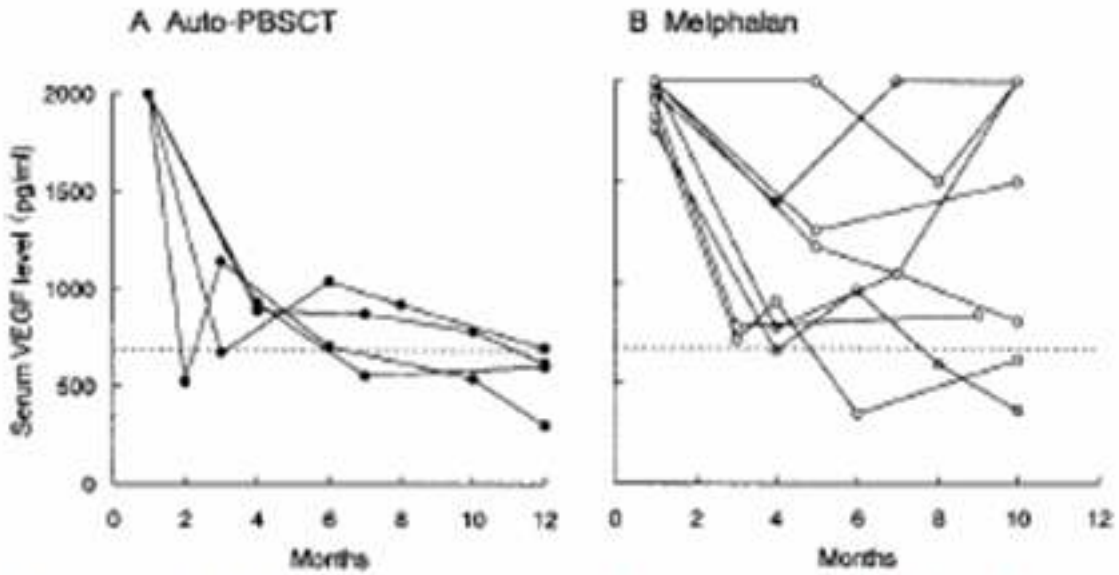

Figure. Serial changes in serum levels of vascular endothelial growth factor (VEGF) after autologous peripheral blood stem cell transplantation (Auto-PBSCT) or conventional melphalan chemotherapy. Dotted lines indicate the normal limit.

Kuwabara et al Neurology 2006; 66:105-7

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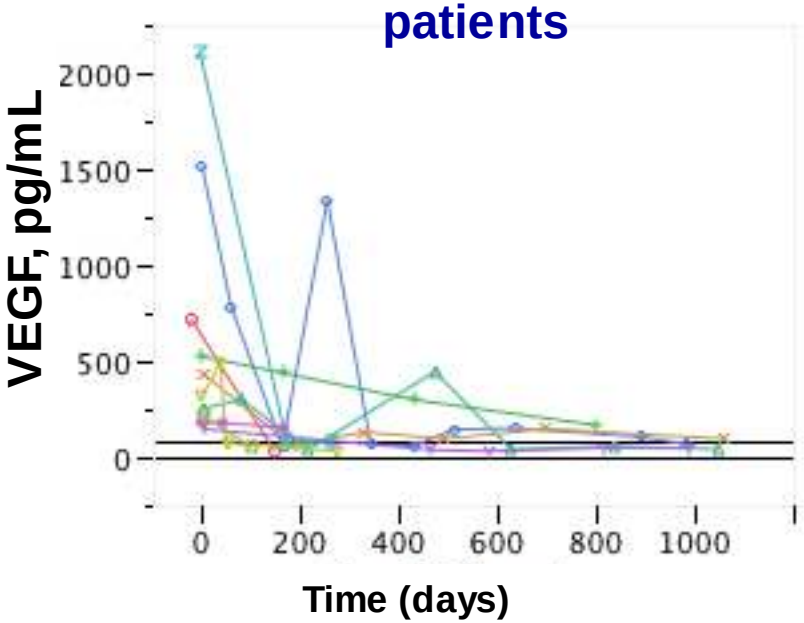
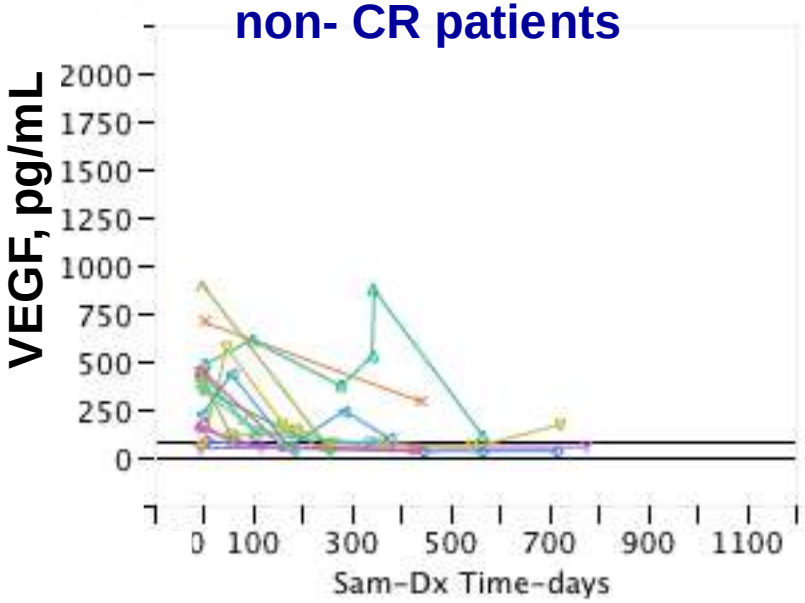
No difference in Plasma VEGF levels among patients achieving CR versus No-CR

Plasma VEGF in CR patients



Plasma VEGF in non- CR patients



Median plasma VEGF[a] at diagnosis (inter quartile range)	CR patients	Non-CR patients
Median VEGF on day 180[b]	131 (n=7)	75 (n=7)
Median VEGF at last follow up	59.5 (n = 10)	69 (n = 15)

D'Souza et al IMW Paris 2011

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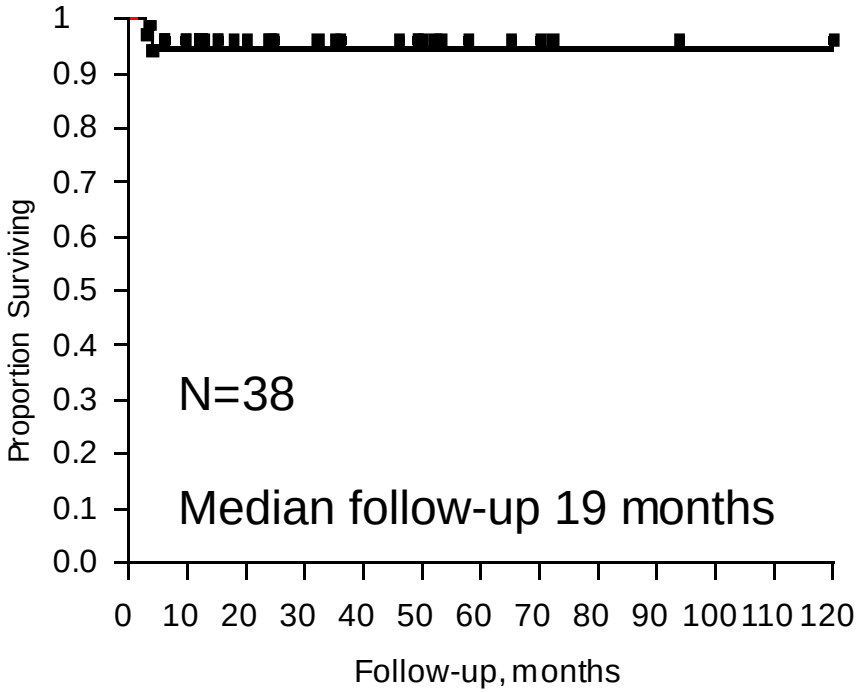
PBSCT for POEMS



Rovira M Br J Haematol2001;115:373–375.
Hogan WJ. BMT 2001;28:305–309.
Jaccard A. Blood 2002;99:3057–3059.
Soubrier M. BMT 2002;30:61–62.
Peggs KS Bone Marrow Transplant 2002;30:401–404.
Dispenzieri A. Blood 2004;104:3400–3407.
Kuwabara S, Neurology 2006;66:105–107.
Sanada S. Am J Kidney Dis 2006;47:672–679
Dispenzieri et al. Eur J Haematol. 2008;80:397-406.

- **Engraftment syndrome ~ 50% of patients**
- **Splenomegaly risk**
- **TRM 3%**
- **Major clinical improvement possible without “hematologic” response as long as VEGF response**

Ganti AK. Am J Hematol 2005;79:206–210.
Giglia F. Neuromuscul Disord 2007;17:980–982.
Laurenti L. Leuk Res 2008;32:1309–1312.
Imai N Neuromuscul Disord 2009;19:363–365.
Barete S, Arch Dermatol 2010;146:615–623.
Kuwabara S. Neurology 2008;71:1691–1695.

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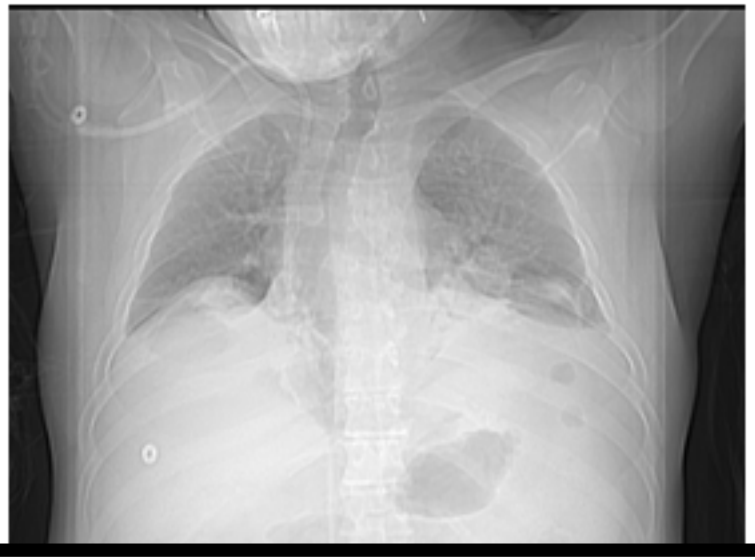
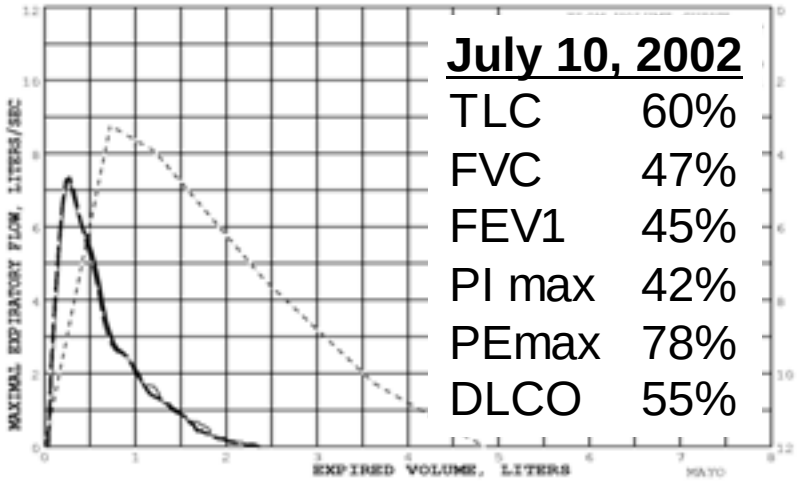
Pre



Predicted Patient Post-dilator



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Novel Treatments--IMiDs

1	Thali after MP	No heme response but improved ascites; stabilized PN, splenomegaly, pulm htn
2	Thali+Dex after CAD	CD/POEMS: impr ascites, effusions, pulm HTN, PN, renal function, IL-6
3	Thali+Dex	N=9; VEGF impr in all; PN impr in 66%; stable in 33%; impr edema; no HCR
4	Thali after VAD, CTX, bevacizumab	Improv cardiopulm status, but no impr PN and rising VEGF
5	Lenalidomide+Dex	Impr ascites, PS, PN, VEGF, testosterone, pulmonary function tests
6	Lenalidomide+Dex	N=9; Hematologic & VEGF response in all; Improved PS, PN, edema

1. Sinisalo, (2004). Am J Hematol 76(1): 66-8.
2. Kim (2006). Ann Hematol 85(8): 545-6.
3. Kuwabara (2008). J Neurol Neurosurg Psychi 79(11): 1255-7.
4. Ohwada (2008). BMT 1-2.
5. Dispenzieri (2007) Blood 110(3): 1075-6.
6. Jaccard (2009) ASH;114:3872-

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Novel Treatments--Bortezomib

1	Bortez + Dex	Improved M-protein, polyneuropathy, hepatomegaly, testosterone; no EMG change
2	Bortez x 5 cycles + thalidomide added at cycle 6 (prior Dex and MP)	Improved anasarca, PN, VEGF, and PET scan with Bortez alone, but thali added for persistent edema, M-protein, PN, and slight ↑ VEGF. With thali, disappearance of pleural effusion, ascites, and M-protein and normalization of VEGF
3	Bortez+AD after VAD, CMP, and AD	Improved M-protein, VEGF, paresthesias, splenomegaly, effusions, muscle strength, gynecomastia, and skin changes
4	Bortezomib dexamethasone*	Improved by 3 cycles (but continued for 6): adenopathy, pleural effusion and ascites, HSM, and IL-6. CR 4 years after completing therapy.

*Castleman's variant of POEMS

1. Kaygusuzet al. Eur J Haematol 2010;84:175-177. 2. Ohguchi et al. Annals of hematology 2010.
3. Tang et al. Eur J Haematol 2009;83:609-610. 4. Sobas et al. Ann Hematol 2010;89:217-219.

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Novel Treatments--Bevacizumab

1	Single	Dead 6 weeks	*RIP*
2	Single	Worsening PN, anasarca, MOF; died of pneumonia 5 weeks after Rx	*RIP*
3	Single	Improved pain, breathing, walking	

1 Kanai (2007). Intern Med 46(6): 311-3.
2 Straume (2006). Blood 107(12): 4972-3.
3 Dietrich (2008). Ann Oncol 19(3): 595.
4 Badros (2005). Blood 106(3): 1135.
5 Ohwada (2008). BMT 1-2.
6 Badros (2006). Blood 107(12): 4973-4.
7 Samaras (2007).Haematologica 92(10): 1438-9.

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How does one define response in patients with POEMS Syndrome?

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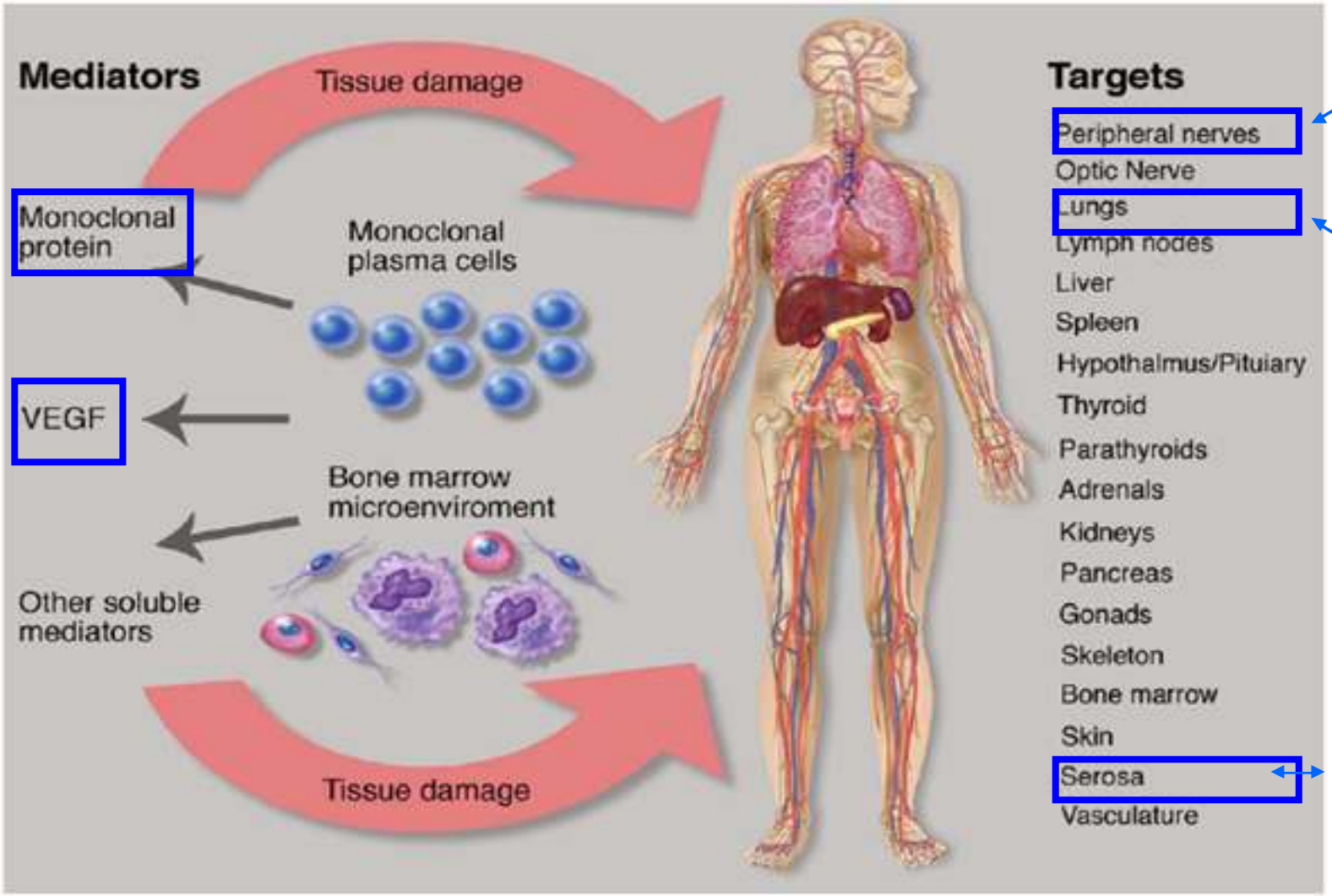
Response Criteria?



Which score?

DLCO

Ascites and effusions: mild, moderate or severe

Dispenzieri et al Blood, in press

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Summary and Future Challenges

1. Essential to recognize syndrome
2. Commonly responsive to therapy
3. VEGF more reliable than M-spike
4. Bone marrow, VEGF, PET/CT useful

5. Need to understand dz mechanism
6. Need formal study of best treatments

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Myeloma, Amyloid, and Dysproteinemia Group

Rochester

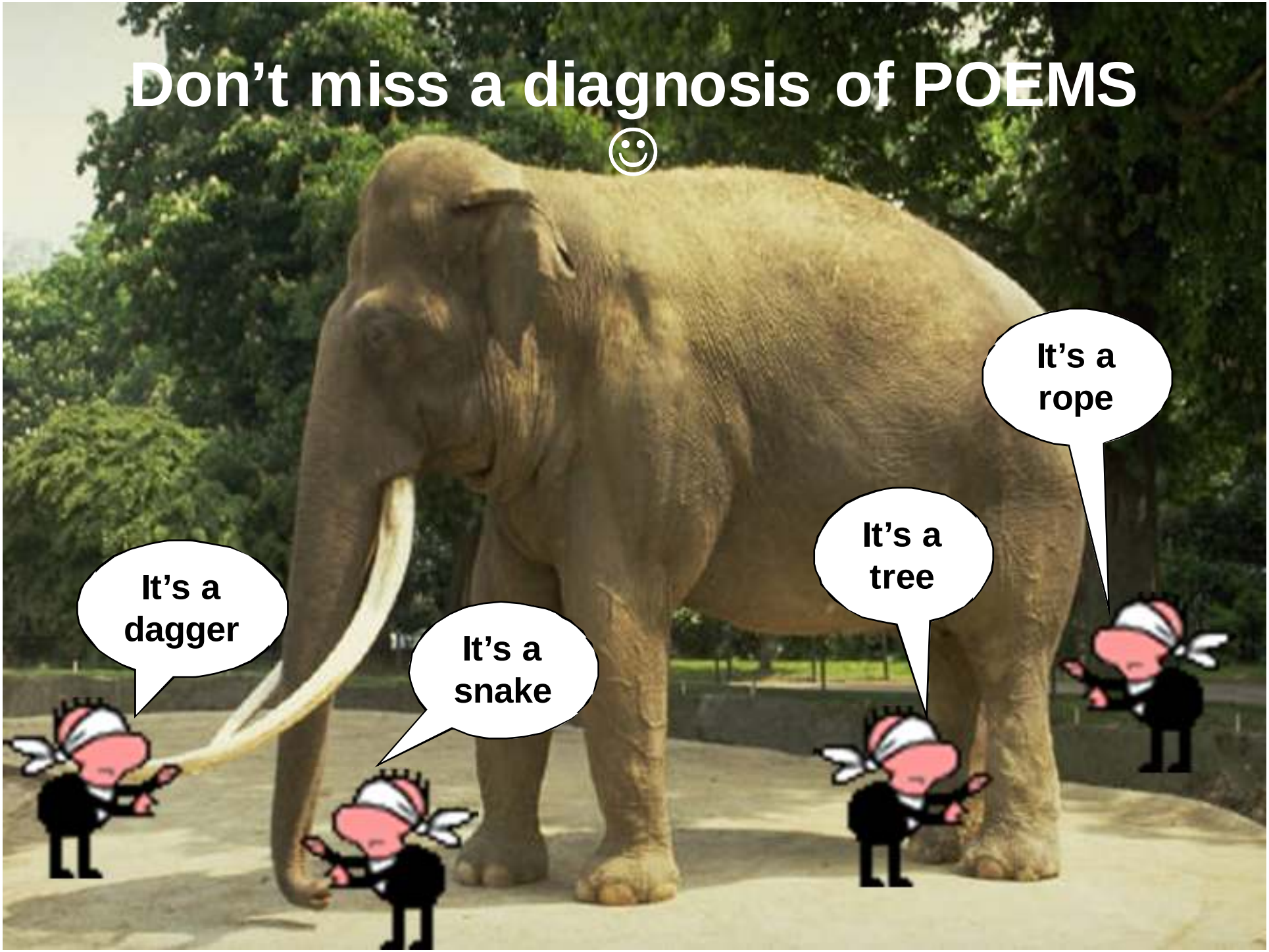
Vince Rajkumar, MD
Francis Buadi, MD
David Dingli, MD, PhD
Morie Gertz, MD
Phil Greipp, MD
Suzanne Hayman, MD
Shaji Kumar, MD
Robert Kyle, MD
Martha Lacy, MD
Nelson Leung, MD
John Lust, MD
Greg Nowakowski, MD
Steve Russell, MD, PhD
Tom Witzig, MD
S Zeldenrust, MD, PhD

Arizona

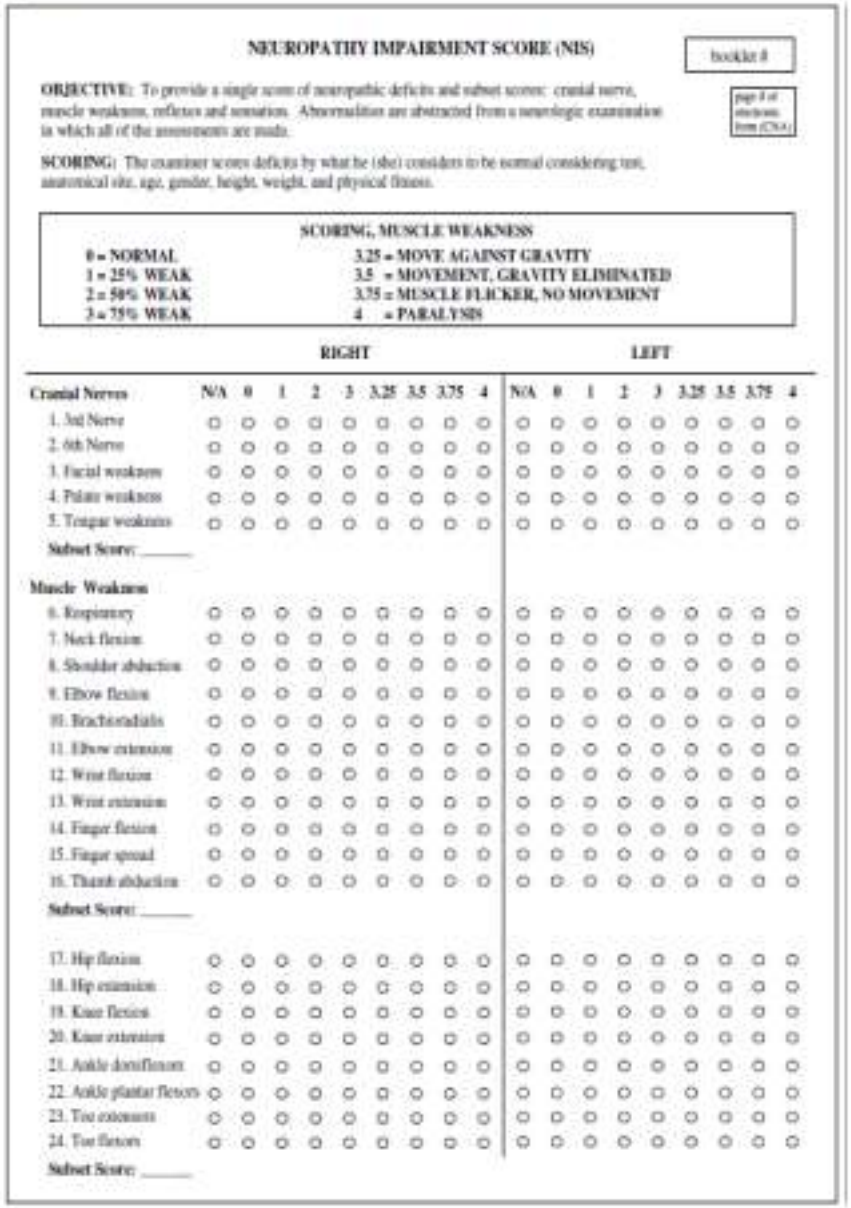
Leif Bergsagel, MD
Rafael Fonseca, MD
Joseph Mikhael
Craig Reeder, MD
Keith Stewart, MD

Jacksonville

Vivek Roy, MD


Don’t miss a diagnosis of POEMS
☺
It’s a dagger
It’s a snake
It’s a tree
It’s a rope

Neuropathy Impairment Score



NEUROPATHY IMPAIRMENT SCORE (NIS)

booklet #

OBJECTIVE: To provide a single score of neuropathic deficits and subset scores: cranial nerve, muscle weakness, reflexes and sensation. Abnormalities are abstracted from a neurologic examination in which all of the assessments are made.

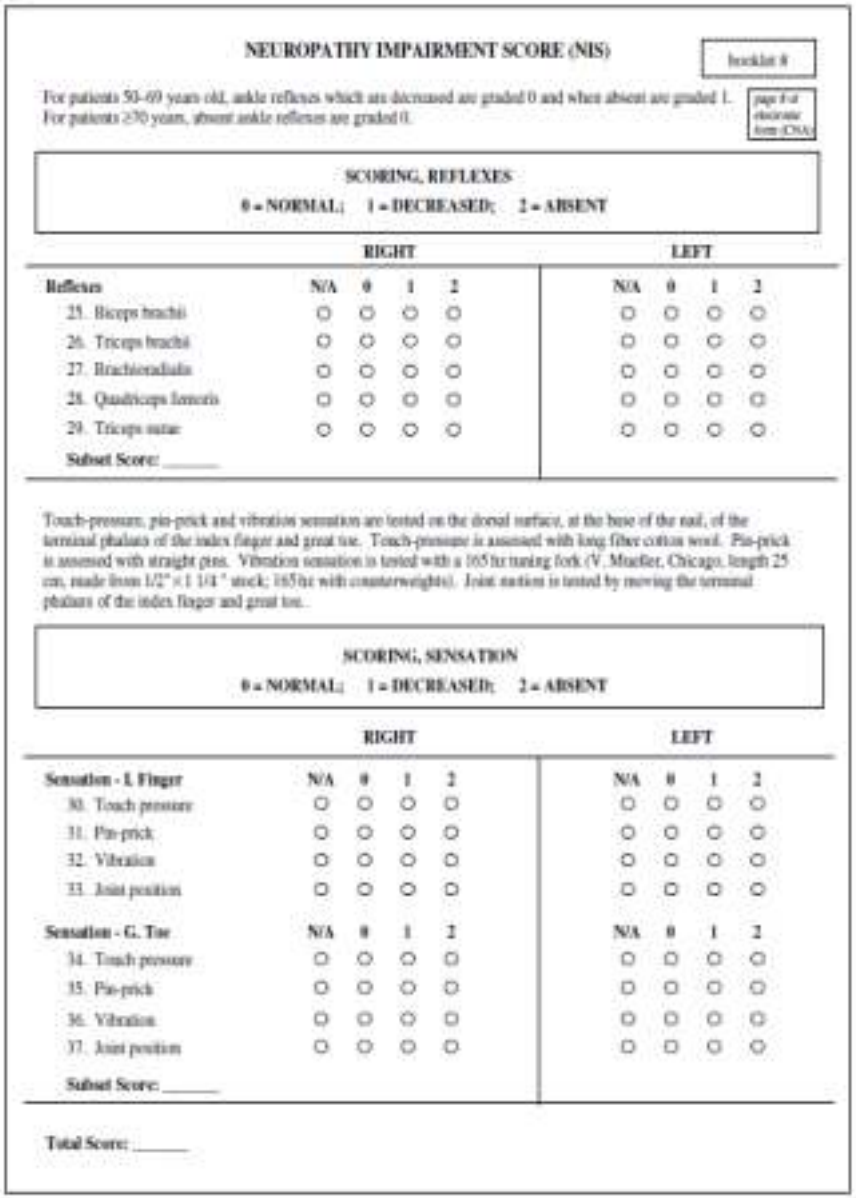
page # of electronic form (CNA)

SCORING: The examiner scores deficits by what he (she) considers to be normal considering test, anatomical site, age, gender, height, weight, and physical fitness.

SCORING, MUSCLE WEAKNESS

0 = NORMAL
1 = 25% WEAK
2 = 50% WEAK
3 = 75% WEAK
3.25 = MOVE AGAINST GRAVITY
3.5 = MOVEMENT, GRAVITY ELIMINATED
3.75 = MUSCLE FLICKER, NO MOVEMENT
4 = PARALYSIS

	RIGHT									LEFT								
Cranial Nerves	N/A	0	1	2	3	3.25	3.5	3.75	4	N/A	0	1	2	3	3.25	3.5	3.75	4
1. 3rd Nerve	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
2. 6th Nerve	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
3. Facial weakness	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
4. Palate weakness	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
5. Tongue weakness	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Subset Score: _____																		
Muscle Weakness																		
6. Respiratory	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
7. Neck flexion	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
8. Shoulder abduction	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
9. Elbow flexion	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
10. Brachioradialis	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
11. Elbow extension	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
12. Wrist flexion	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
13. Wrist extension	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
14. Finger flexion	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
15. Finger spread	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
16. Thumb abduction	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Subset Score: _____																		
17. Hip flexion	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
18. Hip extension	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
19. Knee flexion	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
20. Knee extension	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
21. Ankle dorsiflexion	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
22. Ankle plantar flexors	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
23. Toe extensors	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
24. Toe flexors	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
Subset Score: _____																		



NEUROPATHY IMPAIRMENT SCORE (NIS)

booklet #

For patients 50-69 years old, ankle reflexes which are decreased are graded 0 and when absent are graded 1. For patients ≥70 years, absent ankle reflexes are graded 0.

page # of electronic form (CNA)

SCORING, REFLEXES

0 = NORMAL; 1 = DECREASED; 2 = ABSENT

	RIGHT				LEFT			
Reflexes	N/A	0	1	2	N/A	0	1	2
25. Biceps brachii	○	○	○	○	○	○	○	○
26. Triceps brachii	○	○	○	○	○	○	○	○
27. Brachioradialis	○	○	○	○	○	○	○	○
28. Quadriceps femoris	○	○	○	○	○	○	○	○
29. Triceps surae	○	○	○	○	○	○	○	○
Subset Score: _____								

Touch-pressure, pin-prick and vibration sensation are tested on the dorsal surface, at the base of the nail, of the terminal phalanx of the index finger and great toe. Touch-pressure is assessed with long fiber cotton wool. Pin-prick is assessed with straight pins. Vibration sensation is tested with a 165 hz tuning fork (V. Mueller, Chicago, length 25 cm, made from 1/2" x 1 1/4 " stock; 165 hz with counterweights). Joint motion is tested by moving the terminal phalanx of the index finger and great toe.

SCORING, SENSATION

0 = NORMAL; 1 = DECREASED; 2 = ABSENT

	RIGHT				LEFT			
Sensation - L Finger	N/A	0	1	2	N/A	0	1	2
30. Touch pressure	○	○	○	○	○	○	○	○
31. Pin-prick	○	○	○	○	○	○	○	○
32. Vibration	○	○	○	○	○	○	○	○
33. Joint position	○	○	○	○	○	○	○	○
Sensation - G. Toe	N/A	0	1	2	N/A	0	1	2
34. Touch pressure	○	○	○	○	○	○	○	○
35. Pin-prick	○	○	○	○	○	○	○	○
36. Vibration	○	○	○	○	○	○	○	○
37. Joint position	○	○	○	○	○	○	○	○
Subset Score: _____								

Total Score: _____

Dyck et al Can J Neurol Sci 29:258-266; 2002

MAYO CLINIC

Overall Neuropathy Limitations Scale

Name:
Date:

Overall Neuropathy Limitations Scale (ONLS)

Instructions: The examiner should question **and** observe the patient in order to determine the answers to the following questions. Note should be made of any other disorder other than peripheral neuropathy which limits function at the foot of the page.

ARM SCALE

Does the patient have any symptoms in their hands or arms, eg tingling, numbness or weakness? Yes☐ No☐
(If "no", please go to "legs" section)

Is the patient affected in their ability to:	Not affected	Affected but not prevented	Prevented
Wash and brush their hair	☐	☐	☐
Turn a key in a lock	☐	☐	☐
Use a knife and fork together (or spoon, if knife and fork not used)	☐	☐	☐
Do or undo buttons or zips	☐	☐	☐
Dress the upper part of their body excluding buttons or zips	☐	☐	☐

If all these functions are prevented can the patient make purposeful movements with their hands or arms? Yes☐ No☐ Not applicable ☐

Arm Grade
0=Normal
1=Minor symptoms in one or both arms but not affecting any of the functions listed **SCORE:**___
2=Disability in one or both arms affecting but not preventing any of the functions listed
3=Disability in one or both arms preventing at least one but not all functions listed
4=Disability in both arms preventing all functions listed but purposeful movement still possible
5=Disability in both arms preventing all purposeful movements

LEG SCALE

	Yes	No	Not applicable
Does the patient have difficulty running or climbing stairs?	☐	☐	☐
Does the patient have difficulty with walking?	☐	☐	☐
Does their gait look abnormal?	☐	☐	☐
How do they mobilise for about 10 metres (ie 33 feet)?			
Without aid	☐	☐	☐
With one stick or crutch or holding to someone's arm	☐	☐	☐
With two sticks or crutches or one stick or crutch holding onto someone's arm or frame	☐	☐	☐
With a wheelchair	☐	☐	☐
If they use a wheelchair, can they stand and walk 1 metre with the help of one person?	☐	☐	☐
If they cannot walk as above are they able to make some purposeful movements of their legs, eg reposition legs in bed?	☐	☐	☐
Does the patient use **ankle foot orthoses/braces?** (please circle)	☐	☐ **If yes:** (please circle) **right/left**	

Leg grade
0=Walking/climbing stairs/running not affected
1=Walking/climbing stairs/running is affected, but gait does not look abnormal **SCORE:**___
2=Walks independently but gait looks abnormal
3=Requires unilateral support to walk 10 metres (stick, single crutch, one arm)
4=Requires bilateral support to walk 10 metres (sticks, crutches, crutch and arm, frame)
5=Requires wheelchair to travel 10 metres but able to stand and walk 1 metre with the help of one person
6=Restricted to wheelchair, unable to stand and walk 1 metre with the help of one person, but able to make some purposeful leg movements
7=Restricted to wheelchair or bed most of the day, unable to make any purposeful movements of the legs

Overall Neuropathy Limitation Scale=arm scale (range 0 to 5)+leg scale (range 0 to 7);
(range: 0 (no disability) to 12 (maximum disability)) **TOTAL SCORE:**___
Is there any disorder, other than peripheral neuropathy, which affects the above functions Yes☐ No☐
If yes please describe:

Arm scale 0 to 5

Leg scale 0 to 7

Graham and Hughes J. Neurol. Neurosurg. Psych 77:973-6; 2006