Redefining Polycythemia Vera (PV) in 2014

Carlos Besses, MD, PhD
Hematology Department
Hospital del Mar
Barcelona, Spain

WHO Classification of MPN

- **Classic MPN**
  - Chronic myeloid leukemia
  - Polycythemia vera
  - Primary myelofibrosis
  - Essential thrombocythemia

  Philadelphia-negative

- **Non-classic MPN**
  - Chronic neutrophilic leukemia
  - Chronic eosinophilic leukemia-NOS
  - Mastocytosis
  - MPN, unclassifiable

MPN, myeloproliferative neoplasm; NOS, not otherwise specified

JAK2 Mutations in Classic MPN

	V617F (exon 14)	Exon 12 mutations
PV	95%	3%
PMF	60%	–
ET	60%	–

PMF, primary myelofibrosis; ET, essential thrombocythemia

Cazzola M, et al. *Blood.* 2014;123(24):3714-3719.

2008 WHO Diagnostic Criteria for PV

Major criteria	Minor criteria
1. Hemoglobin (Hb) >18.5 g/dL (men) >16.5 g/dL (women) *or* other evidence of increased red cell volume*	1. Bone marrow biopsy showing hypercellularity for age with panmyelosis
2. Presence of *JAK2*V617F or *JAK2* exon 12 mutation	2. Subnormal serum erythropoietin (EPO) level
	3. Endogenous erythroid colony (EEC) growth

Diagnosis: Both major criteria and one minor criterion *or* first major criterion plus two minor criteria

*Hb or Hematocrit (Hct) >99th percentile of reference range for age, sex, or altitude of residence *or* Hb >17 g/dL in men, >15 g/dL in women if associated with documented and sustained increase of at least 2 g/dL from an individual's baseline value that cannot be attributed to correction of iron deficiency *or* elevated red cell mass (RCM) >25% above mean normal predicted value

Adapted from Barbui T, et al. *Leukemia*. 2014;28(6):1191-1195.

BCSH Modified Diagnostic Criteria for PV

JAK2-positive PV	*JAK2*-negative PV
A1 High hematocrit >0.52 (men), >0.48 (women) **OR** **Raised red cell mass (>25% above predicted)** **A2 Mutation in *JAK2***	A1 Raised red cell mass (>25% above predicted) OR hematocrit ≥0.60 (men), ≥0.56 (women) A2 Absence of mutation in *JAK2* A3 No cause of secondary erythrocytosis A4 Palpable splenomegaly A5 Presence of an acquired genetic abnormality (excluding *BCR-ABL* in the hematopoietic cells B1 Thrombocytosis (platelet count >450x10^9/L) B2 Neutrophil leucocytosis (neutrophil count >10x10^9/L in nonsmokers; >12.5x10^9/L in smokers) B3 Radiological evidence of splenomegaly B4 Endogenous erythroid colonies or low serum erythropoietin
Diagnosis requires both criteria to be present	**Diagnosis requires A1 + A2 + A3 + either another A or two B criteria**

BCSH, British Committee for Standards in Hematology

Adapted from McMullin MF, et al. *Br J Haematol.* 2007;138(6):821-822.

2014 Proposed Revision for WHO Diagnostic Criteria of PV

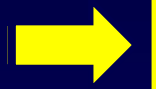
Major criteria	Minor criteria
1. Hemoglobin >16.5 g/dL (men) >16 g/dL (women) *or* Hematocrit >49% (men) >48% (women)	1. Subnormal serum erythropoietin level
2. Bone marrow trilineage myeloproliferation with pleomorphic megakaryocytes	
3. Presence of *JAK2* mutation	

Diagnosis: All three major criteria *or* the first two major criteria and one minor criterion

Tefferi A, et al. *Leukemia.* 2014;28(7):1407-1413.

Differences Between 2008 and Proposed 2014 WHO Diagnostic Criteria for PV

- Hb >18.5 g/dL (men)
  >16.5 g/dL (women)
- RCM >25% normal value
- Hb or Hct >99th percentile of reference range
- Hb >17 g/dL (men), >15 g/dL (women) after increase ≥2 g/dL from baseline value without correction of iron deficiency



Hb >16.5 g/dL (men
>16 g/dL (women)
or
Hct >49% (men)
>48% (women)

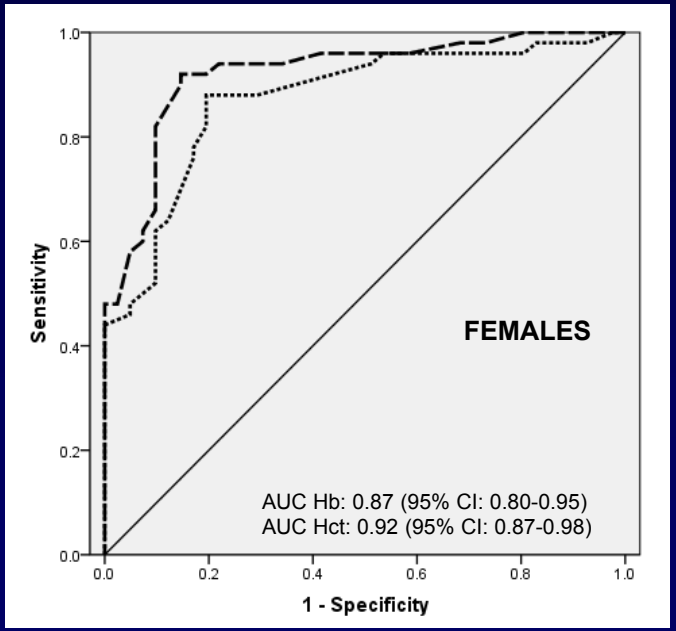
Inclusion of bone marrow morphology as a major criterion

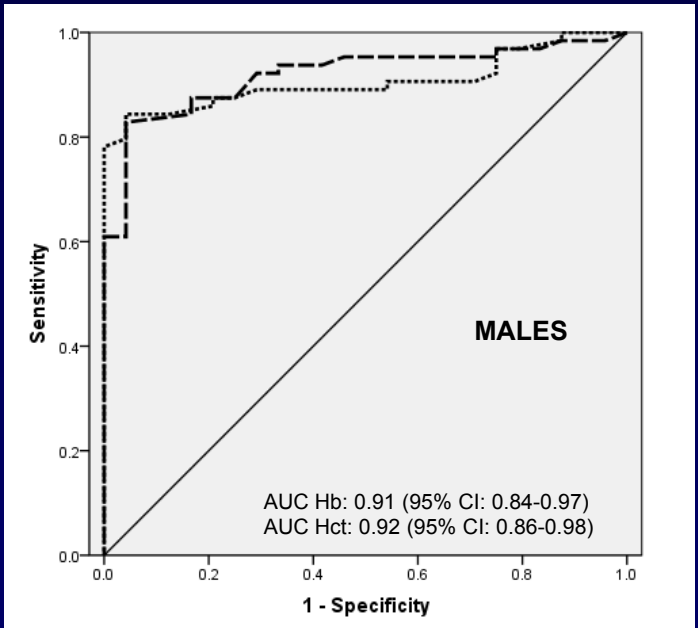
Removal of EEC growth as a minor criterion

Diagnostic Accuracy by ROC Curves of Hemoglobin and Hematocrit as Predictors of an Increased RCM

Whole series (n = 179)

AUC Hematocrit: 0.92, 95% CI: 0.88-0.96
AUC Hemoglobin: 0.88, 95% CI: 0.84-0.93





- - - - - - - Hct
····· Hb

ROC, receiver operating characteristic

Alvarez-Larrán A, et al. *Haematologica.* 2012;97(11):1704-1707.

Diagnostic Accuracy of 2008 WHO Hemoglobin Criteria and Hematocrit Threshold as Predictors of Increased RCM in Patients With a Suspected Diagnosis of PV or Essential Thrombocythemia (ET)

	True + (N)	True – (N)	False + (N)	False – (N)	Sensitivity	Specificity
Male (n = 88)						
Hb >18.5 g/dL	37	24	0	27	58%	100%
Hct >52%	52	23	1	12	81%	96%
Female (n = 91)						
Hb >16.5 g/dL	24	39	2	26	48%	95%
Hct >48%	47	30	11	3	94%	73%

Alvarez-Larrán A, et al. *Haematologica.* 2012;97(11):1704-1707.

Diagnostic Accuracy of Different Combination of PV Criteria in 47 PV, 78 ET, and 49 Non-Clonal Erythrocytosis

	False + (N)	False – (N)	Sensitivity	Specificity
WHO 2008 + low EPO	0	26	45%	100%
BCSH	4	10	79%	97%
BCSH + low EPO	3	16	66%	98%
BCSH + *JAK2*V617F >35%	2	15	66%	98%
BCSH + *JAK2*V617F >35% + low EPO	5	8	83%	96%

Alvarez-Larrán A, et al. *Br J Haematol.* 2014;167(3):411-417.

RESEARCH ARTICLE

AJH

Discriminating between essential thrombocythemia and masked polycythemia vera in *JAK2* mutated patients

Tiziano Barbui,[1,2*] Jürgen Thiele,[3] Alessandra Carobbio,[1] Paola Guglielmelli,[4] Alessandro Rambaldi,[2] Alessandro M. Vannucchi,[4] and Ayalew Tefferi[5]

PV patients with WHO-defined morphology
N = 397

	Overt PV	Masked PV
	n = 257 65%	N = 140 35%
Follow-up (median)	4.5 years	3.8 years

Barbui T, et al. *Am J Hematol.* 2014;89(6):588-590.

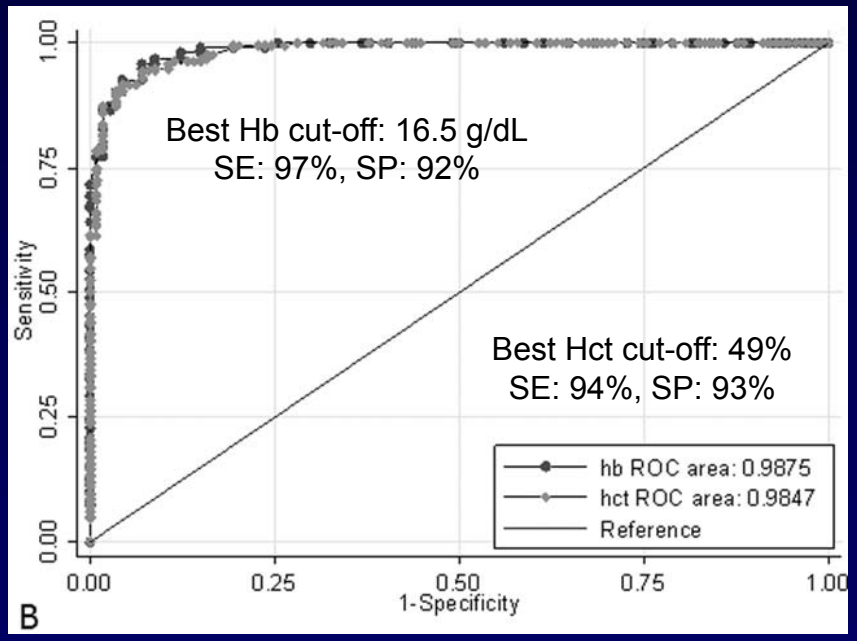
Main Features of 397 PV Patients at Diagnosis and During Follow-Up According to 2008 WHO and BCSH Criteria

	2008 WHO			BCSH		
	Masked PV	Overt PV	*P*	Masked PV	Overt PV	*P*
N (%)	140 (35)	257 (65)	—	59 (15)	338 (85)	—
Male / female, %	76/24	43/57	<.0001	80/20	50/50	<.0001
Platelets ($x10^9$/L), median	567	457	<.0001	623	487	.010
Fibrosis, %	18	10	.028	22	11	.022
Previous thrombosis, %	31	15	<.0001	27	20	.184
arterial, %	21	10	.002	20	13	.136
venous, %	10	6	.128	7	7	.867
Thrombosis rate (pt/y)	1.83	1.99	.788	1.67	1.98	.620
Overall survival rate (pt/y)	1.16	0.57	.011	1.35	0.64	.019

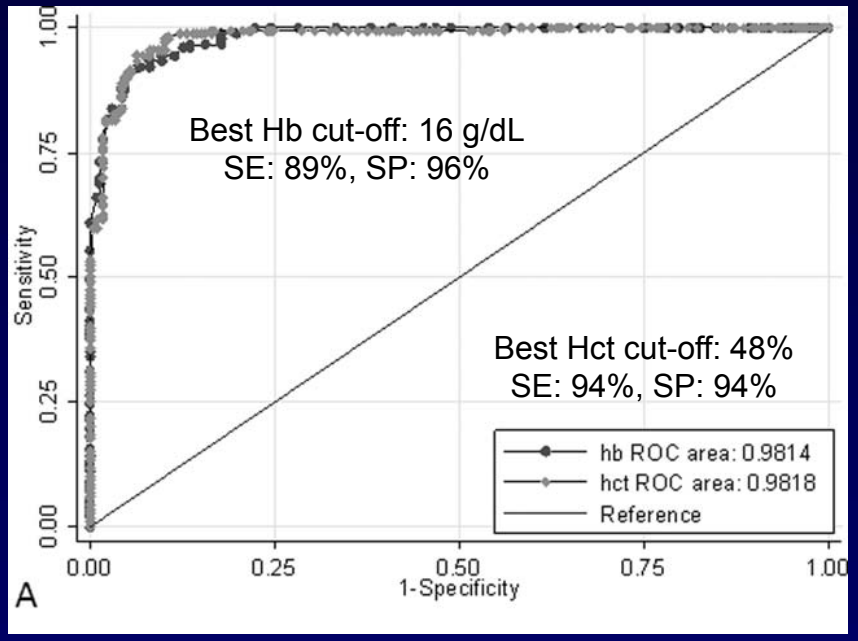
Adapted from Barbui T, et al. *Am J Hematol.* 2014;89(2):199-202.

ROC Curves of Hemoglobin and Hematocrit for the Discrimination Between ET and PV in *JAK2*V617F Mutated Patients

Males



Females



Overt PV (n = 257)
Masked PV (n = 140)
ET (n = 369)

Modified from Barbui T, et al. *Am J Hematol.* 2014;89(6):588-590.

Bone Marrow Features in PV (at Diagnosis)

- Hypercellular for age
- Panmyelosis (trilineage proliferation)
- Loose clusters of mature megakaryocytes of different size with polymorphous aspect
- Normal reticulin fiber network (80%)
- Lack of stainable iron
- Reactive nodular lymphoid aggregates (20%)

Thiele J, et al. Critical Issues About the Diagnosis of MPNs: Bone Marrow Histopathology. In: Barbui T, ed. *Myeloproliferative Neoplasms*. Berlin and Heidlberg, Germany: Springer-Verlag; 2012:19-35.

World Health Organization-defined classification of myeloproliferative neoplasms: Morphological reproducibility and clinical correlations—The Danish experience

Ann Brinch Madelung,[1*] Henrik Bondo,[1] Inger Stamp,[1] Preben Loevgreen,[2] Signe Ledou Nielsen,[3] Anne Falensteen,[3] Helle Knudsen,[3] Mats Ehinger,[4] Rasmus Dahl-Sørensen,[5] Nana Brochmann Mortensen,[5] Kira Dynnes Svendsen,[6] Theis Lange,[6] Elisabeth Ralfkiaer,[7] Karsten Nielsen,[1] Hans Carl Hasselbalch,[5] and Jürgen Thiele[8]

	Histological consensus rate
Step 1: Blinded, only morphological study	53%
Step 2: Re-evaluation of fiber grading	60%
Step 3: Clinico-pathological correlation	83%

Madelung AB, et al. *Am J Hematol.* 2013;88(12):1012-1016.

Clinicians Agreement With Blinded Morphological Consensus Diagnoses After Fiber Re-evaluation in 97 MPN

Morphological diagnosis	ET	PV	pre PMF	PMF
No. of cases with morphological consensus	12	17	43	25
No. of cases with clinical concordance	4/12	13/17*	22/43**	16/25***
Agreement (%)	33	76	51	64

*Clinical diagnosis of pre MF (n = 2) and PMF (n = 2)
**Clinical diagnosis of PV (n = 16), PMF (n = 3), EP (n = 1), and MPN unclassifiable (n = 1)
***Clinical diagnosis of PV (n = 2), ET (n = 1), preMF (n = 5), and CML (n = 1)

Madelung AB, et al. *Am J Hematol.* 2013;88(12):1012-1016.

Diagnostic Accuracy of Bone Marrow Histopathology in 211 MPN Patients

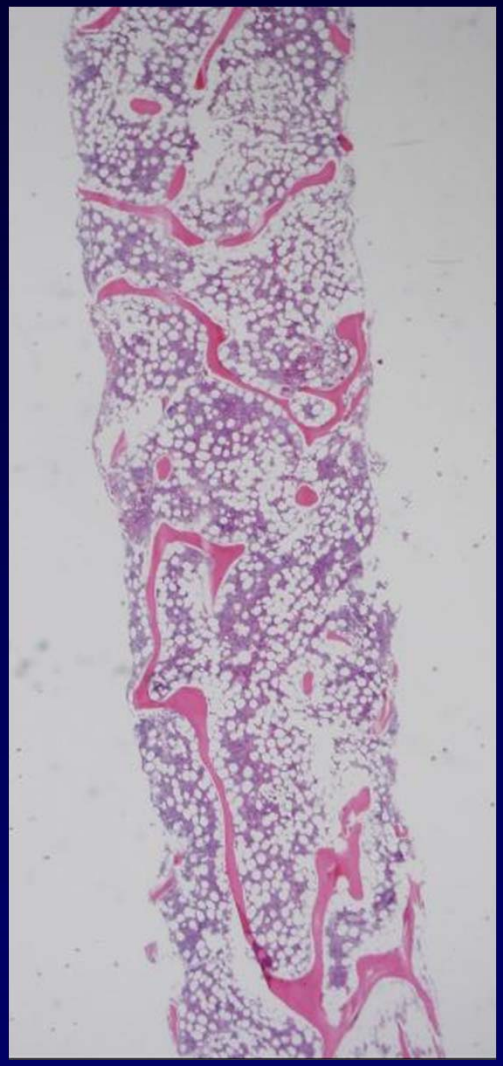
	Histological diagnosis (N)	Clinical diagnosis (N)	False +	False -	Sensitivity	Specificity
PV	13	40	0	27	32.5%	100%
ET	78	143	1	66	54%	98.5%
MF						
including pre MF	37	28	15	6	79%	92%
excluding pre MF	25	28	4	7	75%	98%

Modified from Alvarez-Larrán A, et al. *Br J Haematol*. 2014;166(6):911-919.

Clinical Case

- Woman, 66 years old, platelet count 671x10^9/L
- Mother with ET
- No palpable spleen; asymptomatic

- Hb 16.1 g/dL, Hct 48.8%, WBC 9.8x10^9/L
- *JAK2*V617F: 34%
- EPO: <1.0 mU/mL
- Bone marrow
  - Slight increase in cellularity (40%, normal 30%)
  - No increase in erythroid and granulocytic series
  - Megakaryocytes increased: loose clusters, giant size, no atypia
  - Lack of stainable iron
  - No reticulin fibrosis
- Red cell mass increased



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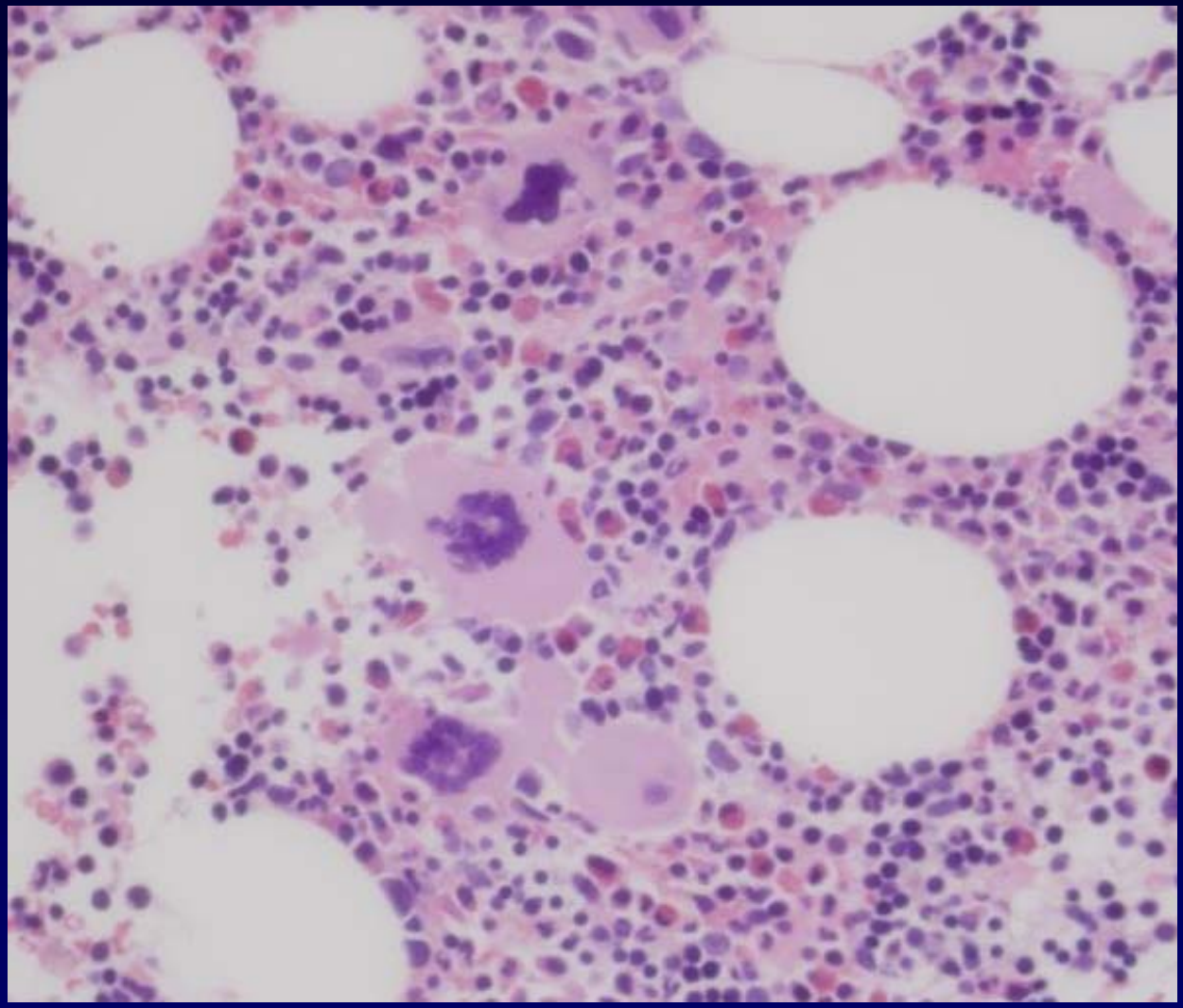

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Pathologist Diagnosis: ET
Clinician Diagnosis: PV

WHO 2008	BCSH	WHO 2014 (proposal)
• Hb 16.1 g/dL: NO	• Hct 48.8%: YES	• Hb 16.1 g/dL/Hct 48.8%: YES
• *JAK2* mutated: YES	• *JAK2* mutated:YES	• *JAK2* mutated: YES
• BM findings: NO		• BM findings: NO
• Low EPO: YES		
DOES NOT MEET DIAGNOSTIC CRITERIA	MEETS DIAGNOSTIC CRITERIA	DOES NOT MEET DIAGNOSTIC CRITERIA

Clinical Features at Presentation and During the Clinical Course of 1545 Patients With PV

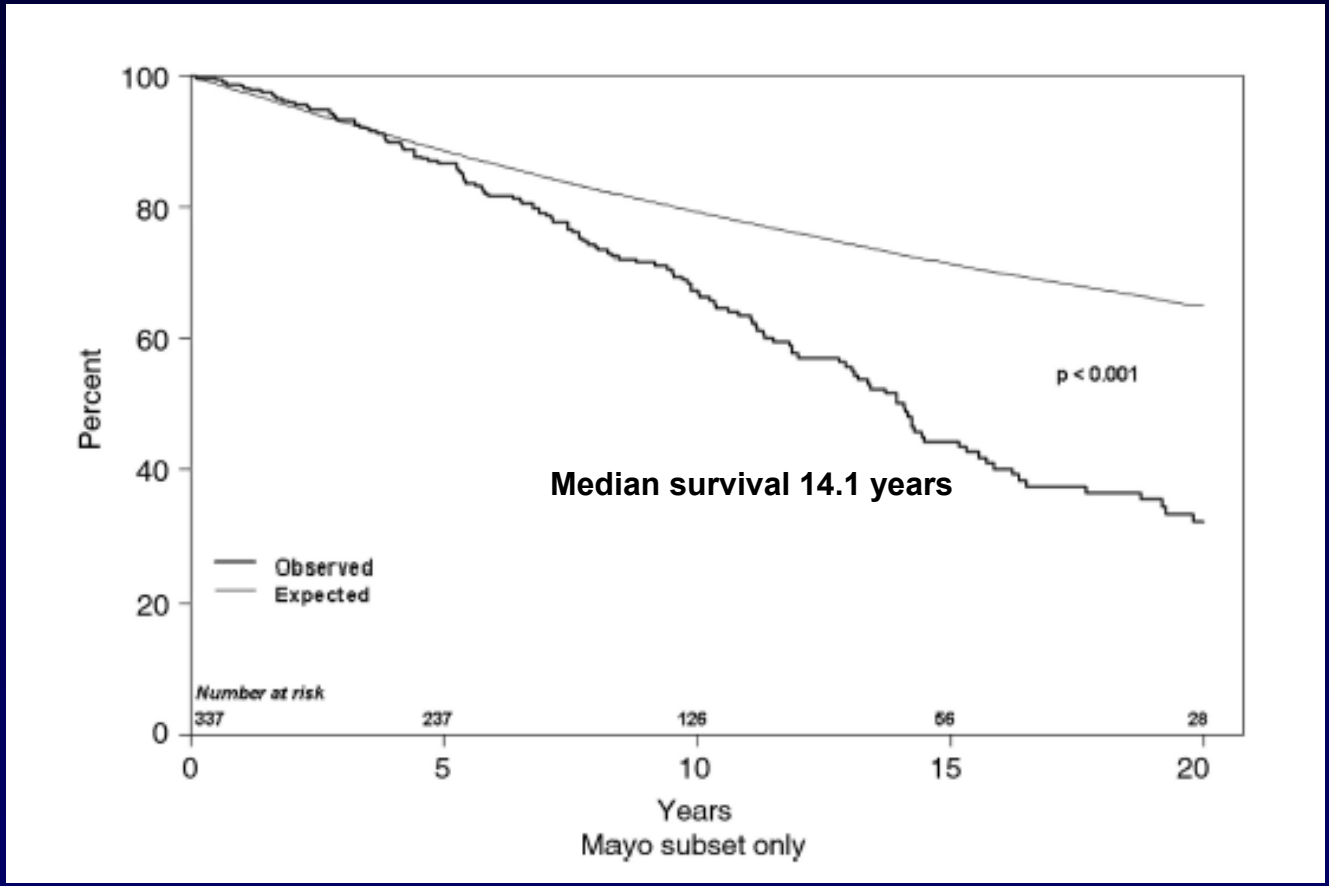
	At presentation	During follow-up
Median age, years	61 (18-95)	—
Palpable spleen	36%	—
Arterial thrombosis*	16%	12%
Venous thrombosis*	7%	9%
Major bleeding*	4%	4%
Leukemic transformation	—	3%
Progression to MF	—	9%

*Before / at diagnosis

Median follow-up 6.9 years (0-39)

Adapted from Tefferi A, et al. *Leukemia.* 2013;27(9):1874-1881.

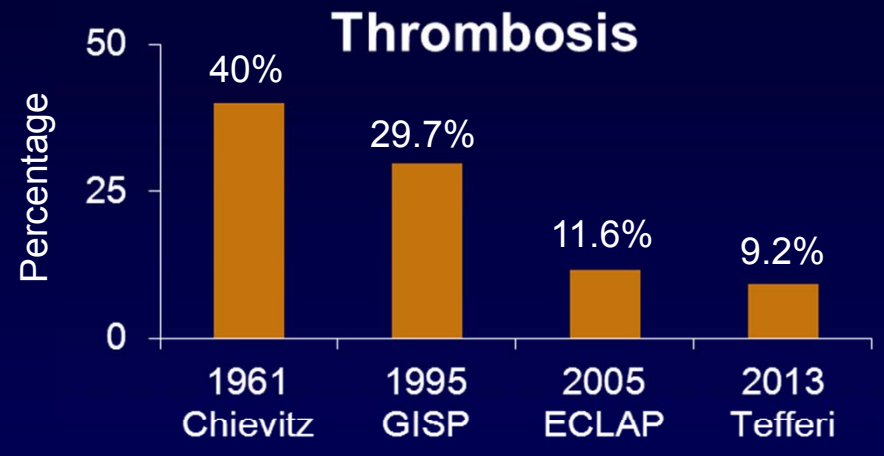
Median Survival in Patients With PV

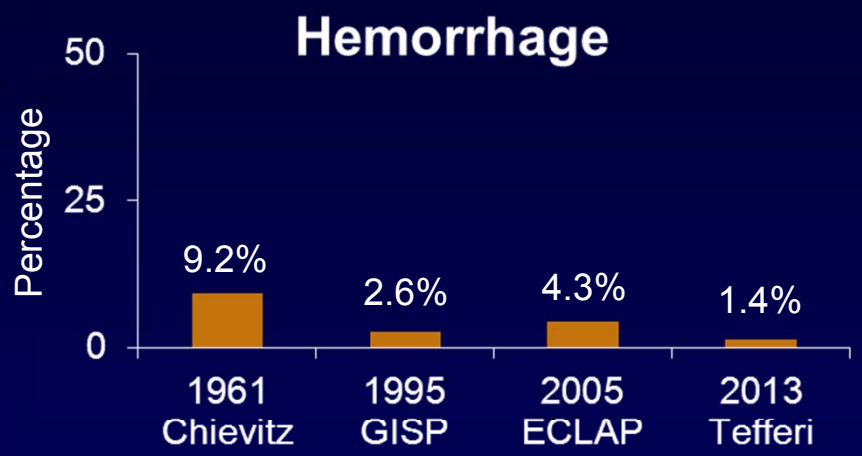


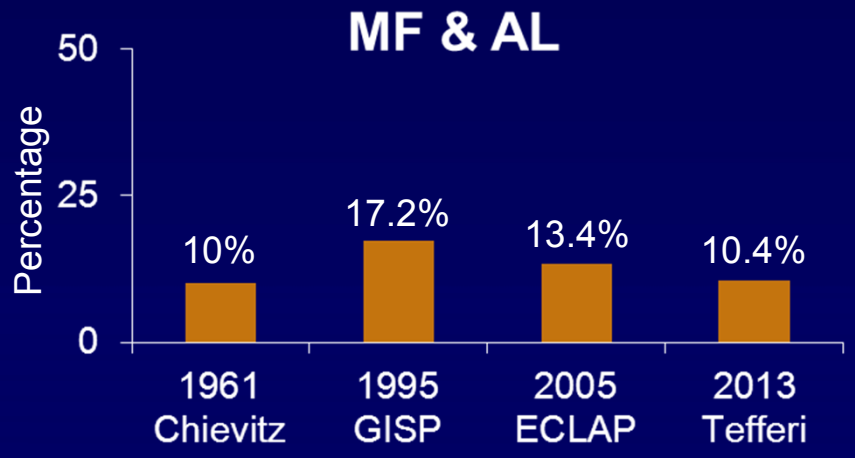
Survival in 337 Mayo Clinic patients with PV (44% followed to death) compared with expected survival based on individuals of the same age and gender from the US population

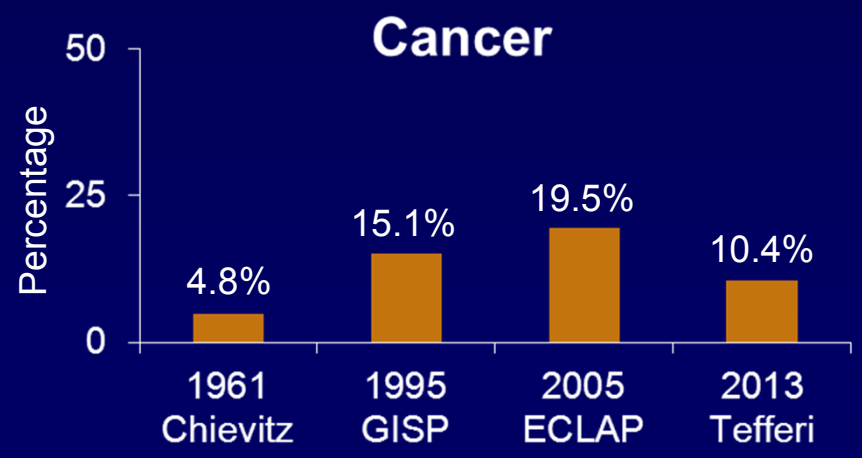
Tefferi A, et al. *Leukemia.* 2013;27(9):1874-1881.

Causes of Death in PV Patients







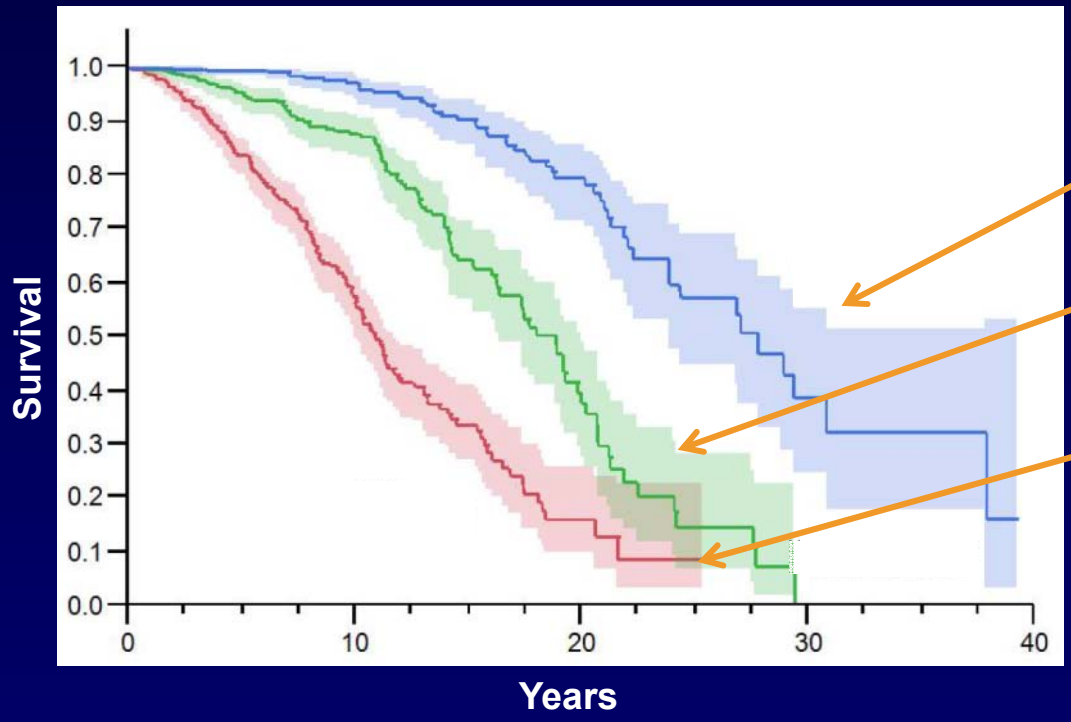


Thiede T, et al. *Acta Med Scand.* 1961;170:443-448. Gruppo Italiano Studio Policitemia. *Ann Intern Med.* 1995;123(9):656-664. Marchioli R, et al, *J Clin Oncol.* 2005;23(10):2224-2232. Tefferi A, et al, *Leukemia.* 2013;27(9):1874-1881.

Prediction of Survival in PV

Risk factors	
Age ≥67 years	5 points
Age 57-66 years	2 points
Leukocyte count ≥15 × 10^9/l	1 point
Venous thrombosis	1 point

Risk categories / score	
Low	0
Intermediate	1-2
High	≥ 3



N = 503 — 27.8 years

N = 474 — 18.9 years

N = 568 — 10.9 years

Median follow-up: 6.9 years (0-39)

Tefferi A, et al. *Leukemia.* 2013;27(9):1874-1881.

Take-Home Messages

- 2008 WHO PV criteria are inadequate for diagnosing a substantial number of patients who do not fulfill hemoglobin thresholds
- Hematocrit is a sensitive and specific surrogate of an increased red cell mass
- The inclusion of bone marrow morphology as a major diagnostic criterion requires a broad consensus among pathologists and hematologists