Primary Budd-Chiari Syndrome (Hepatic Venous Outflow Tract Obstruction)

Dominique-Charles Valla

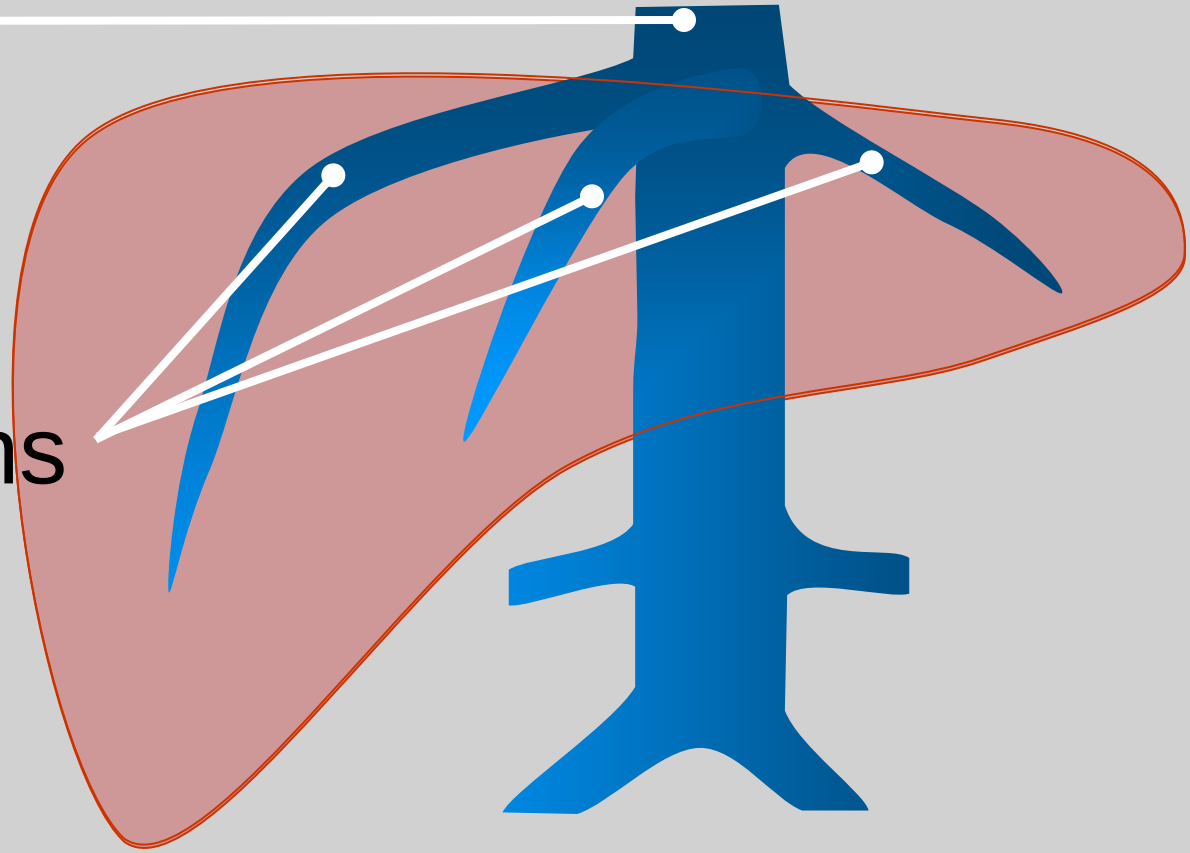
DHU UNITY
Service d'Hépatologie, Hôpital Beaujon (AP-HP), Clichy;
CRI-UMR1149, Université Paris-Diderot and Inserm U1149, Paris, France

BCS – Level of Obstruction in Europe

2% IVC

49% Combined

49% Hepatic veins



EN-Vie BCS Cohort. Darwish Murad. Ann Intern Med 2009

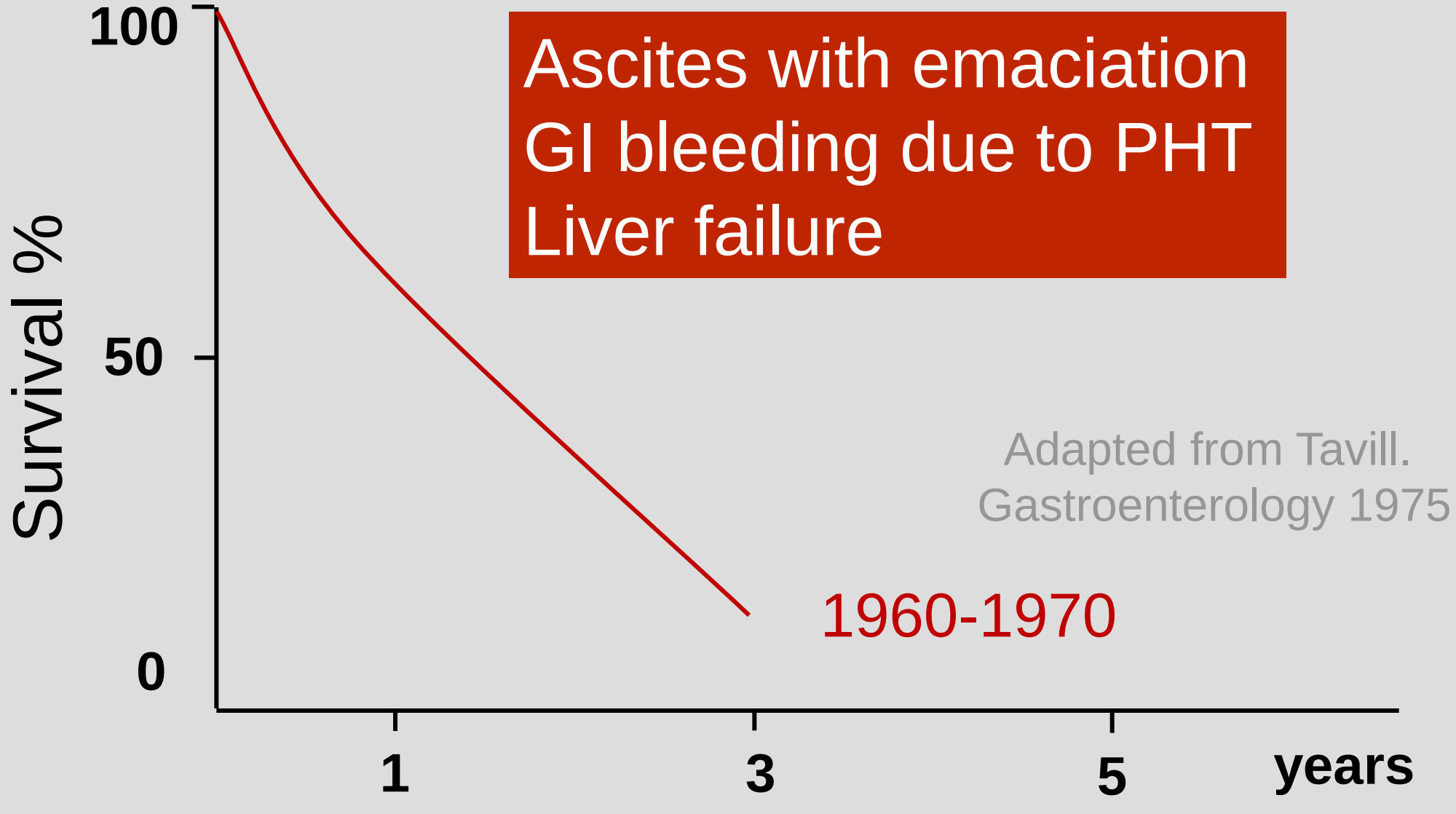
Epidemiology of BCS – France, 2010

	Questionnaire survey	Discharge code
Incidence (per 10^6 per yr)	0.37	0.80
Prevalence (per 10^6)	5.9	5.2

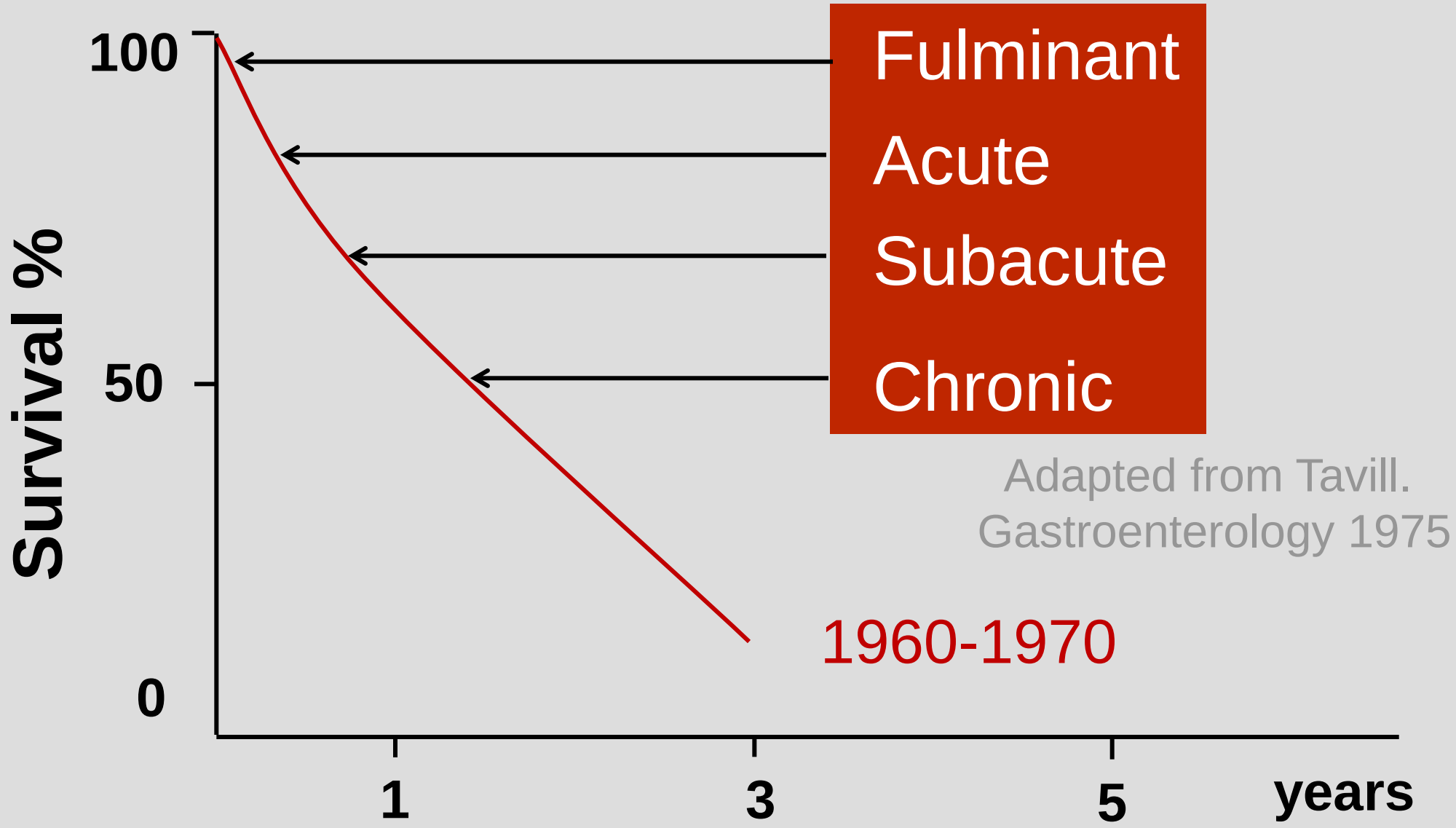
Romania: 100 – 150 cases ?

I. Ollivier and Réseau Français des Maladies Vasculaires du Foie. ILC Vienna 2015

Primary BCS – Natural History



Primary BCS – Natural History



Adapted from Tavill.
Gastroenterology 1975

Primary Budd-Chiari Syndrome

- Etiology
- Diagnosis
- Treatment
- Challenges

Prothrombotic Conditions in Western Budd-Chiari Syndrome

- At least one condition 87%
- Multiple conditions 48%
- Local factor 5%

A multifactorial systemic disorder

EN-Vie BCS Cohort. Darwish Murad Ann Intern Med 2009

Western Budd-Chiari Syndrome
Prevalence of Major Causes

- Myeloproliferative neoplasm 49%
- Paroxysmal nocturnal hemoglobinuria 10%
- Antiphospholipid syndrome 20%
- Factor V Leiden 12%

An underlying blood disorder is the rule

EN-Vie BCS Cohort. Darwish Murad Ann Intern Med 2009

Prothrombotic Disorders
Diagnostic Pitfalls

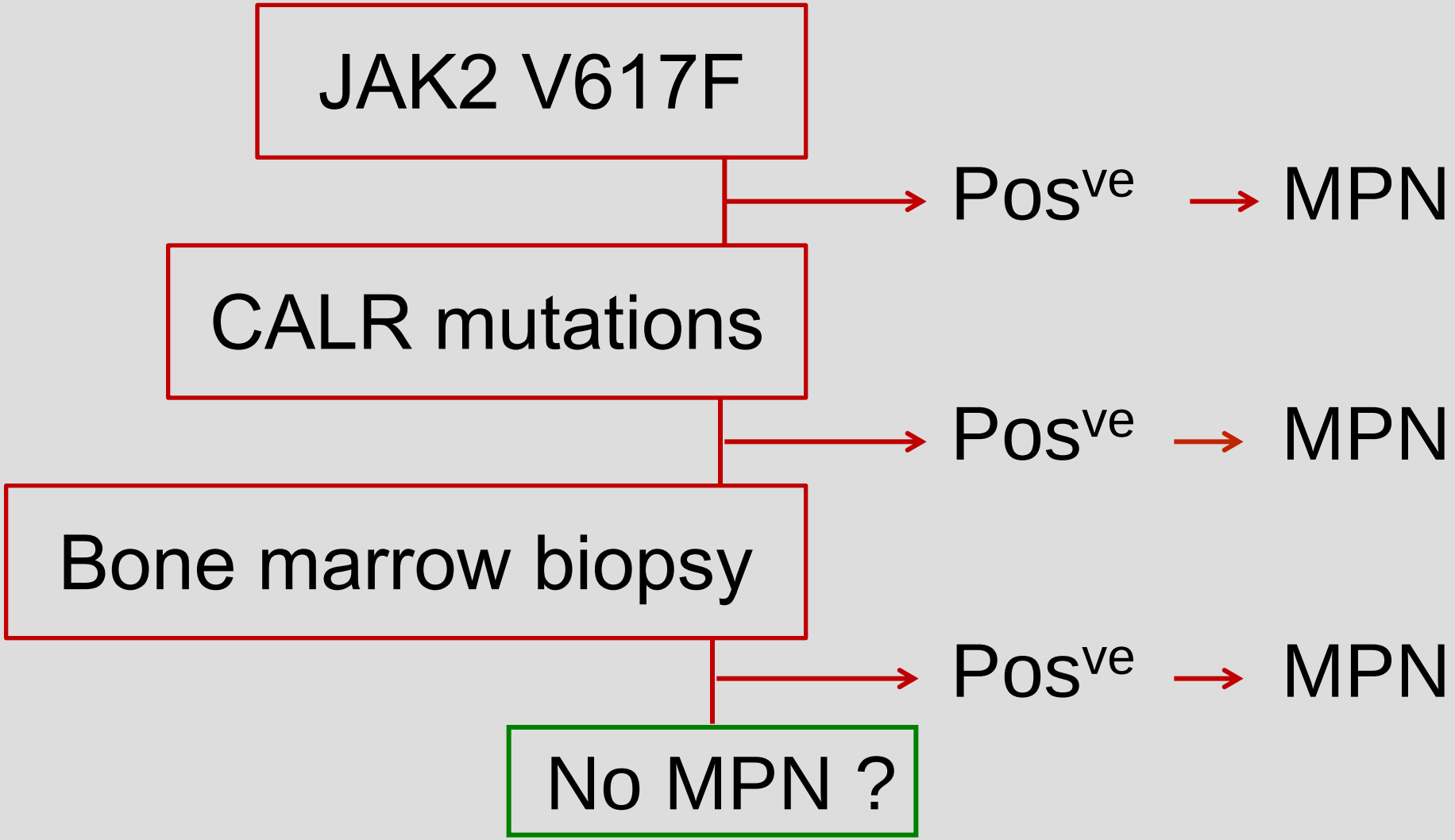
1. Liver dysfunction decreases PC, PS and AT plasma levels

→ *Molecular analyses*

2. Portal hypertension masks MPN. Hypersplenism decreases blood cell counts.

→ *V617F JAK2 & CALR mutations*

→ *Clusters of dystrophic megacaryocytes (BMB)*



Turon, J Hepatol 2014, Rautou, ILC 2015

Prothrombotic Conditions in Western Budd-Chiari Syndrome

- At least one condition 87%
- Multiple conditions 48%
- Local factor 5%

What is the local factor ?

EN-Vie BCS Cohort. Darwish Murad Ann Intern Med 2009

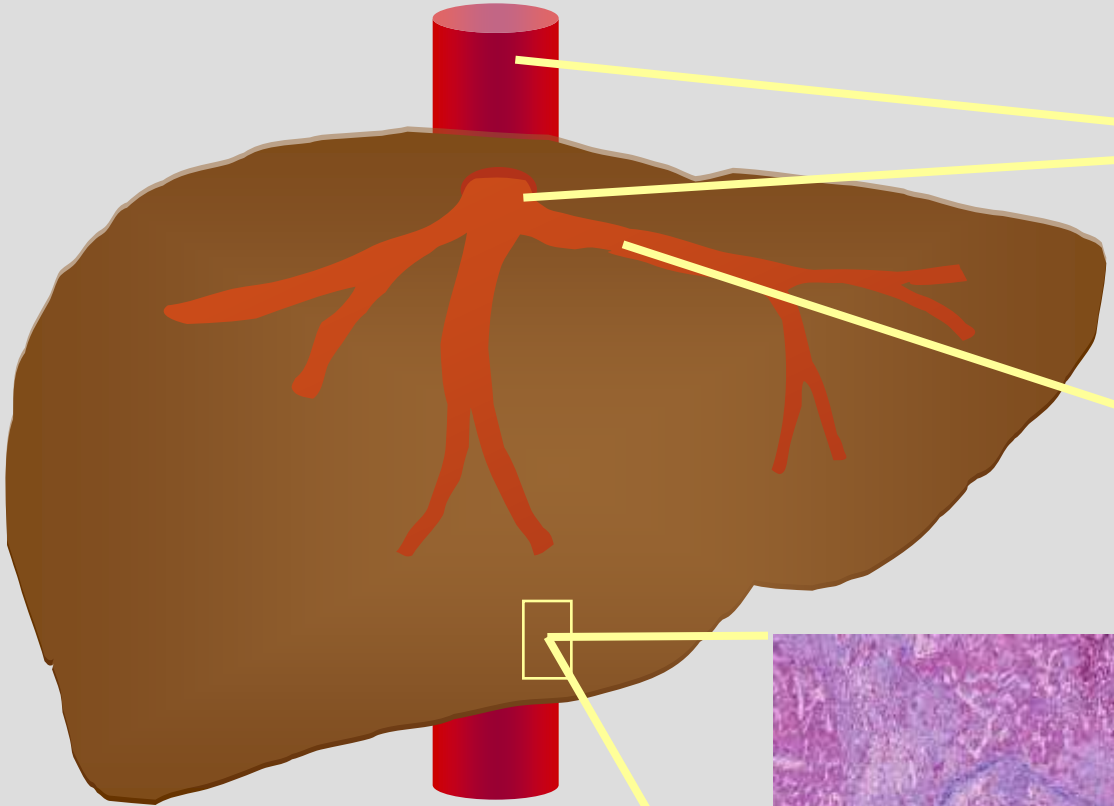
Site Specificity for Thrombosis in MPN

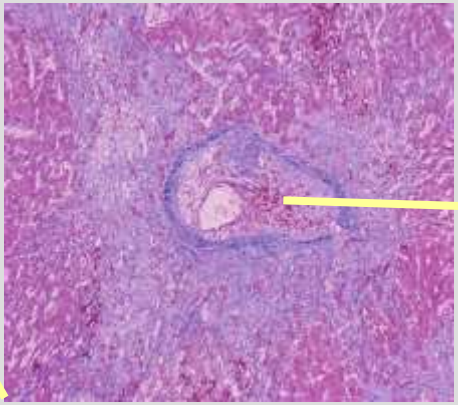
	V617F *JAK2*
Hepatic vein thrombosis	35-50%
Portal vein thrombosis	20-35%
Extra-splanchnic thrombosis	2%
General population	0,2%

Specificity of portal/hepatic venous endothelium ?

Mercier, NEJM 2007. Pardanani, Leukemia 2007.
Plessier, Hepatology 2009. Kiladjian, Blood 2008, Dentali, Blood 2009. Qi, APT 2011.

Primary Budd-Chiari Syndrome
Site Specificity in Prothrombotic Disorders





- Behcet's D.
- V Leiden
- Low SES

- MPD
- OC

- PNH

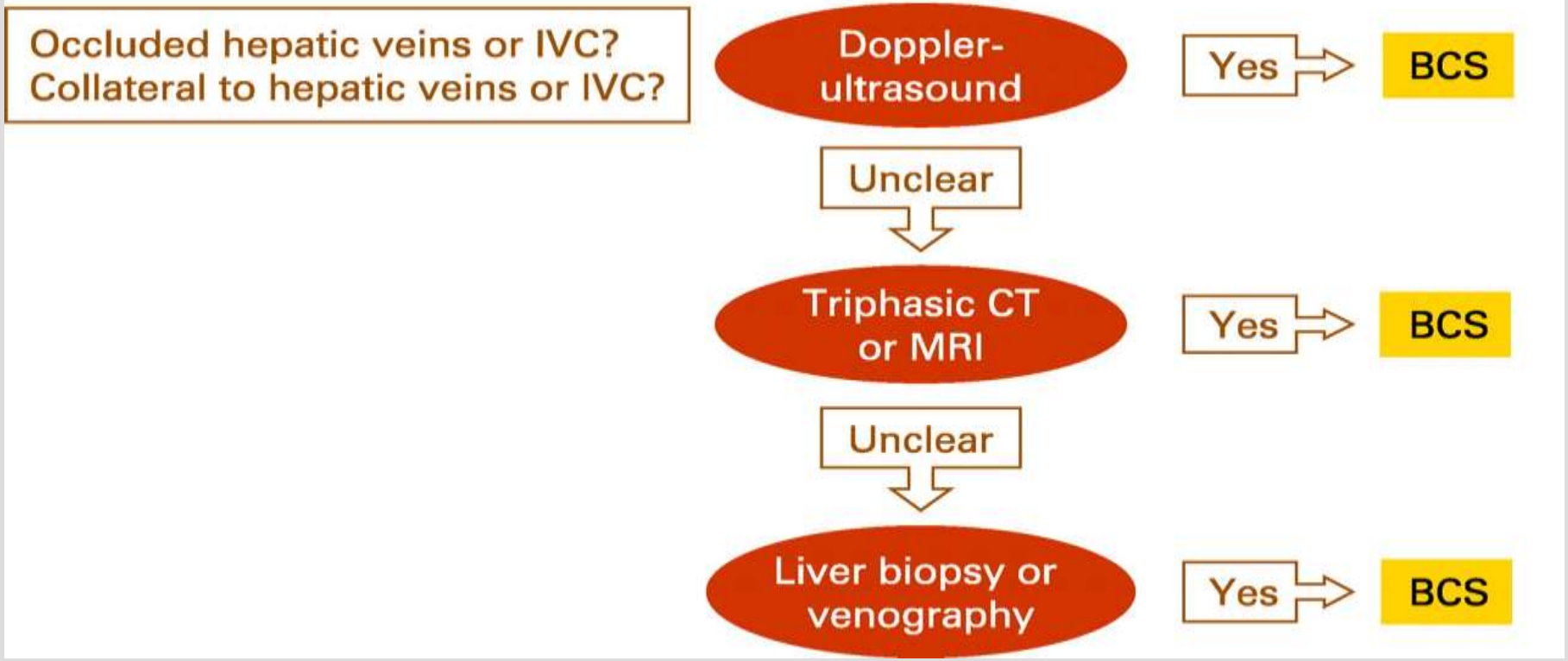
Valla J Hepatol 2009

Primary Budd-Chiari Syndrome

- Etiology
- Diagnosis
- Treatment
- Challenges

Diagnostic Strategy

Any patient with acute or chronic, symptomatic or asymptomatic liver disease

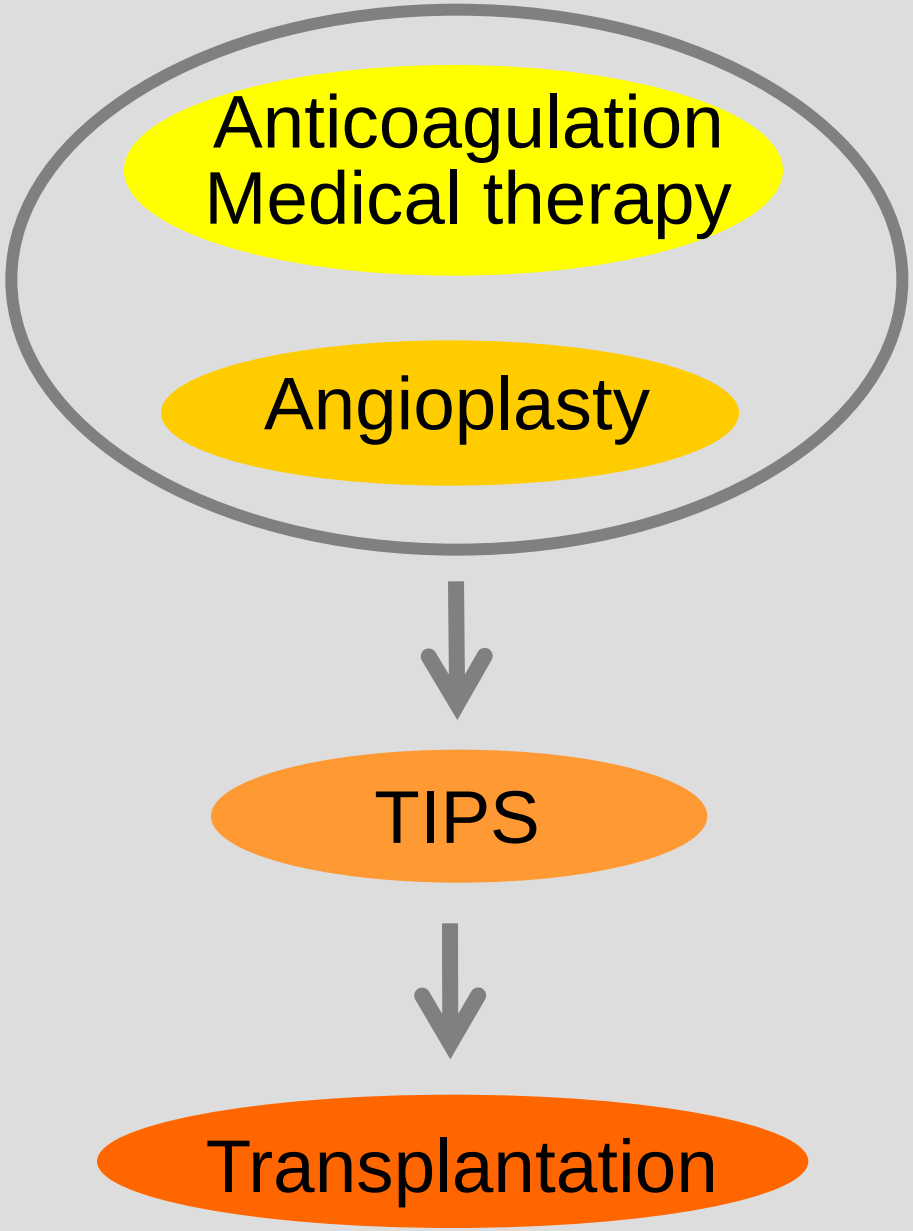


Valla, D-C Gut 2008;57:1469-1478

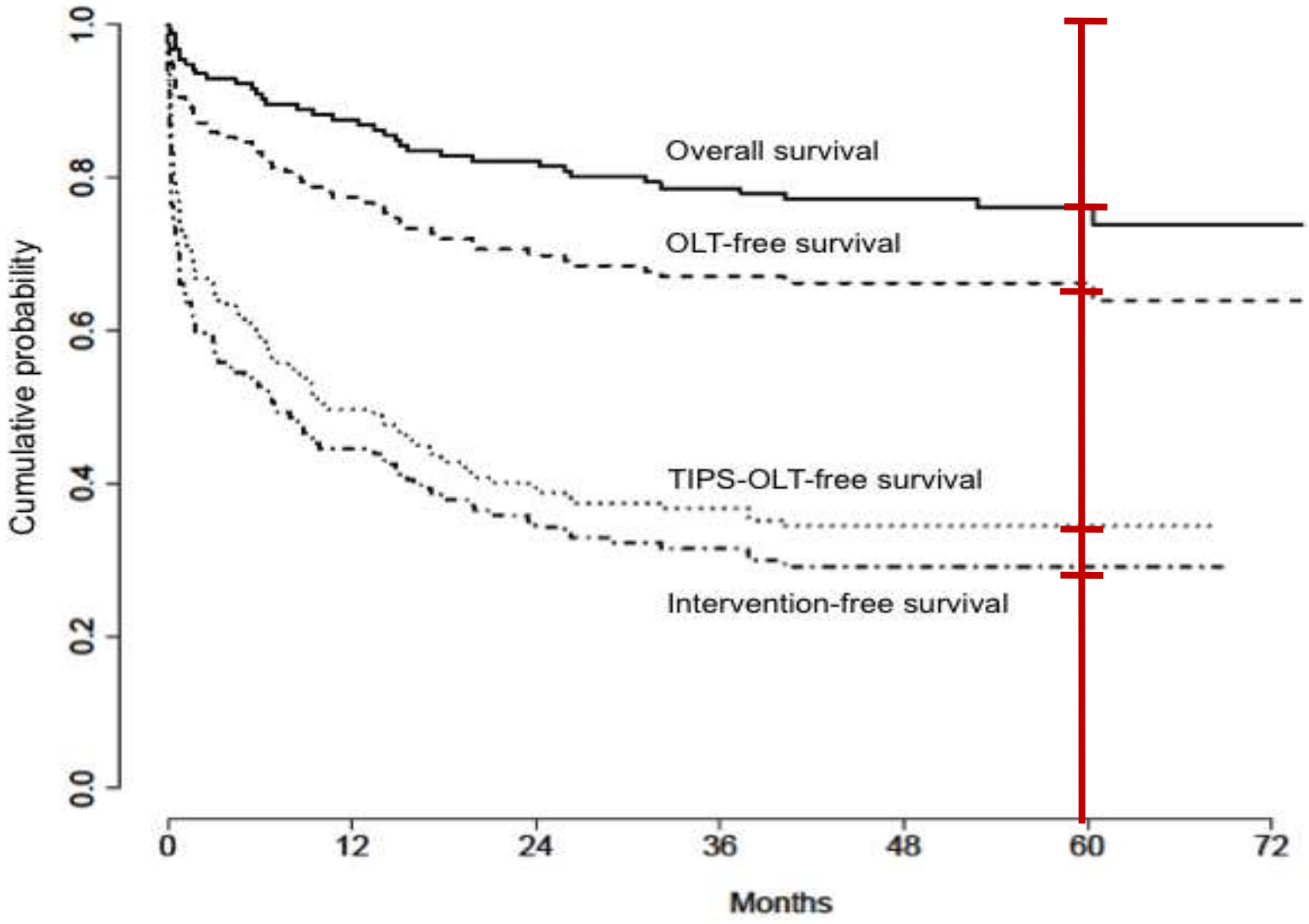
Primary Budd-Chiari Syndrome

- Etiology
- Diagnosis
- Treatment
- Challenges

EASL, Prague 2001. Baveno, 2005, 2010, 2015



Budd-Chiari Syndrome - Survival



26% †

13% LTx

39% TIPS

27% Tt méd.

EN-Vie cohort. Seijo. Hepatology 2013

Primary Budd-Chiari Syndrome

- Etiology
- Diagnosis
- Treatment
- Challenges

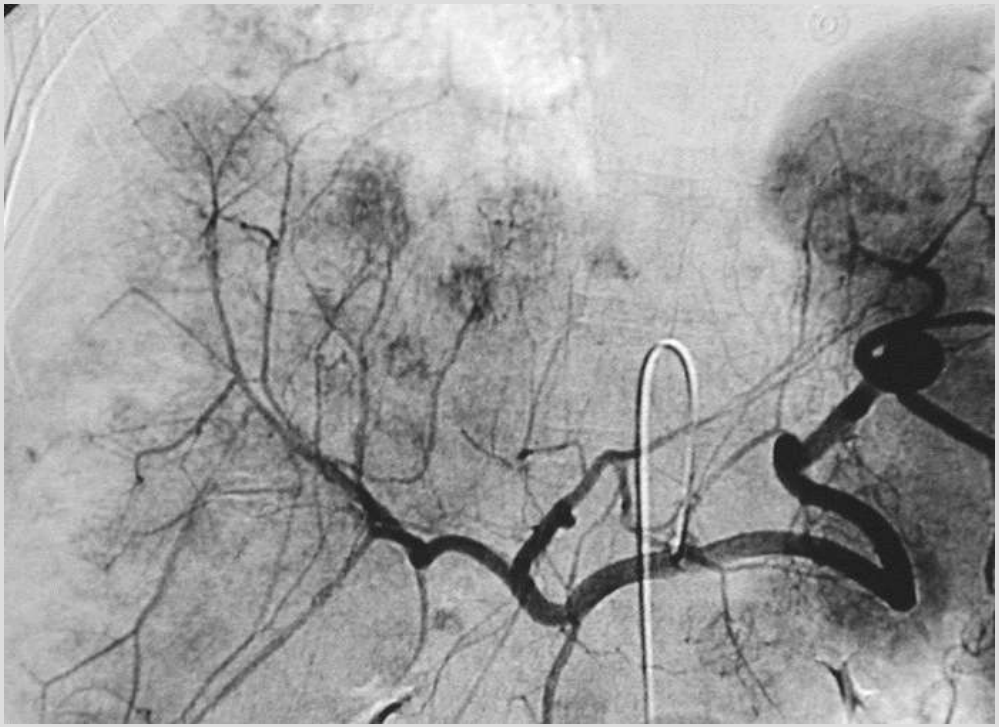
Budd-Chiari Syndrome
Current Challenges

- Complications of therapy
  - Encephalopathy related to TIPS
  - Bleeding related to anticoagulation therapy
- Prediction of treatment response
- Complications of blood disease
- Regenerative nodules and HCC

Cazals-Hatem, Hepatology 2003. Chait, Br J Haematol 2005. Moucari, Gut 2008. Garcia-Pagan, Gastroenterology 2008. Rautou, J Hepatol 2011. Seijo, Hepatology 2013.

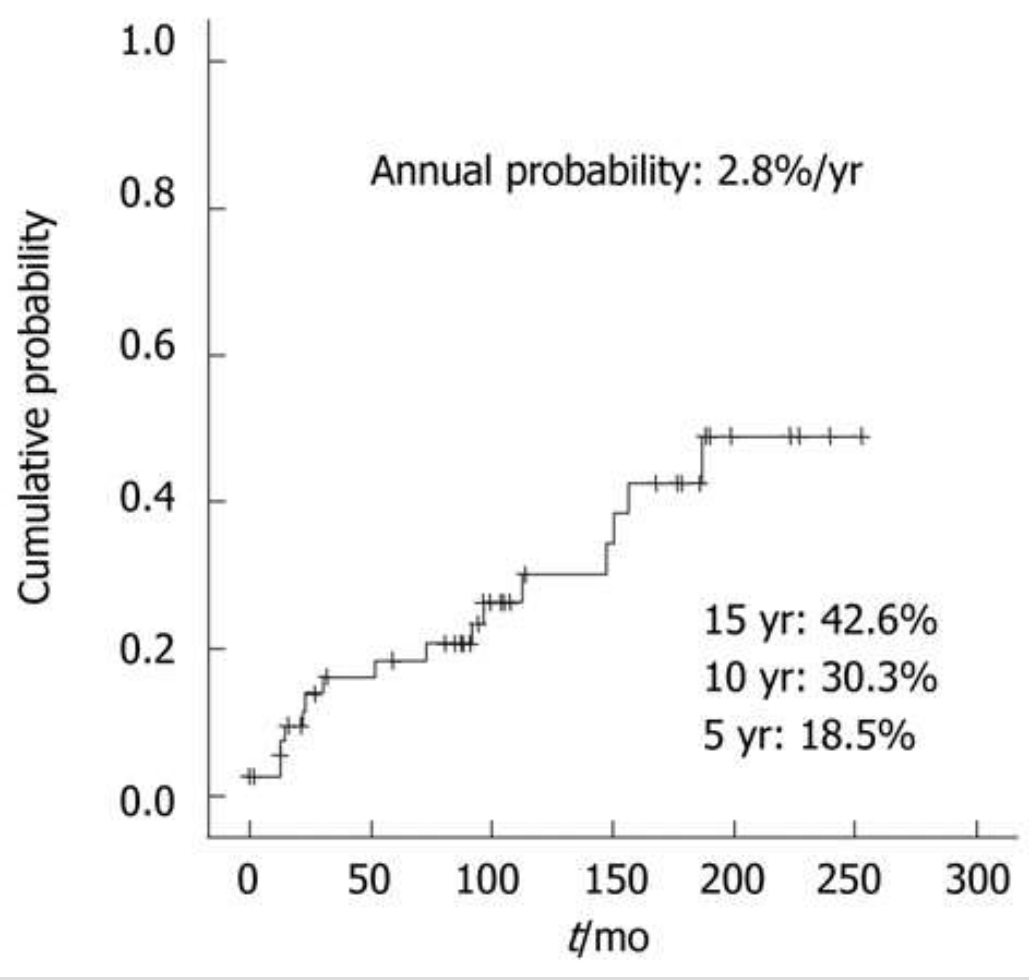
Budd-Chiari Syndrome

Regenerative changes
Macronodules



Cazals-Hatem. Hepatology 2003

BCS complicated by HCC



Park, WJG 2012.

1988-2008	N
Primary BCS	67
HCC	17

Pooled Prevalence
15.4%

Ren, EJGH 2013

BCS - HCC vs benign regenerative nodule

- Larger size (> 4cm)
- AFP > 20 ng/L
- Heterogeneous
- Hyperenhanced at arterial phase
- Wash-out at portal and/or late phase
- IVC obstruction

Moucari. Gut 2008. Gwon, Radiology 2010.
Liu, BMC Gastro 2013. Zhang Eur J Radiol 2012
Ren, EJGH 2013

Budd-Chiari syndrome - Conclusions

- A spontaneously fatal liver disease.
- Underlying blood disorder is the rule, with myeloproliferative neoplasm in the first place.
- BCS must be considered – and assessed with Doppler-US – in any patient with liver disease.
- Prognostication at baseline is not satisfactory.

Budd-Chiari syndrome - Conclusions

- Good results of a therapeutic strategy based on minimal invasiveness and stepwise approach.
- Severe treatment related complications
- Long-term outcome jeopardized by malignancy (underlying blood disease and HCC).
- Expert centers concentrating experience are needed.

BCS – Level of Obstruction

Country	Year	% IVC	% IVC+HV	% HV
Europe	2009	2	49	49
Japan	1995	13	81	6
China	2012	19	53	28
India	1994	20	56	24
Korea	2012	84	9	7

Darwish Murad, Ann Intern Med 2009. Sakr, WJG 2011. Dilawari, Medicine 1994. Okuda, J Hepatol 1995. Uskudar WJS 2008. Park WJG 2012. Han Radiology 2012

V617F-JAK2 in Xi'an, China

Primary BCS	4/77	5.2%
Primary portal vein thrombosis	15/55	27.3%
Cirrhotic portal vein thrombosis	1/64	1.6%

Qi. J Gastroenterol Hepatol 2012

Endemicity and clinical picture of liver disease due to obstruction of the hepatic portion of the inferior vena cava in Nepal

SANTOSH M SHRESTHA,* KUNIO OKUDA,† TOSHIKAZU UCHIDA,‡ KRISHNA GOPAL MAHARJAN,* SHOBHANA SHRESTHA,§ BISHNU L JOSHI,# STIG LARSSON** AND YOGESH VAIDYA††

	IVC obstruction ($n = 150$)	Control ($n = 150$)
Residence		
Rural	124 (83%)	87 (58%)
Urban	26 (17%)	63 (42%)
Economic status		
Low	134 (89%)	58 (39%)
Middle	16 (11%)	89 (59%)
High	0	3 (2%)
Profession		
Farmer	113 (75%)	45 (30%)
Others	37 (25%)	105 (70%)
Educational level		
Illiterate*	117 (78%)	71 (47%)
Middle school	29 (19%)	43 (29%)
High school	4 (3%)	36 (24%)

*Never went to school. The literacy rate in Nepal is 35% according to the Statistical Pocket Book, 1990.

Shresta J Gastroenterol Hepatol 1996

Meta-analysis - Thrombophilia and BCS

	OR	95% CI
FV Leiden	1.8	1.1 - 3.1
Prothrombin G20210A	5.0	3.0 - 8.3
C677T MTHFR +/+	2.0	1.1 - 3.61
Hyperhomocysteinemia	2.6	1.2 – 5.5
Antithrombin deficiency	8.9	2.3 - 33.7
Protein C deficiency	17.6	2.0 - 158.2
Protein S deficiency	8.0	1.6 - 39.9

Qi. J Gastroenterol Hepatol 2013, Hepatol Research 2014, Clin Gastroenterol Hepatol 2014

Vascular Liver Diseases	*N*	254
DNA available	*N*	206
Selective PC or PS deficiency	*N*	35

PC deficiency (mean level 53%)	*N*	18
Deleterious *PROC* mutation	*N*	5
	%	28

PS deficiency (mean level 44%)	*N*	17
Deleterious *PROS1* mutation	*N*	4
	%	24

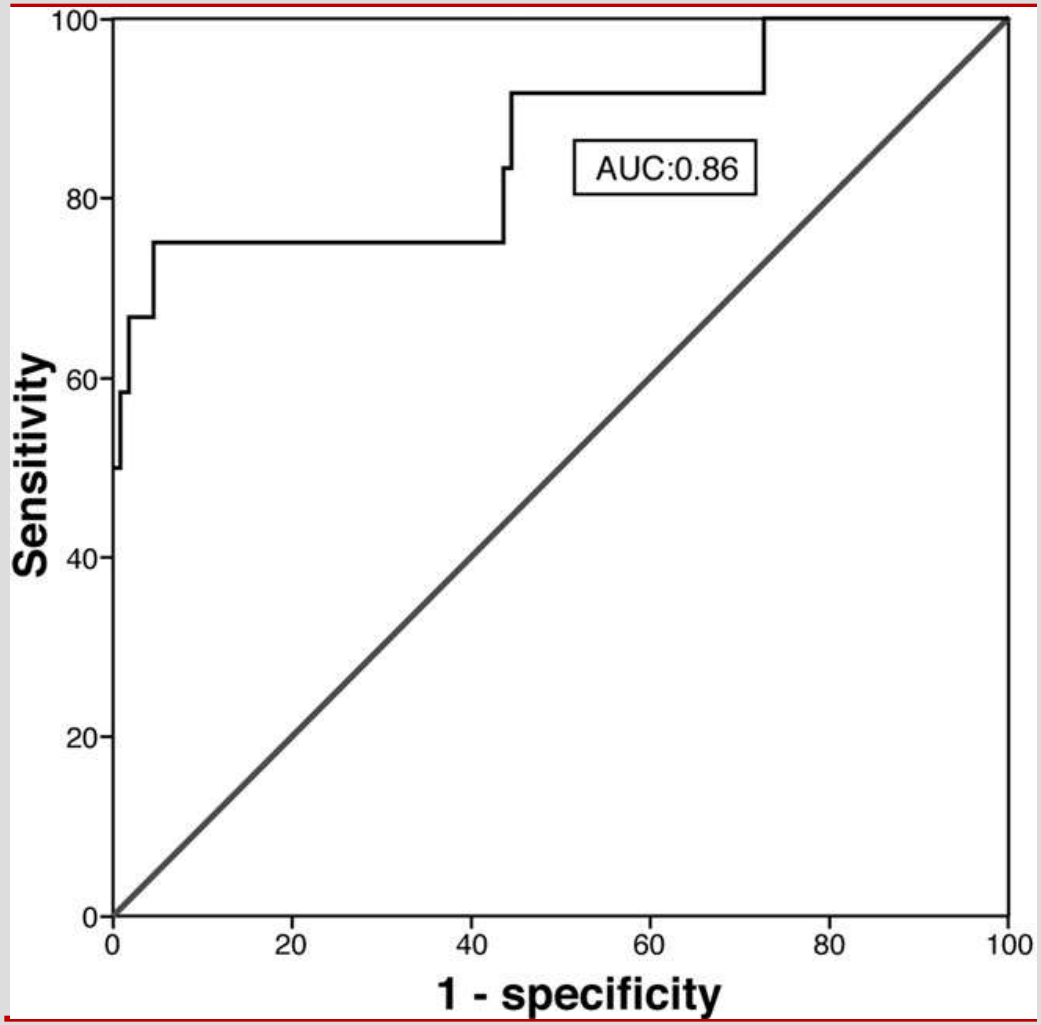
Plessier, Alhenc-Gelas et al., AFEF 2014 – BCS 74, PVT 150, OPV 30

Prognostic Scores for BCS

	Survival without LTx	
	AUROC	ρ^2
Child-Pugh	0.666	0.16
MELD	0.693	0.27
Clichy	0.619	0.22
Rotterdam	0.670	0.14

Rautou. Am J Gastro 2009

Prognostic Scores for BCS



OLT-free survival

BCS TIPS PI Score
0.08 x age +
0.16 x bilirubin +
0.63 x INR

Garcia-Pagan, Gastroenterology 2008

BCS – Level of Obstruction

Country	Year	% IVC	% IVC+HV	% HV
Europe	2009	2	49	49
Turkey	2008	23	30	47
Egypt	2011	3	17	74
Japan	1995	13	81	6
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Darwish Murad, Ann Intern Med 2009. Sakr, WJG 2011. Dilawari, Medicine 1994. Okuda, J Hepatol 1995. Uskudar WJS 2008. Park WJG 2012. Han Radiology 2012

Budd-Chiari Syndrome – TIPS

Hepatic Encephalopathy

• Total number of patients	127
• 1-year probability *%*	21
• Median time to 1st episode *months*	1.2
• Number transient	22
• Number recurrent	4

Garcia-Pagan Gastroenterology 2008

BCS - Bleeding on Anticoagulation Therapy

	N		N Death	
Prolonged Anticoagulation	139	89%		
Bleeding	24	17%	3	2%
Portal hypertension	14		2	
Intracranial	3		1	
Other	7		0	

Seijo. Hepatology 2013

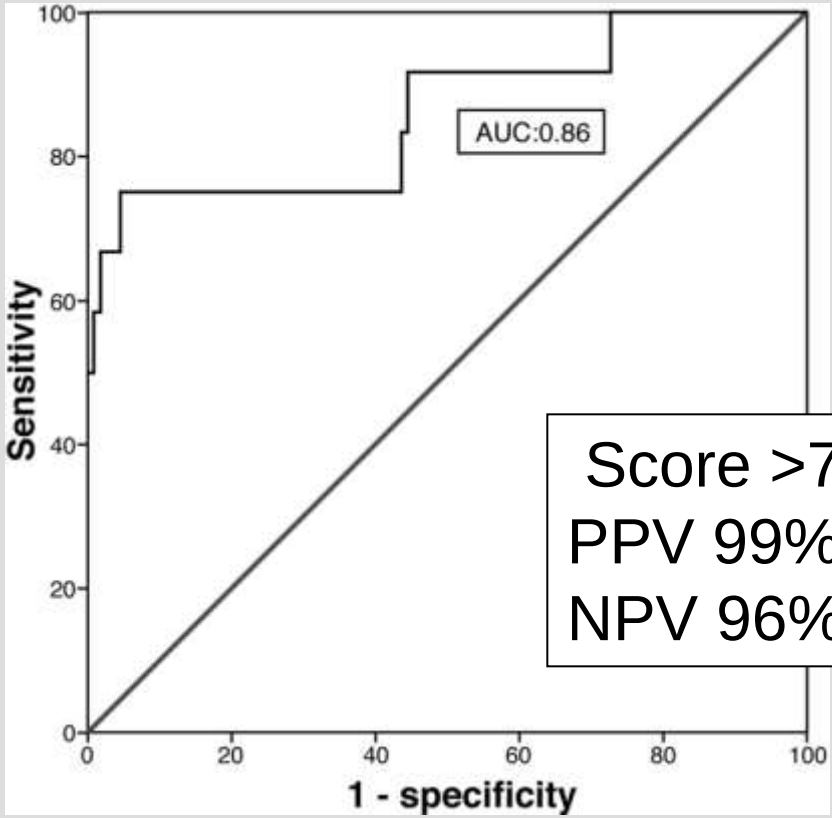
Anticoagulation
Medical therapy

Angioplasty

TIPS

Transplantation

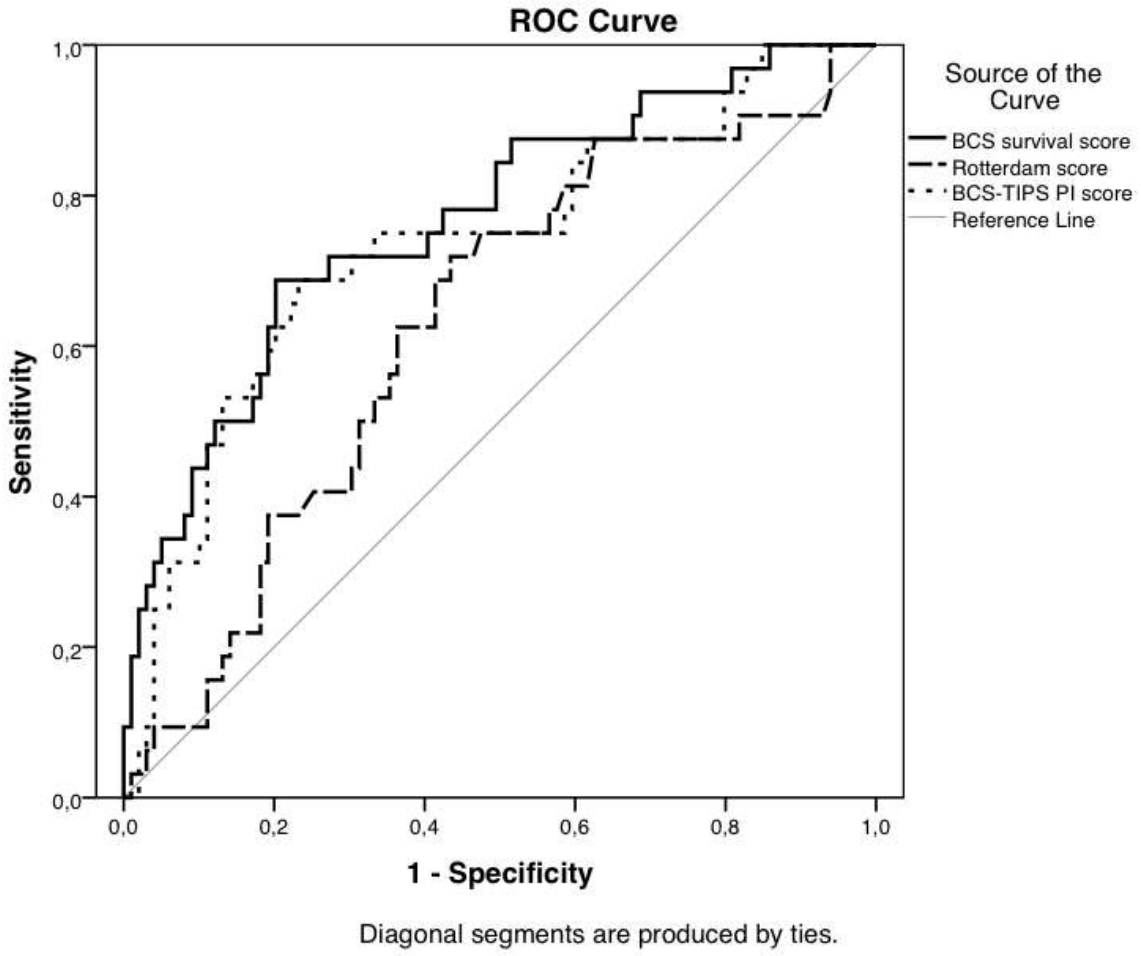
BCS TIPS PI Score
0.08 x age +
0.16 x bilirubin +
0.63 x INR



Score >7 :
PPV 99%
NPV 96%

1-yr OLT-free survival

Prognostic Scores for BCS



Rotterdam score

1.27 x encephalopathy +
1.04 x ascites +
0.72 x prothrombin time +
0.004 x bilirubin

AUC 0.640

BCS TIPS PI Score

0.08 x age +
0.16 x bilirubin +
0.63 x INR

AUC 0.734

BCS Survival score

0.37 x age/10 +
0.809 x ln creatinine +
0.496 x ln bilirubin

AUC 0.767

Seijo. Hepatology 2013

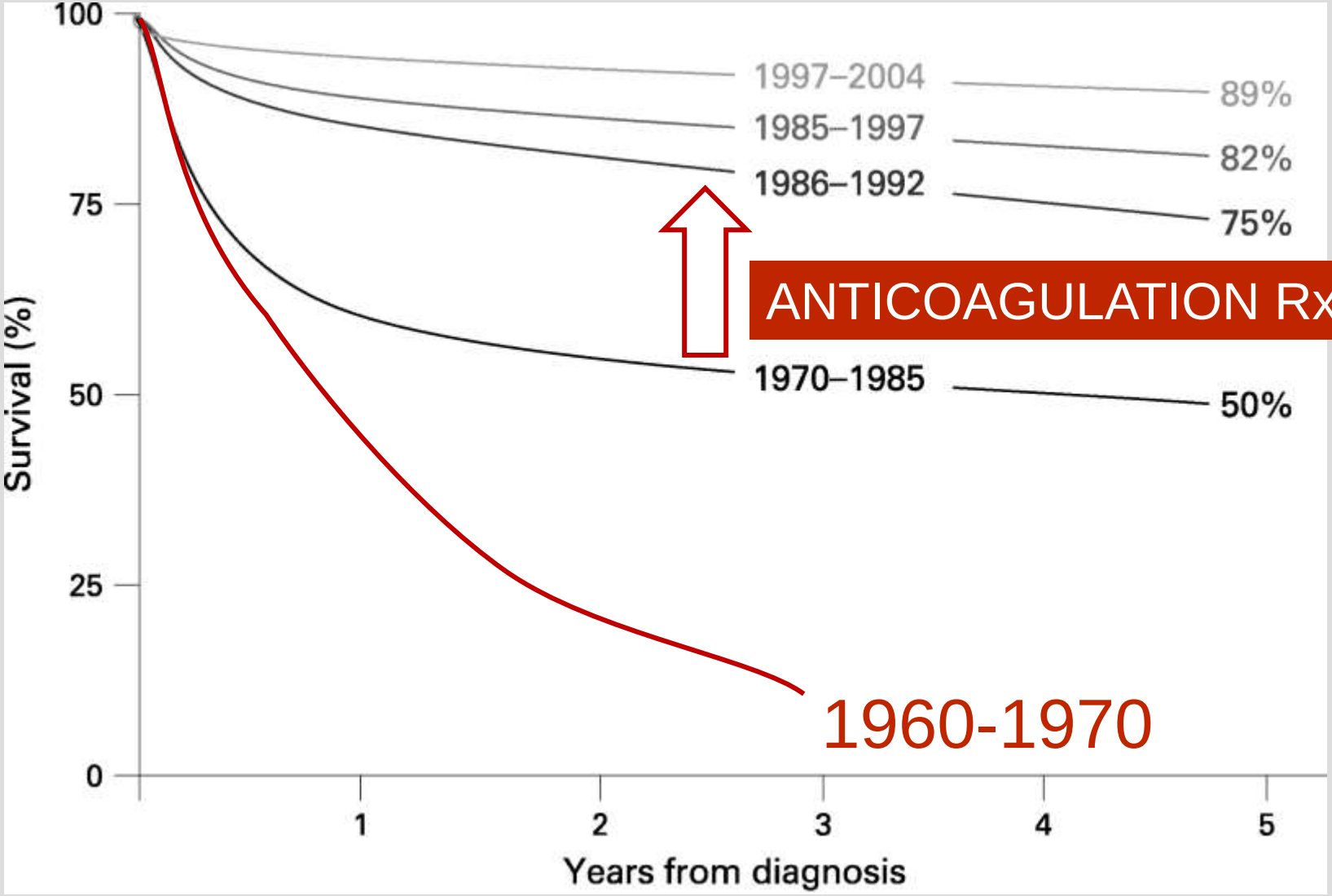
HCC - BCS vs HBV

- Peripheral
- Pauci-nodular
- Well differentiated
- Portal venous invasion uncommon

Selective TACE well tolerated ?

Shin Eur J Gastroenterol Hepatol 2004. Liu, BMC Gastro 2013. Gwon, Radiology 2010

BCS - Improved survival over 50 years



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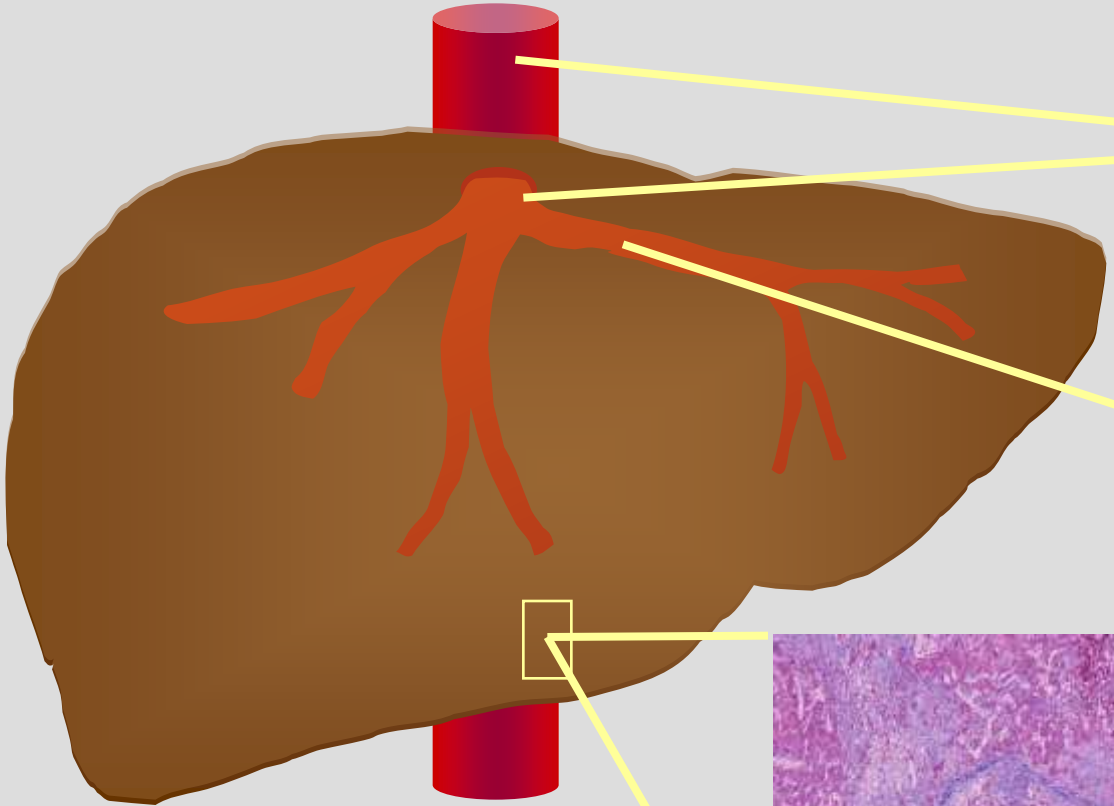
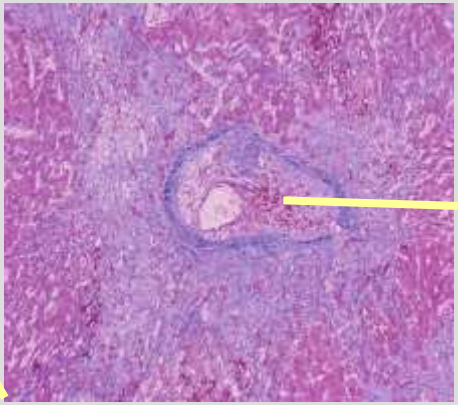
Primary Budd-Chiari Syndrome
Site Specificity in Prothrombotic Disorders





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- MPD
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Valla J Hepatol 2009