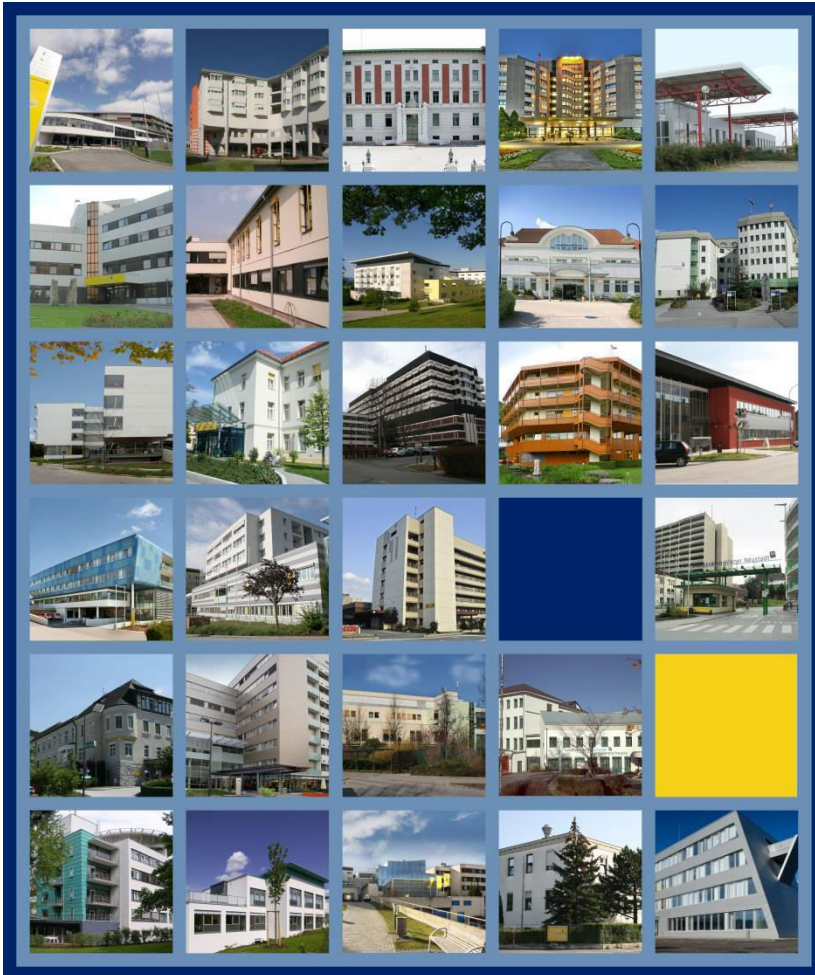


Metabolische Veränderungen nach Leberresektion

Friedrich LÄNGLE

Chirurgische Abteilung



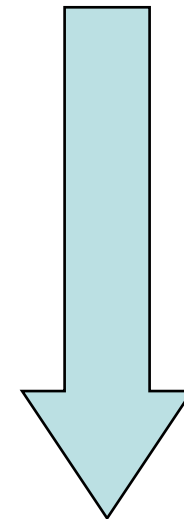
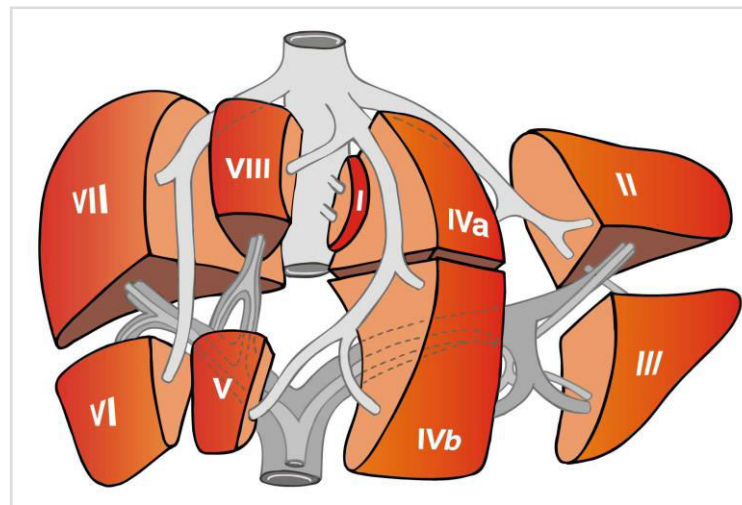
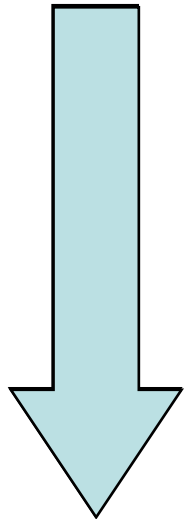
2012 Liver resections in the 21st century: we are far from zero mortality

Domak S., Belghiti J. HPB 2013

- Liver resections from 2000-2009
- Pts operated for malignancy 66,4% in 2000 - 82,3% in 2009
- Mortality: 3,5%
 - malignant lesions: 4,5% vs benign lesions: 0,7%
 - older, greater comorbidity, parenchymal disease
- Risk factors for mortality (multivariate analysis)
 - Age > 60
 - ASA classification ≥ 3
 - Major resection
 - Vascular procedure
 - Severe fibrosis (F3-F4)
 - Steatosis > 30%

Technical resectability

Functional resectability

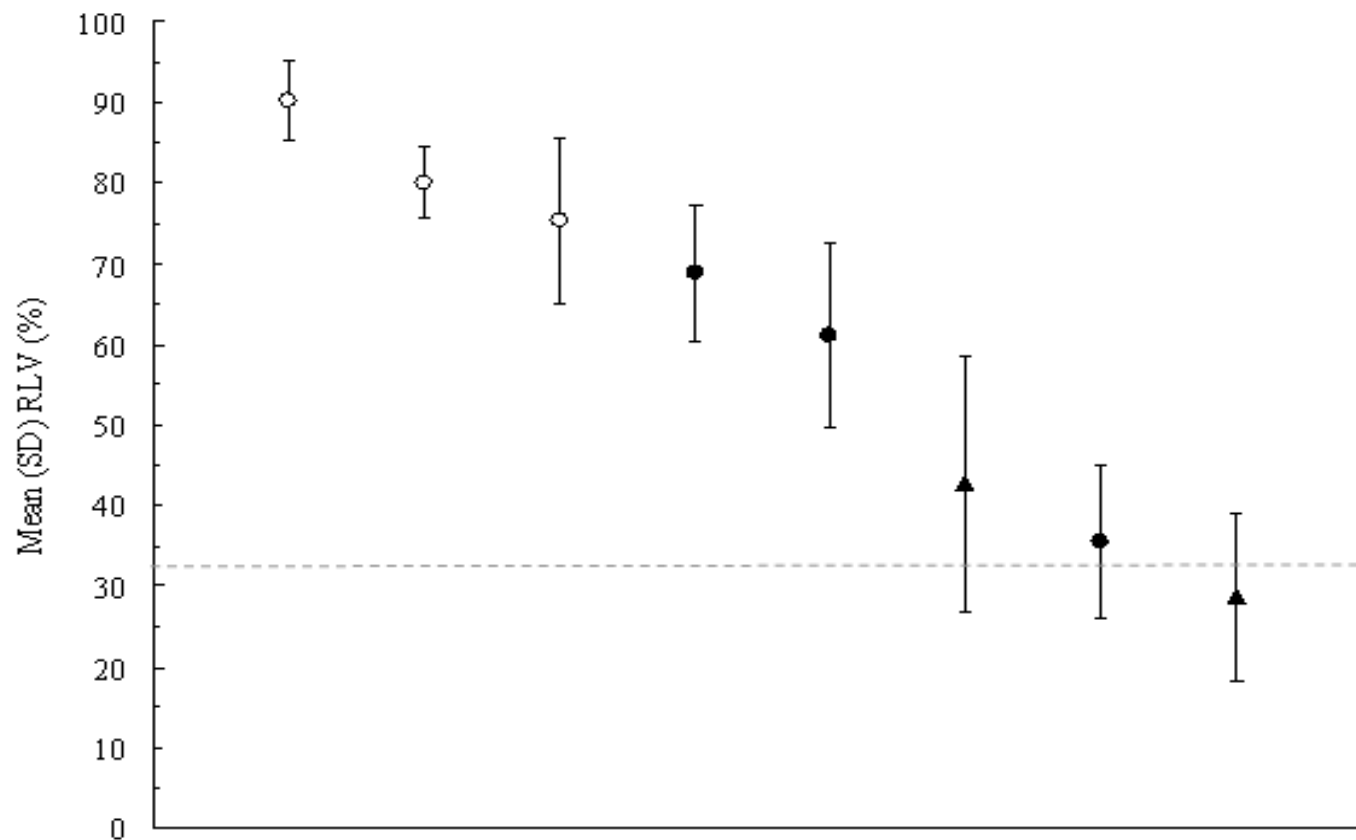


Type of resection
R0



Liver remnant

Restleber-Volumen und Art der Resektion

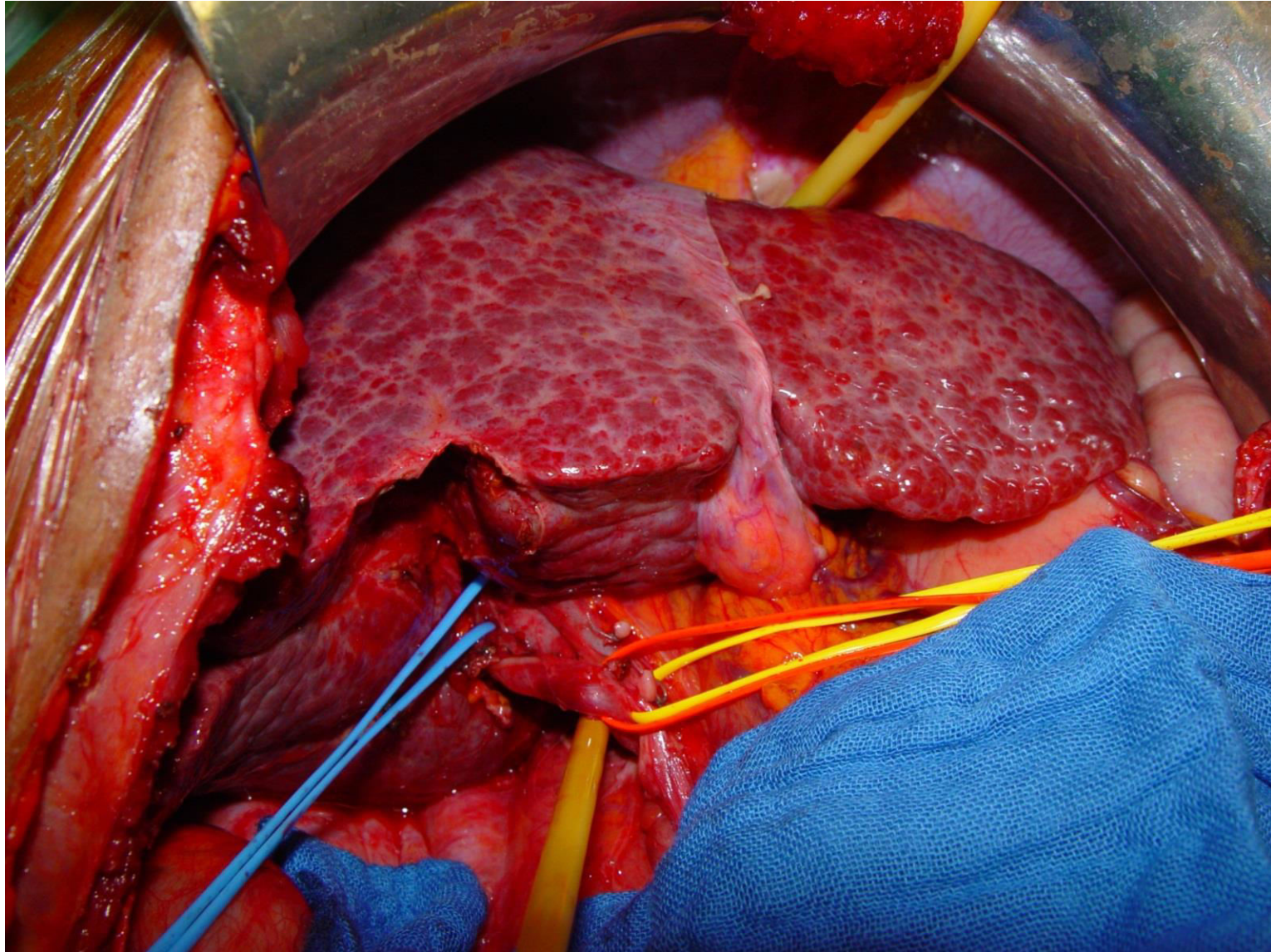


Volumen der Restleber
(25-30% RLV)

Prä-operative Faktoren
(Fibrose, Zirrhose,
CASH, Ikterus, Adipositas)

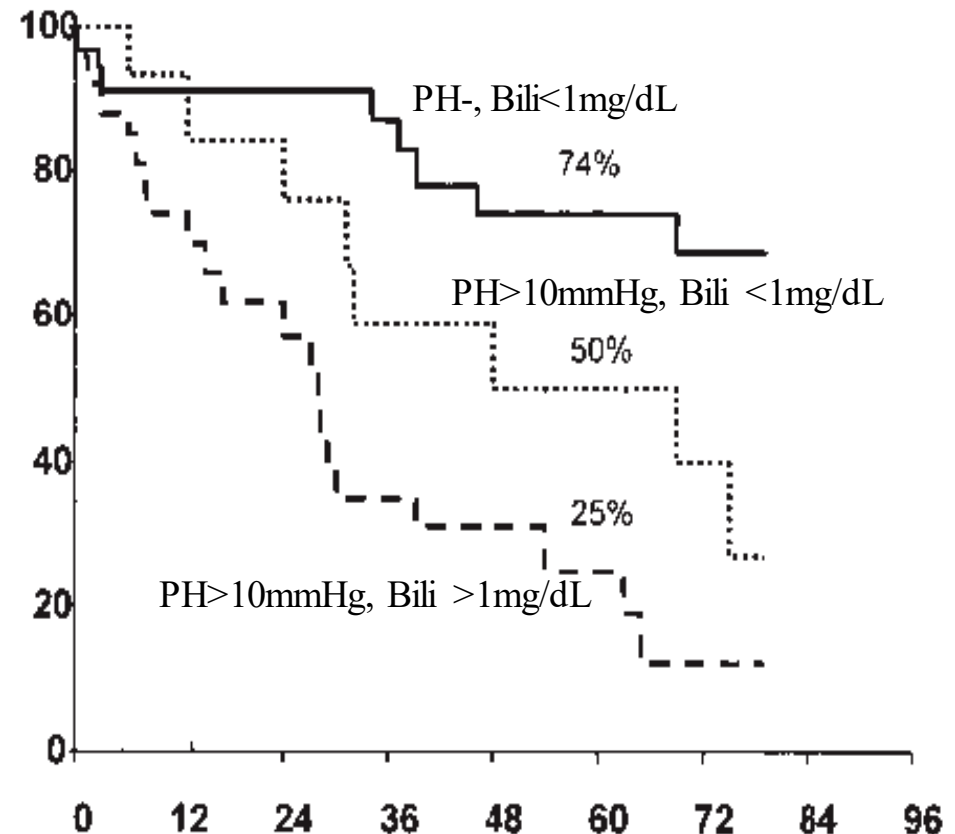
Intra-operative Faktoren
(Pringle, Blutung,
OP Zeit,...)

Funktion der Restleber

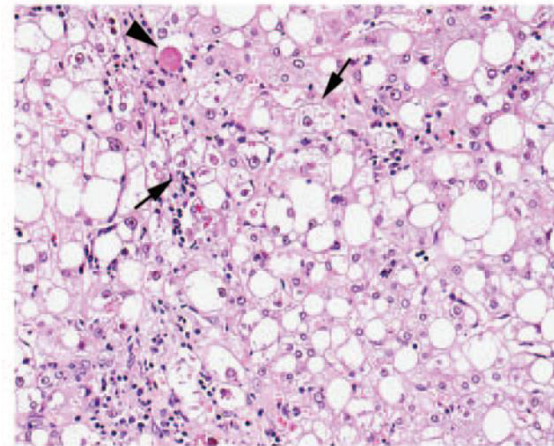
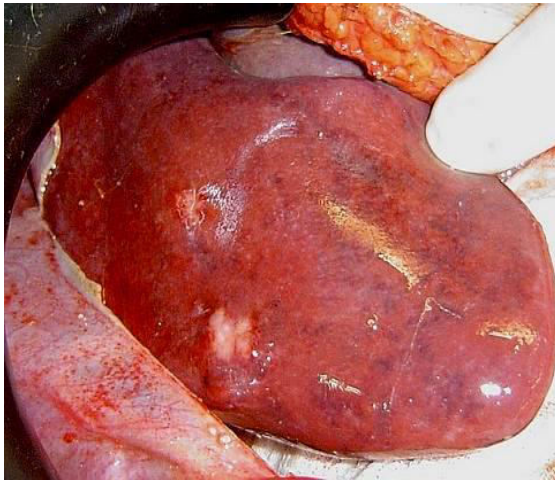
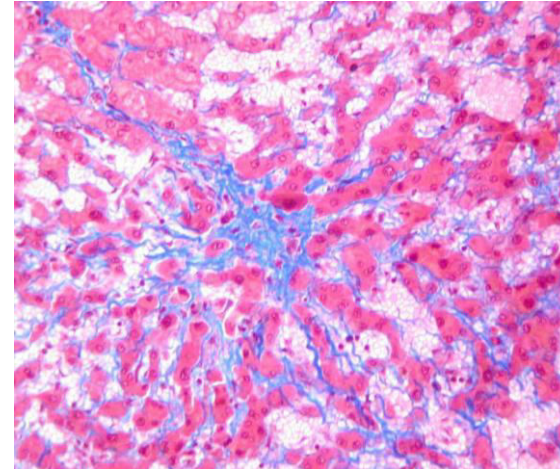
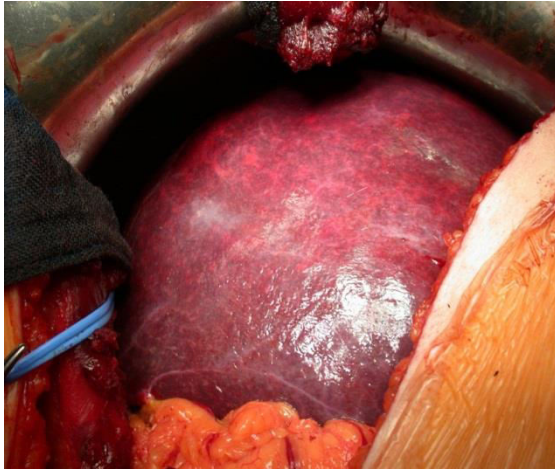


Optimal candidates for long-term survival

- well preserved liver function
- absence of clin. rel. port. hypertension
- normal bilirubin
- small asymptomatic tumour



Neoadjuvante Chemotherapie



Courtesy of Professor Gilles Mentha, University of Geneva
Vauthey J-N, et al. *J Clin Oncol* 2006; 24: 2065–2072.

Influence of Preoperative Chemotherapy on the Risk of Major Hepatectomy for Colorectal Liver Metastases



Mehdi Karoui, MD,* Christophe Penna, MD,* Mohamed Amin-Hashem, MD,† Emmanuel Mitry, MD,‡
 Stephane Benoist, MD, PhD,* Brigitte Franc, MD,† Philippe Rougier, MD,‡
 and Bernard Nordlinger, MD*

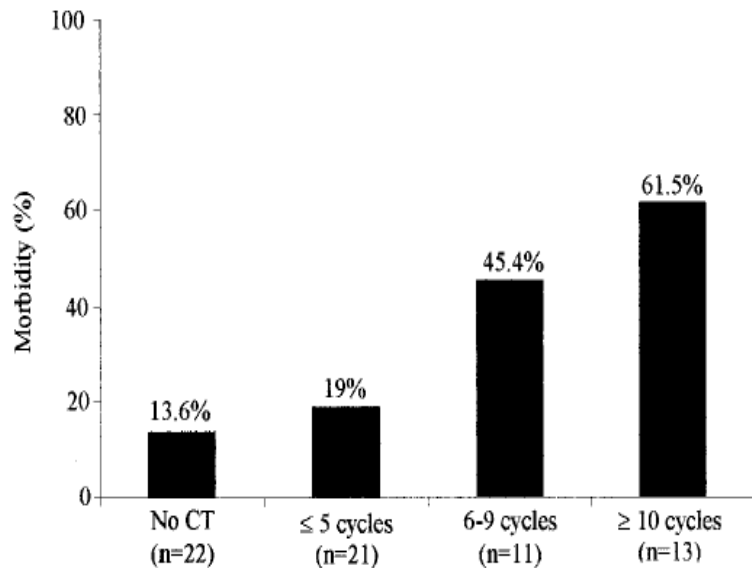


TABLE 5. Predictive Factors for Postoperative Morbidity: Logistic Regression Model

Variable	Odds Ratio	95% CI	P
Associated GI procedure			
No	1	2.3–86.0	0.004
Yes	14.0		
Blood transfusion			
No	1	1.6–24.5	0.008
Yes	6.2		
Preoperative chemotherapy			
No	1	1.03–29.8	0.046
Yes	5.5		

Was bedeutet „Leberfunktion“ ?

Synthese: Proteine, Zucker, Fettsäuren, Galle

Störung: Blutgerinnung, Aszites

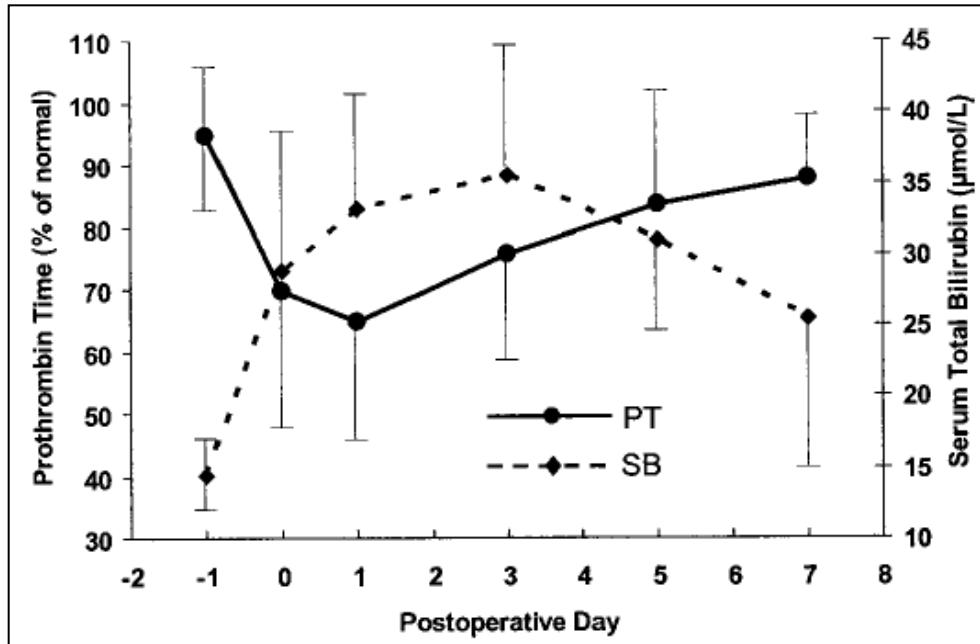
Entgiftung: körpereigene und –fremde Stoffe

Störung: Hyperammonämie, Enzephalopathie, Ikterus

Abwehr: Phagozytose von Mikroorganismen

Synthese von Akutphaseproteinen

Störung: Infektion



„50 – 50 Regel“

Gesamt Serumbilirubin (>50µmol/l) und Prothrombinzeit (<50%)
am 5. postoperativen Tag = 50% Mortalität nach Leberresektion

Posthepatectomy liver failure: A definition and grading by the International Study Group of Liver Surgery (ISGLS)

Table II. Consensus definition and severity grading of posthepatectomy liver failure (PHLF) by the International Study Group of Liver Surgery (ISGLS)

Definition	A postoperatively acquired deterioration in the ability of the liver (in patients with normal and abnormal liver function) to maintain its synthetic, excretory, and detoxifying functions, characterized by an increased INR (or need of clotting factors to maintain normal INR) and hyperbilirubinemia (according to the normal cut-off levels defined by the local laboratory) on or after postoperative day 5. If INR or serum bilirubin concentration is increased preoperatively, PHLF is defined by an increasing INR (decreasing prothrombin time) and increasing serum bilirubin concentration on or after postoperative day 5 (compared with the values of the previous day). Other obvious causes for the observed biochemical and clinical alterations such as biliary obstruction should be ruled out.
Grade	
A	PHLF resulting in abnormal laboratory parameters but requiring no change in the clinical management of the patient.
B	PHLF resulting in a deviation from the regular clinical management but manageable without invasive treatment.
C	PHLF resulting in a deviation from the regular clinical management and requiring invasive treatment.

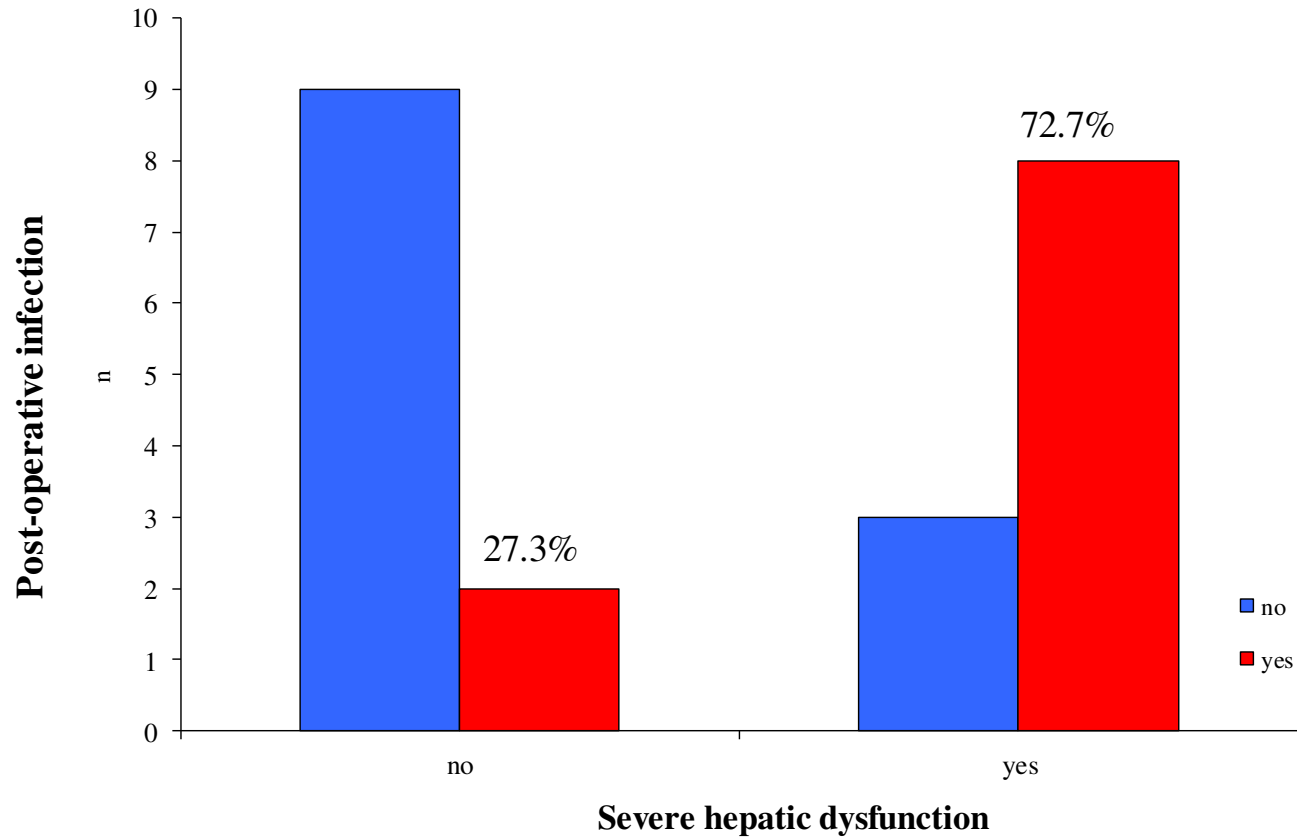
Definition of Post-operative Hepatic Dysfunction and its Correlation with Residual Liver Volume

Table 1 Definition of postoperative hepatic dysfunction based on results from blood tests and clinical observation

Total serum bilirubin ($\mu\text{mol/l}$)	≤ 20	21–60	>60
Prothrombin time (seconds above normal)	<4	4–6	>6
Serum lactate (mmol/l)	≤ 1.5	1.6–3.5	>3.5
Encephalopathy grade	No	1 and 2	3 and 4
	0	1	2
Severity of hepatic dysfunction	None (0), mild (1–2), moderate (3–4), severe (>4)		

M J Schindl, D N Redhead, K C H Fearon, O J Garden, S J Wigmore, on behalf of the Edinburgh Liver Surgery and Transplantation Experimental Research Group (eLISTER)
Gut 2005;54:289–296.

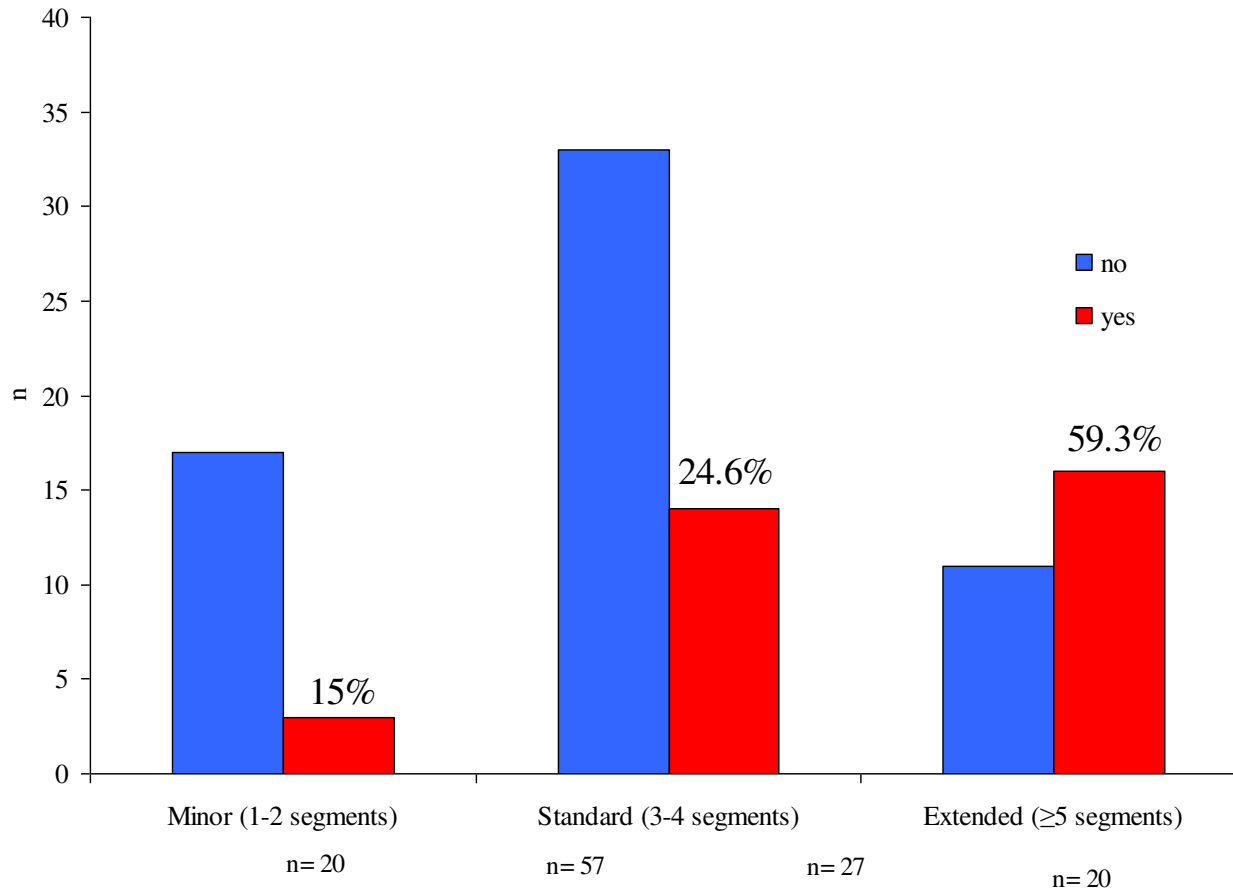
The association between hepato-cellular function and infection



Post-op infection after liver resection with small residual liver volume (<26.6%): Fisher's Exact Test , p=0.030

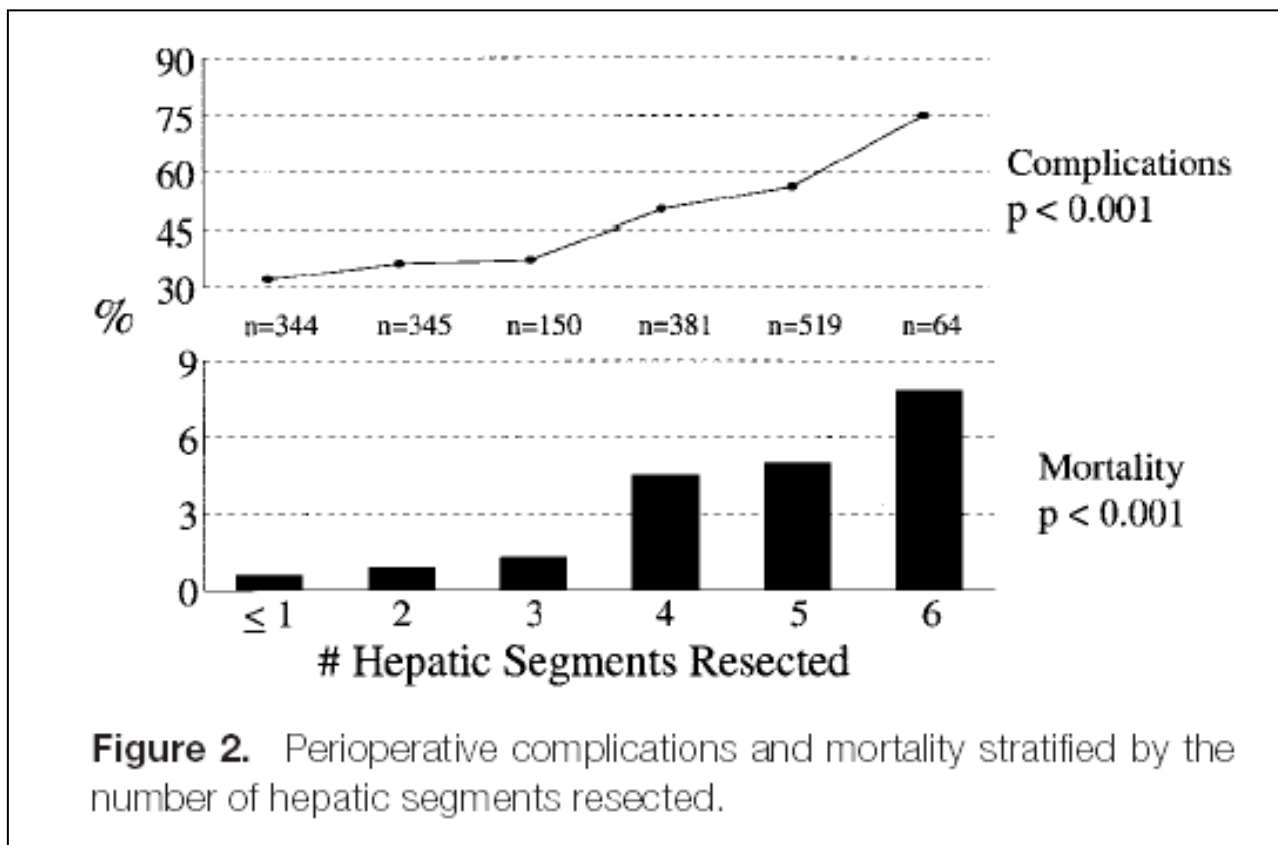
Post-operative infection increases with the extent of liver resection

Metabolische Veränderungen - Leberresektion



Post-operative infection in relation to extent of resection: Pearson Chi-Square , p=0.001

The incidence of post-operative complications increases with the extent of liver resection



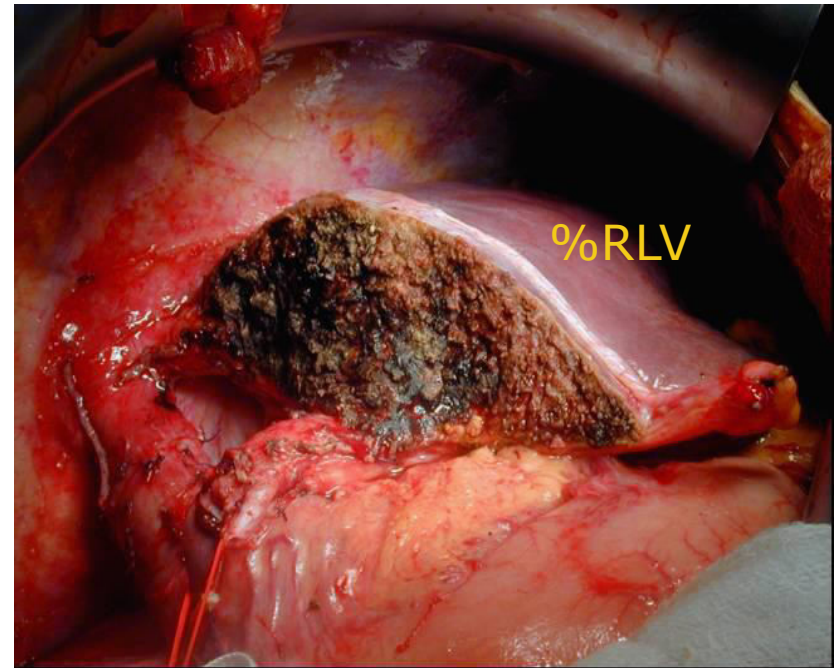
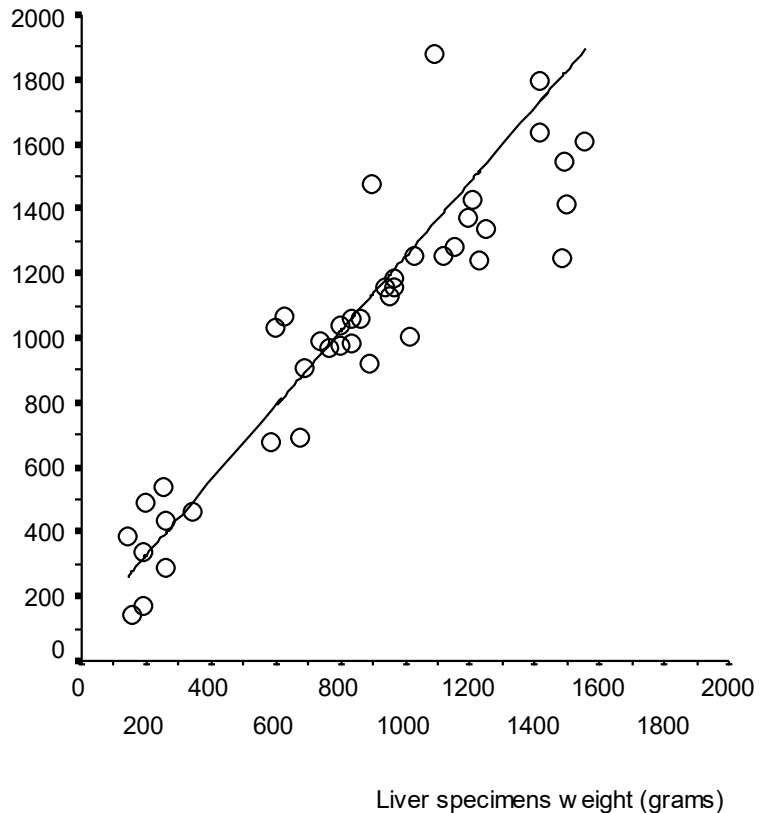
Improvement in Perioperative Outcome After Hepatic Resection
Analysis of 1,803 Consecutive Cases Over the Past Decade

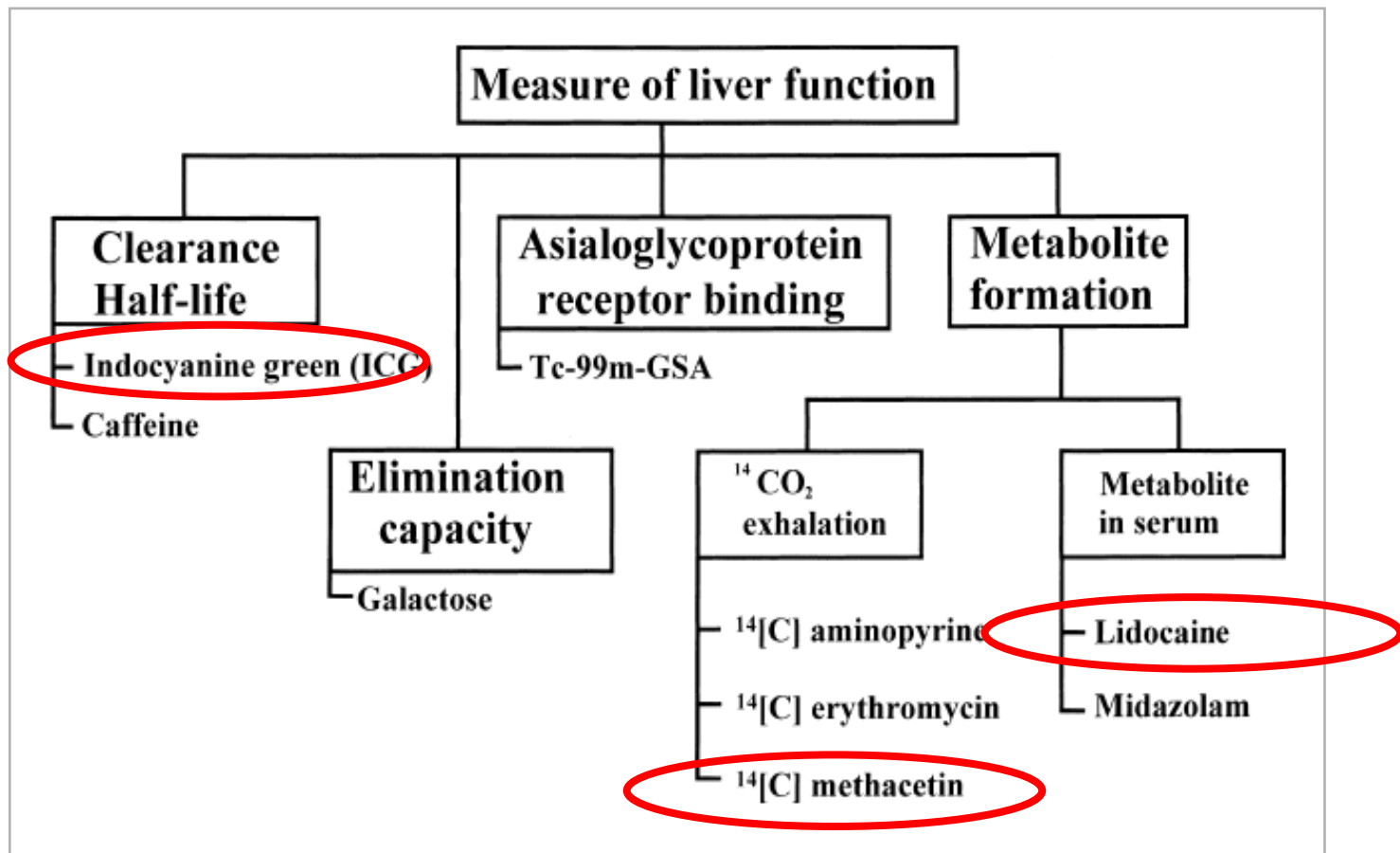
W.R. Jarnagin, Y. Fong and Leslie H. Blumgart (Memorial Sloan-Kettering Cancer Centre, New York)
ANNALS OF SURGERY 2002; 236 (4): 397-407

Präoperative Beurteilung der Leberfunktion

Anamnese:	Hepatitis B/C, Alkohol, Chemotherapie
Klinisch:	Ikterus, Aszites, Adipositas Ösophagusvarizen, Caput medusae
Blutlabor:	Bilirubin, Prothrombinzeit, Cholinesterase, Albumin, g-Globulin, Thrombozyten, gGT, ALT, Alkalische Phosphatase
Funktionstest:	ICG, MEGX, GEC
Radiomorphologie:	Volumetrie (Hypertrophie – Atrophie)

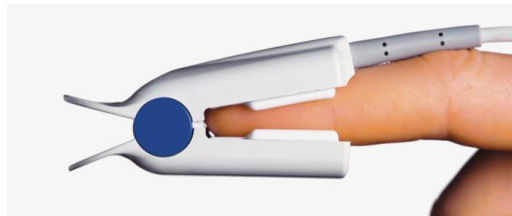
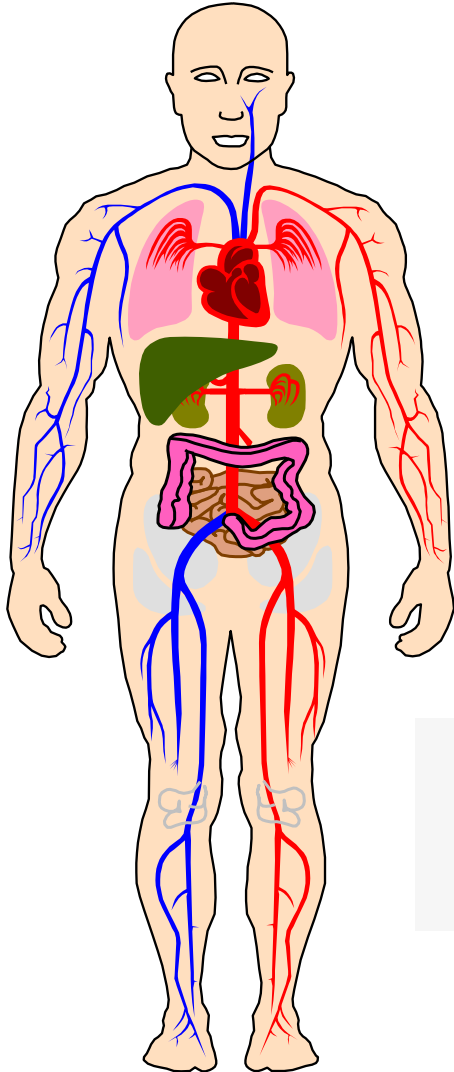
Leber - Volumen und CT





Zimmermann H, Reichen J (2000) Assessment of the liver function in the surgical patient. In: Blumgart LH, Fong Y (eds) Surgery of the liver and biliary tract. Saunders, London, pp 35-64

Indocyanin Grün (ICG) Clearance



Parameter Normal Range

PDR (%/min) **18 – 25**

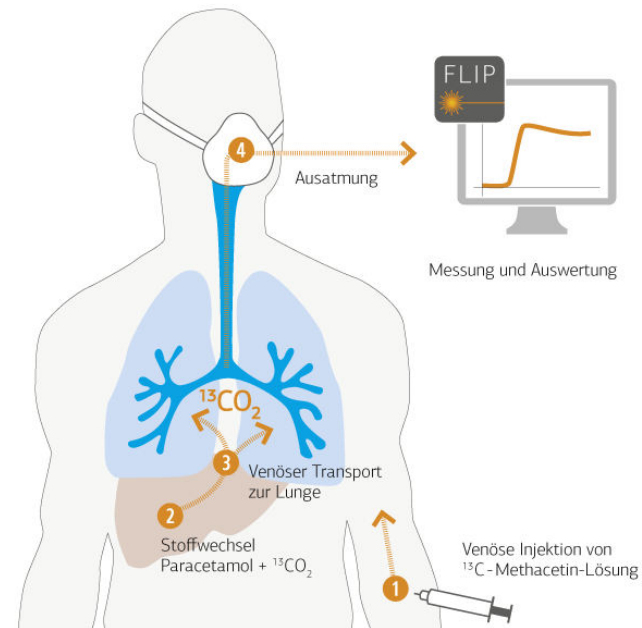
R15 (%) **0 – 10**

Plasma Disappearance rate (PDR)

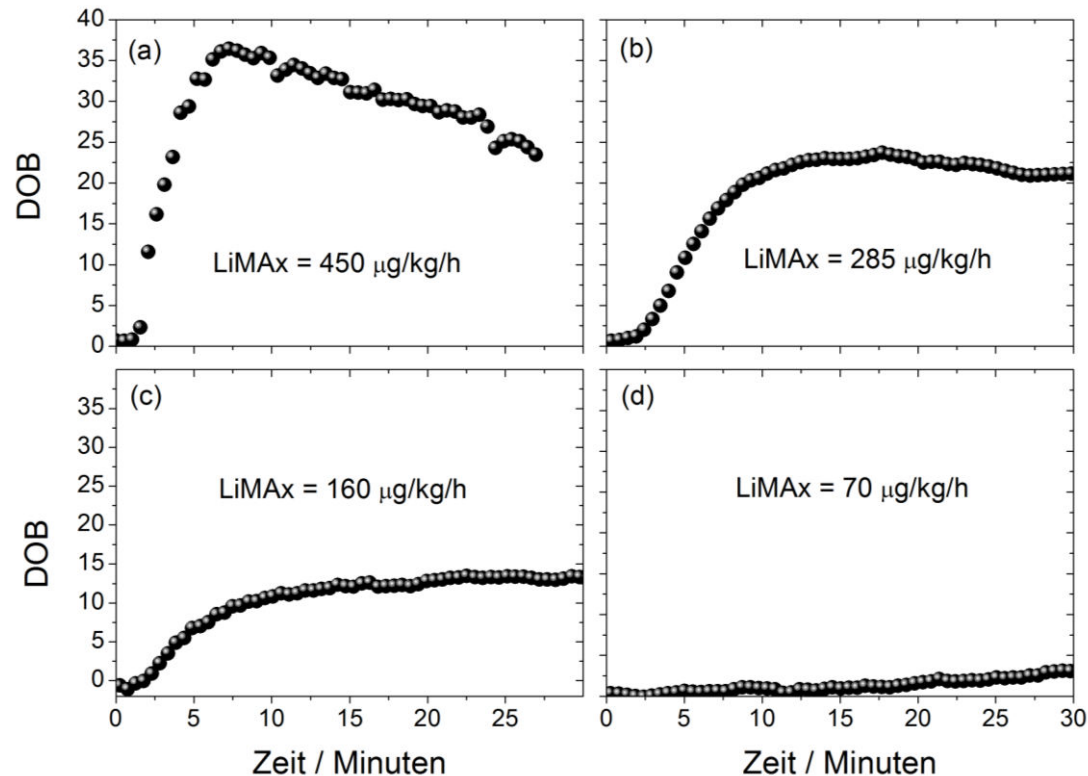
Plasma Retention rate (R15)

Prinzip LiMAx-Test in vivo real-time Leberenzym-Aktivitätstest

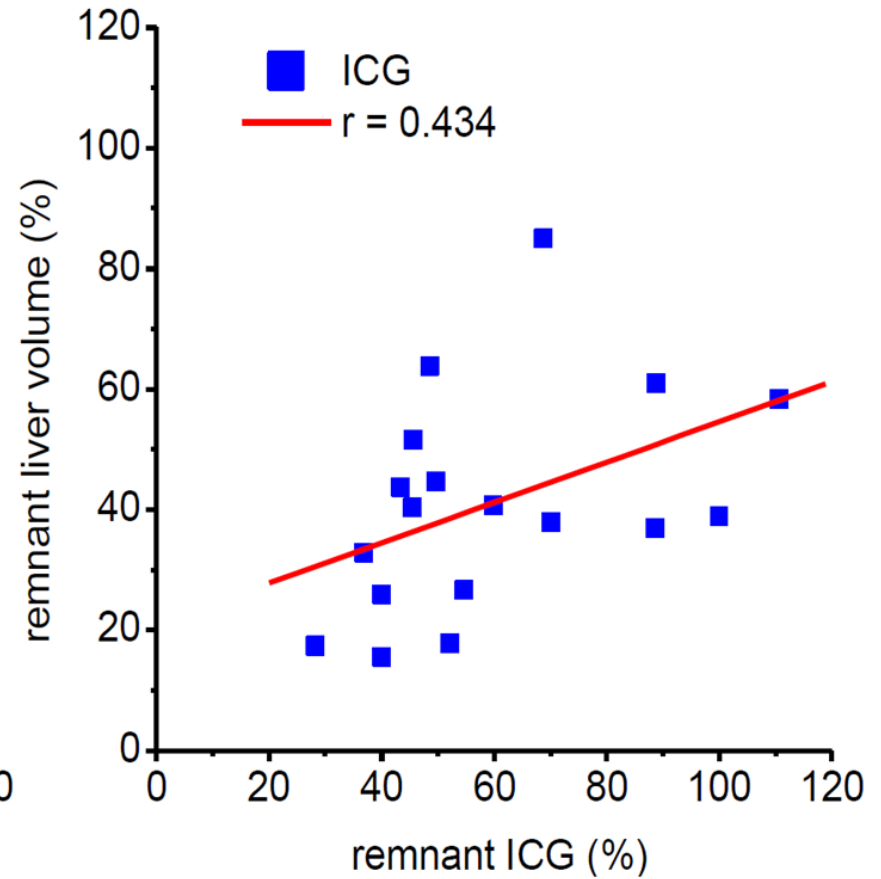
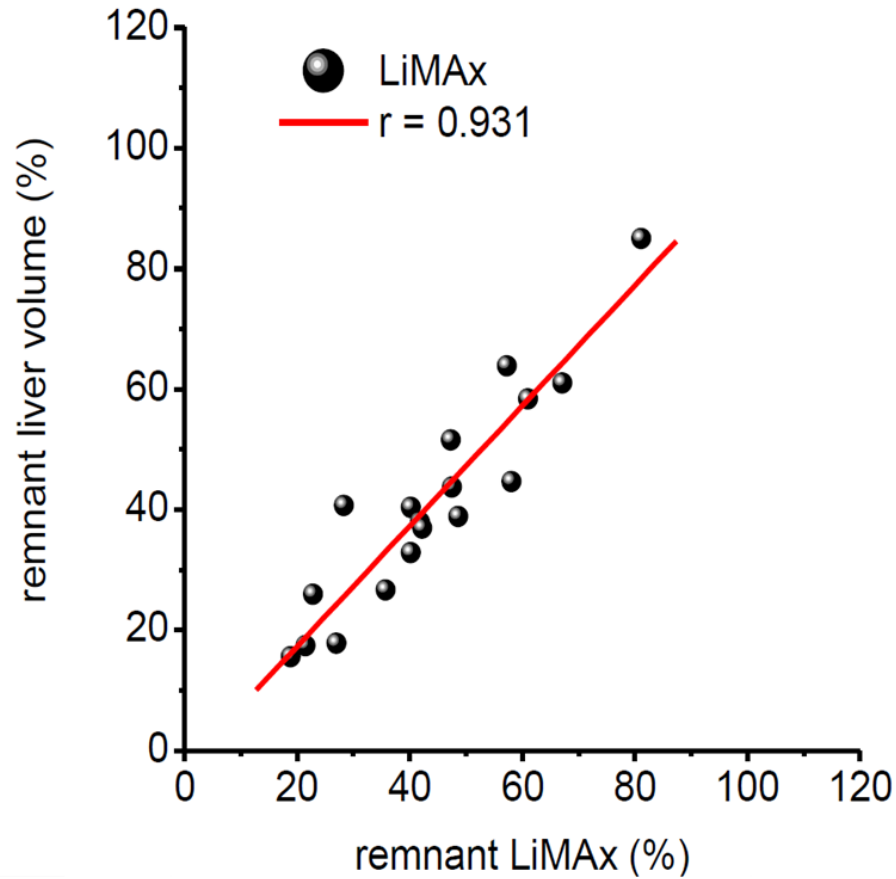
- Messprinzip basiert auf der Umsetzung eines intravenös applizierten Wirkstoffs (^{13}C -Methacetin)
- Wirkstoff wird in der Leber exklusiv durch das Enzym CYP 1A2 umgesetzt
- Endprodukte der Umsetzung:
 - Paracetamol
 - $^{13}\text{CO}_2$



- Operationsplanung (präoperativer LiMAx-Test)
- Monitoring / Identifikation von Einschränkungen (postoperativer LiMAx-Test)



Patients without cirrhosis n=23



TRANSHEPATIC METABOLISM OF TNF- α , IL-6, AND ENDOTOXIN IN THE EARLY HEPATIC REPERFUSION PERIOD AFTER HUMAN LIVER TRANSPLANTATION

RUDOLF STEININGER, ERICH ROTH,¹ REINHOLD FÜGGER, SUSANNE WINKLER, FRIEDRICH LÄNGLE,
THOMAS GRÜNBERGER, PETER GÖTZINGER, THOMAS SAUTNER, AND FERDINAND MÜHLBACHER

TABLE 1. Comparison of GOT, LDH, and prothrombin time (PT) of patients with and without complications after LTX

	12 hr po			3 po days		
	GOT (IU/L)	LDH (IU/L)	PT (%)	GOT (IU/L)	LDH (IU/L)	PT (%)
PNF ^a (OLT 257)	419	2111	44	2000	6110	16
PNF (OLT 274)	103	442	69	484	1670	13
Dysf. (OLT 258) + rej.	205	980	70	700	1255	59
Dysf. (OLT 259) + inf.	486	1960	58	674	846	69
Without complications (n = 9)—exc. function	666±376	2089±1246	57±9	91±52	321±57	85±14

^a PNF, primary nonfunction; dysf., dysfunction; inf., infection; rej., rejection; exc., excellent.

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TABLE 2. Concentration differences of endotoxin (ET), tumor-necrosis factor (TNF- α), and interleukin-6 (IL-6) across the liver (HV-P and HV-A) and gut (P-A)

	Liver		Gut— P-A
	HV-P	HV-A	
ET (ng/ml)			
Septic patient	+ ^b 29±13 ^a	+29±14 ^a	+2±12 ^a
8 Patients with moderate endotoxemia	0±14	-2±16	0±15
TNF- α (pg/ml)			
4 Patients with poor organ function	+160±122 ^{**c}	+137±101 ^{*c}	-25±27
9 Patients with good organ function	+7.3±9.7	+3.9±12	-3±7
IL-6 (pg/ml)			
2 patients	-210±81 ^a	-20±15 ^a	+170±73 ^a
Patient	-125±15 ^a	-9±17 ^a	+109±51 ^a
Mean of 11 patients	-17±20	+26±30	+45±56

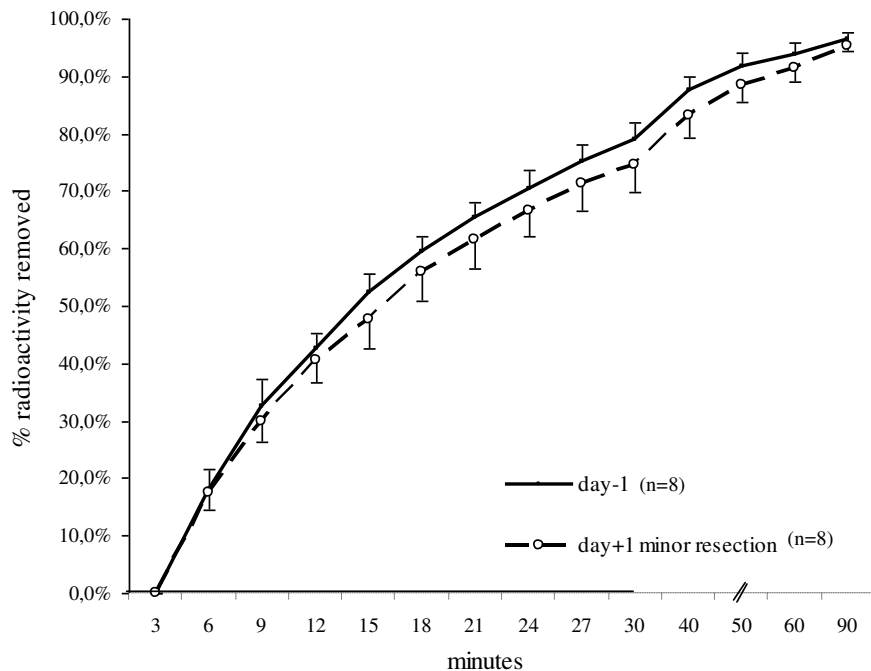
^a Mean of 5 different time points.

^b (+) release; (-) uptake.

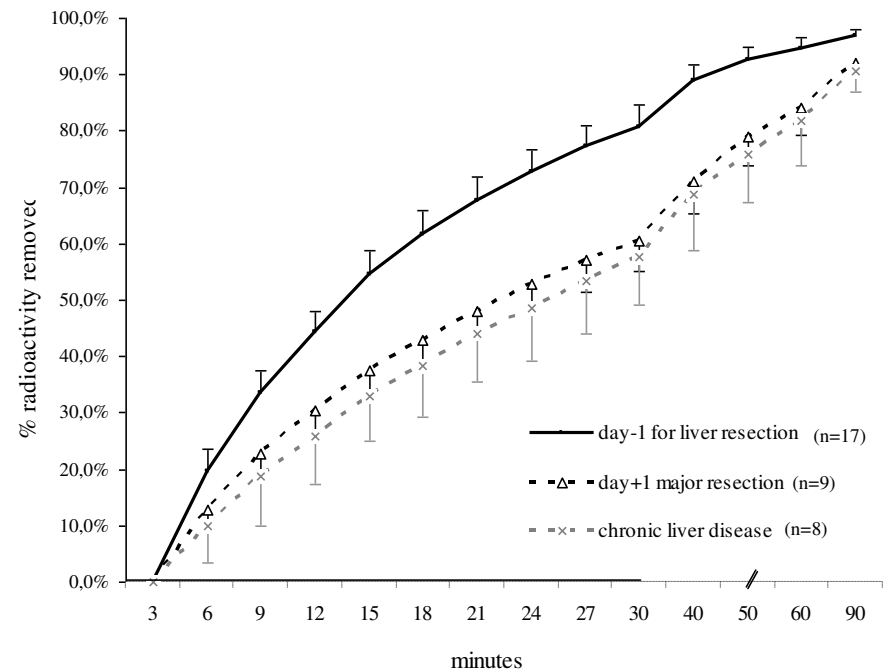
^c (**) P <0.01; (*) P <0.5 vs. patients with good organ function.

Reduktion der Phagozytosekapazität nach erweiterter Leberresektion

Standard Leberresektion



Erweiterte Leberresektion



The Adaptive Response of the Reticuloendothelial System to Major Liver Resection in Humans
Martin J. Schindl et al. Ann Surg 2006;243: 507-514

L-ARGININE DEFICIENCY AFTER LIVER TRANSPLANTATION AS AN EFFECT OF ARGINASE EFFLUX FROM THE GRAFT

INFLUENCE ON NITRIC OXIDE METABOLISM

ERICH ROTH,¹ RUDOLF STEININGER, SUSANNE WINKLER, FRIEDRICH LÄNGLE, THOMAS GRÜNBERGER,
REINHOLD FÜGGER, AND FERDINAND MÜHLBACHER

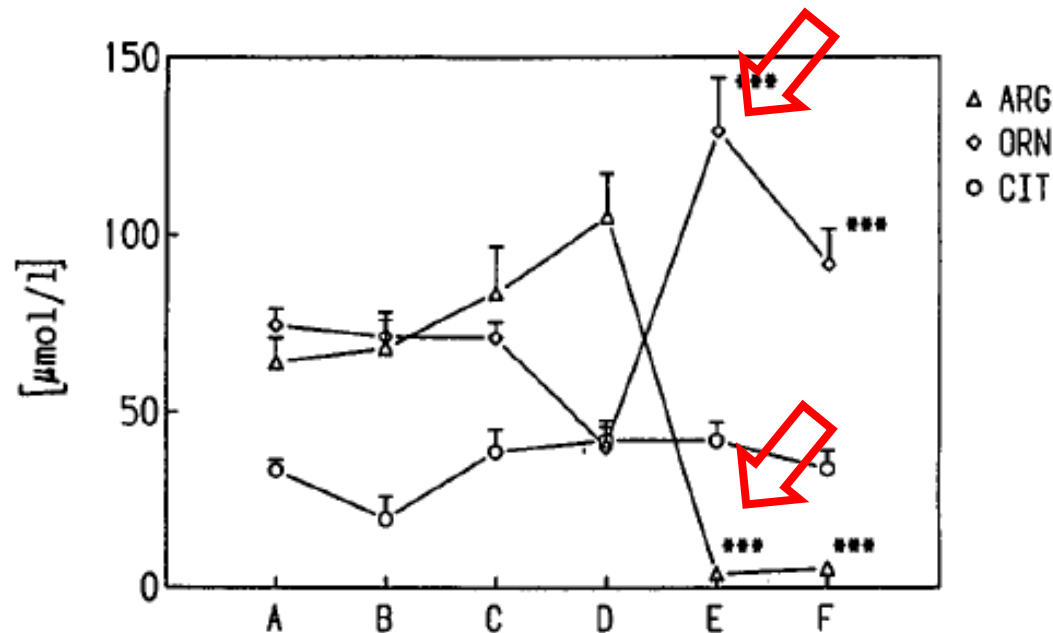


FIGURE 1. Course of plasma levels of arginine (Δ), ornithine (\diamond), and citrulline (\circ) in 10 patients during OLT. Significant alterations were found between the end of the anhepatic phase (D) versus 5 min after reperfusion (E) and the end of operation (F), $***P < 0.001$ E and F versus D.

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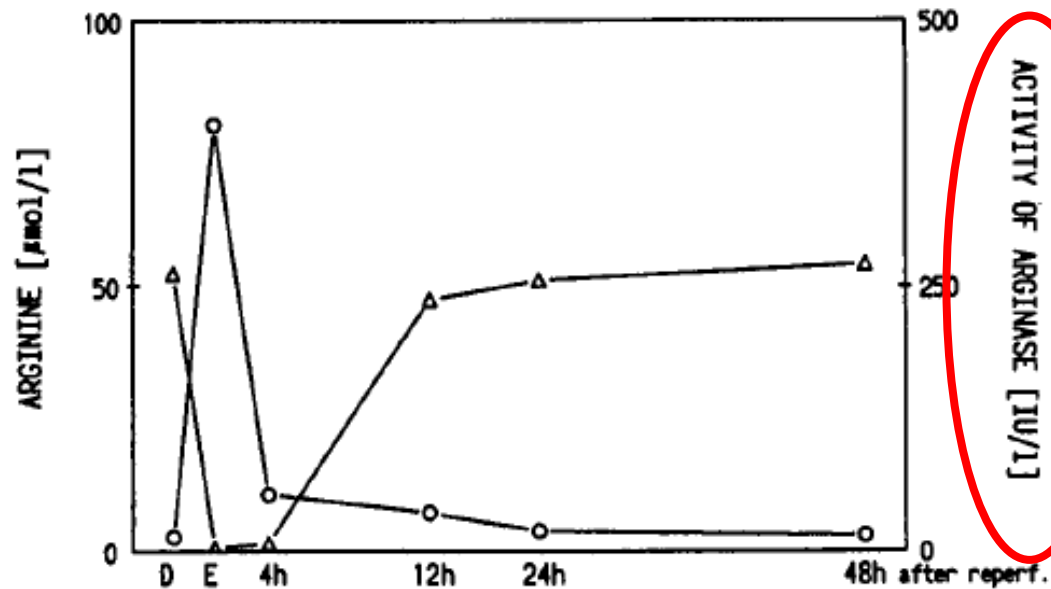


FIGURE 4. Plasma concentrations of L-arginine (Δ) and arginase (\circ) at the end of the anhepatic phase (D), 5 min after reperfusion (E), and at 4, 12, 24, and 48 hr after reperfusion. There was a negative correlation between L-arginine and arginase levels in the posttransplantation period.

L-ARGININE DEFICIENCY AFTER LIVER TRANSPLANTATION AS AN EFFECT OF ARGINASE EFFLUX FROM THE GRAFT

INFLUENCE ON NITRIC OXIDE METABOLISM

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REINHOLD FÜGGER, AND FERDINAND MÜHLBACHER

TABLE 1. Plasma concentrations of arginase, nitrite (NO₂⁻),
and nitrate (NO₃⁻) before and 5 min after reperfusion
in 5 OLT patients

	NO ₂ ⁻ (μmol/L)	NO ₃ ⁻ (μmol/L)	Activity of arginase (IU/L)
F. K.			
Before reperfusion	2.1	113	9.2
After reperfusion	0.82	89	1,701
M. A.			
Before reperfusion	1.4	63	16
After reperfusion	0.50	58	3,023
E. J.			
Before reperfusion	1.5	72	12
After reperfusion	0.98	59	400
N. A.			
Before reperfusion	1.97	46	37
After reperfusion	0.96	24	1,441
O. S.			
Before reperfusion	1.30	85	15
After reperfusion	0.75	85	472

ARGINASE RELEASE FOLLOWING LIVER REPERFUSION

EVIDENCE OF HEMODYNAMIC ACTION OF ARGINASE INFUSIONS

FRIEDRICH LÄNGLE,¹ ERICH ROTH,² RUDOLF STEININGER,² SUSANNE WINKLER,² AND FERDINAND MÜHLBACHER

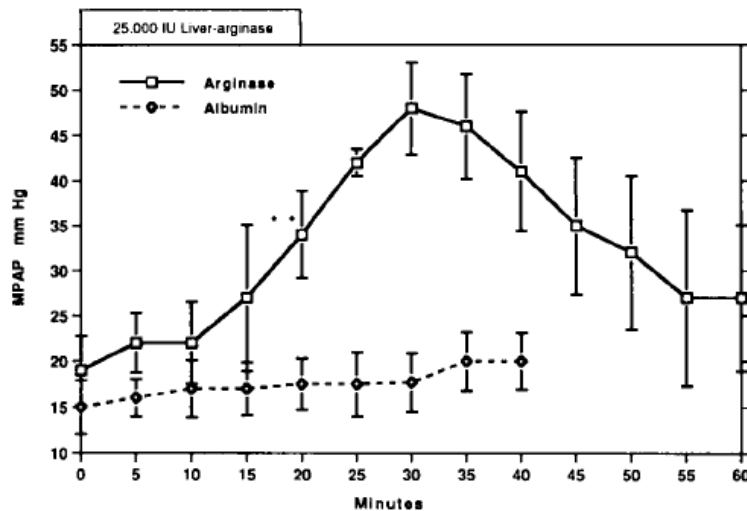


FIGURE 4. Increase of MPAP after administration of 25,000 IU of bovine liver arginase in comparison with constant MPAP after infusion of 100 ml of bovine albumin over a 20-min period (n=5). ** $P < 0.01$ 20 min vs. 0 min.

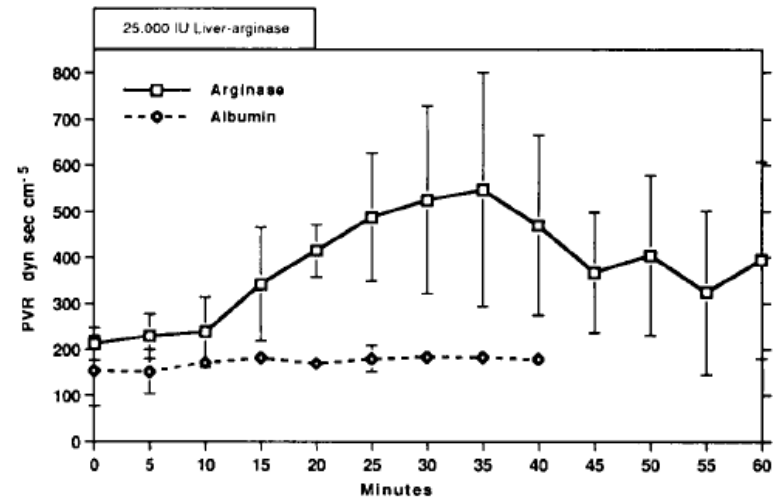


FIGURE 5. Increase of PVR (in dynes sec cm⁻⁵) after application of 25,000 IU of bovine liver arginase in comparison with constant PVR after infusion of 100 ml of bovine albumin over a 20-min period (n=5).

ARGINASE RELEASE FOLLOWING LIVER REPERFUSION

EVIDENCE OF HEMODYNAMIC ACTION OF ARGINASE INFUSIONS

FRIEDRICH LÄNGLE,¹ ERICH ROTH,² RUDOLF STEININGER, SUSANNE WINKLER,² AND FERDINAND MÜHLBACHER

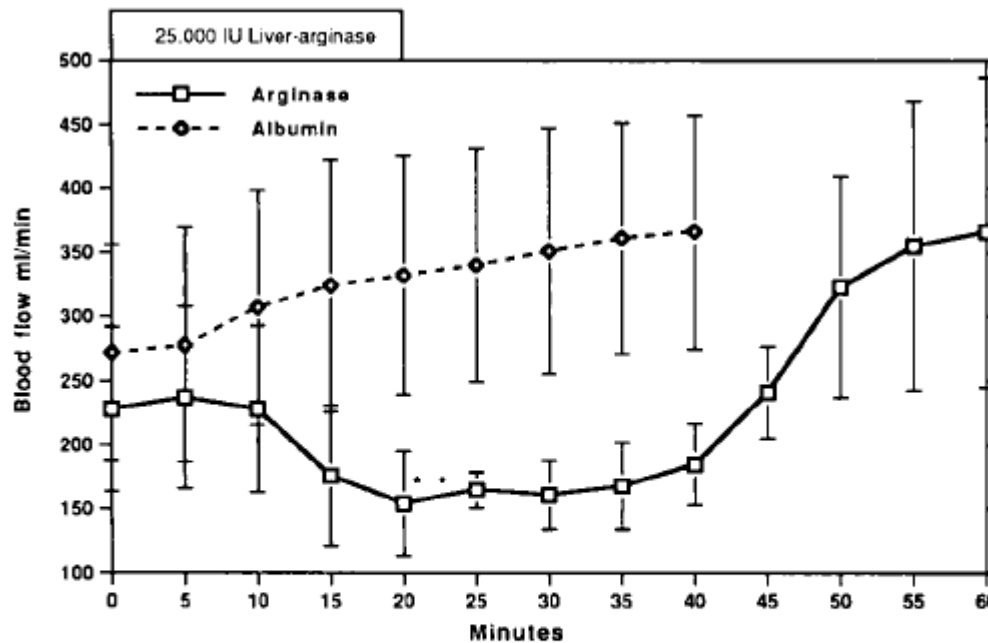


FIGURE 6. Decrease of flow of the hepatic artery after administration of 25,000 IU of bovine liver arginase in comparison with constant increasing flow of the hepatic artery after infusion of 100 ml of bovine albumin over a 20-min period ($n=5$). $**P<0.01$ 20 min vs. 0 min.

IMPROVEMENT OF CARDIAC OUTPUT AND LIVER BLOOD FLOW AND REDUCTION OF PULMONARY VASCULAR RESISTANCE BY INTRAVENOUS INFUSION OF L-ARGININE DURING THE EARLY REPERFUSION PERIOD IN PIG LIVER TRANSPLANTATION

Langle, Friedrich; Steining, Rudolf; Waldmann, Elke; Grunberger, Thomas; Benditte, Heike; Mittlbock, Martina; Soliman, Thomas; Schindl, Martin; Windberger, Ursula; Muhlbacher, Ferdinand; Roth, Erich

Transplantation. 63(9):1225-1233, May 15, 1997.

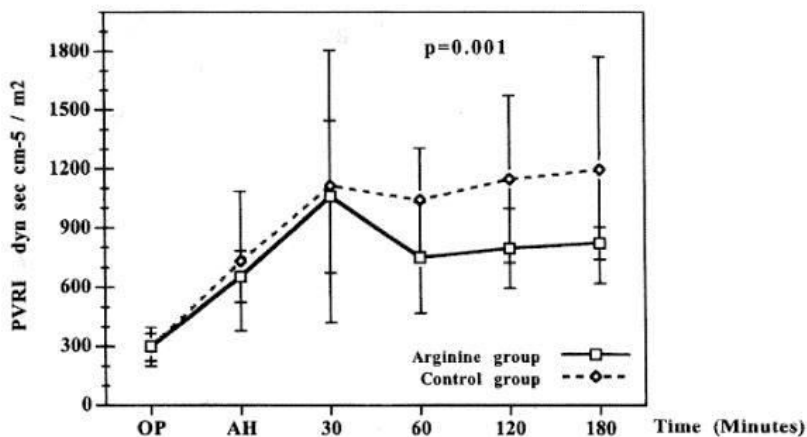
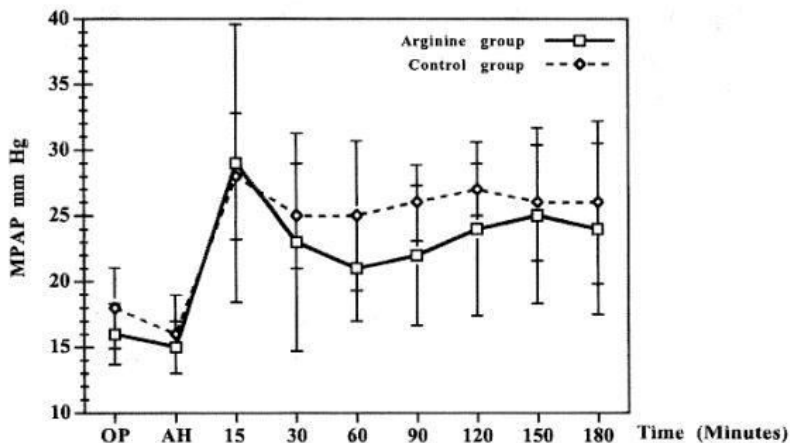


Figure 1 . Effect of intravenous infusion of L-arginine (500 mg/kg body weight, starting at the end of the anhepatic period) on the time course of MAP heart rate during liver transplantation. MAP decreased about 50% after liver reperfusion without any difference between the arginine group and the control group. After liver revascularization, heart rate was statistically significantly higher in the arginine group (P=0.017). Abbreviations used in figure legends: OP, beginning of the recipient operation; AH, end of anhepatic phase, 15-180 min after liver revascularization.

IMPROVEMENT OF CARDIAC OUTPUT AND LIVER BLOOD FLOW AND REDUCTION OF PULMONARY VASCULAR RESISTANCE BY INTRAVENOUS INFUSION OF L-ARGININE DURING THE EARLY REPERFUSION PERIOD IN PIG LIVER TRANSPLANTATION

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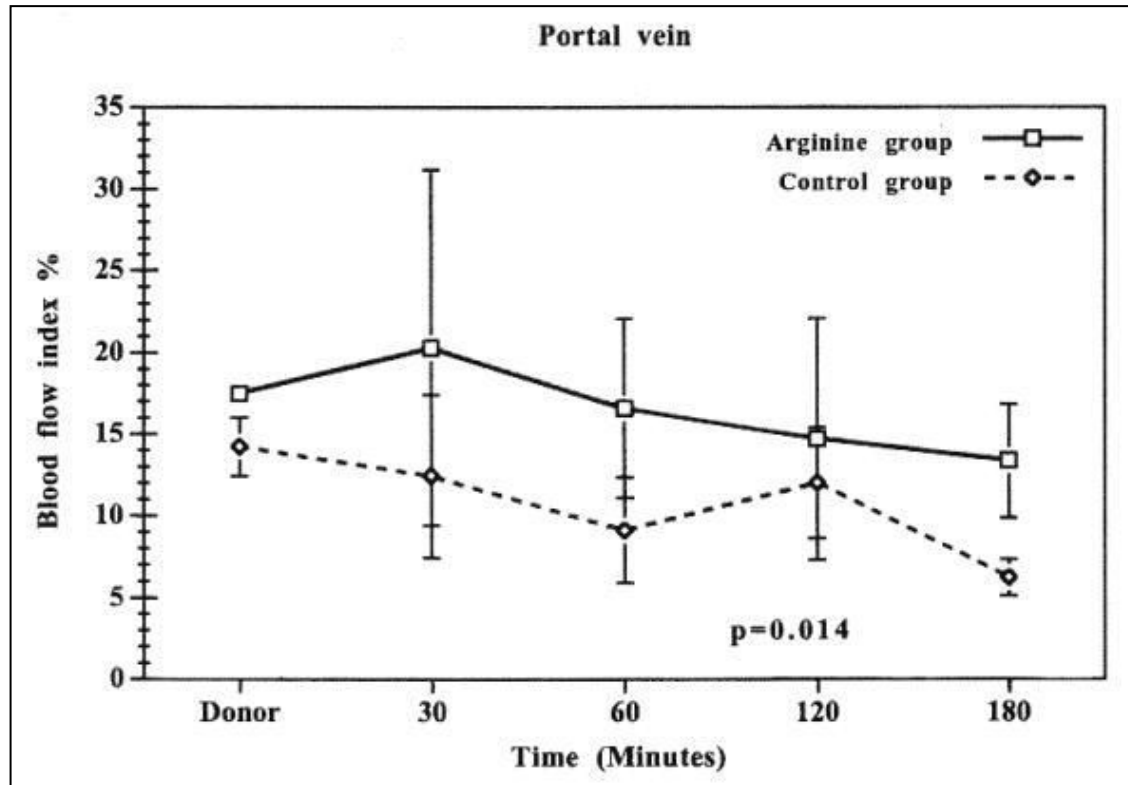


Figure 5 . Effect of intravenous infusion of L-arginine (500 mg/kg body weight, starting at the end of anhepatic period) on the time course of portal venous blood index during liver transplantation. Blood flow of the portal vein was monitored by electrodynamic flow measurements. To compare single periods of flow measurements, the percentile flow of the portal vein was calculated by the following formula: (flow/CI)x100. Blood flow levels of the donor liver were used as baseline levels. Portal venous blood flow was significantly higher in the arginine group (P=0.014).

- increase in heart rate (+61%, $P=0.017$)
- cardiac index (+53%, $P=0.005$)
- reduction in pulmonary capillary wedge pressure (-54%, $P=0.014$)
- increased oxygen consumption (+65%, $P=0.003$),
- reduced pulmonary vascular resistance index ($P=0.001$)
- stimulated portal venous blood flow ($P=0.014$)
- elevated body temperature during the reperfusion period ($P=0.007$).

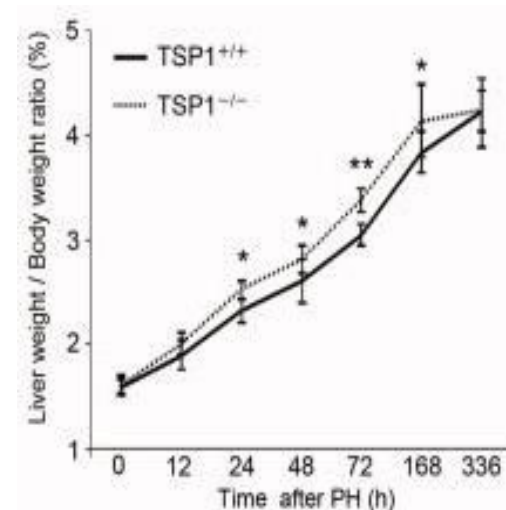
Plasma Thrombospondin 1 as a Predictor of Postoperative Liver Dysfunction

P. Starlinger, S. Hägele, D. Wanek, S. Zikeli, D. Schauer, L. Alidzanovic,
E. Fleischmann, B. Grünberger, T. Grünberger, C. Brostjan



TSP-1 und Leberresektion

- *Hayashi et al. (2012)* im Mausmodell
- TSP-1 unmittelbar nach OP ausgeschüttet (Peak 6h)
- TSP-1 via TGF- β 1 hemmend für Leberregeneration nach LR
- Resultierende TGF- β ₁ Konversion
 - → Zellzyklusblockade
 - → Apoptose



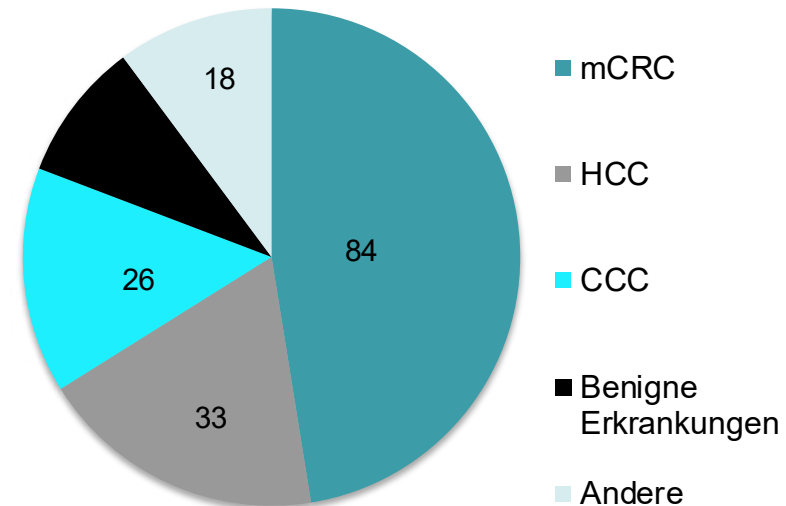
- **TSP-1 als hemmendes Element der Leberzellregulation**

Setting

- Evaluations-Set (Beobachtung):
 - 228 Patienten von 2001 bis 2009
 - mCRC
 - Retrospektive Auswertung

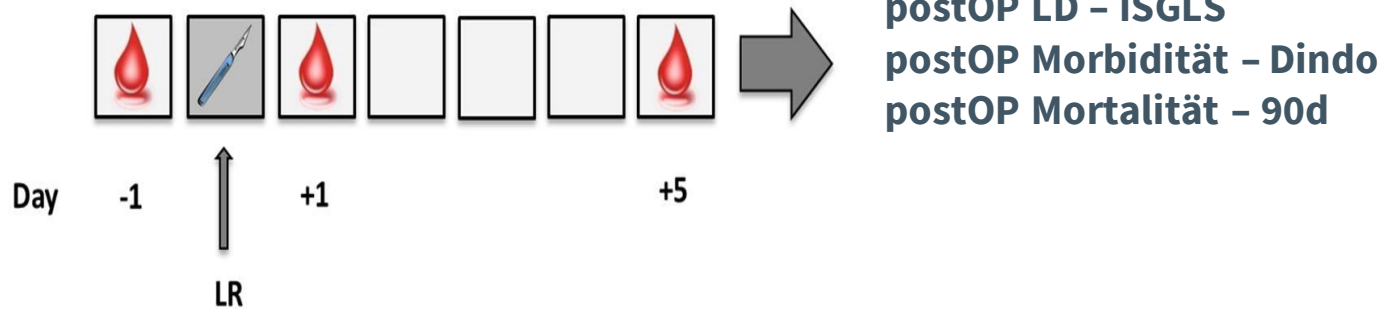
- Validierungs-Set (Bestätigung):
 - 177 Patienten von 2010 bis 2014
 - Klinisches Routine Setting
 - Prospektive Validierung

Validierungs Kohorte



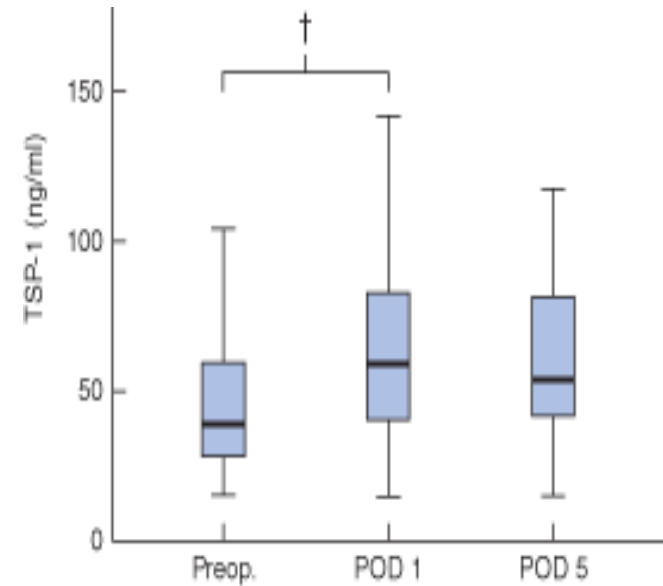
Studiendesign

- Prospektive Validierungskohorte:
85 Patienten (Jan. 2012 – Sep 2013)



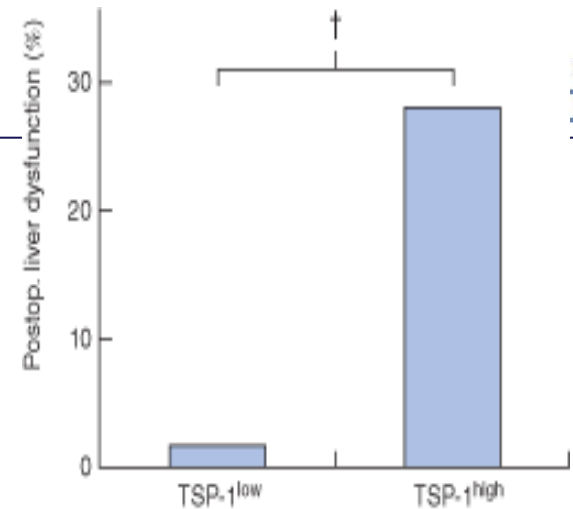
Ergebnisse

- POD1 allgemein Erhöhung der TSP-1 Werte ($p=0,001$)
- POD5 (Verfügbarkeit 69%) leichter Rückgang, aber dennoch erhöht
- **Verlauf ähnlich dem Mausmodel**

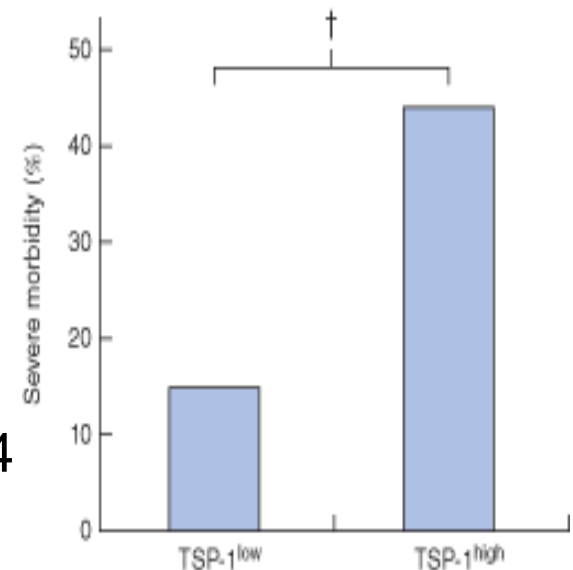


Ergebnisse: TSP-1 und klinische Performance

- Cut Off 80 ng/dl für TSP-1^{high}
 - Spezifität 76%, Sensitivität 87%
- TSP-1^{high} häufigere Leberdysfunktion
 - 28% (7/25) vs 2% (1/60) | $p < 0,001$
- TSP-1^{high} höhere intervent. Morbidität
 - 44% (11/25) vs 15% (9/60) | $p = 0,004$



a Overall liver dysfunction

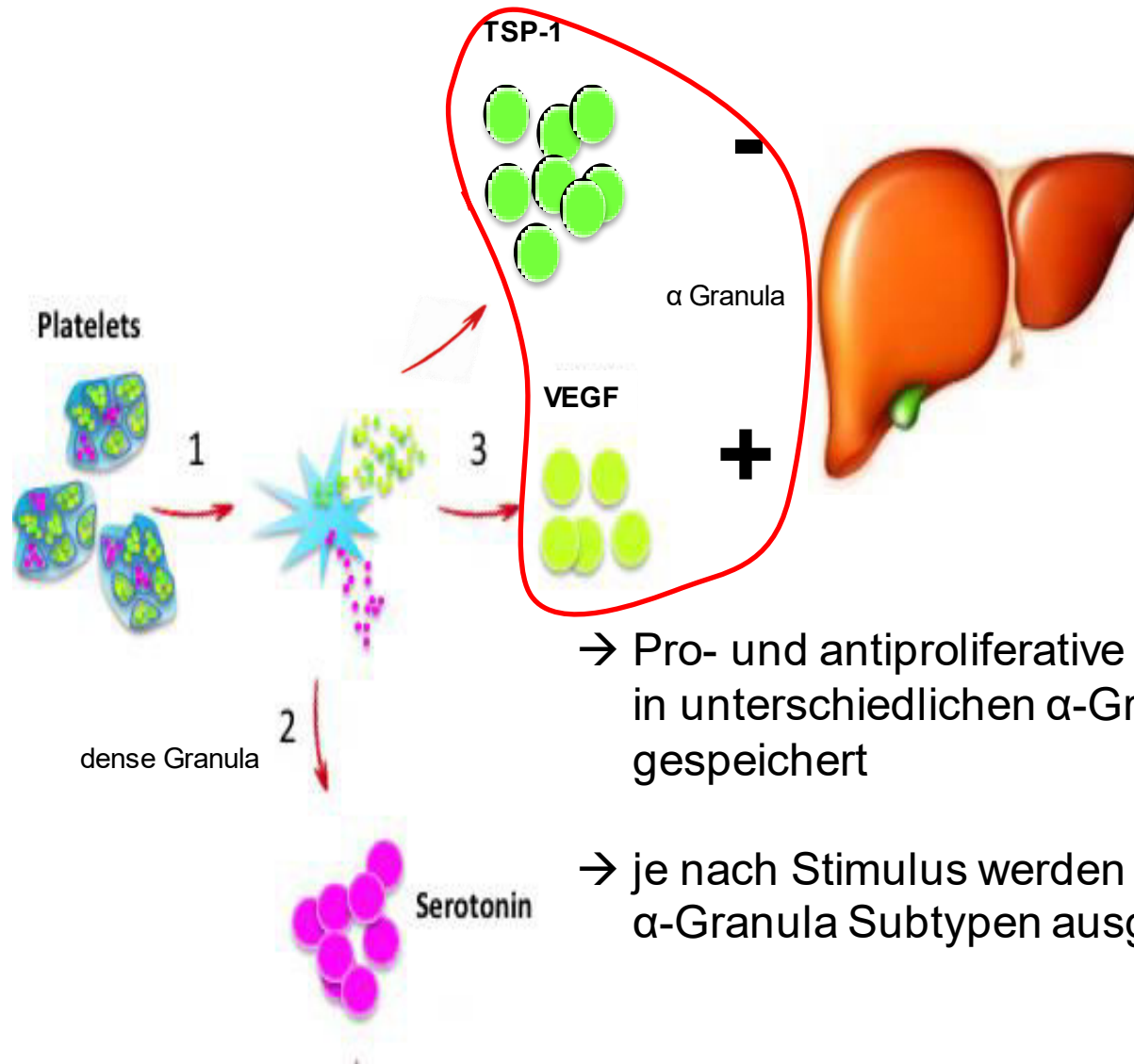


c Severe morbidity

Conclusio

- Daten zeigen, dass TSP-1
 - ... unmittelbar nach OP ausgeschüttet wird
 - ... korreliert mit postoperativer LD
- TSP-1 Cut-Off (80ng/dl) identifiziert High-Risk Gruppe mit
 - ... erhöhter Rate an schwerer postoperativer Morbidität
 - ... verlängertem Krankenhausaufenthalt (9,9d vs 19,7d)

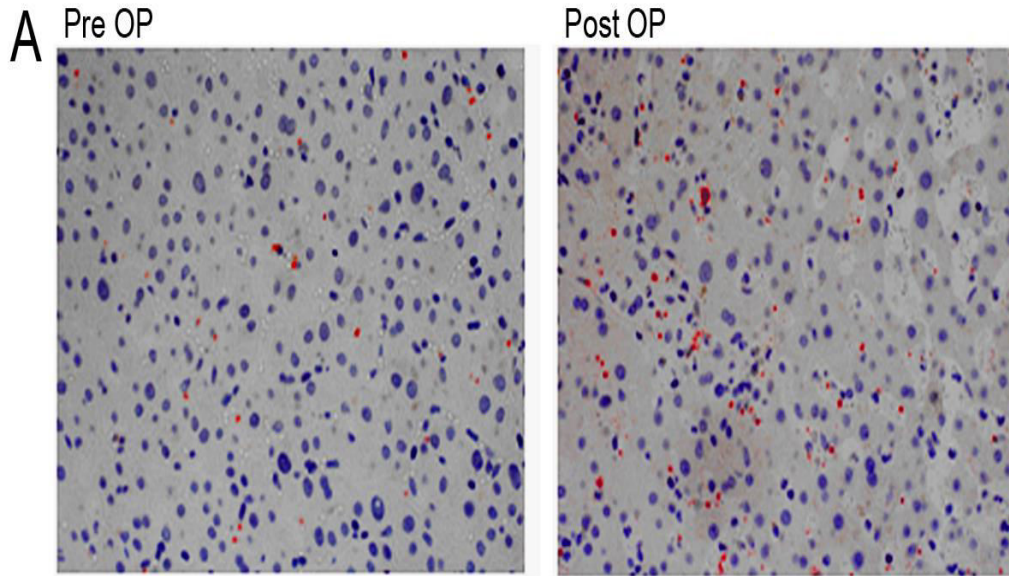
Thrombozytäre Granula



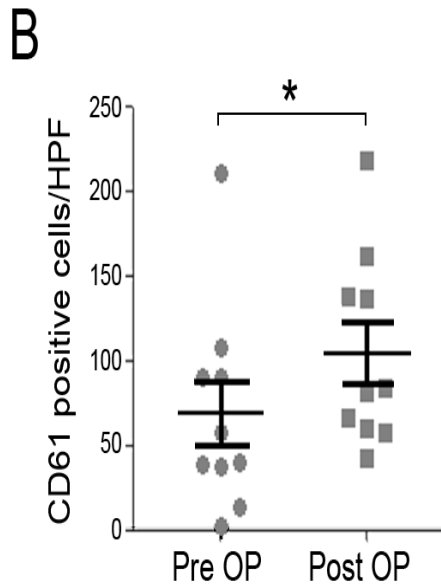
→ Pro- und antiproliferative Faktoren sind in unterschiedlichen α-Granula gespeichert

→ je nach Stimulus werden verschiedene α-Granula Subtypen ausgeschüttet

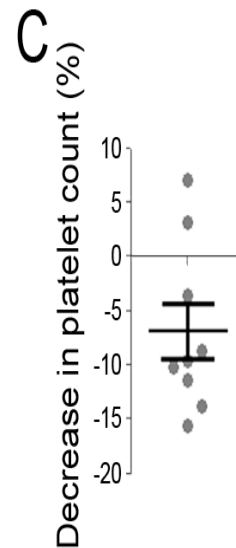
Was geschieht in der Leber?



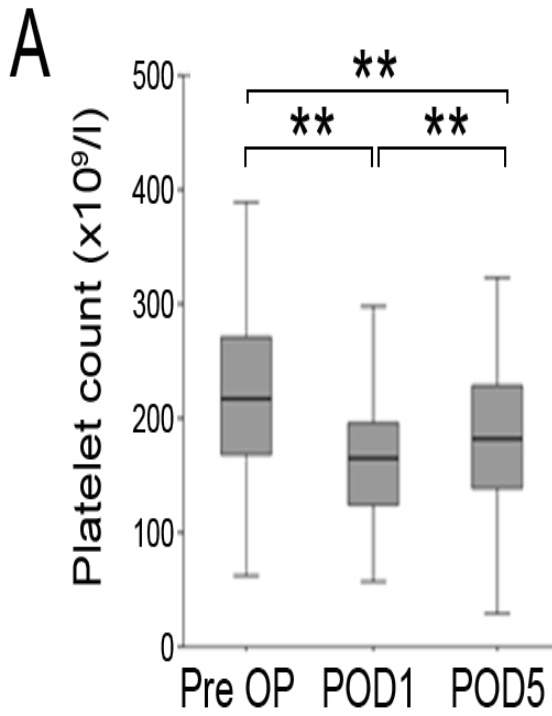
→ Thrombozyten akkumulieren nach partieller Hepatektomie in der Leber



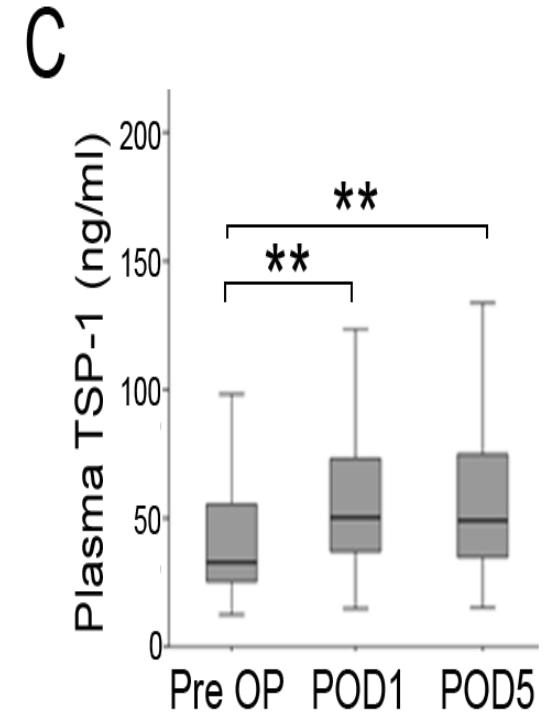
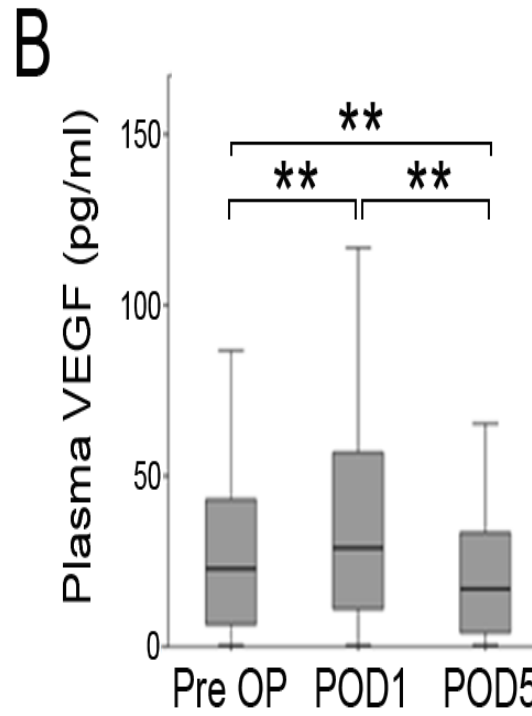
* $p < 0,05$
** $p < 0,005$



→ Verringerte Thrombozytenzahl nach Leberpassage



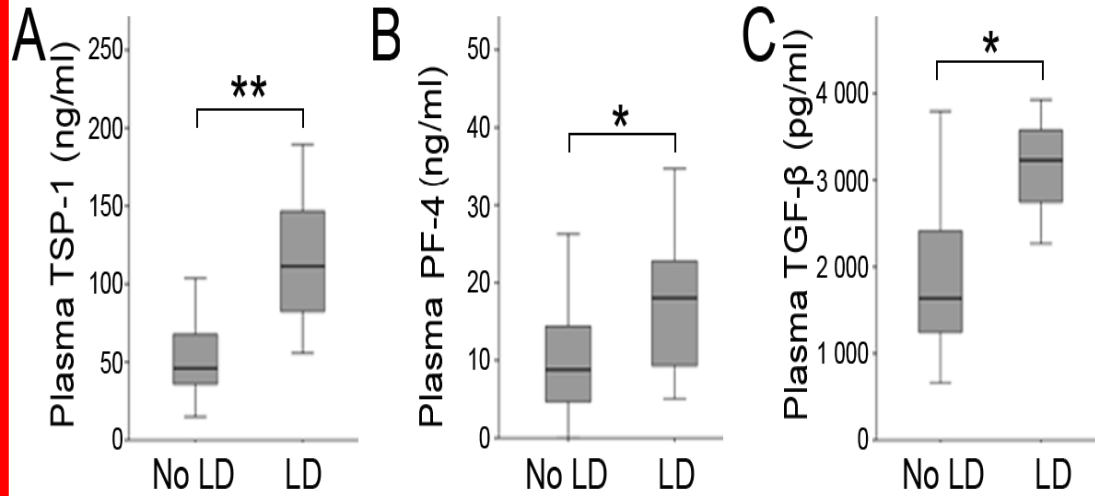
* $p < 0,05$
** $p < 0,005$



→ Anstieg an α -Granula-Proteinen an POD1

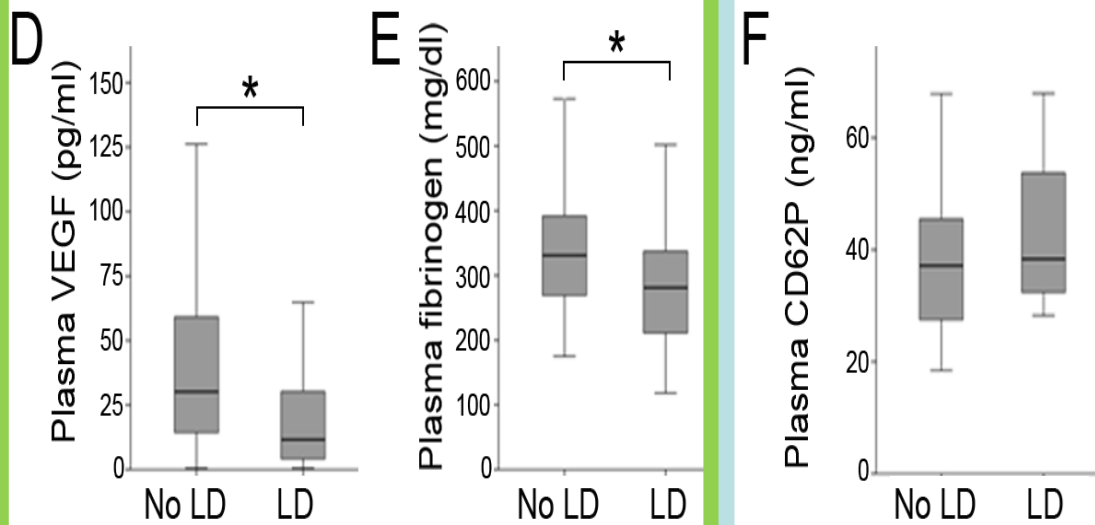
Korrelation mit Leberdysfunktion

proliferativ



antiproliferativ

→ TSP-1, PF-4, TGF-β bei Patienten mit LD erhöht

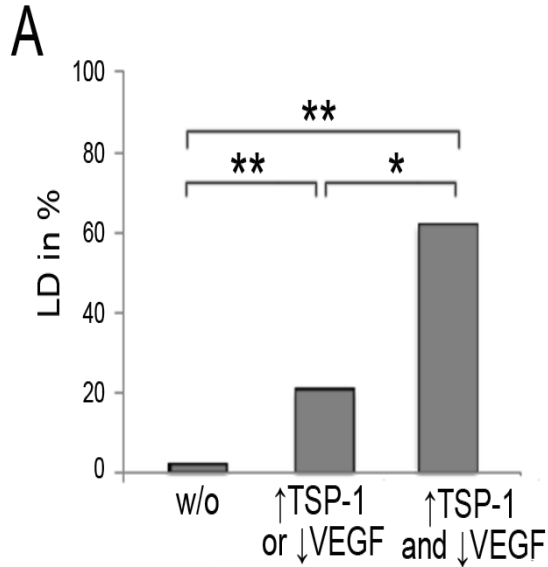


ubiquitär

→ VEGF und Fibrinogen bei Patienten mit LD vermindert

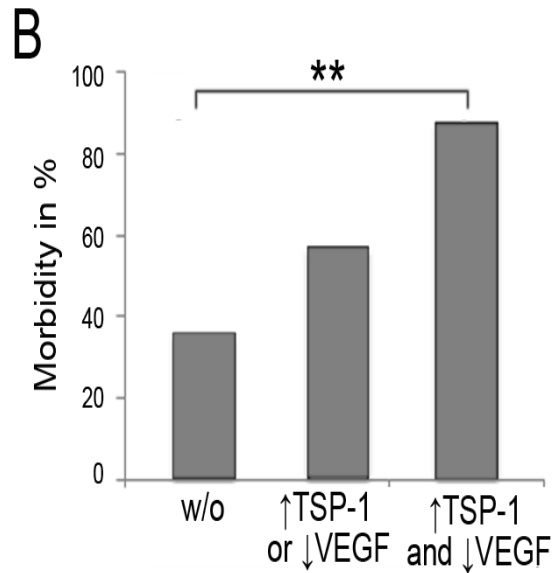
* p < 0,05
** p < 0,005

Risikogruppen

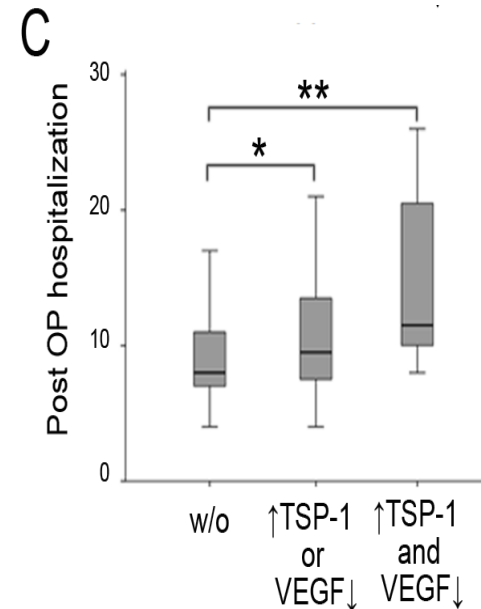


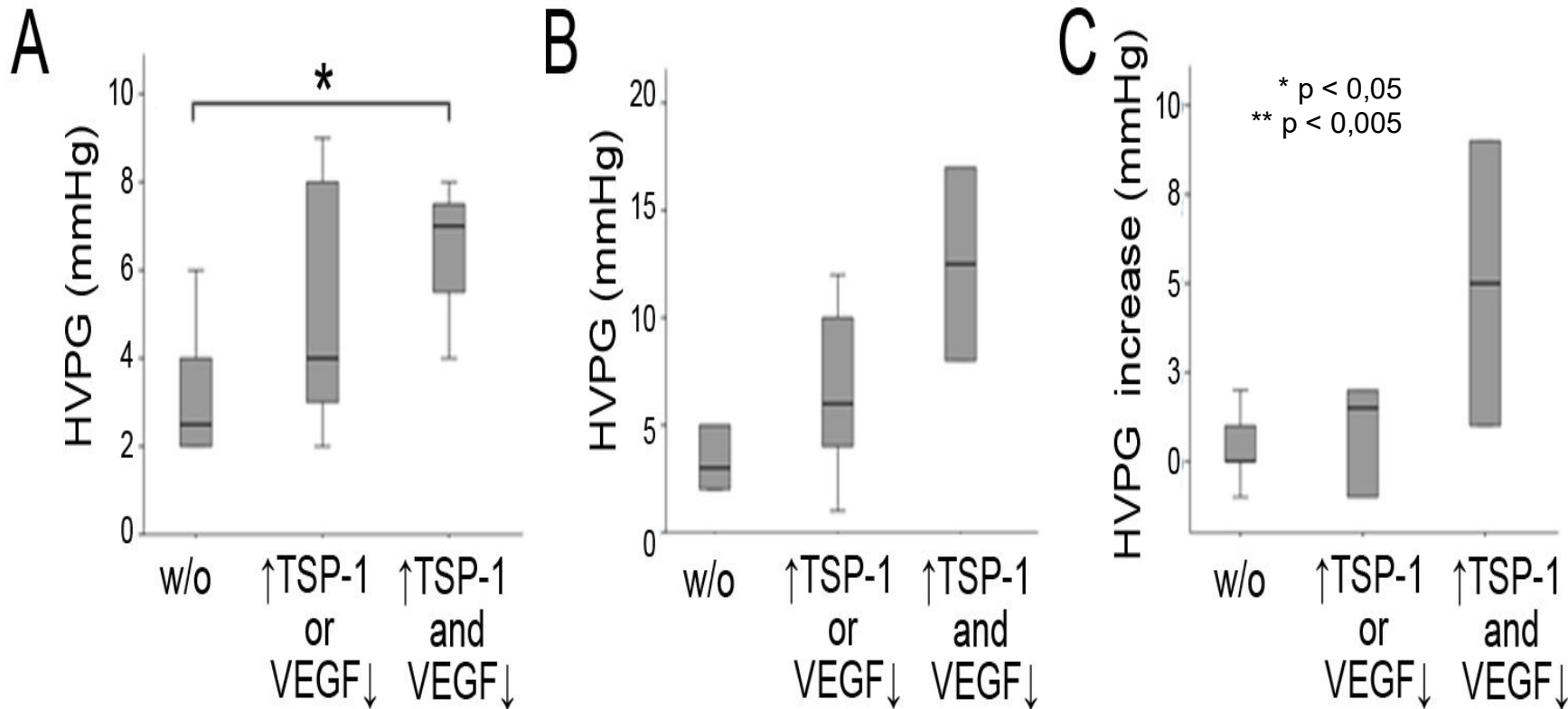
- Low-risk: ↓TSP-1 AND ↑VEGF
- Intermediate-risk: ↑TSP-1 OR ↓VEGF
- High-risk: ↑TSP-1 AND ↓VEGF

→ Patienten in der high-risk Gruppe hatten signifikant schlechtere postoperative klinische Verläufe



* p < 0,05
** p < 0,005





- High-risk Gruppe hatte präoperativ erhöhten HVPG
- Postoperativer HVPG Anstieg fällt in der high-risk Gruppe stärker aus

Conclusio

- Thrombozyten akkumulieren nach partieller Hepatektomie in der Leber
- Die Sekretion von α -Granula-Subtypen wahrend Leberregeneration scheint spezifisch reguliert
- Der PVD stellt womoglich einen entscheidenden Stimulus fur die selektive α -Granula Sekretion dar
- Pharmakologische Einflussnahme auf den PVD stellt in Zukunft eine potentiell wesentliche Therapie dar

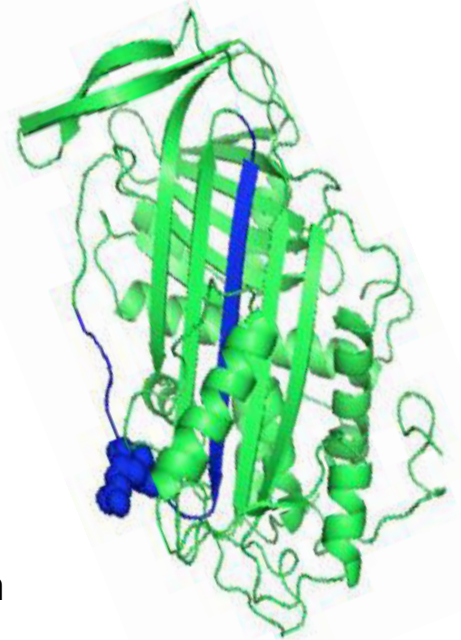
Antithrombin III – Aktivität und postoperatives Outcome nach Leberresektion



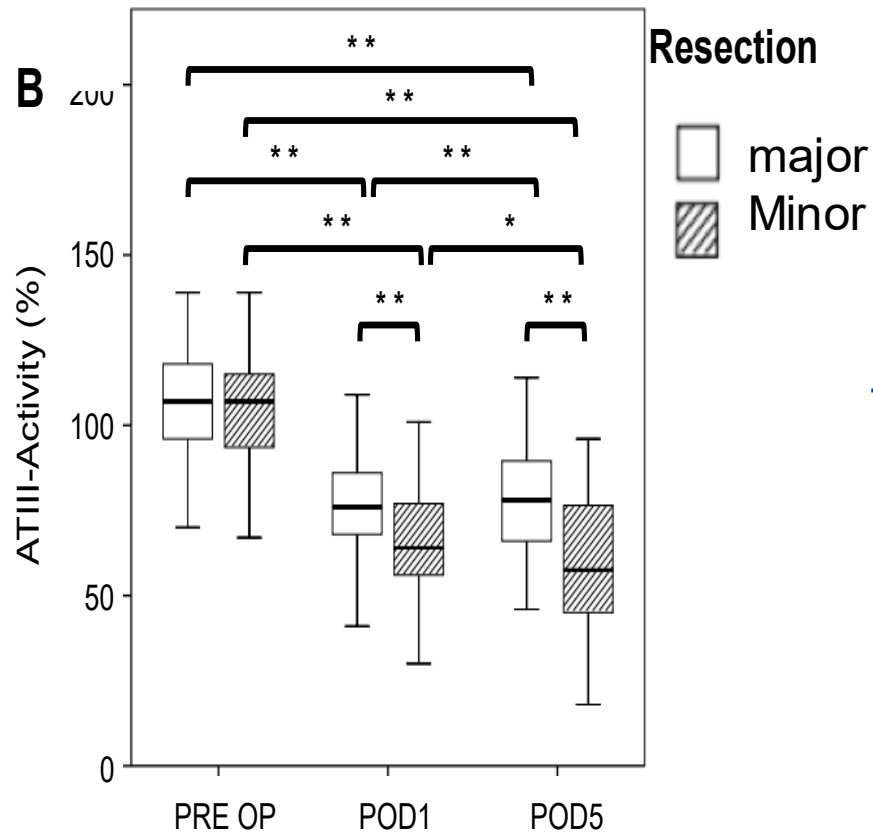
David Pereyra, Florian Offensperger, Stefanie Hägele, Lukas Öhlberger, Paul Bräuer, Christian Schwarz, Clemens Haselmann, Thomas Grünberger, Christine Brostjan, Patrick Starlinger

Antithrombin III

- AT III Levels in zirrhotischen Patienten vermindert
 Tang W. et al. Eur J Gastroenterol Hepatol 2015
 Bianchini M. et al. Dig Dis 2014
- Prädiktives Potential für Leberdysfunktion in HCC Patienten
 Iwako H. et al. Ann Surg Onc 2012
 Mizuguchi T. et al. Hepatogastroenterology 2012
- Postoperative ATIII-Administration verbessert Outcome in HCC Patienten
 Kuroda S. et al. Dig Surg 2015



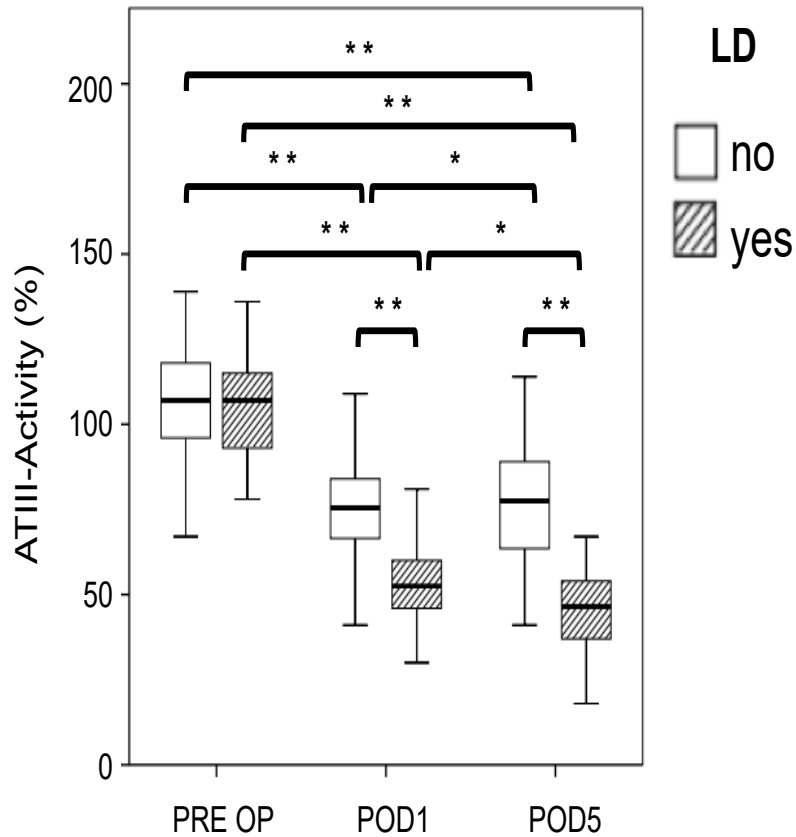
Ergebnisse



Resektionsausmaß spiegelt sich in der postoperativen ATIII-Aktivität wieder

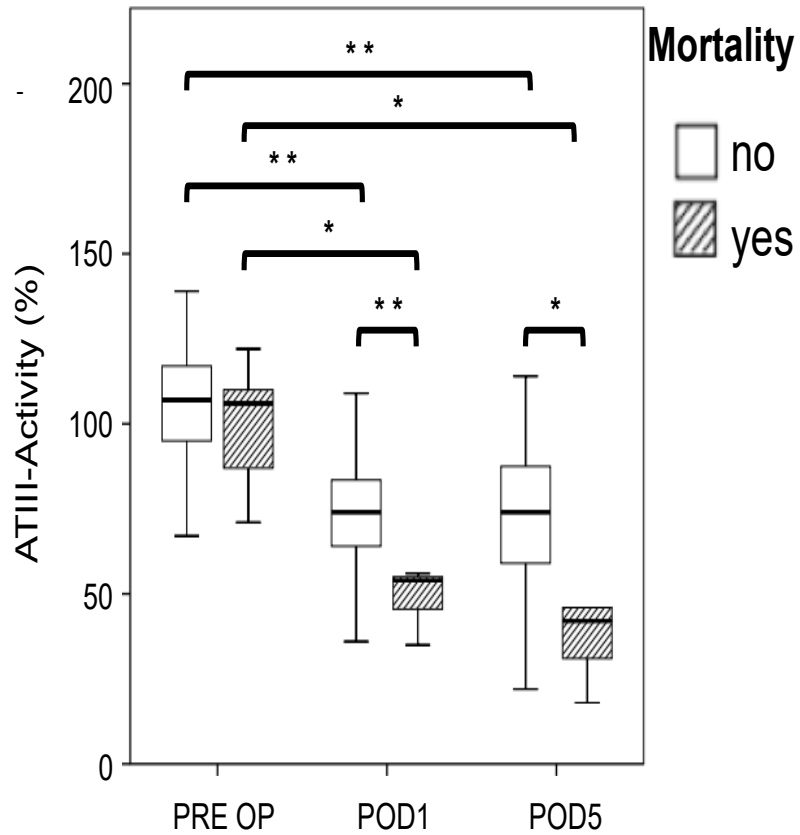
- Hypothese: ATIII ist ein Synthesemarker für die Leberfunktion

Ergebnisse



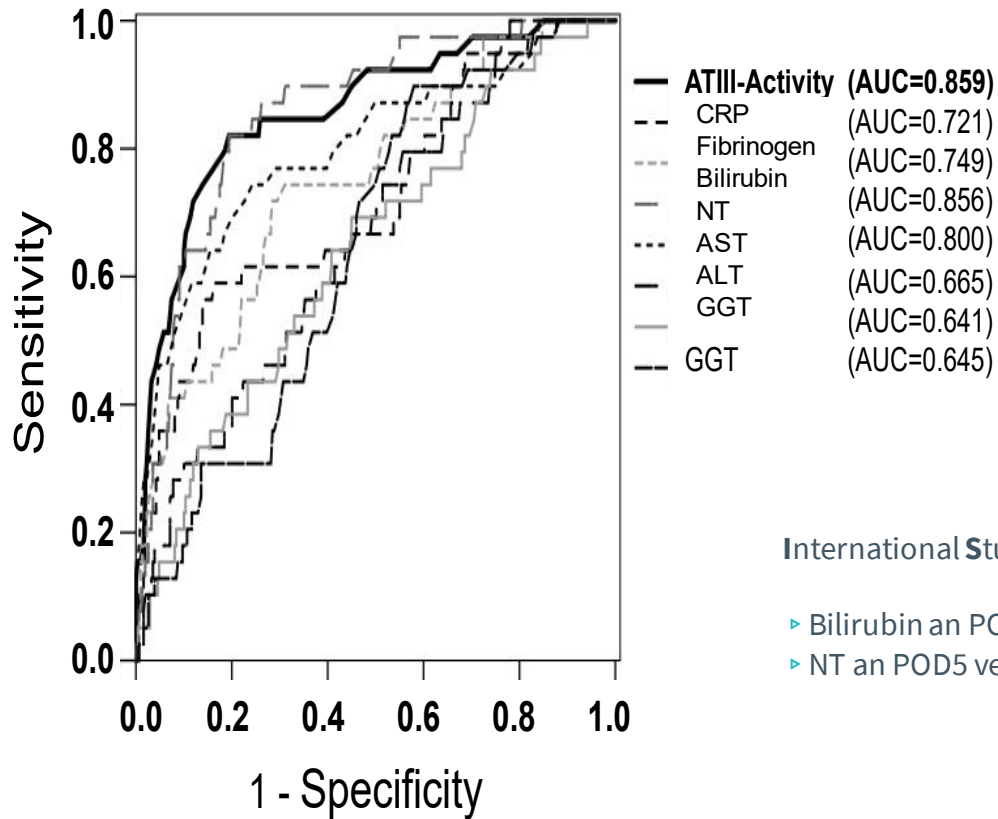
- Patienten mit postoperativer LD haben postoperativ signifikant verminderte Levels an ATIII-Aktivität

Ergebnisse



- Postoperatives Outcome korreliert mit niederen Levels postoperativer ATIII-Aktivität

Ergebnisse



- Postoperative ATIII-Aktivität übertrifft bekannte Marker für postoperative LD

International Study Group of Liver Surgery:

- Bilirubin an POD5 erhöht
- NT an POD5 verringert

Conclusio

- ATIII-Aktivität ist ein unabhängiger prädiktiver Marker für postoperative Leberdysfunktion
- Niedrige ATIII-Aktivität am ersten postoperativen Tag korreliert mit postoperativem Outcome und Gesamtüberleben
- Hochrisiko-Patienten können mit einem Cut-Off von 57% identifiziert werden

Beurteilung der Resektabilität in Abhängigkeit von Diagnose und klinischer Situation

- ✓ Patienten ohne Hinweis auf chronische Lebererkrankung
- ✓ Patienten mit chronischer Lebererkrankung (Fibrose / Zirrhose)
- ✓ Patienten mit Ikterus

How far can we go?