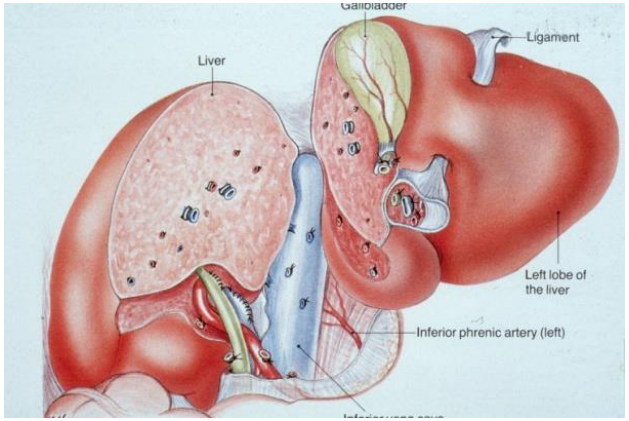
1st Maastricht E-AHPBA Post-Graduate HPB Course

Assessment of Hepatic Volume and Function



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Disclosure slide for speakers at further training events

Disclosure of speaker's interests	
(Potential) conflict of interest	**None/See below**
Potentially relevant company relationships in connection with event [1]	**Company names**
• Sponsorship or research funding[2] • Fee or other (financial) payment[3] • Shareholder[4] • Other relationship, i.e. …[5]	• • • •

Assessment of hepatic volume and function

- The single most important determinant of mortality after liver resection is postresectional liver failure
  (Reported mortaliity up to 90%)

Van den Broek et al, Liv Int 2008
Kauffmann R, Fong Y, Hepatobiliary Surg Nutr 2014

Assessment of hepatic volume and function

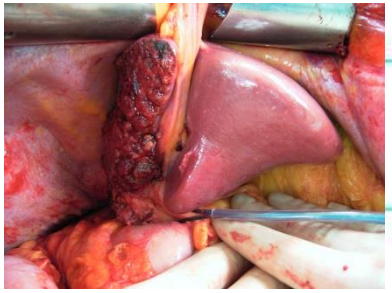
- The single most important determinant of mortality after liver resection is postresectional liver failure
  (Reported mortaliity up to 90%)

- Too small liver remnant
  Too little volume (= function?)

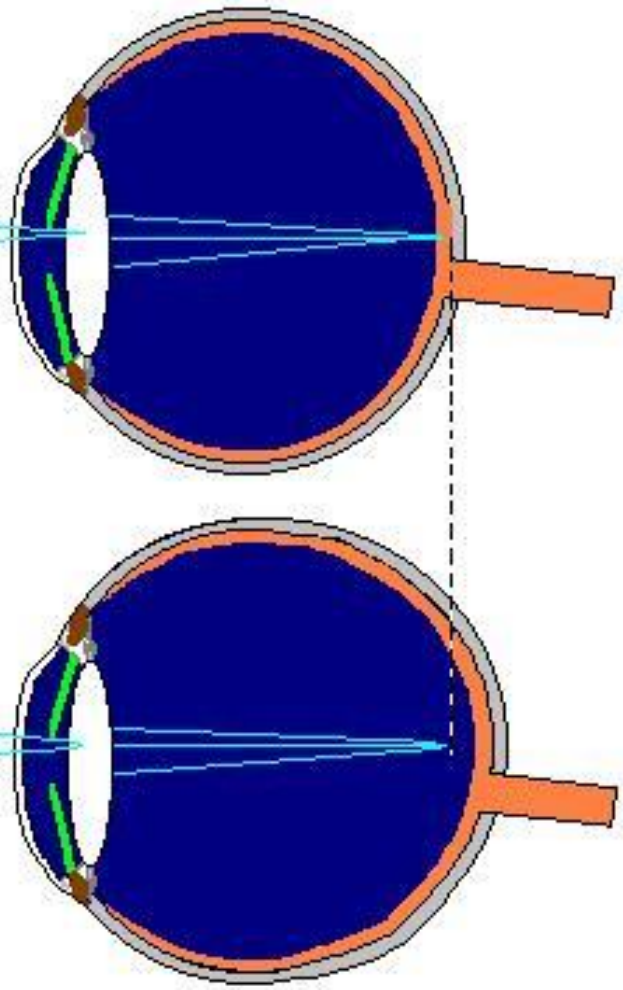
HOW TO ASSESS?

Eyeball assessment

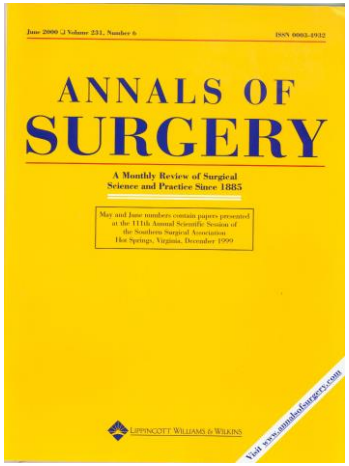
Liver remnant on CT



Liver remnant after resection



Annals of Surgery ***2002****; 236(4):397-407*



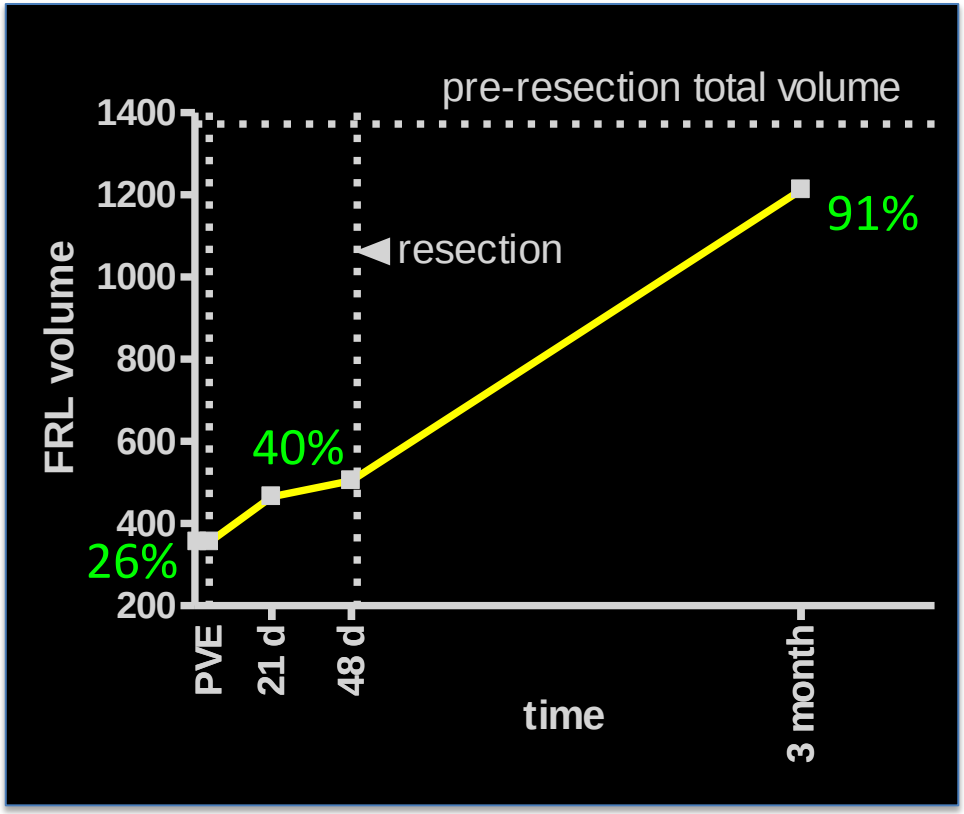
Improvement in Perioperative Outcome After Hepatic Resection
Analysis of **1,803** Consecutive Cases Over the Past Decade

William R. Jarnagin, Mithat Gonen, Yuman Fong, Ronald P. DeMatteo, Leah Ben-Porat, Sarah Little, Carlos Corvera, Sharon Weber, Leslie H. Blumgart.

The *number of hepatic segments resected* and *operative blood loss* were the only predictors of both perioperative **morbidity (45%)** and **mortality (3.1%)**

Volumetric studies

- CT-volumetry (FRLV)
- Standardized FRLV (BSA)
- FRL/body weight ratio (0.5%)



Remnant liver volume 1240cc

Truant et al, J Am Coll Surg 2007
Kishi et al, Ann Surg 2009
vd Esschert et al, J Gastrointest Surg 2009

Standardized FRL volume

$$\frac{\text{RLV (measured by CT volumetry)}}{\text{TLV (based on BSA or body weight)}}$$

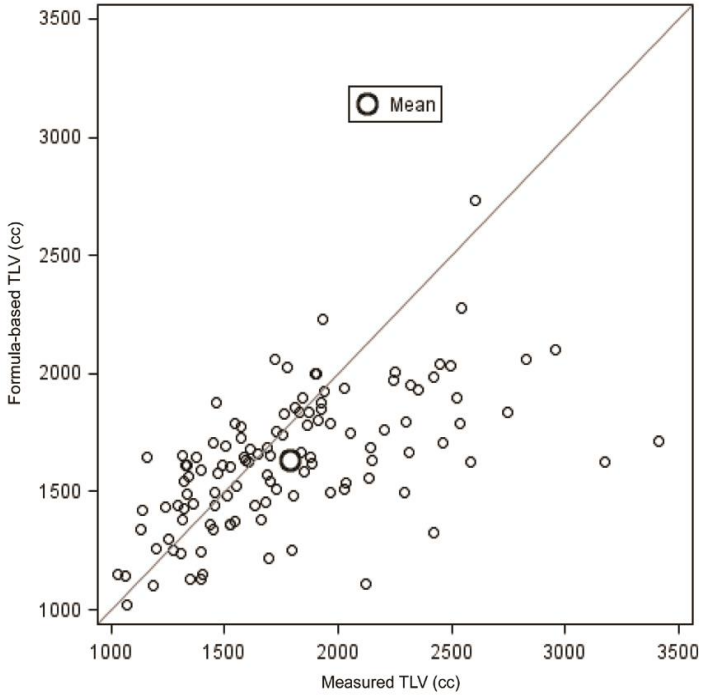
TLV = -794.41 + 1,267.28 x BSA (square meters)
TLV = 191.80 + 18.51 x weight (kilograms)

Vauthey et al, Surgery, 2000
Vauthey et al, Liver Transplantation, 2002
Abdalla, Arch Surg, 2002

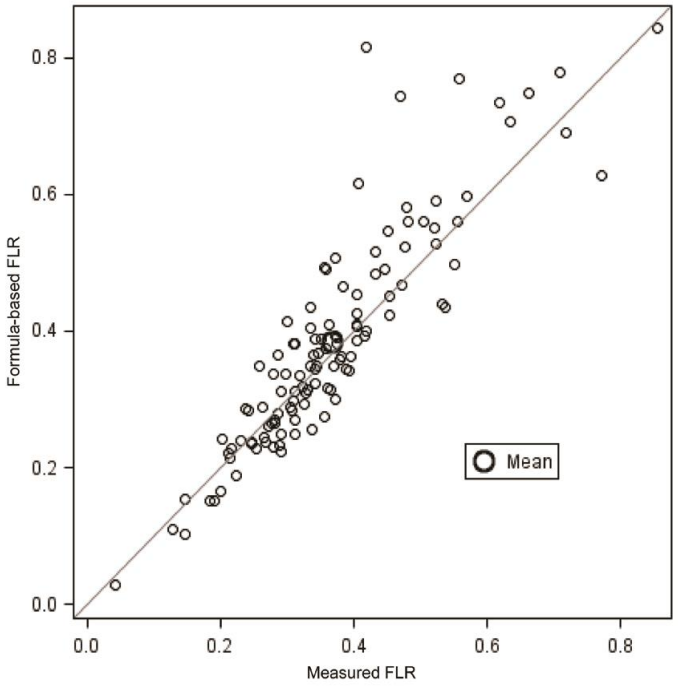
Measured vs standardized FRL volume

116 patients

TLV

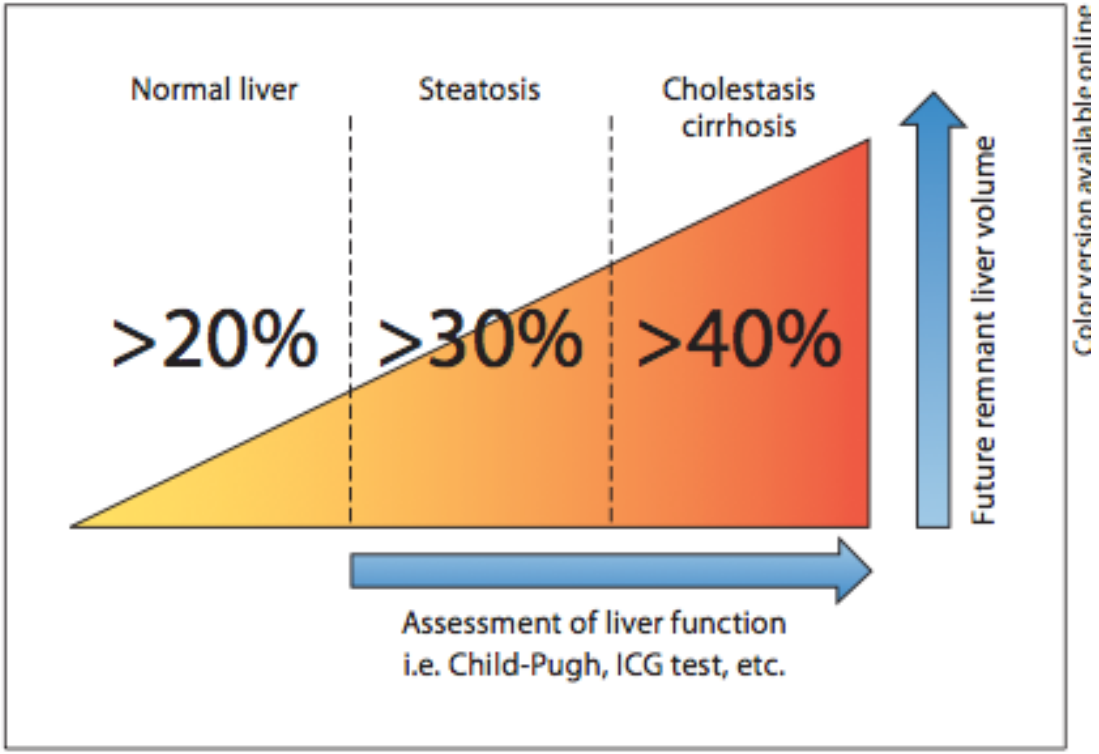


FRL



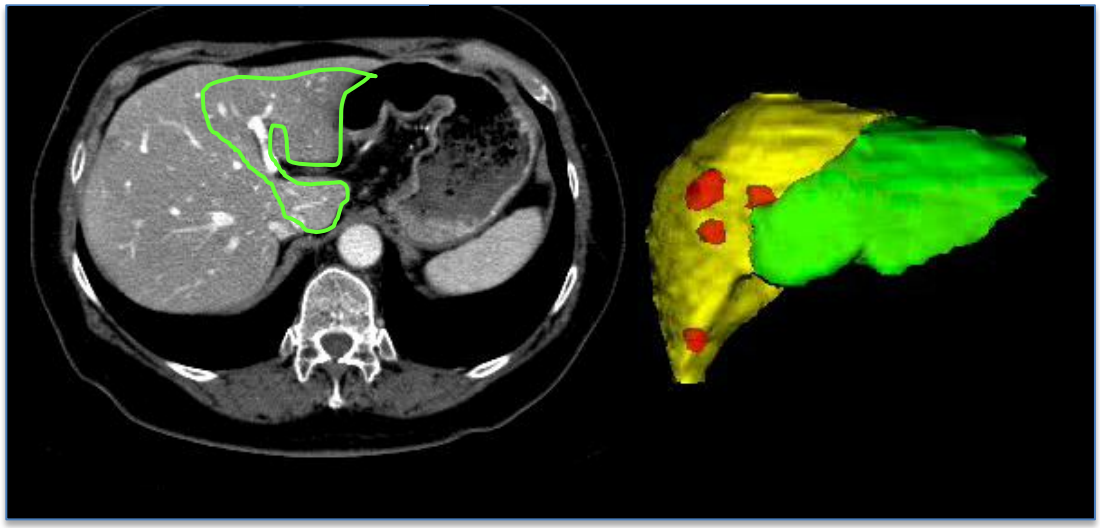
Martel et al, HPB 2015

Volumetric studies



HOW MUCH DO WE NEED? > 20-30%?

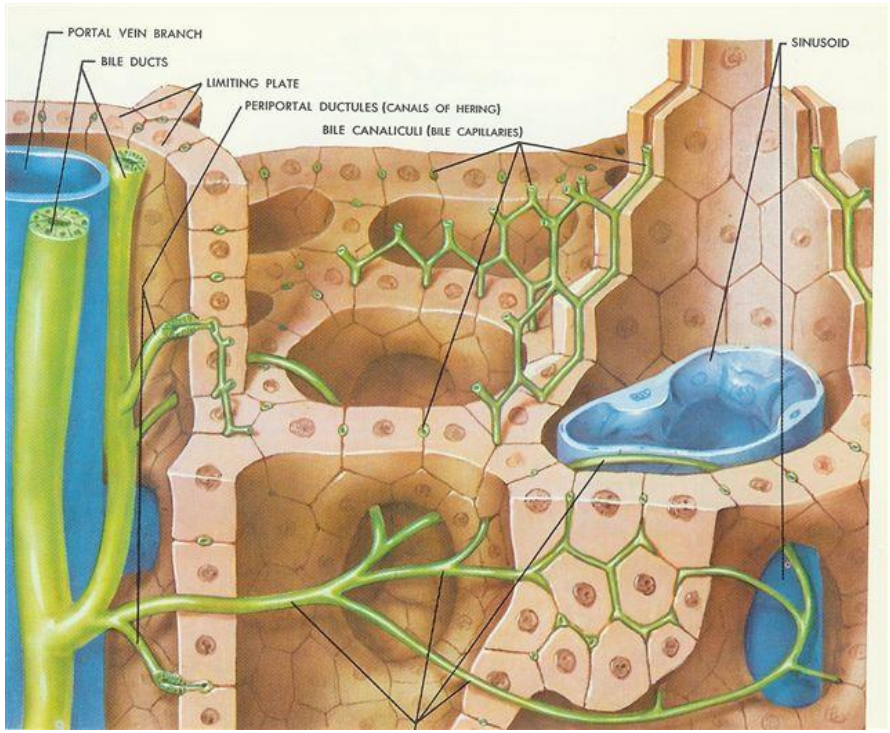
Assessment of hepatic volume and function



Volume ≠ Function

Liver function

- Uptake
- Synthesis
- Biotransformation
- Excretion



Hoekstra et al, Ann Surg 2012
Cieslak et al, DigSurg 2014

Assessment of hepatic volume and function

- There is not one single test that can predict all liver functions

Conventional tests	Function and/or event measured
Serum bilirubin	Uptake, conjugation, excretion
Serum bile acids	Excretion, shunting
Alkaline phosphatase	Cholestasis
Gamma-glutamyl transpeptidase	Cholestasis, enzyme induction, alcohol abuse
Transaminases	Necrosis
Coagulation factors, prothrombin time	Synthesis
Albumin	Synthesis, loss
Quantitative tests	**Function tested**
Aminopyrine breath test	Microsomal function
Antipyrine clearance	Microsomal function
Caffeine clearance	Microsomal function
Lidocaine clearance (MEGX)	Microsomal function
Methacetin breath test	Microsomal function
Galactose elimination capacity (GEC)	Cytosolic function
Low-dose galactose clearance	Hepatic perfusion (liver blood flow)
Sorbitol clearance	Hepatic perfusion (liver blood flow)
Indocyanine green disappearance	Hepatic perfusion, anion excretion
Albumin synthesis	Synthetic function
Urea synthesis	Synthetic function
^{99m}Tc-GSA	Functional hepatocyte mass

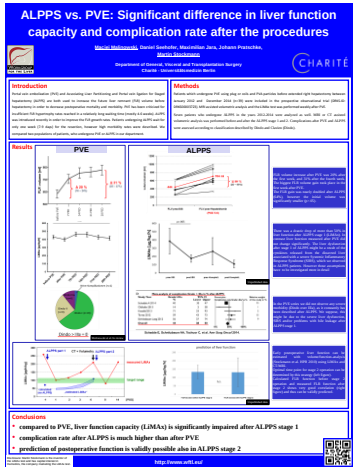
Hoekstra et al, Ann Surg 2012
Cieslak et al, DigSurg 2014

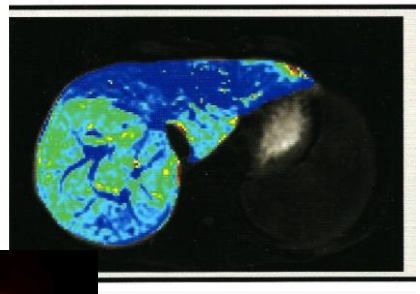
Quantitative biochemical tests

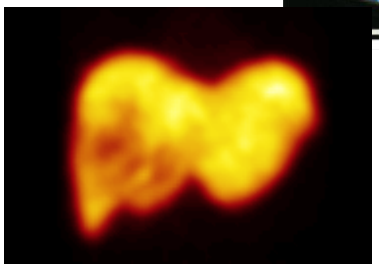
- ICG clearance test (hepatic perfusion)
- Galactose elimination test (hepatic cell mass)
- Caffeine elimination test (cytochrome P450 activity)
- Amino acid clearance (protein synthesis)
- Aminopyrine breath test (cytochrome P450 activity)
- Lidocaine elimination test (MEGX test)

Quantitative liver function tests

- ICG clearance test
  Lau et al, BJS 97
- Limax test (Aminopyrine breath test)
  Stockmann et al, HPB 2010
- Functional imaging using MRI
  Nilsson, B J Rad 2013
- Scintigraphic methods
  De Graaf et al, J Nucl Med 2010







Indocyanine green (ICG) clearance test

- ICG tricarbocyanine dye that binds to albumin and alpha-1-lipoproteins
- Uptake by OATP:
  organic anion transporting polypeptide
- Excretion through MRP2:
  multidrug resistance related protein
- Determined by blood sampling or
  pulsed spectrophotometry
- Safe clearance values: ICG C-15 > 86%

The ICG clearance test is the best discriminating preoperative test for evaluating hepatic functional reserve in patients with HCC

H Lau et al, BJS, 1997

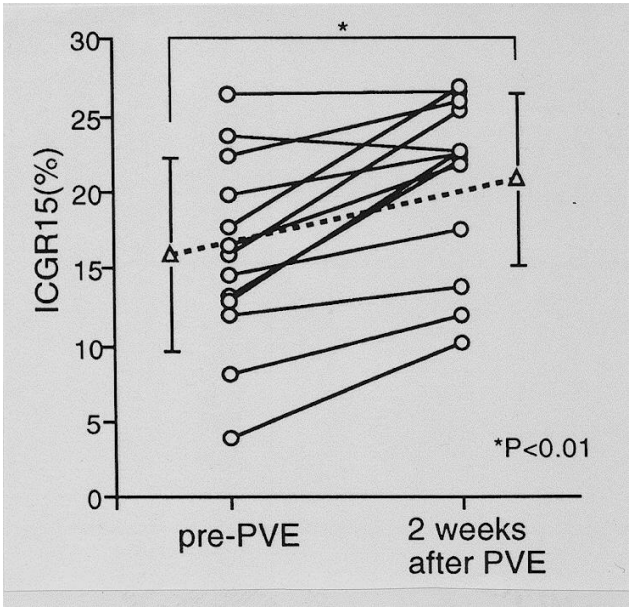
Drawbacks:

- Influence of hepatic bloodflow
- Regional variations within the liver are not detected
- Influence of hyperbilirubinemia

Influence of hepatic bloodflow on ICG clearance

- ICG-15 clearance test worsened at 2 weeks after portal vein embolization (PVE)

  Wakabayashi H, Jpn J Surg, 1997



- Return to baseline values 6-8 weeks after PVE

Scintigraphic imaging studies

- Provides simultaneous morphologic (visual) and physiologic (functional) information
- Defines regional hepatic function
- Dynamic SPECT allows measurement of functional volume of the liver
- Two phases: hepatic uptake and excretion

Liver scintigraphic studies

- Tc-99m-galactosyl serum albumin (GSA) binds to asialoglycoprotein receptors
  - relation with hepatoycyte cell mass?
  - influence of hepatic bloodflow?
  - no biliary excretion phase
  - availability of radiopharmaceutical?
- Tc-99m-colloid Kupffer cell mass
- Tc-99m-IDA (Mebrofenin)

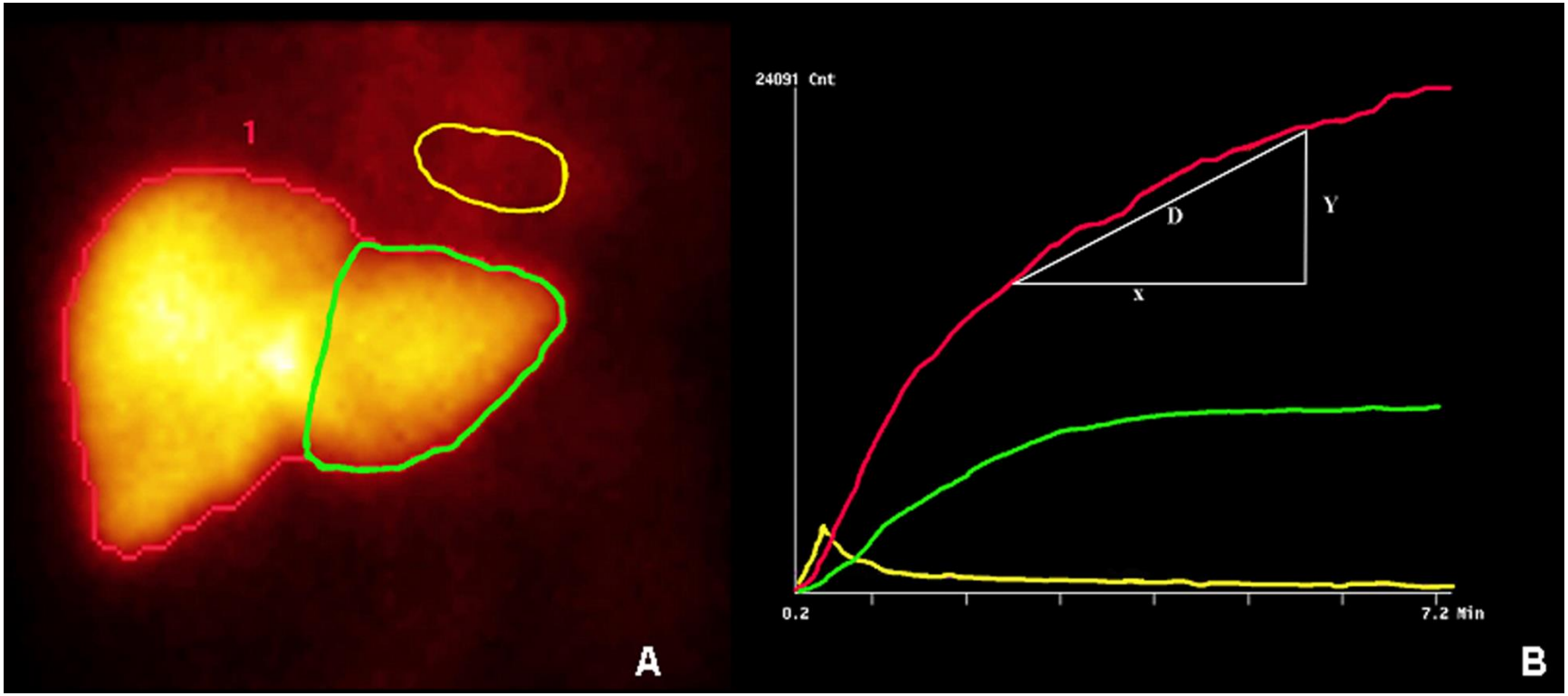
^{99m}Tc-mebrofenin HBS

Mebrofenin

- Iminodiacetic acid (IDA) analogue
- Uptake exclusively in the liver
- Hepatic transport similar to organic anions and to ICG
- Mebrofenin is excreted in the bile canaliculi

Hoekstra et al, Ann Surg 2012

Functional hepato-biliary scintigraphy
^{99m}Tc-mebrofenin



Liver uptake:

% Tc-mebrofenin/min

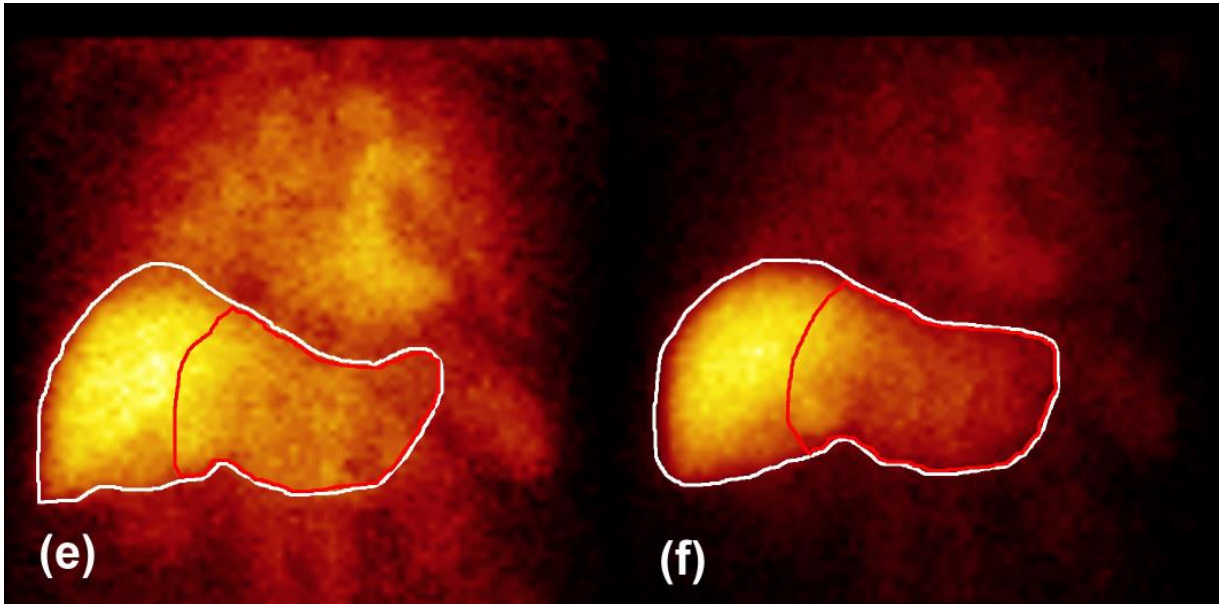
Hoekstra et al, Ann Surg 2012

Parameters:

- total liver function
- FRL function

Functional hepato-biliary scintigraphy ^{99m}Tc-mebrofenin

Biliary excretion phase represents
the run-off of bile to the gut

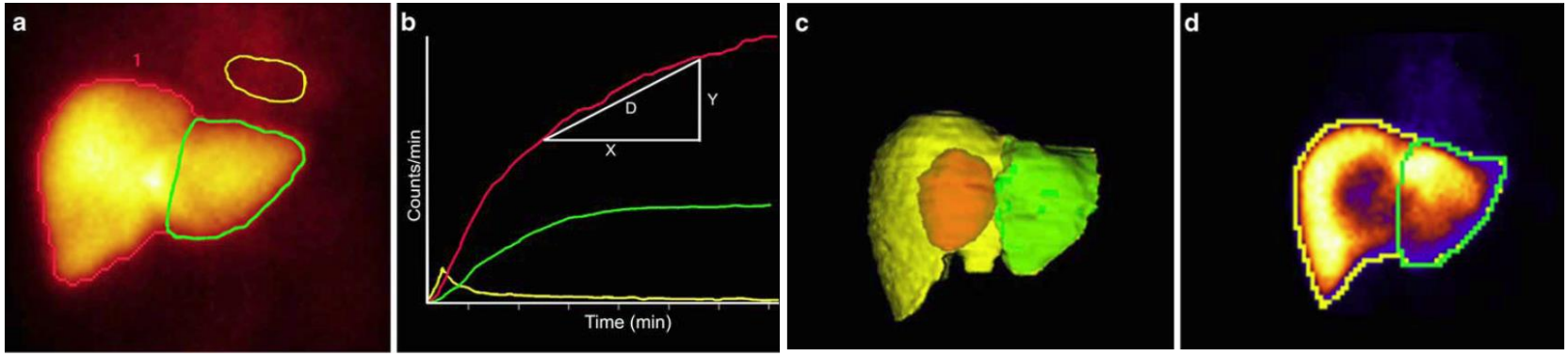


Cieslak 2014

Hepatobiliary scintigraphy

- In the uptake phase:
  provides simultaneous regional and functional information

- In the excretion phase:
  defines the quality of biliary drainage

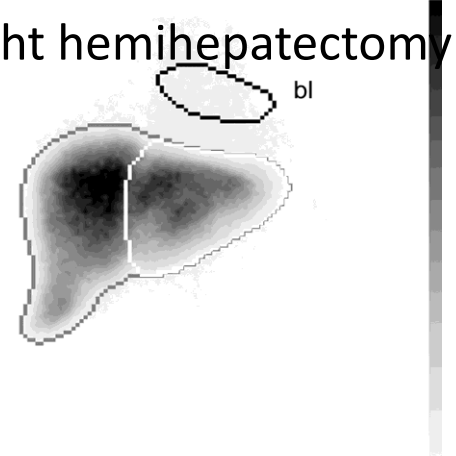


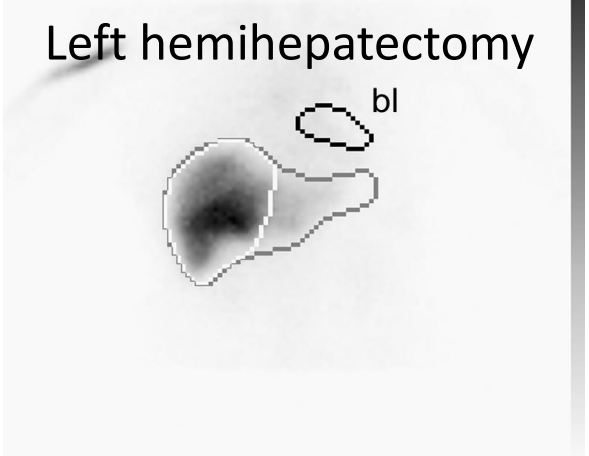
n=15

Right hemihepatectomy

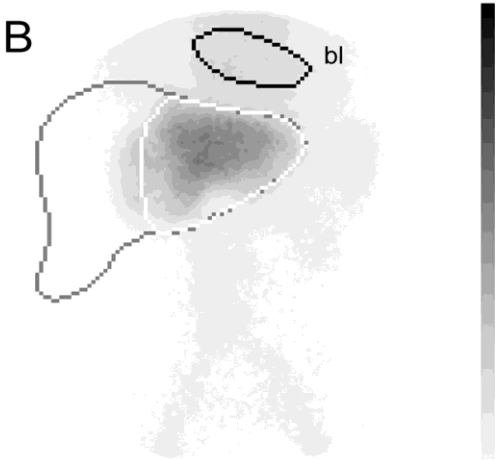
Left hemihepatectomy

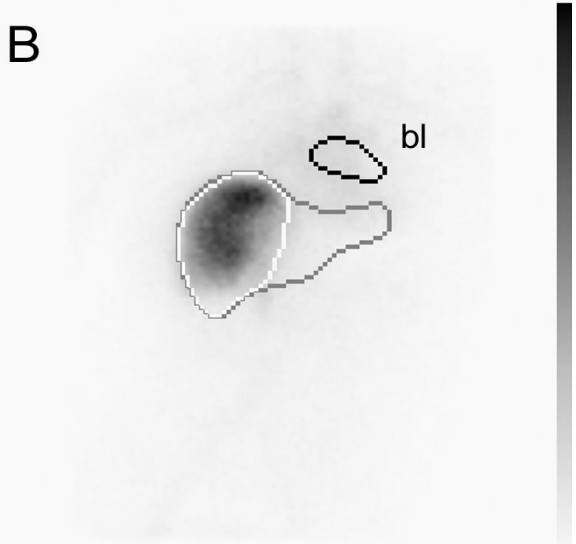
Pre-operative



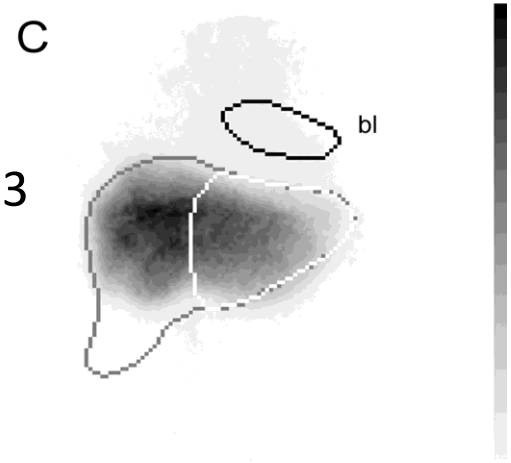


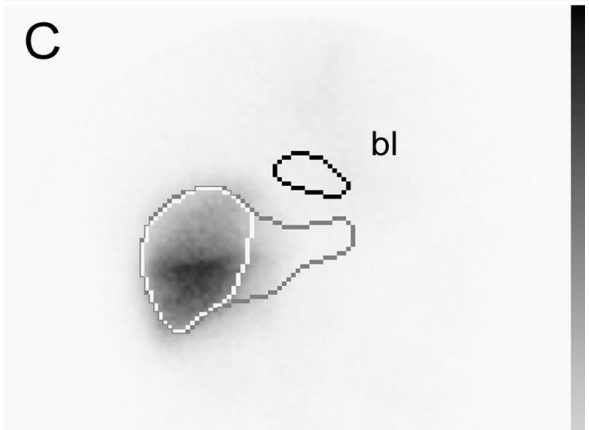
Post-operative day1



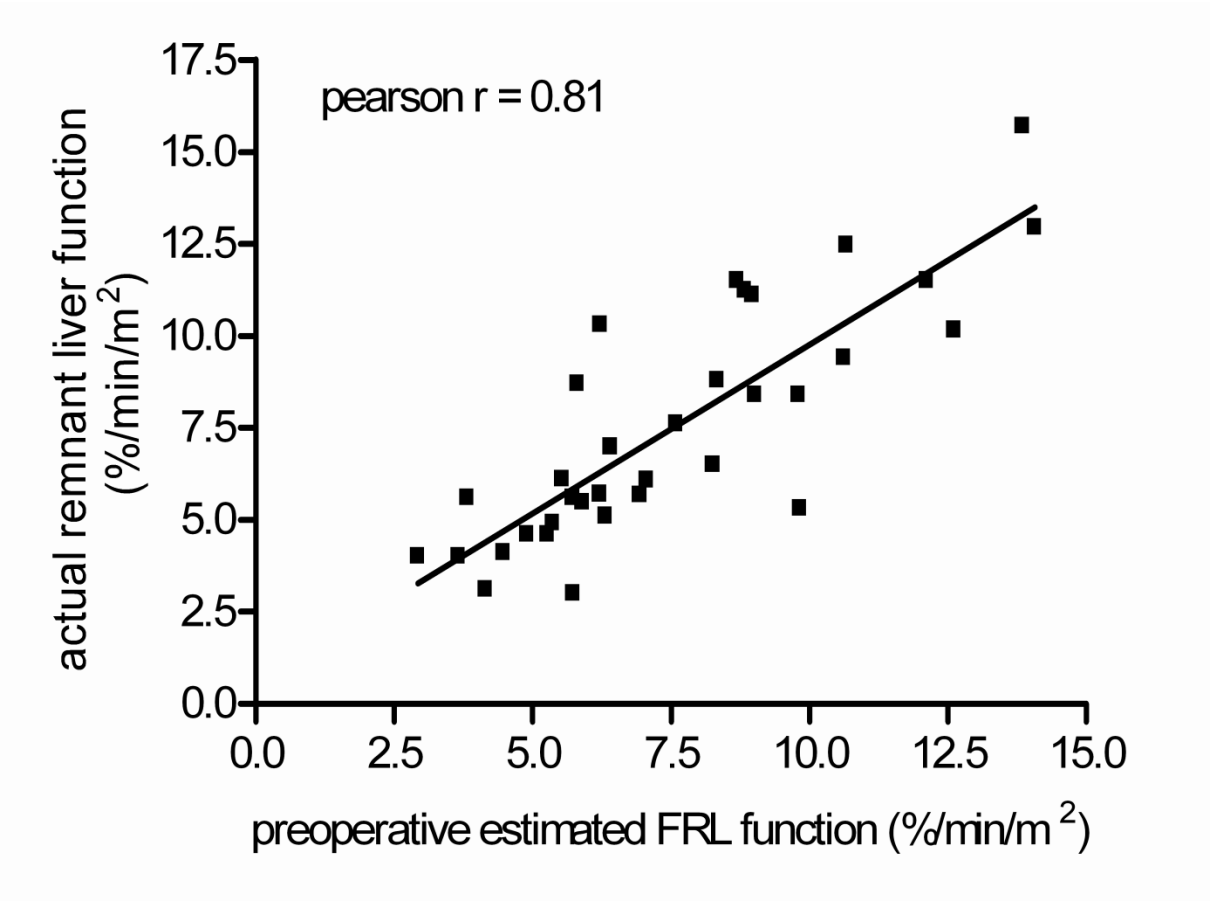


Post-operative month 3





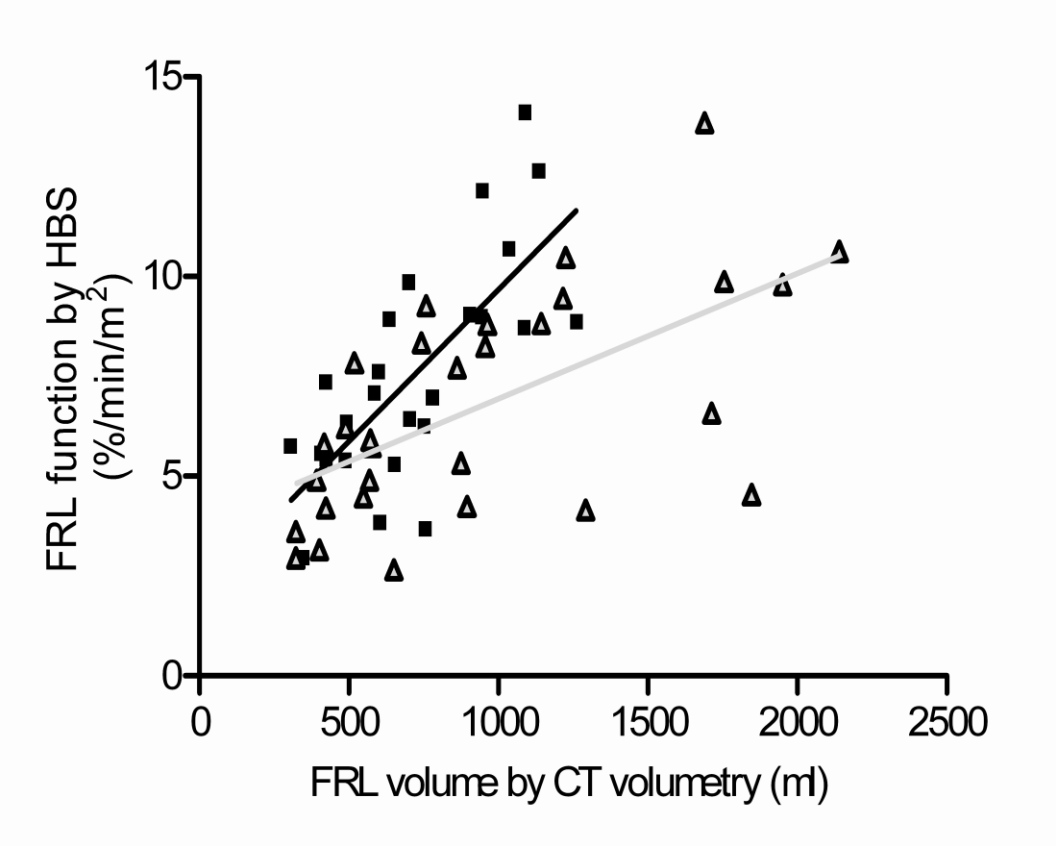
Dynamic ^{99m}Tc-mebrofenin HBS



Pearson r=0.81, p<0.0001, n=33)

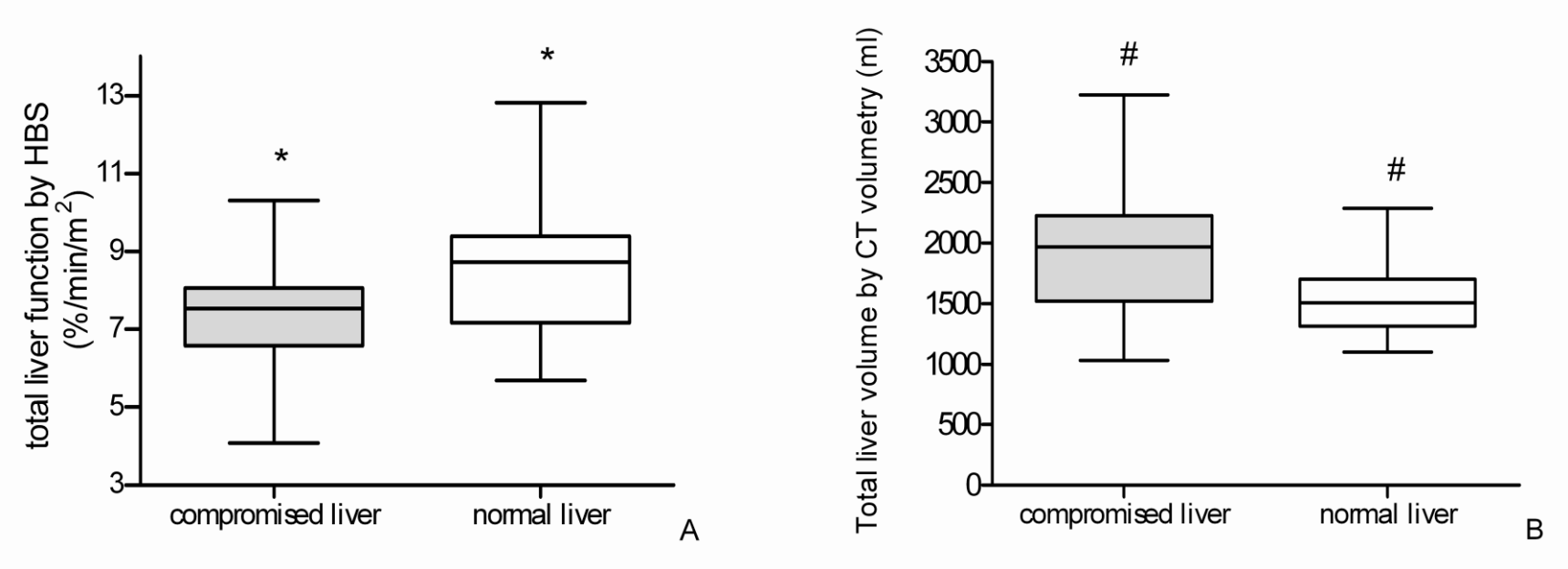
Bennink et al, J Nucl Med 2004

FRL function vs FRL volume



Normal patients (black line): Pearson r = 0.71, p= 0.0001
Compromised patients (grey line): Pearson r=0.61 p< 0.0003

Dynamic ^{99m}Tc-mebrofenin HBS

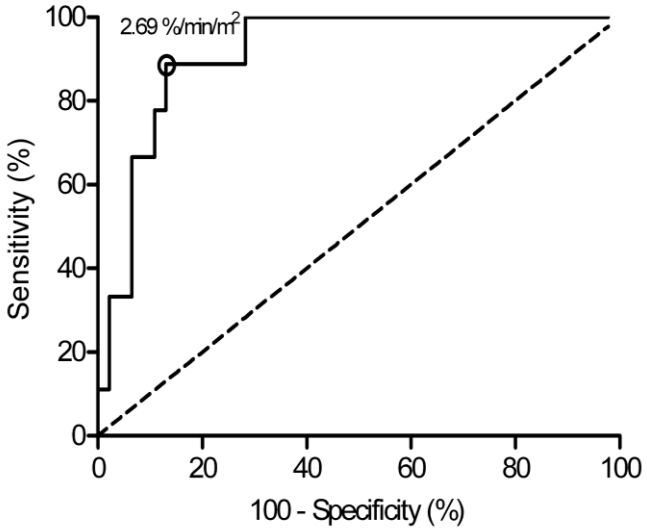


De Graaf et al, BJS 2011

Preoperative prediction of postoperative liver failure in 55 patients undergoing major liver resection

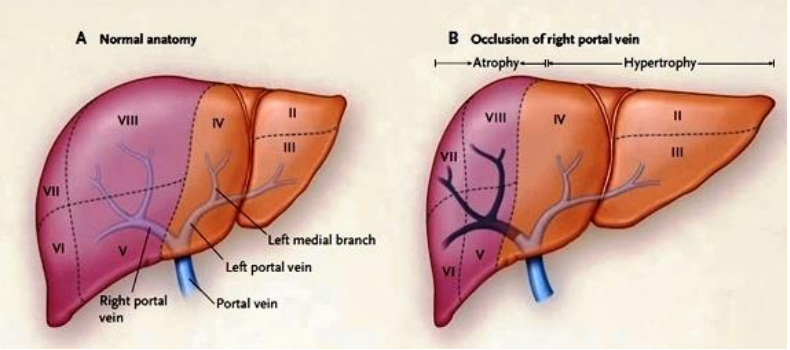
Outcome parameter	FRL function	FRL/TLV ratio	Standardized FRL
Cut-off value	2.69 %/min/m^2	Normal liver < 30% Compromised liver < 40%	Normal liver < 30% Compromised liver < 40%
Sensitivity	89%	78%	67 %
Specificity	87%	80%	87 %
PPV	57%	44%	50 %
NPV	98%	95%	93 %
LR+	6.8	4.0	5.1
LR-	0.12	0.19	0.38

Cut-off 2.7 %/min/m^2



De Graaf et al, J Gastrointest Surg 2010

Modulation of future remnant liver (FRL)



- Portal vein embolization (PVE)
- Portal vein ligation (PVL)
- PVL in combination with two-stage procedure
- PVL in combination with *in situ* liver split – ALPPS
  (Associating liver partition with portal vein ligation for staged hepatectomy)

Hepatic volume and function in PVE

Table 2 Results of the (first) preoperative FRL assessment using CT-volumetry and ^{99m}Tc-mebrofenin hepatobiliary scintigraphy with SPECT-CT

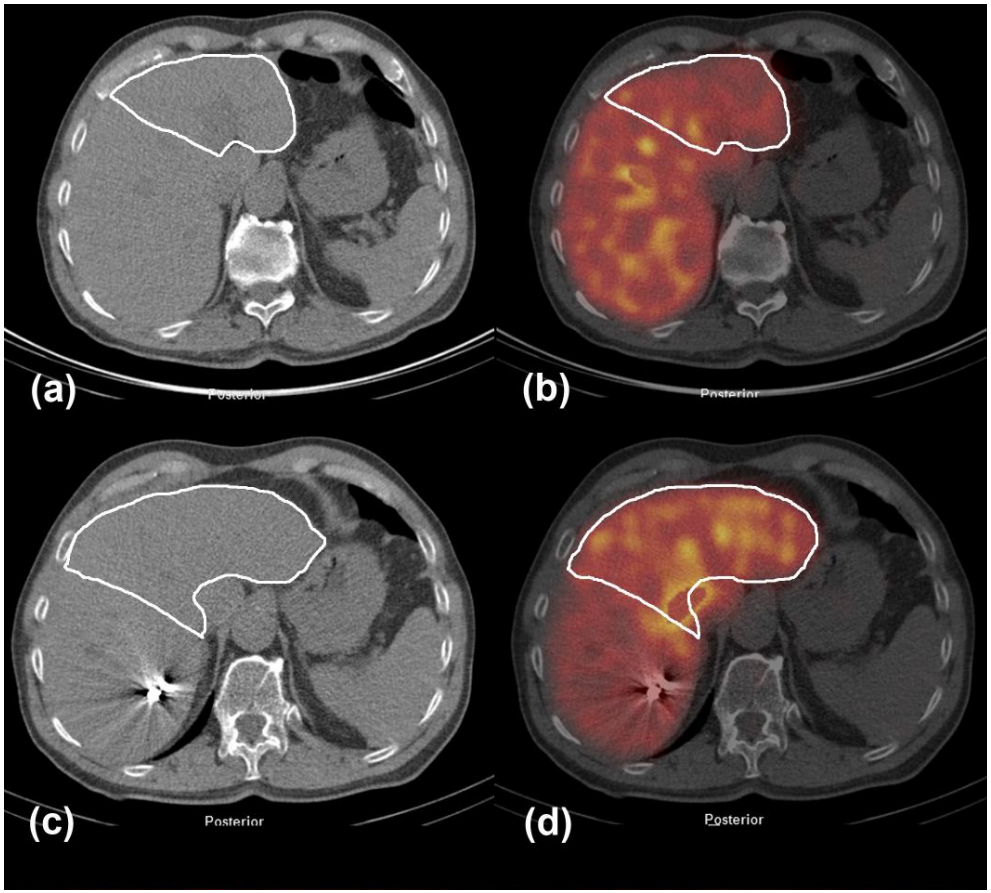
163 patients undergoing major liver resection (>3 segments)

	FRL-volume, % (IQR 25-75)	**FRL-function, %/min/m^2 (IQR 25-75)**	**Standardized FRL-volume, % (IQR 25-75)**	**FRL-BWR ≥ 0.5% weight, *n* (%)**
All patients, (*n* = 163)	49.3 (37.3 – 70.1)	4.6 (3.3 – 6.39)	54.3 (38.9 – 77.9)	161 (98.8)
PVE patients, (*n* = 29)	23.7 (18.7 – 27.8) **21 pts**	1.93 (1.5 – 2.36) **29 pts**	24.5 (18.3 – 29.4) **18 pts**	16 (55.2) **13 pts**
Non-PVE patients, (*n* = 134)	53.9 (37.4 – 73.5)	5.00 (3.49 – 7.10)	57.2 (41.6 – 79.7)	133 (99.3)

FRL, future remnant liver; FRL-volume, percentage FRL of the total liver volume; FRL-BWR, future remnant liver/body weight ratio; PVE, portal vein embolization; IQR, interquartile range.

Cieslak et al, in press HPB 2016

Hepatic volume and function in PVE

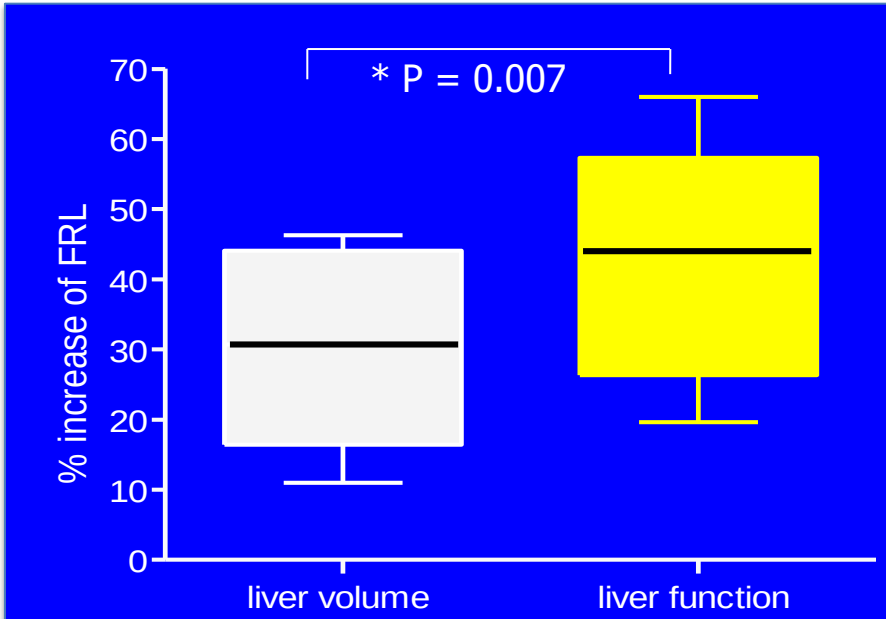


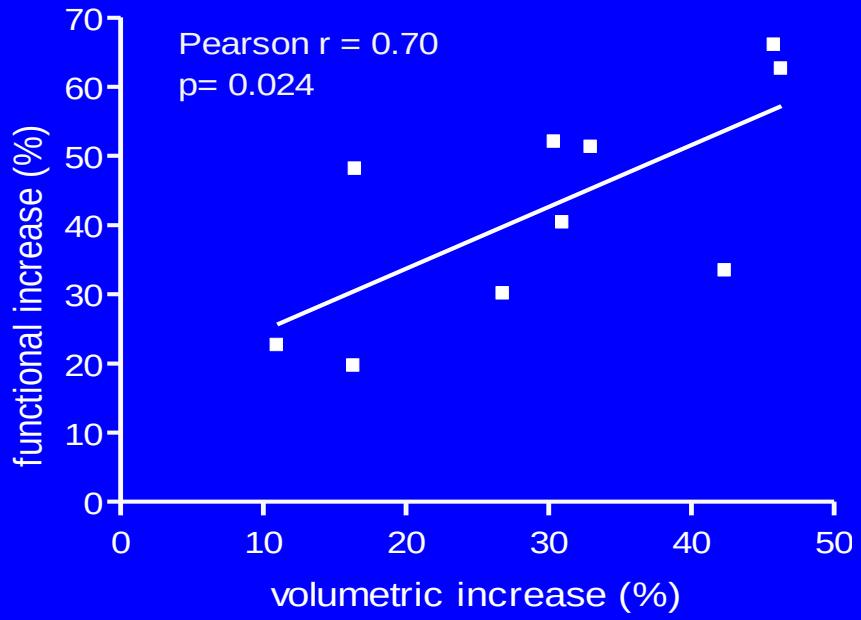
T=0

T=21d

Cieslak et al, in press HPB 2016

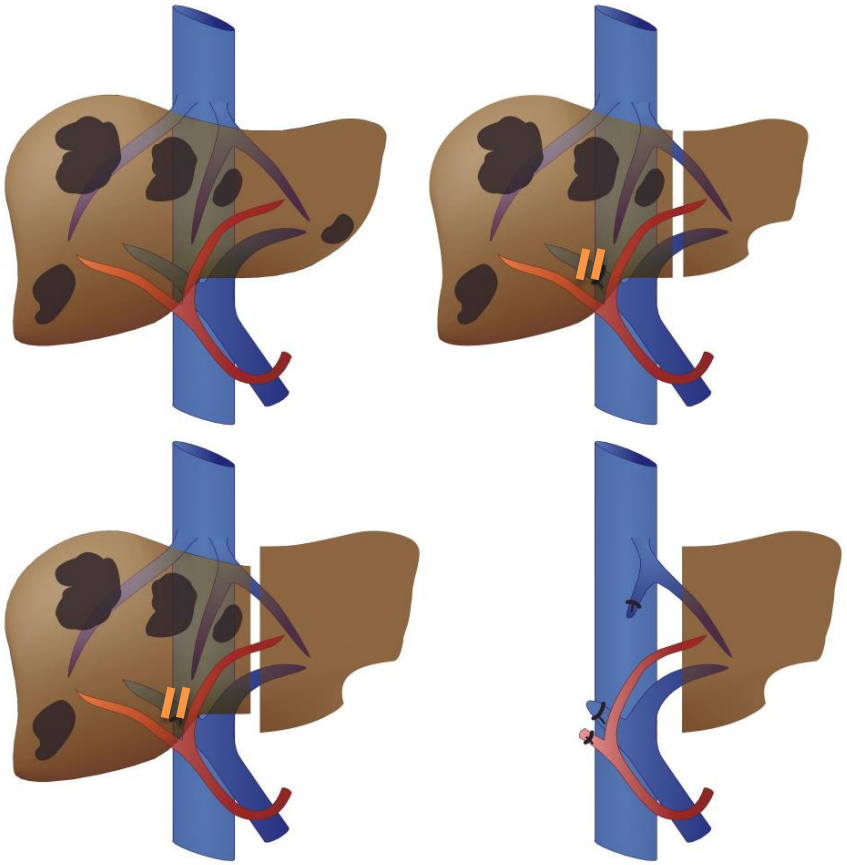
Increase of liver function (^{99m}Tc-mebrofenin uptake) exceeds liver volume (CT) after PVE





De Graaf et al, BJS 2011

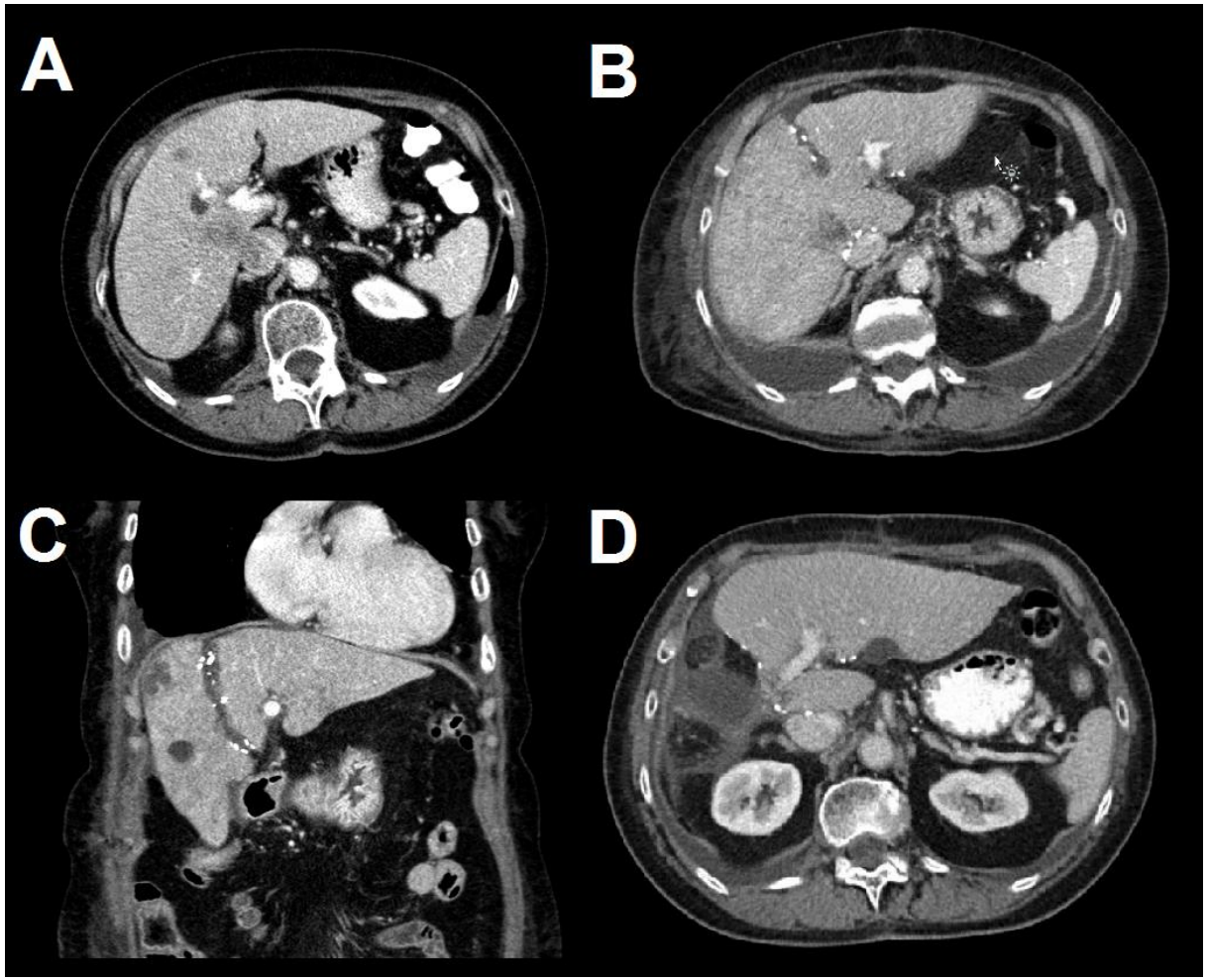
Hepatic volume and function in **ALPPS**



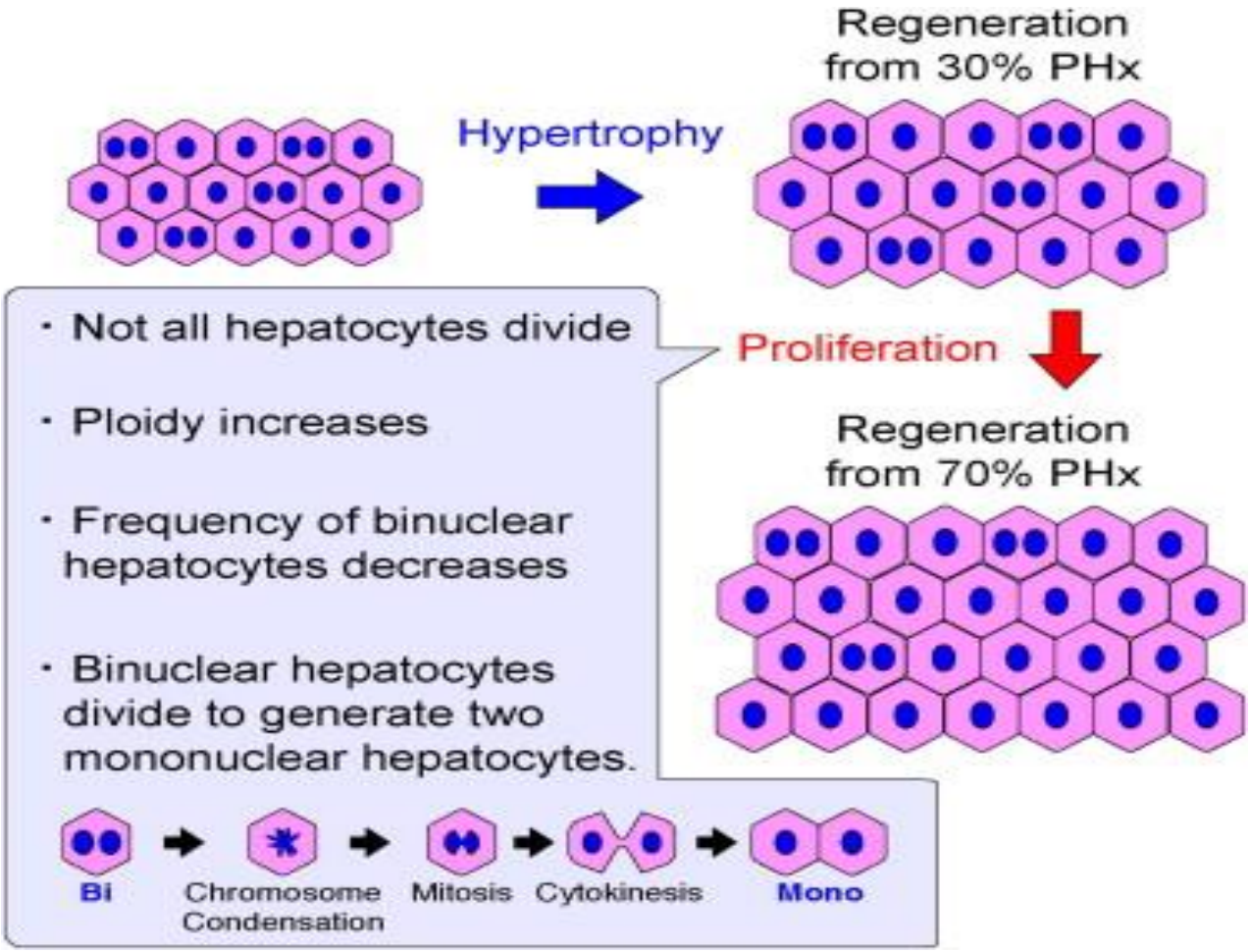
Association of Liver Partition and Portal vein ligation for Staged hepatectomy

Schnitzbauer et al, Ann Surg 2012

In situ split-technique



Hepatocellular hypertrophy → Hyperplasia → FRL hypertrophy

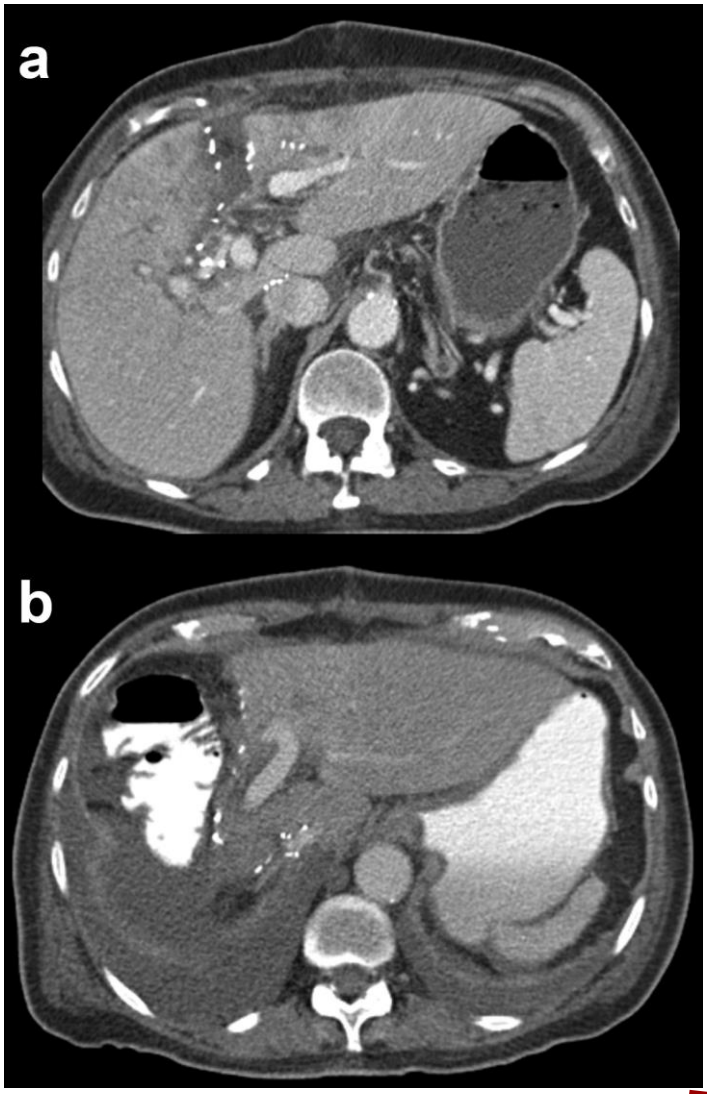


Miyaoka 2012

79-year-old patient with CLM
ALPPS/ext right hemihepatectomy

Stage I
CT POD 3

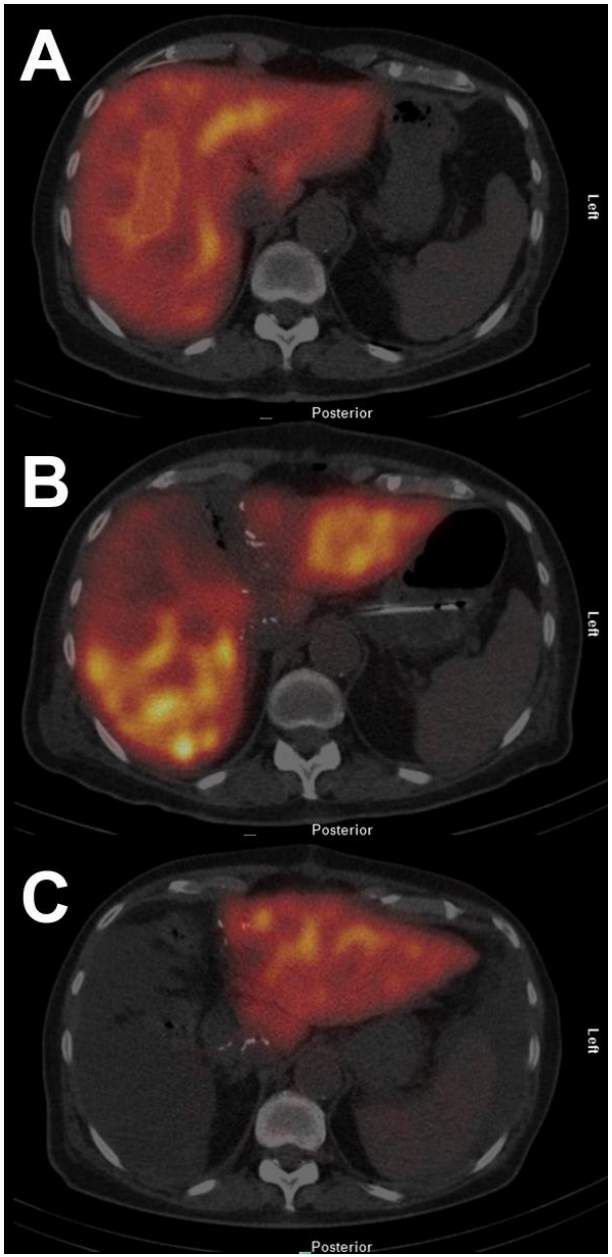
Stage II undertaken on POD 8
CT POD 20



Baseline

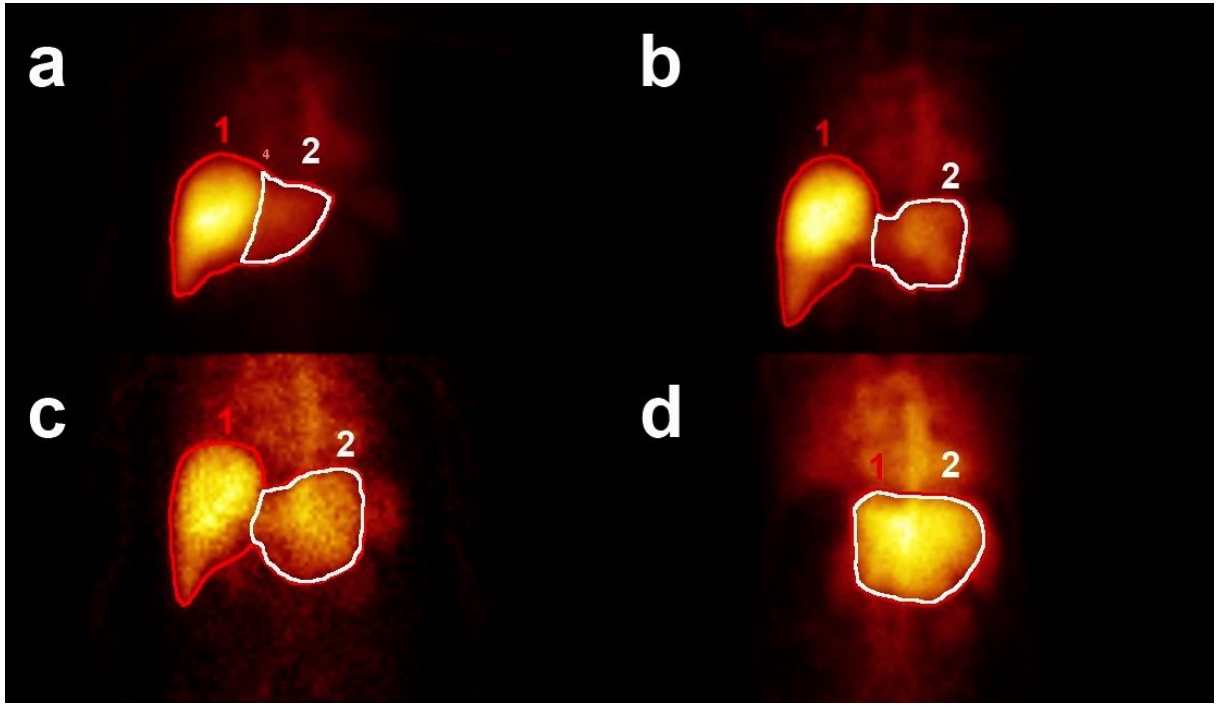
Stage I POD 3

Stage II POD 8
HBS POD 20



Baseline

Stage I POD 3



Stage I POD 8

Stage II POD 20

HBS
Cut-off 2.7 %/min/m²

TABLE 1. Scintigraphic and volumetric measurements of the FRL in a patient who underwent ALPSS

Event	Total liver function [%/min]	FRL function [%/min]	Total liver volume [cm^3]	FRL volume [cm^3]	FRL volume [% of total liver volume]
Preoperative assessment	12.2	1.5	1204	236	19.6
1st stage of ALPPS					
POD 3	13.3	2.0	1462	383	26.2
POD 8/POD 6	11.9	2.9	1554	412	26.5
2nd stage of ALPPS					
POD 20	6.25	3.4		759	63.0*

ALPPS Associating Liver Partition and Portal vein Ligation for Staged hepatectomy, *FRL* future remnant liver, *POD* postoperative day; * expressed as percentage of the pre preoperative total liver volume

CONCLUSIONS (I)

- CT volumetry is useful in patients with normal liver parenchyma
- In compromised patients measurement of liver volume is preferably combined with a quantitative liver function test
- The value of standardized CT volumetry (FRLV) and FRL/body weight ratio (>0.5%) needs further clinical assessment

CONCLUSIONS (II)

- ICG-15 clearance is the most widely used quantitative test but variability and discrepancies with clinical outcome have been reported
- Hepatobiliary scintigraphy (HBS) enables "Functional imaging" providing simultaneous morphological and physiological information
- Hepatobiliary scintigraphy shows regional (segmental) functional differences in the liver
- Hepatobiliary scintigraphy provides information on quality of biliary drainage

CONCLUSIONS (III)

- Hepatobiliary scintigraphic mehods are particularly useful in timing of resection after PVE or ALPPS stage 1

  - earlier resection after PVE (3 weeks)
  - more reliable timing of ALPPS stage II (8-10 days)