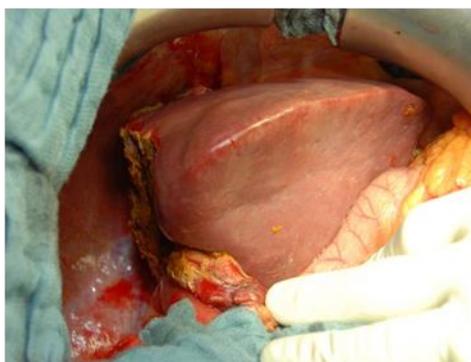
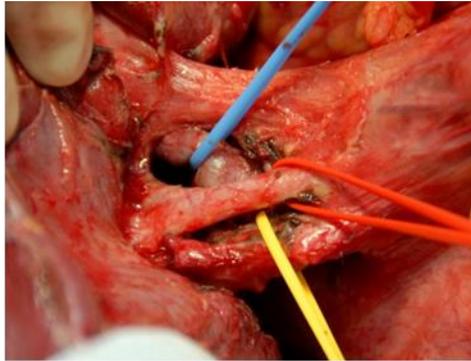


Two-stage hepatectomy and ALPPS



Hauke Lang

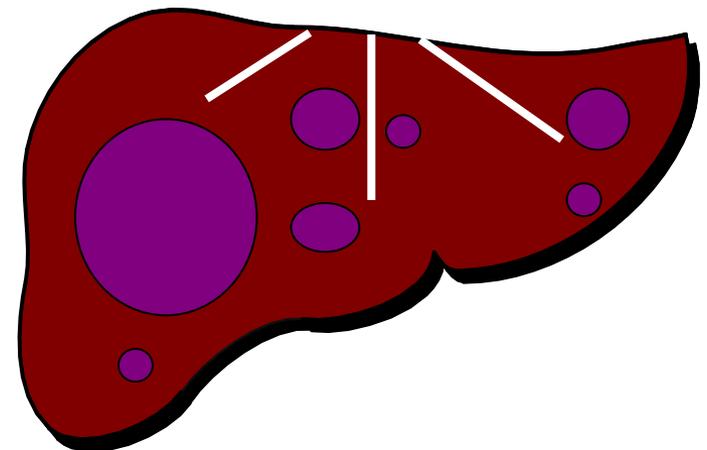
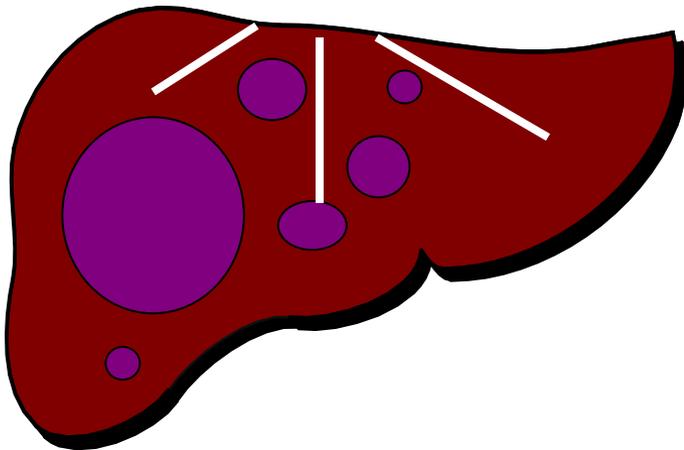
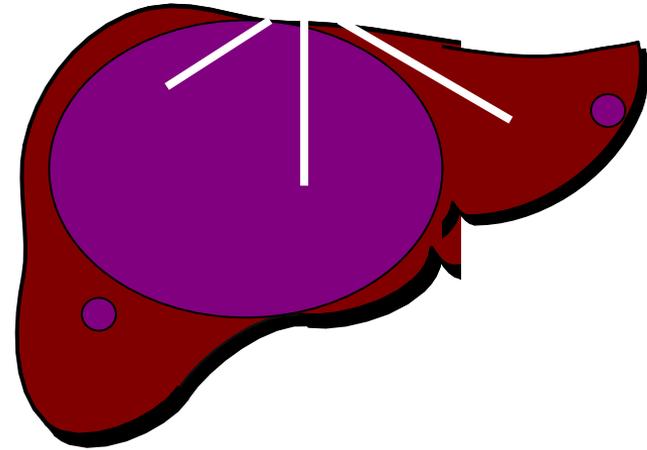
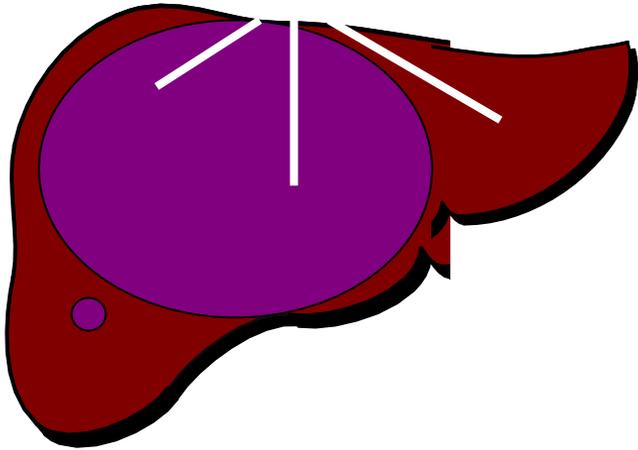
Department of General, Visceral and
Transplantation Surgery, Mainz



UNIVERSITÄTS**medizin.**

MAINZ

Functional Irresectability



Extended hepatectomy/right trisectionectomy



**minimum of functional
residual volume?**

Volume/liver function

quality of parenchyma, i.e. steatosis, cholestasis etc.

Liver *volume* \neq Liver *function*

Variations of liver anatomy

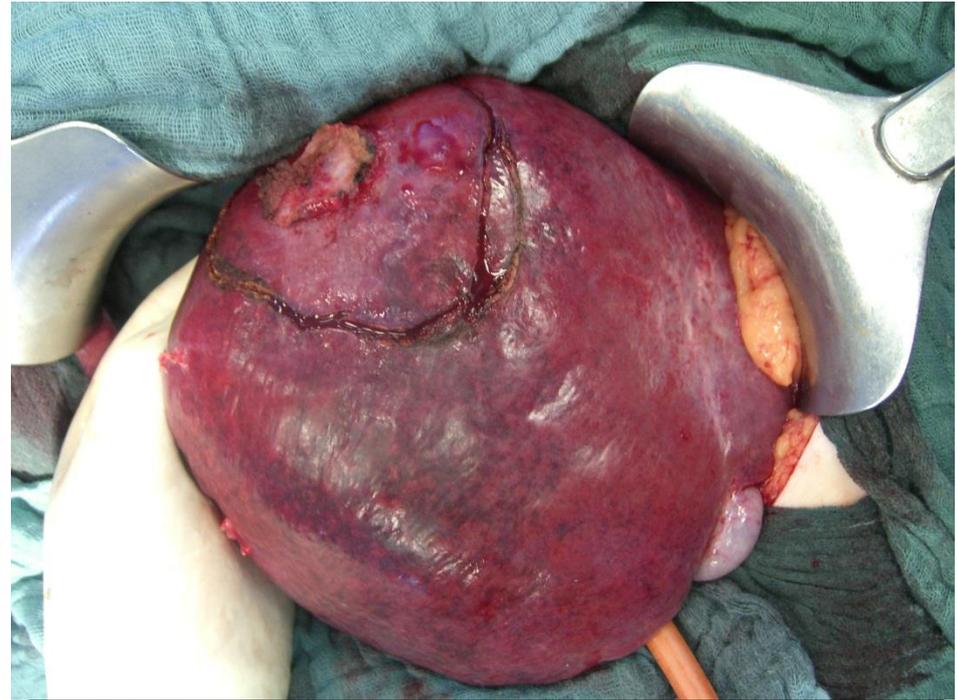
Liver remnant *volume* \neq Perfused liver remnant *volume*

Liver damage due to chemotherapy



Irinotecan

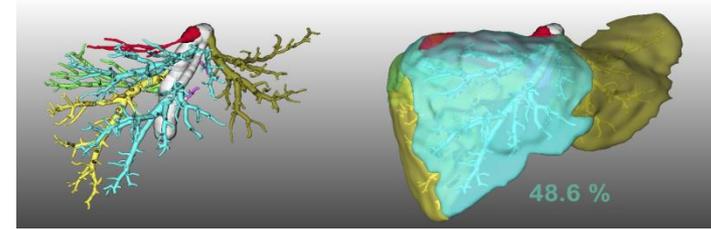
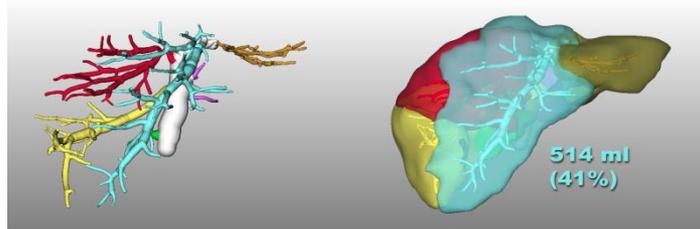
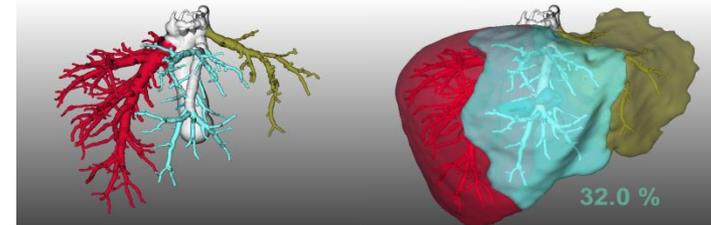
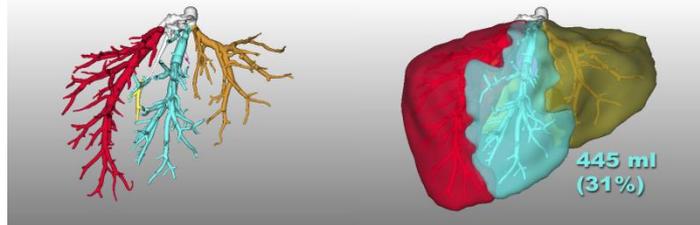
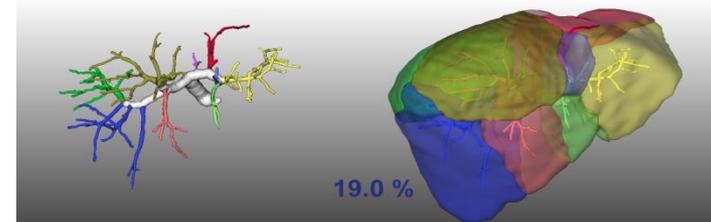
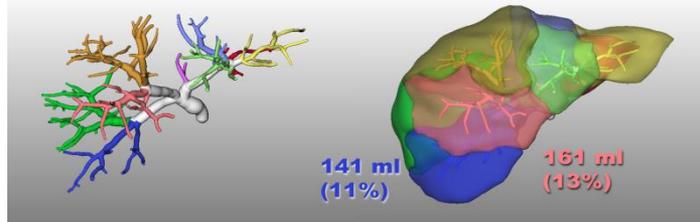
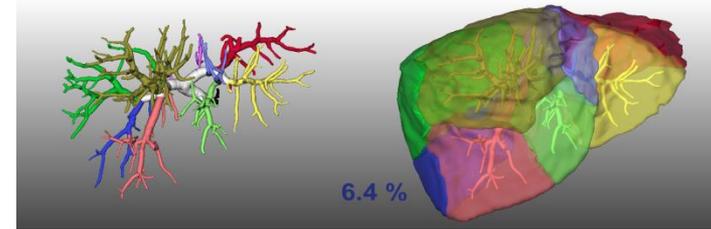
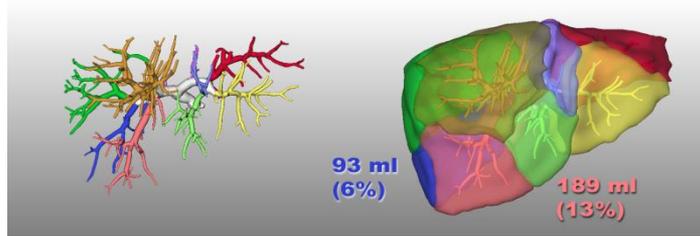
Steatosis, Steatohepatitis



Oxaliplatin

sinusoidale obstruction
„Blue Liver Syndrome“

Computerassisted 3-dimensional reconstruction – Variation of vascular territories



Trisectionectomy

Author/year

right trisectionectomy

left trisectionectomy

n

mortality

n

mortality

Iwatsuki/1988

126

5.5%

16

12.5%

Blumgart/1999

-

51

8.0%

Melendez/2001

189

5.3%

37

10.8%

Nishio/2005

-

70

9.0%

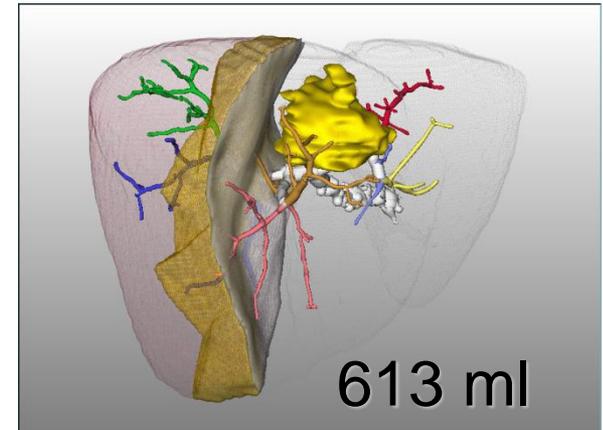
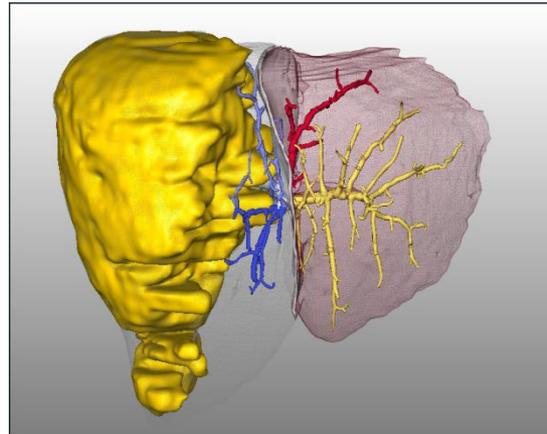
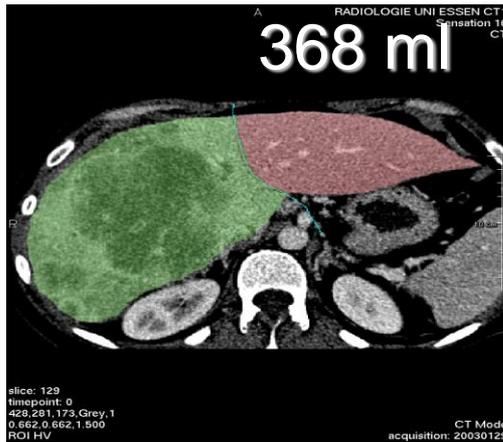
Lang/2006

121

5.8%

55

11.5%



Lang H et al., J Am Coll Surg 2006

Required Volume of the liver remnant

normal quality

≥ 25% liver volume

≥ 20% eTLV (sFRL)

$$eTLV = -794.41 + 1,267.28 \times \text{body surface}$$

$$sFRL = \text{remnant volume} / eTLV$$

≥ 0.5% of body weight (BWR = liver volume/Bw)

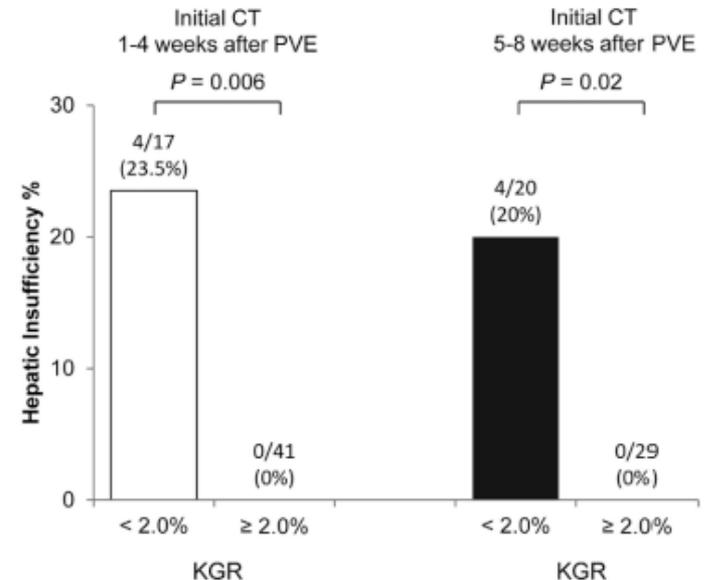
Kinetic growth rate

sFRL = volume in CT / eTLV

DH = Degree of hypertrophy (%) sFRL2 – sFRL1

KGR = DH/time (weeks)

	Best cut-off value	AUC (95% CI)	SE	P
KGR	2.0% per week	0.830 (0.736-0.923)	0.048	0.002
DH	7.5%	0.727 (0.539-0.915)	0.096	0.03
sFLR	29.6%	0.665 (0.486-0.845)	0.096	0.12



Volume of the liver remnant

Liver *volume*

≠

Liver *function*

History of hypertrophy induction

Portal vein embolization (PVE)

Makuuchi M, et al. Surgery 1990



Two-Stage hepatectomy

Adam R, et al. Ann Surg. 2000



Two-Stage hepatectomy + PVL

Jaeckel

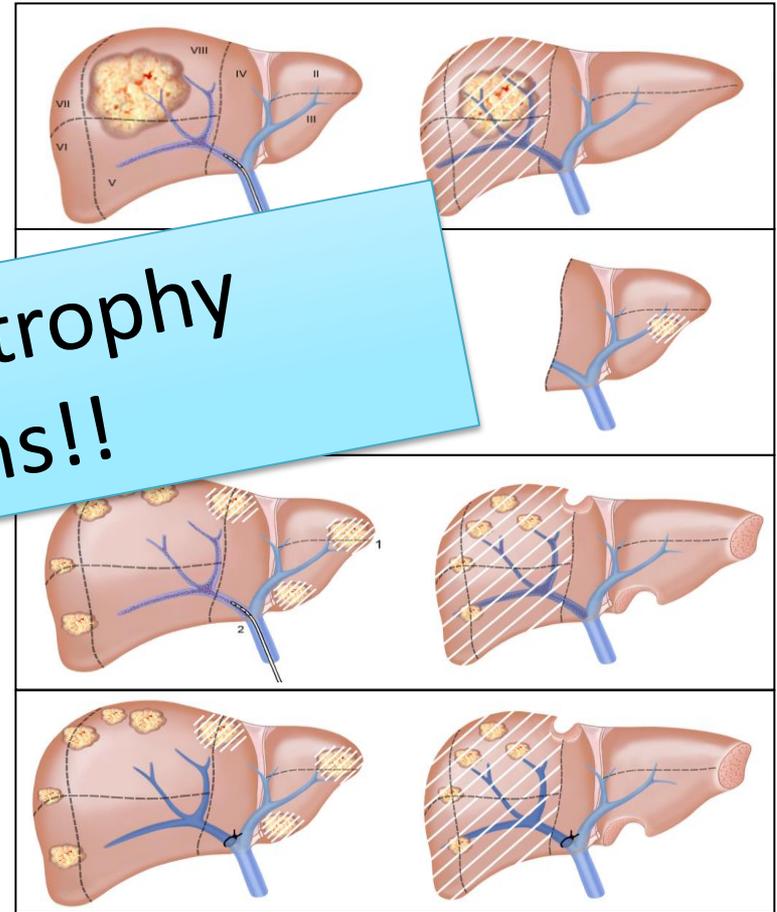
Two-Stage hepatectomy + PVL

J Belghiti et al. Hepatology 2008



Hepatic Vein embolization

Hwang et al. Ann Surg 2009



**30-50% hypertrophy
2-4 months!!**

Two-Stage Hepatectomy: A Planned Strategy to Treat Irresectable Liver Tumors

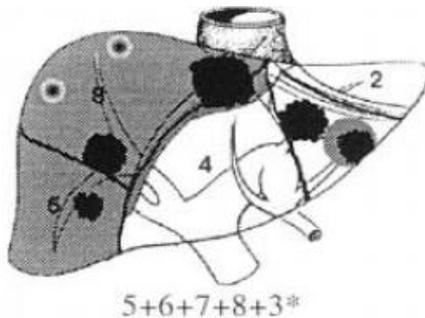
René Adam, MD, PhD, Alexis Laurent, MD, Daniel Azoulay, MD, PhD, Denis Castaing, MD, and Henri Bismuth, MD, FACS (Hon)

From the Centre Hépato-Biliaire, Hôpital Paul Brousse, Villejuif, and Université Paris-Sud, France

- **16 patients** with multiple CR liver metastases

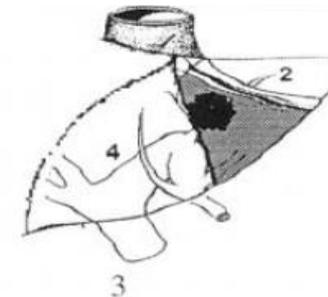
1° Stage (non-curative)

Resection of most diseased side **“difficult side”**



2° Stage (curative)

Clean-up of liver remnant **“easy side”**



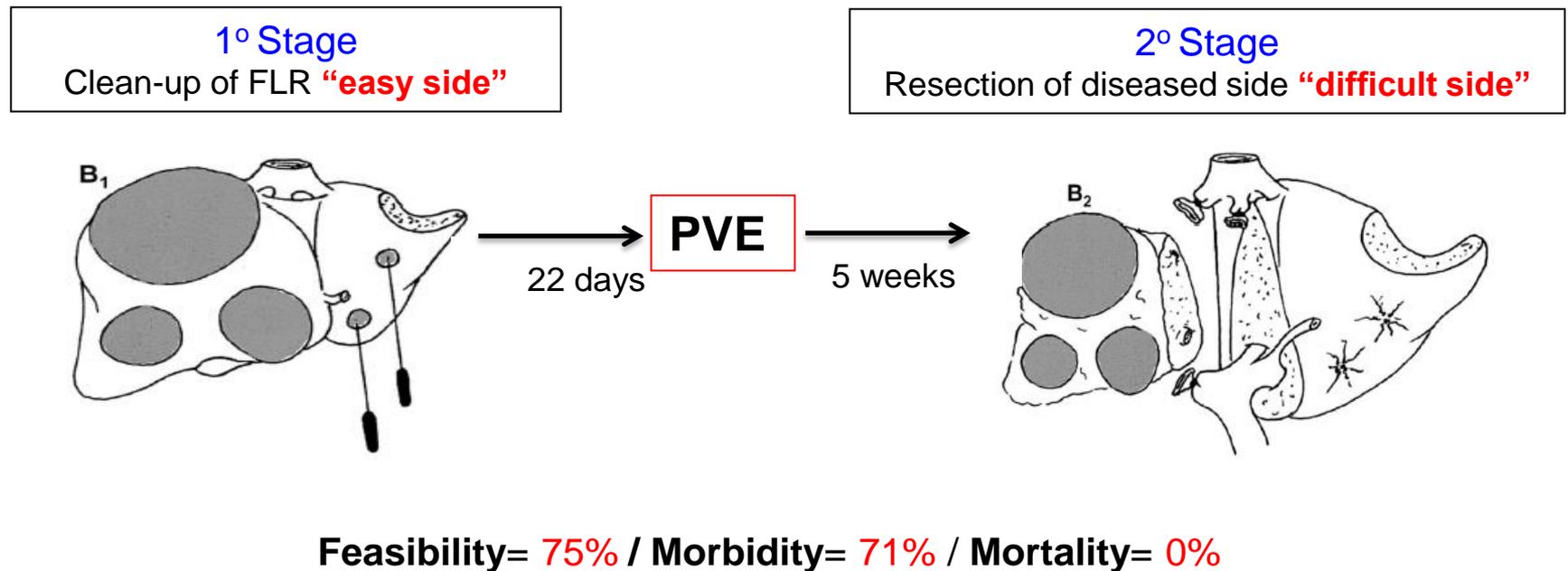
4 months (r 2-14)

Feasibility= 81% / Morbidity= 76% / Mortality= 15%

A Two-Stage Hepatectomy Procedure Combined With Portal Vein Embolization to Achieve Curative Resection for Initially Unresectable Multiple and Bilobar Colorectal Liver Metastases

Daniel Jaeck, MD, PhD, FRCS, Elie Oussoultzoglou, MD,* Edoardo Rosso, MD,* Michel Greget, MD,† Jean-Christophe Weber, MD, PhD,* and Philippe Bachellier, MD**

- **33 patients** with unresectable bilateral CR liver metastases

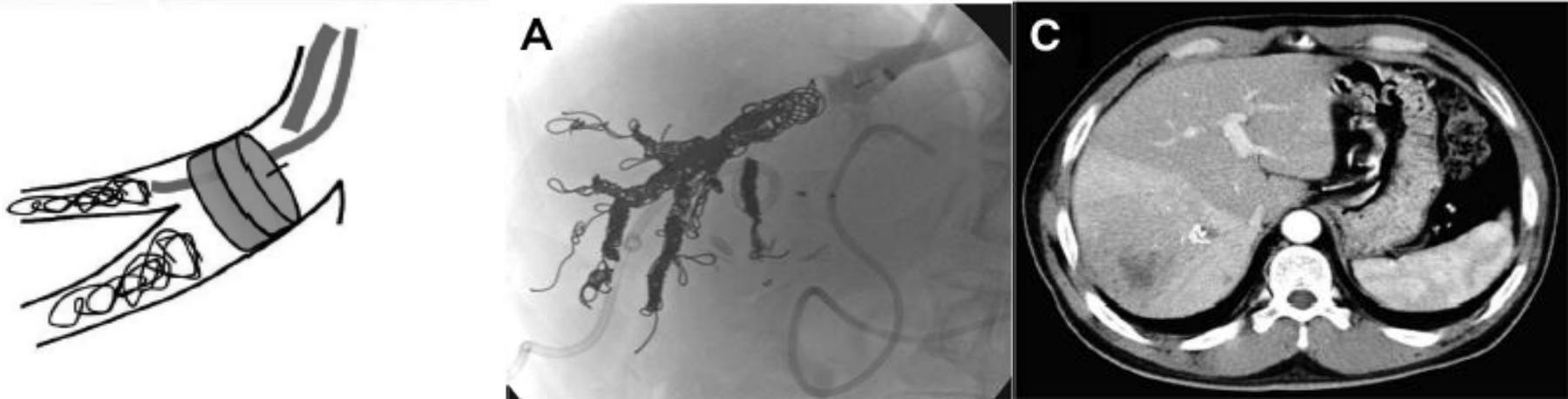


Sequential Preoperative Ipsilateral Hepatic Vein Embolization After Portal Vein Embolization to Induce Further Liver Regeneration in Patients With Hepatobiliary Malignancy

Shin Hwang, MD, Sung-Gyu Lee, MD,* Gi-Young Ko, MD,† Bum-Soo Kim, MD,* Kyu-Bo Sung, MD,† Myung-Hwan Kim, MD,‡ Sung-Koo Lee, MD,‡ and Hea-Nam Hong, PhD§*

Annals of Surgery • Volume 249, Number 4, April 2009

- Sequential right hepatic vein embolization two weeks after PVE.

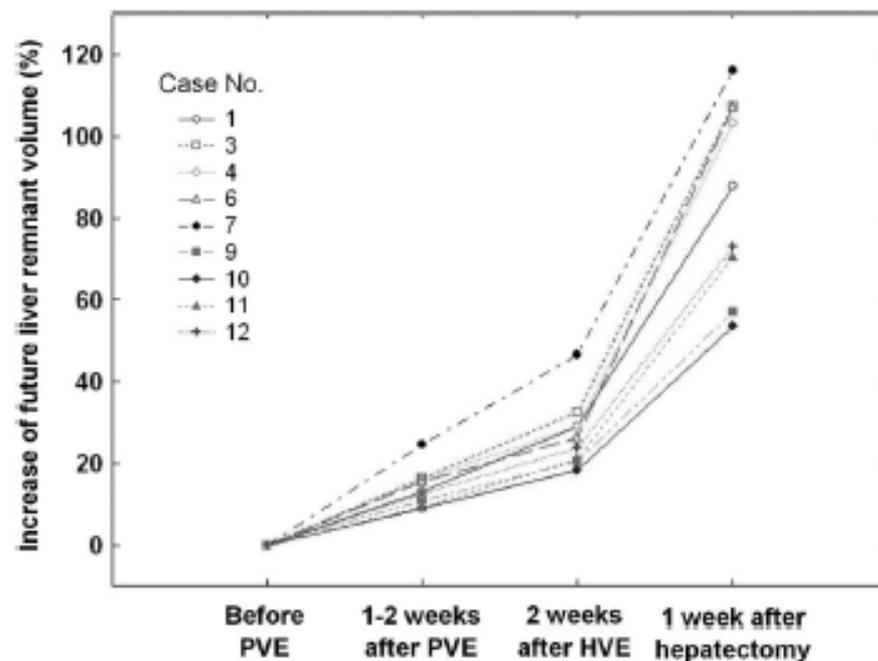


The sequential application of PVE and HVE appears safe and effective in facilitating contralateral liver regeneration by inducing more liver damage than PVE alone.

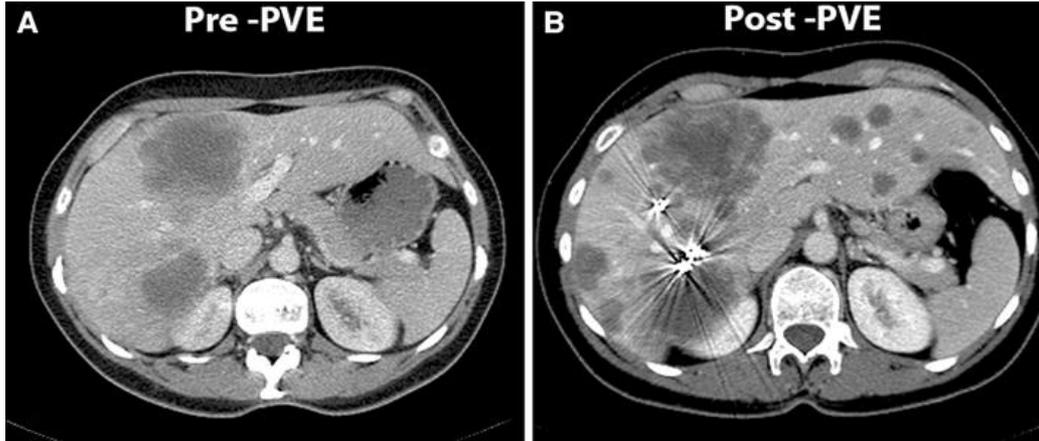
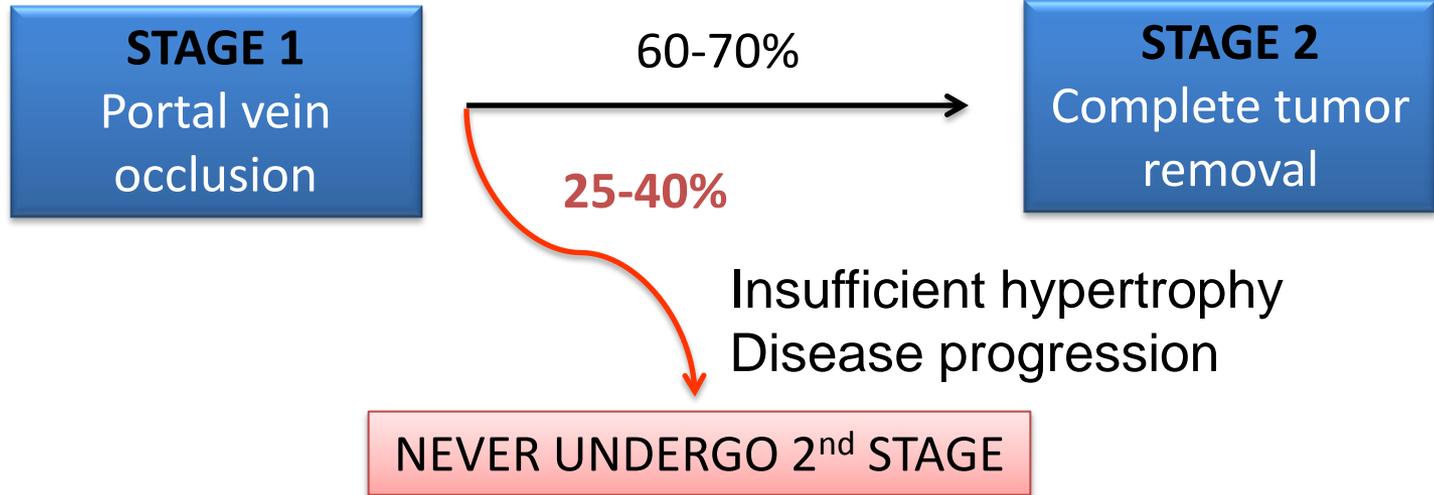
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	FLR Volume (mL)	FLR Volume/TLV (%)
Before PVE	561.1 ± 43.1	34.8 ± 1.6
1-2 wk after PVE	640.6 ± 53.5	39.7 ± 0.6
2 wk after HVE	714.8 ± 61.1	44.2 ± 1.1
1 wk after hepatectomy	1043.9 ± 149.5	64.5 ± 6.2



Hypertrophy induction



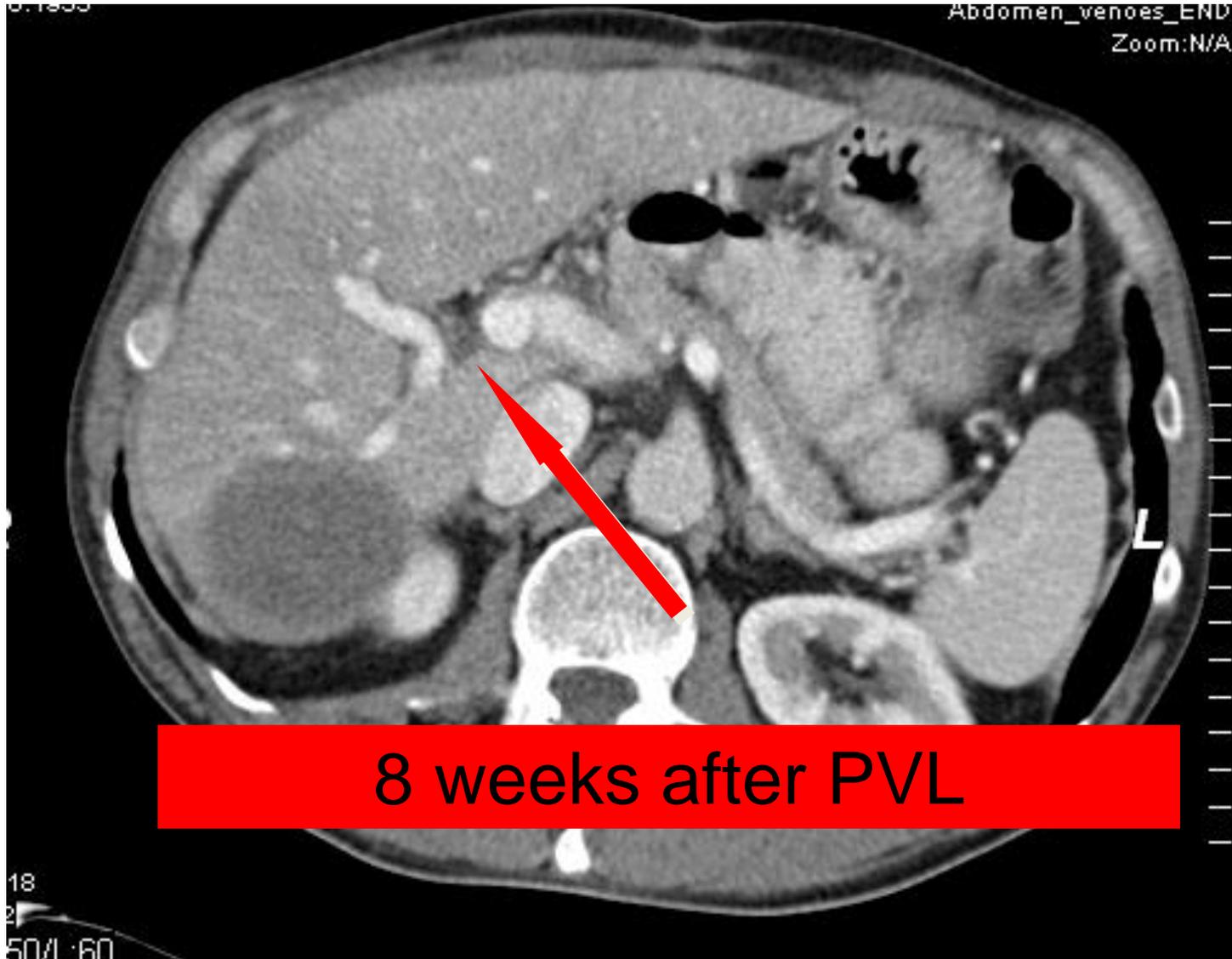
Elias D, et al. Br J Surg 1999 .
Kokudo N, et al. Hepatology 2001
Mueller L, et al. Ann Surg Oncol 2008.

De Graaf W, et al. Ann Surg Oncol 2009

- Portal vein ligation (PVL) / Portal vein embolization (PVE) -

Author	Year	Patients (n)	PVE (n) PVL (n)	Increase of liver volume (%)	Time intervall (d)	
Shindoh	2013	144	144	62 (0.3-379)	34 (12 – 385)	Seg. II/III
Capussotti	2008	48	31	53,4	29	Seg. II/III
			17	43,1	40	Seg. II/III
Aussilhou	2007	35	18	35 ± 38	49 ± 3	Seg. II/III
			17	38 ± 26	56 ± 3	Seg. II/III
Farges	2002	27	PVE normal hepatic function (n =13)	44 ± 19	49 ± 13	Seg. I-IV
			PVE hepatic dysfunction (n = 14)	35 ± 28		

- PVL -



ALPPS (In situ Splitting)

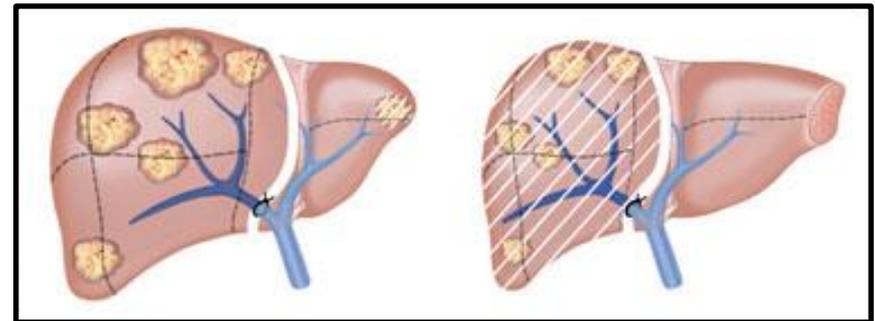
FEATURE

Right Portal Vein Ligation Combined With In Situ Splitting Induces Rapid Left Lateral Liver Lobe Hypertrophy Enabling 2-Staged Extended Right Hepatic Resection in Small-for-Size Settings

Andreas A. Schnitzbauer, MD, Sven A. Lang, MD,* Holger Goessmann, MD,† Silvio Nadalin, MD,§
Janine Baumgart, MD,|| Stefan A. Farkas, MD,* Stefan Fichtner-Feigl, MD,* Thomas Lorf, MD,¶
Armin Goralczyk, MD,¶ Rüdiger Hörbelt, MD,# Alexander Kroemer, MD,* Martin Loss, MD,* Petra Rümmele, MD,‡
Marcus N. Scherer, MD,* Winfried Padberg, MD,# Alfred Königsrainer, MD,§ Hauke Lang, MD,||
Aiman Obed, MD,¶ and Hans J. Schlitt, MD**

Schnitzbauer/Schlitt et al. *Ann Surg* 2012

- **German multicentric experience**
- **25 patients** with insufficient FLR
- **FLR hypertrophy: 74% in 9 days**
- **R0 resection: 100%**



- ALPPS – case report -

- August 2009: 33-year-old woman with ICC
- **Body weight: 83 kg**
- Bilirubin 7 mg/dl → no cholangitis
- PV-infiltration?



Volume Seg. II/III

400ml

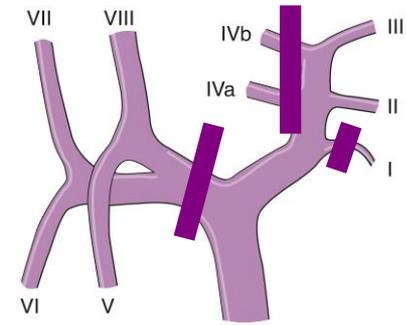
LR/BW = 0.48

- Case Report I -

Operative procedure Step I:

In-situ-Split with

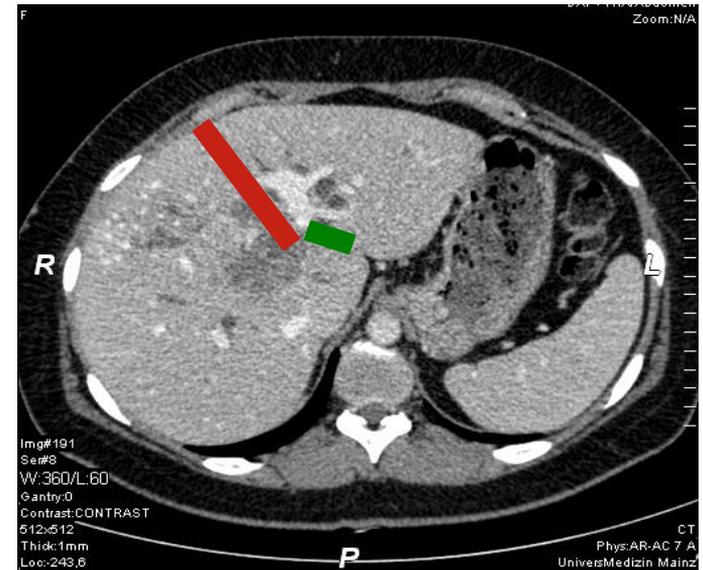
complete right portal vein dissection
(division of all branches Seg. IV-VIII and I)



- **complete mobilization** of right liver lobe, **division of all minor hepatic veins;**
- **complete parenchymal transection** along the Lig. Falciforme; hereby **division of the MHV**
- **Division of the left bile duct** and reconstruction with Y-Roux-Hepaticojejunostomy

but

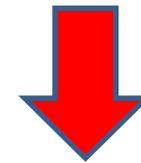
- **Preserving the right liver lobe in situ** (A. hep. dextra, V. hepatica dextra + Ductus hep. dexter (resp. Ductus choledochus))



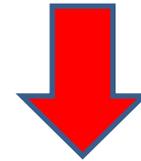
- ALPPS – case report -



Volume Seg. II/III



700ml



**Hypertrophy of 75%
within 7 days**

- ALPPS – case report -



**Patient had intrahepatic recurrence
2 years after ALPPS treated with repeated
hepatectomy ;**

**the patient is alive now 80 months after
ALPPS without recurrence**

ALPPS (In situ Splitting)

FEATURE

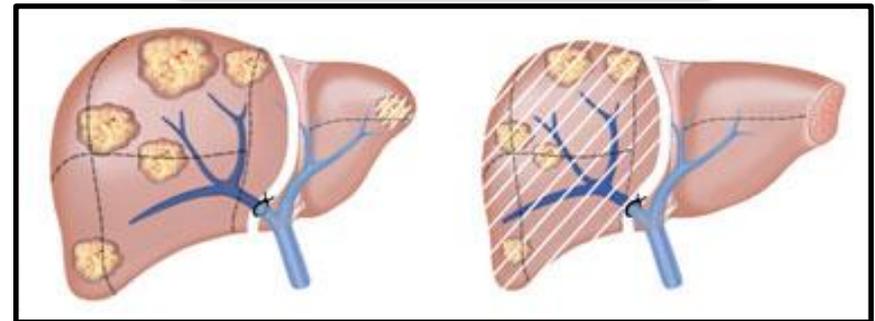
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Aiman Obed, MD,¶ and Hans J. Schlitt, MD**

Schnitzbauer/Schlitt et al. *Ann Surg* 2012

- German multicentric experience
- 25 patients with insufficient FLR
- FLR hypertrophy: 74% in 9 days
- R0 resection: 100%
- Morbidity: 64%
- Mortality: 12%.

New 2-stage strategy:
Liver partition+ PVL



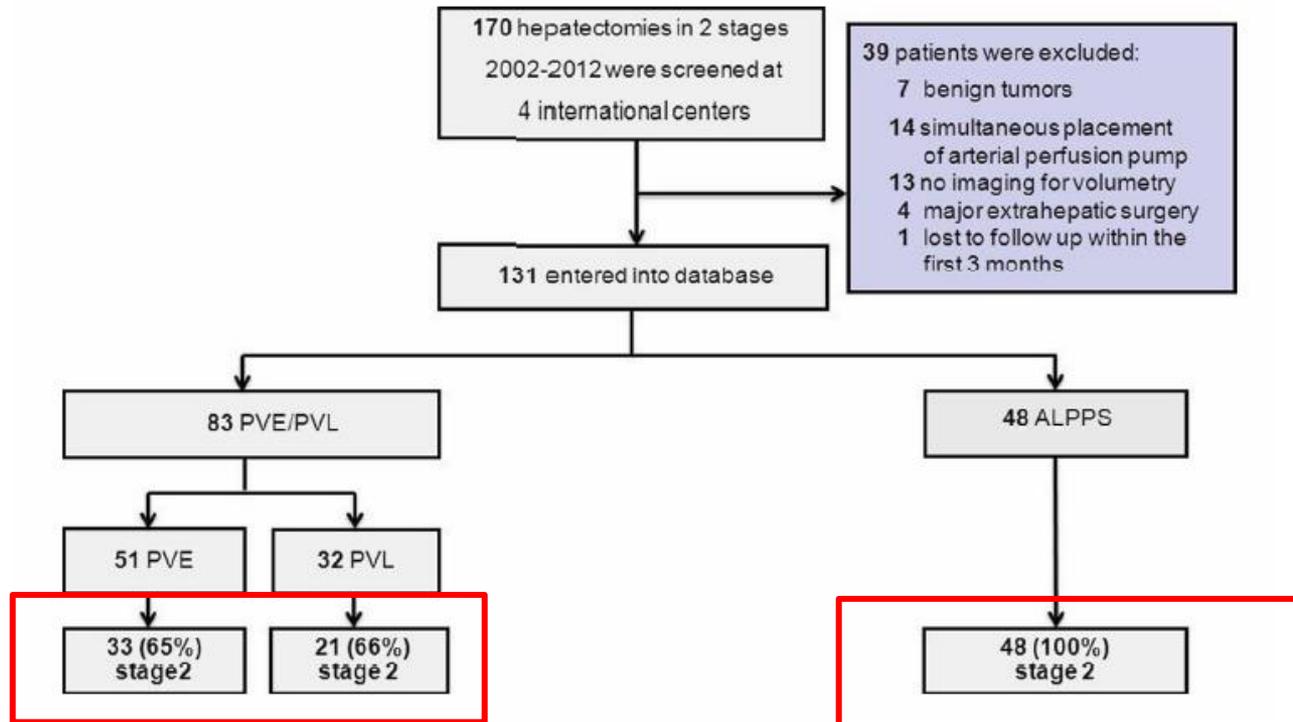
ALPPS offers a better chance of complete resections in patients with primarily unresectable liver tumors compared with conventional-staged hepatectomies

Swiss HPB Center,
Zürich

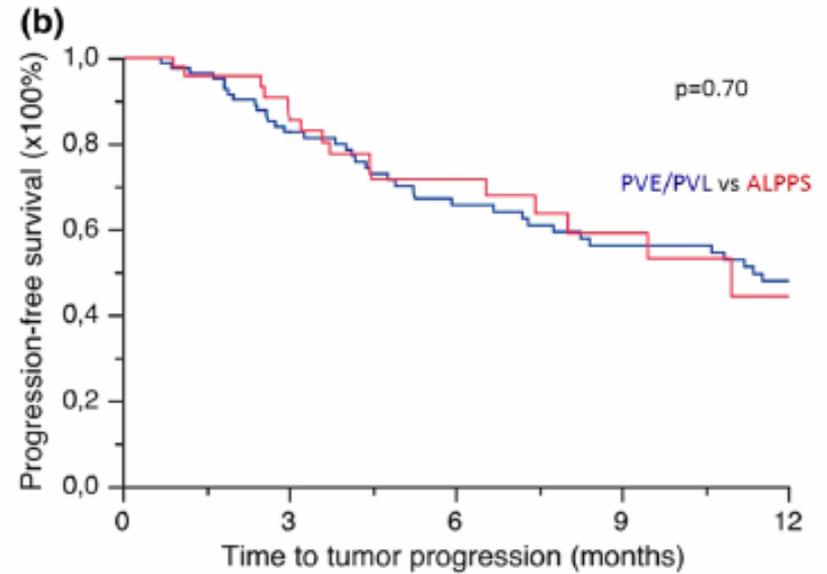
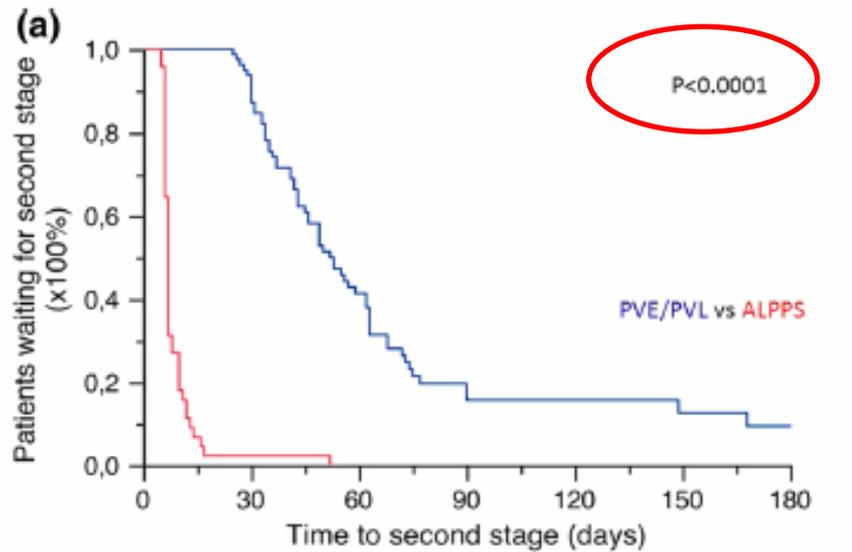
 HOSPITAL ITALIANO
de Buenos Aires

 UNIVERSITÄTSmedizIN.
MAINZ

Division of HPB Surgery,
London, ON, Canada



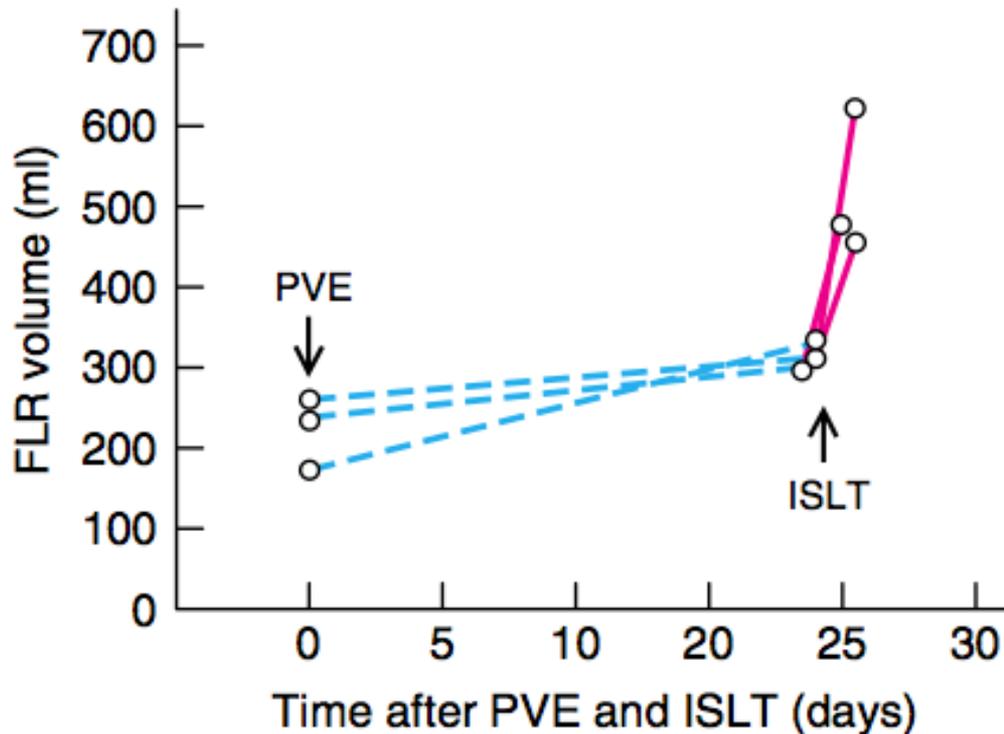
ALPPS offers a better chance of complete resections in patients with primarily unresectable liver tumors compared with conventional-staged hepatectomies



ALPPS – after failed PVE -

In up to 9% of patients who undergo PVE, sufficient hypertrophy is not achieved.

Wichert DA, et al. Br J Surg. 2010

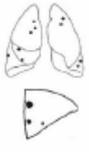
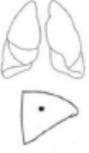
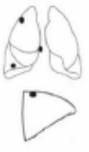


45-92% FLR hypertrophy when using ALPPS after a failed PVE

Knoefel et al, Brit J Surg 2013

ALPPS for CRLM: effective hypertrophy but early tumor recurrence?

n = 6 (83%) recurrence after a median time of
8 months (range 3 – 13 months)

Patient	Location before ALPPS	RFS ¹ (months)	Location of Recurrence	OS ² (months)
1		13	 + bone	Dead 25
2		7	 + bone + peritoneum	Alive 20
3		8	 + lymphnode + peritoneum	Dead 8
4		13	 + lymphnode	Alive 18

Patient	Location before ALPPS	RFS ¹ (months)	Location of Recurrence	OS ² (months)
5		6	 + lymphnode	Dead 11
6		3	 + lymphnode	Alive 15
7		11	 Increase in CEA	Alive 12

Early Survival and Safety of ALPPS

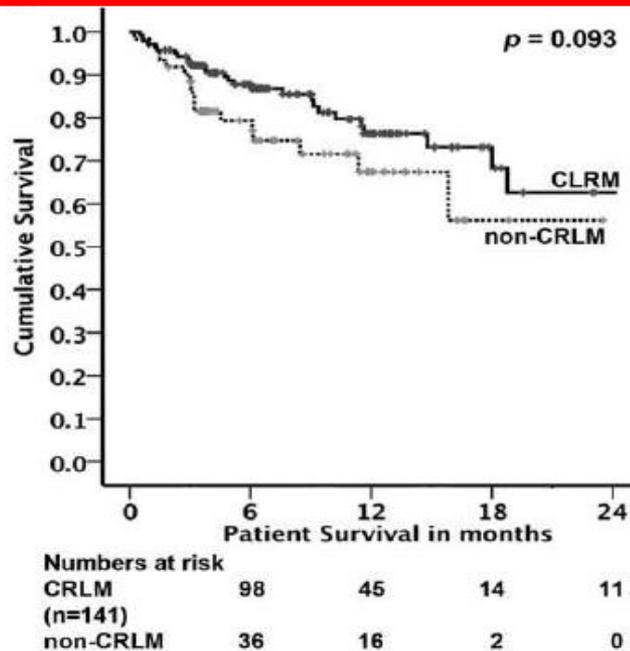
First Report of the International ALPPS Registry

- Total ALPPS n = 202 ALPPS for CRLM n = 140

right hepatectomy	106 (52%)
right trisect. +/- Seg I	86 (42%)
other	10 (5%)



- 90-day-mortality rates for CRLM 11/141 (8%)



Two-stage hepatectomy for multiple bilobar CLM

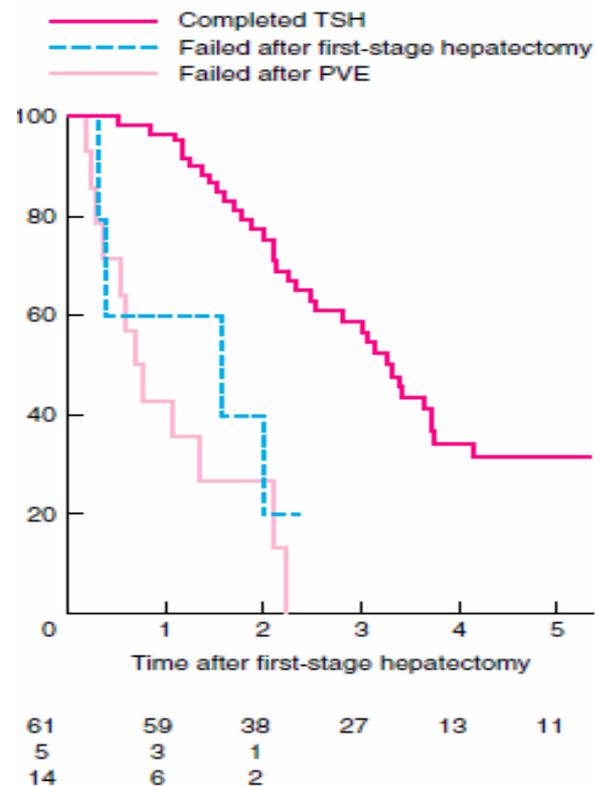
CRLM: total 753

TSH (intended) 80/753 (10.6%)

TSH (completed) 61/80 (76%): mortality : 0%

Reasons for failure to proceed to step 2:

tumor progression:	11
insuff. hypertrophy:	5
left PV thrombosis:	1
injury of left PV by RFA	1
Cardiac failure	1



Two-stage hepatectomy for multiple bilobar CLM

time between step 1 and PVE: median 25 (4-289) days

time between PVE and step 2: median 62 (34-228) days

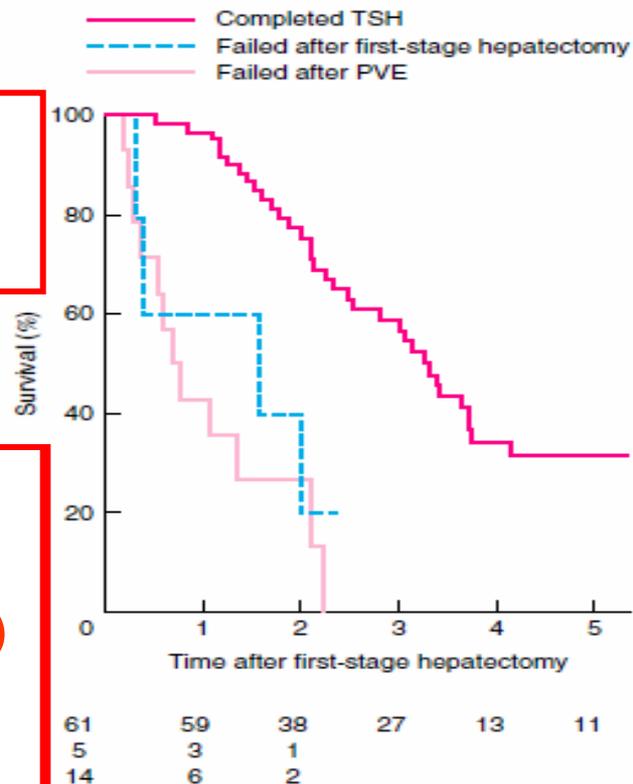
Risk factors for not achieving step 2:



Multivariate

3 or more CRLM in FLR at 1 step

age > 70 years



Portal vein embolization and its effect on tumour progression for colorectal cancer liver metastases

E. Simoneau¹, M. Hassanain^{2,4}, M. Shaheen¹, M. Aljiffry⁵, N. Molla³, P. Chaudhury^{1,2}, S. Anil⁴,
A. Khashper³, D. Valenti³ and P. Metrakos¹

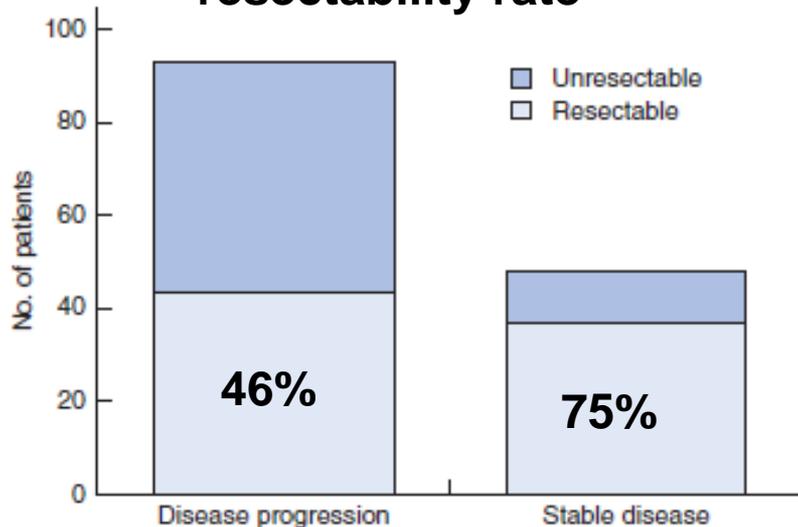
n = 141 PVE in CRLM



n = 93 (66%) had tumor progression after PVE

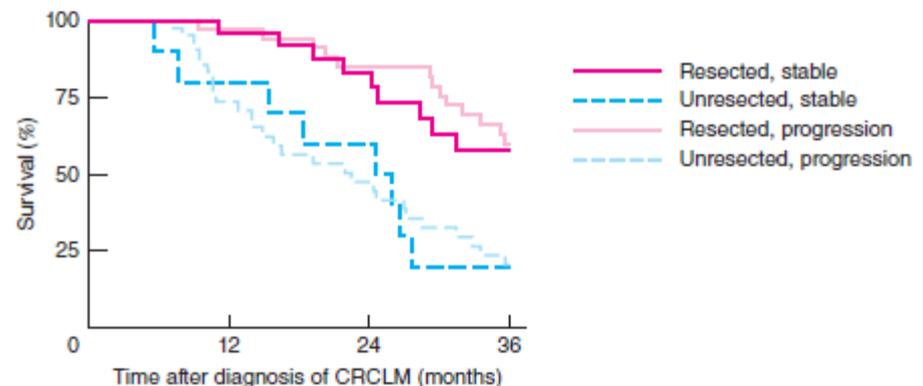
n = 17 (12%) had new tumor in FLR

resectability rate



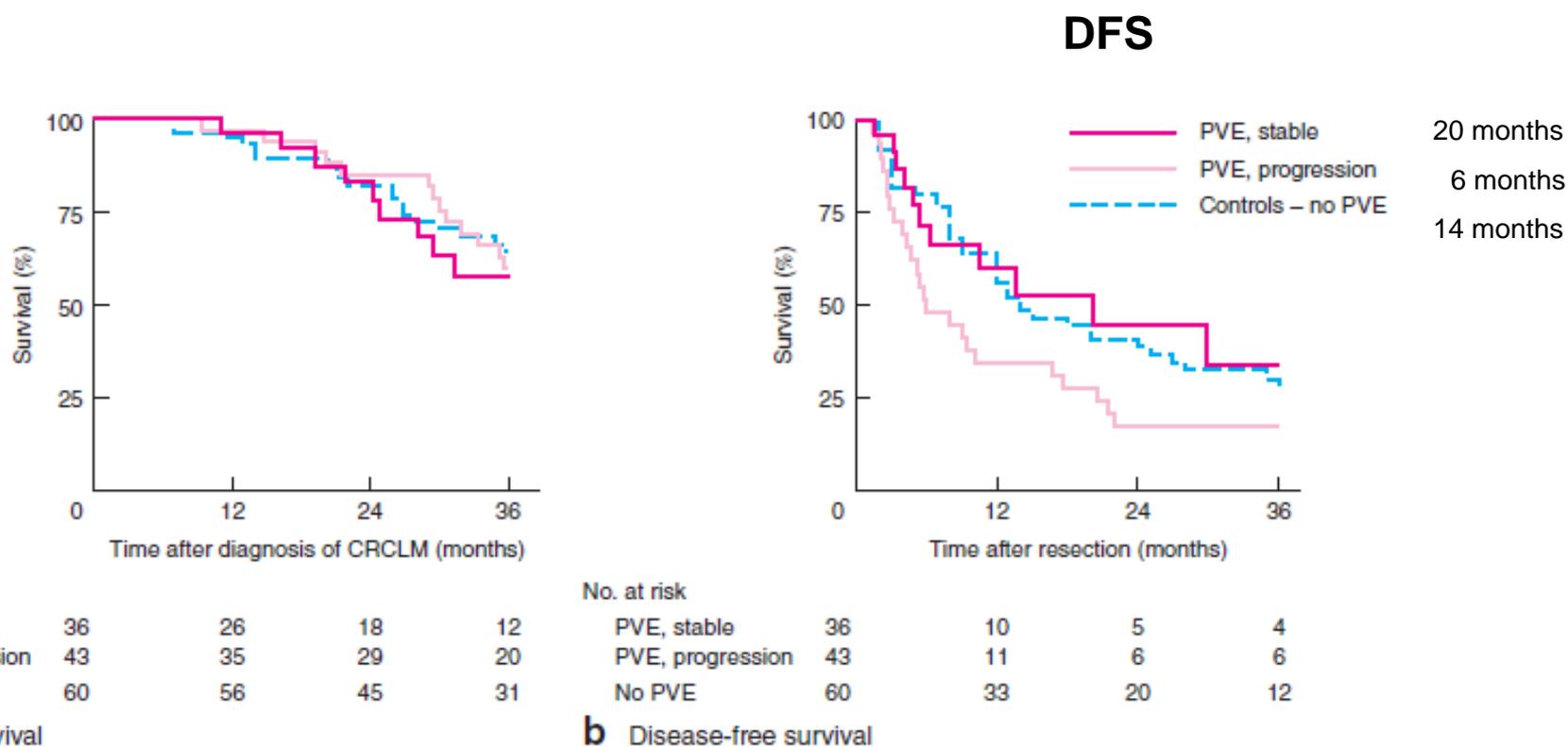
P = 0.001

survival



Portal vein embolization and its effect on tumour progression for colorectal cancer liver metastases

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Early Survival and Safety of ALPPS

First Report of the International ALPPS Registry

- Total ALPPS n = 202 ALPPS for CRLM n = 140
- 90-day-mortality rates for CRLM 11/141 (8%)

Risk factors for M and M

Schadde et al., Ann Surg 2014

- Operating time stage 1 327 min (+/- 119 min)

Associating Liver Partition
and Portal Vein Ligation
for Staged Hepatectomy
(ALPPS): What Is Gained
and What Is Lost?

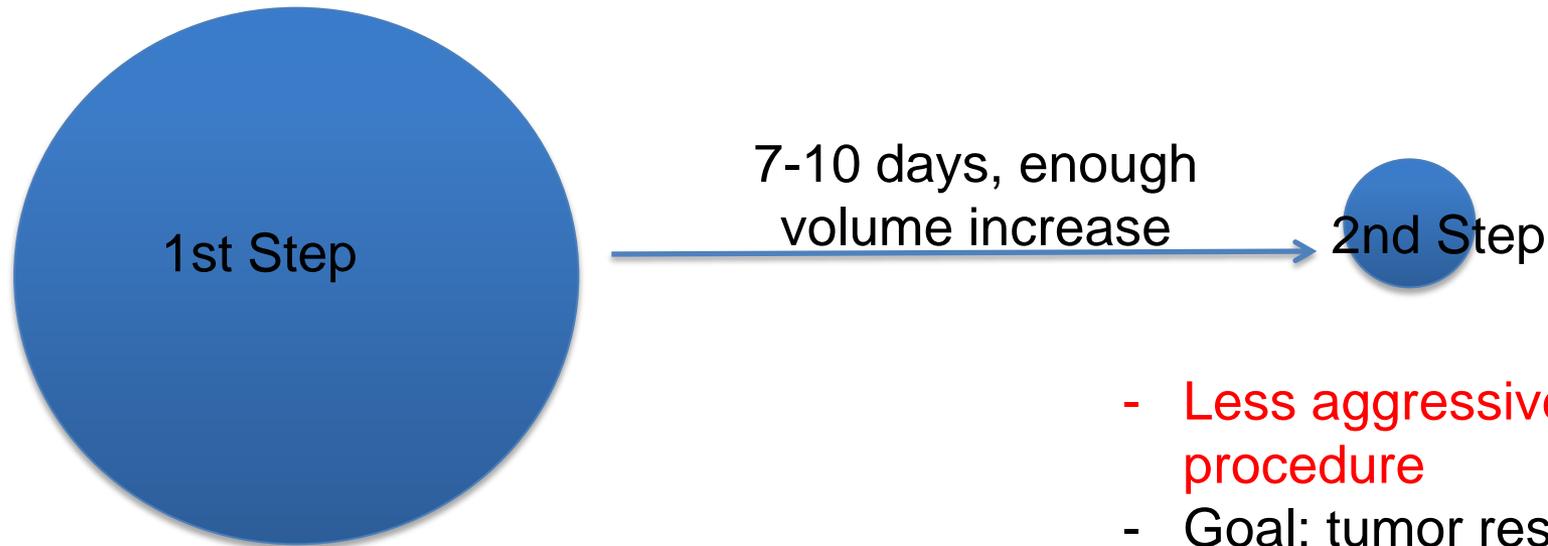
Thomas A. Aloia, MD
Jean-Nicolas Vauthey, MD

Ann Surg 2012

„.....the tumor is physically manipulated and left for about one week in an environment of inflammation and enriched with growth factors...

Changing the paradigm in ALPPS

The current paradigm



- **More aggressive surgical procedure**
- Complete parenchymal transection
- FLR clean-up
- Lymphadenectomy
- Simultaneous procedures
- Goal: FLR volume increase

- **Less aggressive surgical procedure**
- Goal: tumor resection

Changing the paradigm in ALPPS

The future paradigm!
Mini ALPPS

1st Step

Patient in good
condition, normal LF
test, enough function
increase

2nd Step

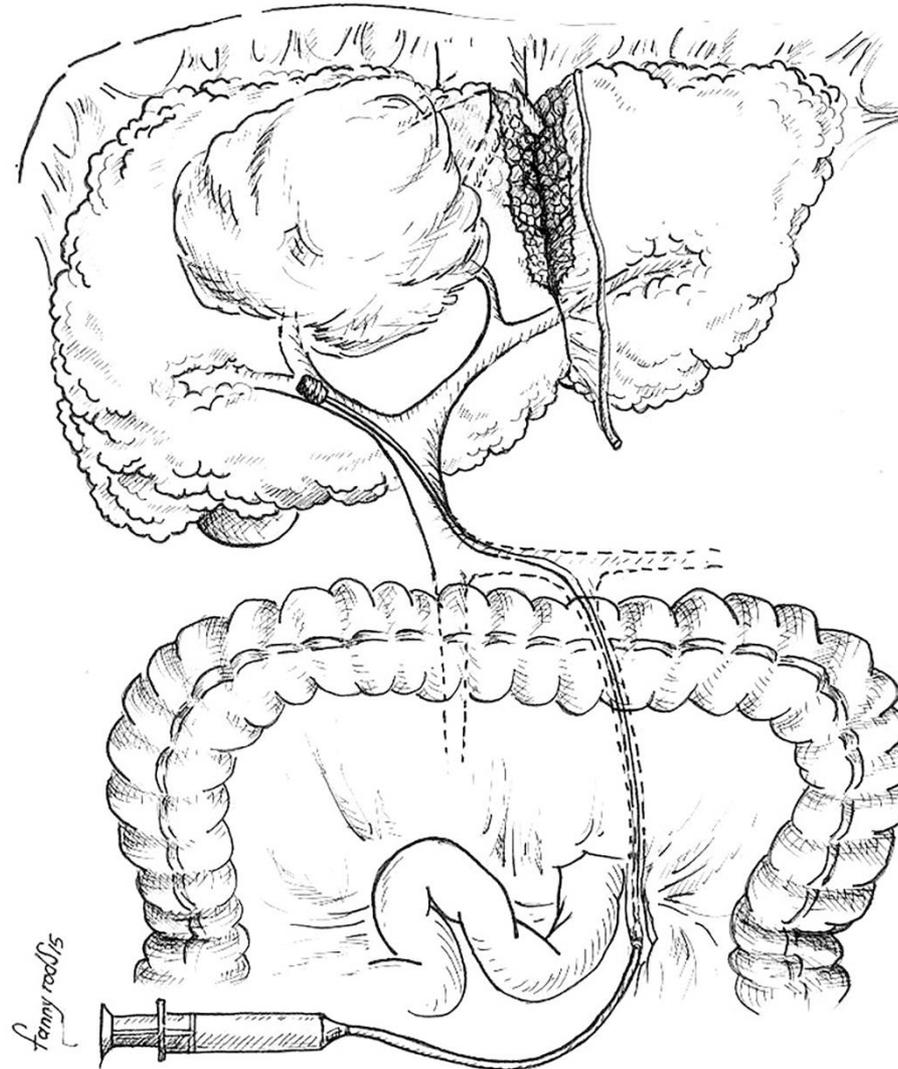
- Less aggressive as possible surgical procedure
- Partial parenchymal transection
- FLR clean-up
- Simultaneous procedure only in CR
- **Goal: FLR function increase**

- More aggressive surgical procedure
- Other simultaneous procedures (HJ, lymphadenectomy etc)
- **Goal: tumor resection**

Inverting the AL PPS paradigm by minimizing first stage impact: the Mini-AL PPS technique

Langenbecks Arch Surg 2016

Eduardo de Santibañes^{1,2} & Fernando A. Alvarez¹ & Victoria Ardiles¹ & Juan Pekolj¹ & Martin de Santibañes¹



Inverting the AL PPS paradigm by minimizing first stage impact: the Mini-AL PPS technique

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Langenbecks Arch Surg 2016

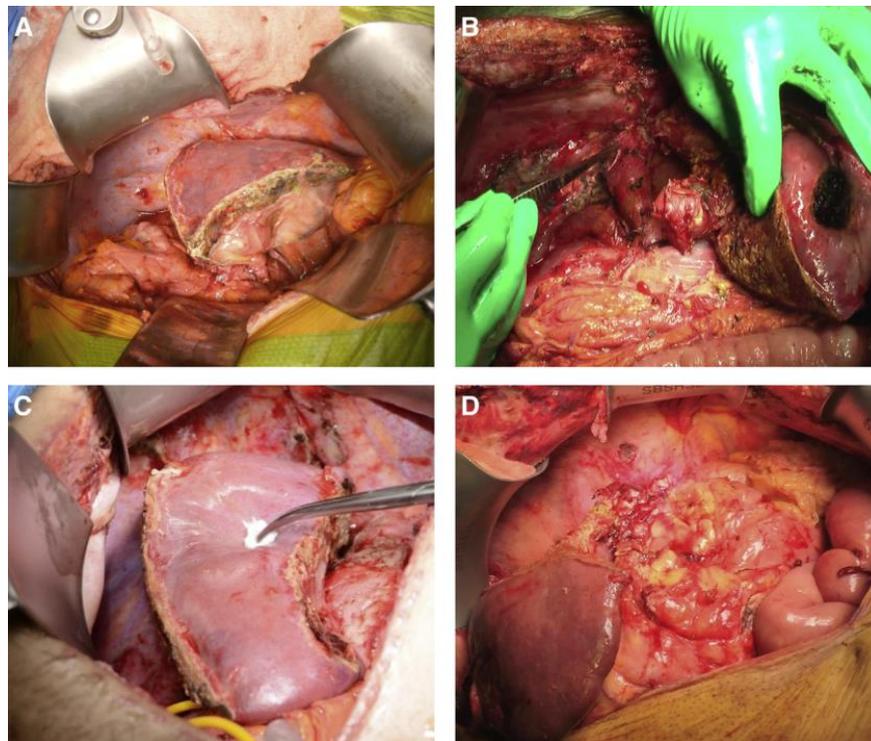
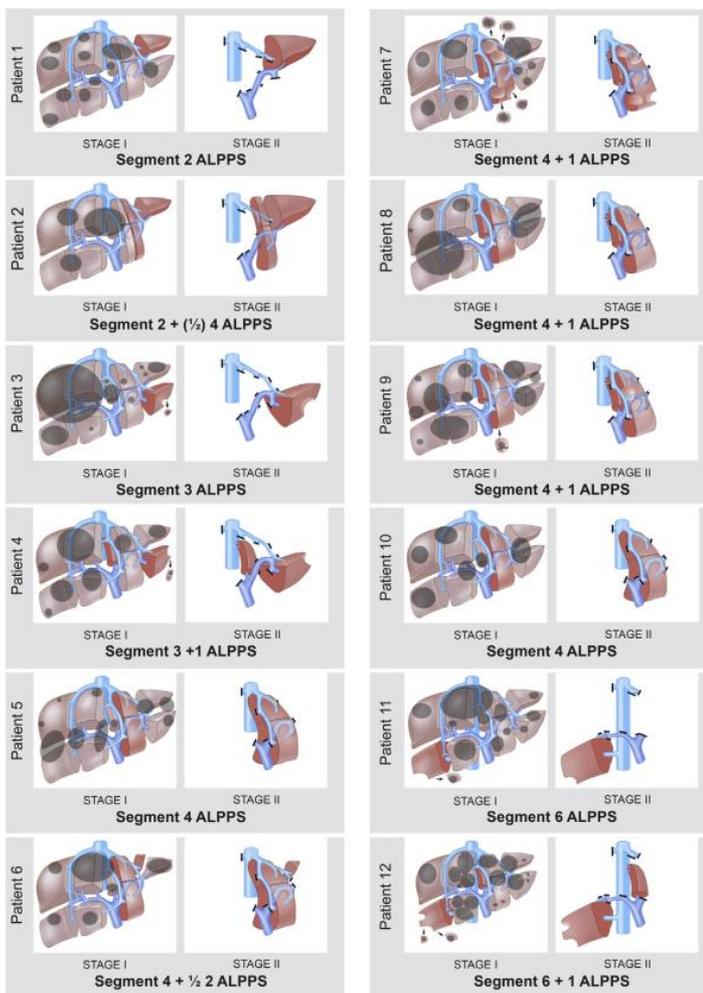
a

c



Monosegment ALPPS hepatectomy: Extending resectability by rapid hypertrophy

- n = 12

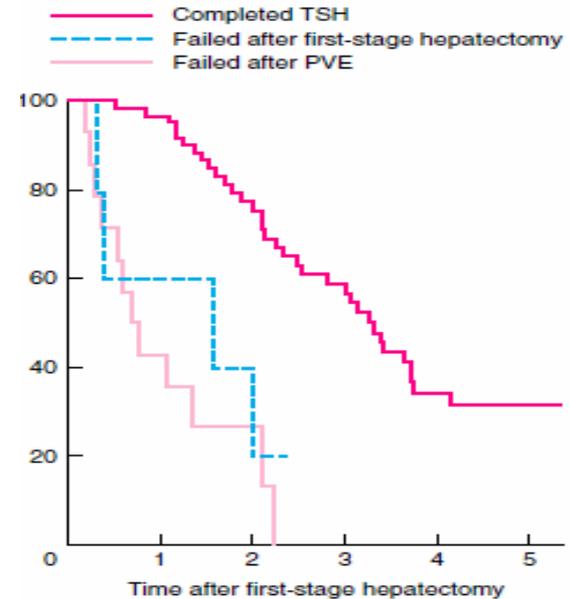
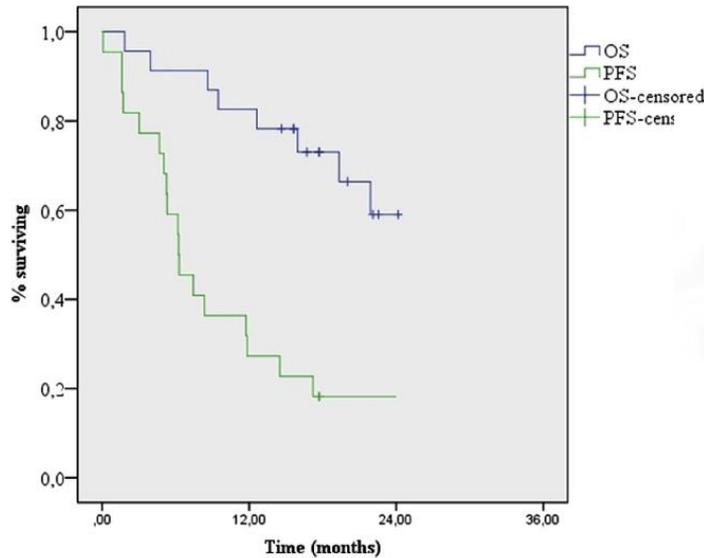


- hypertrophy rate: 160 (93-250)%
- 90-day-mortality: 0%age
- 1 Year SR 80%
- 1 Year DFS 50%

Comparison Two-stage hepatectomy ALPPS

Narita, BJ Surg 2011

Björnsson et al., EJSO 2016



Resection rate 40%

Intent to treat

OS: 2 year: 59%

DFS: 1 year 27%

median 6.4 months



Resection rate 70%

after completed TSH

OS: 3 year: 59%

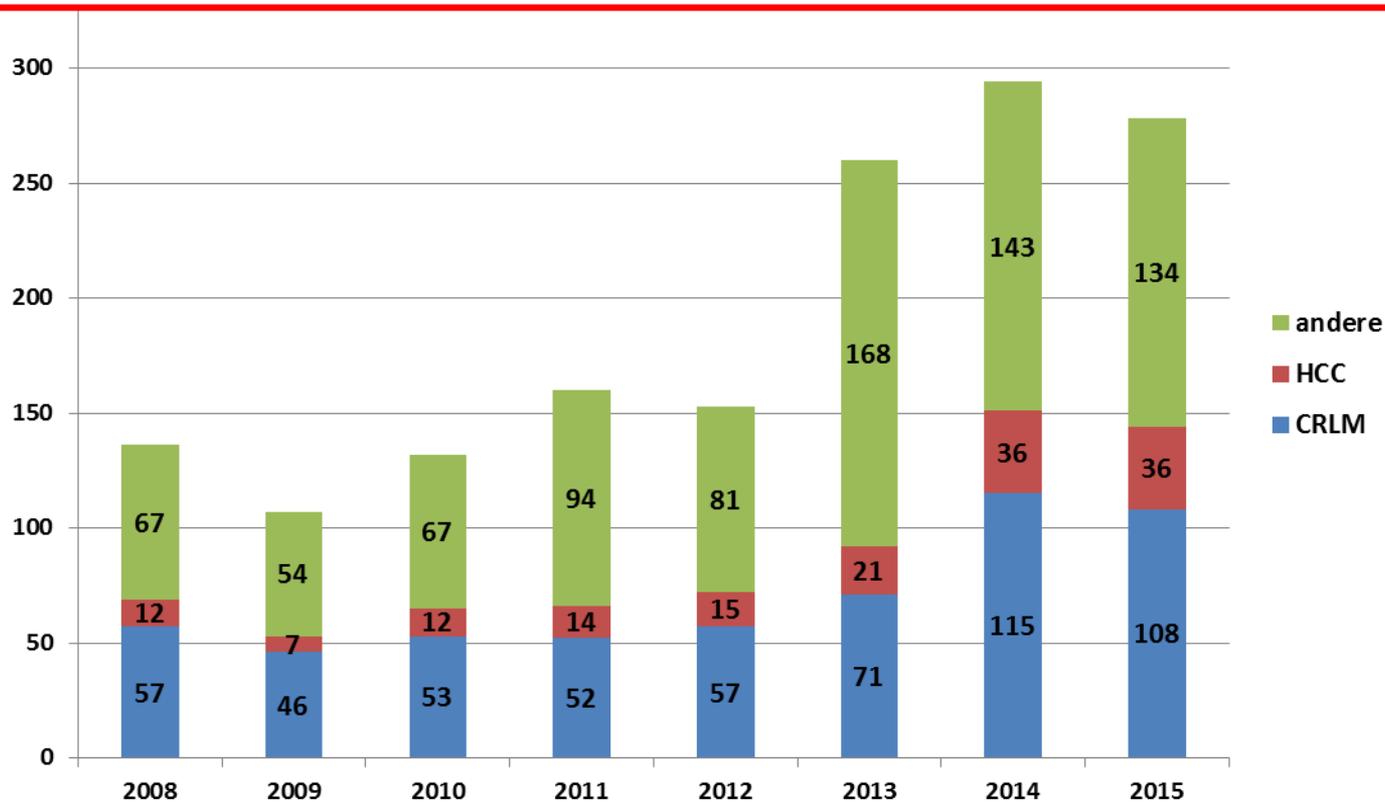
DFS; 1 year 45%

median 9.4 months

Liver resection AVTC Unimedizin Mainz

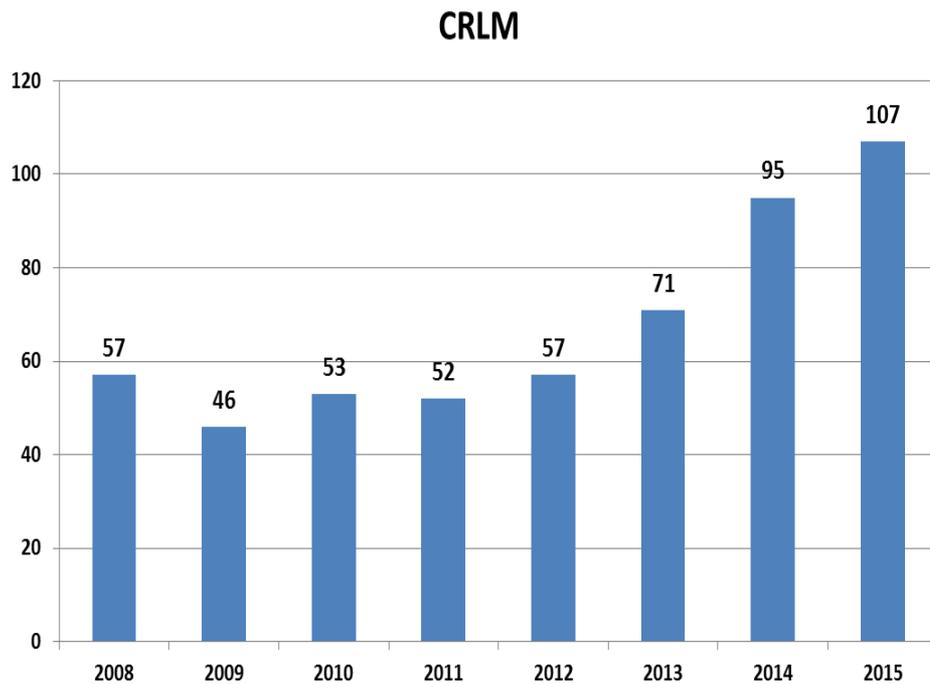
2008-2015: n = 1495

ALPPS: n = 15 ~ 1%

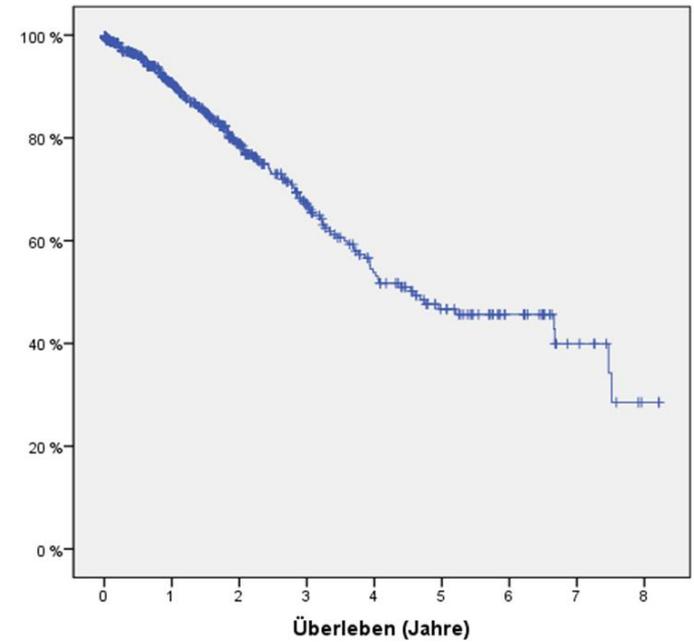


Liver resection in CRLM – Mainz data

01.01.2008 – 31.12.2015



Total: n = 553



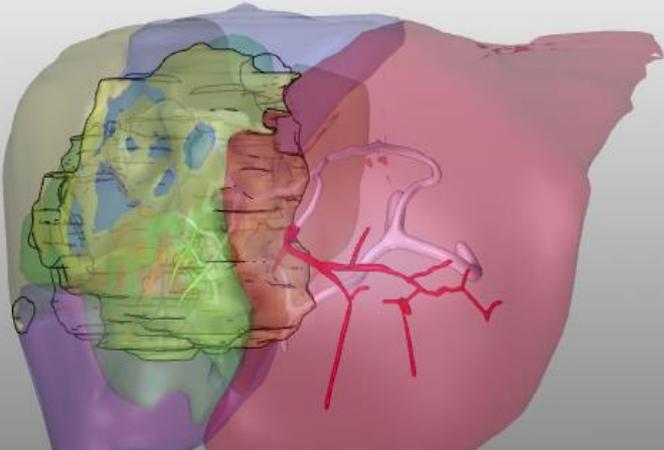
60-day mortality: 0.7%

where PVE and ALPPS don't not work

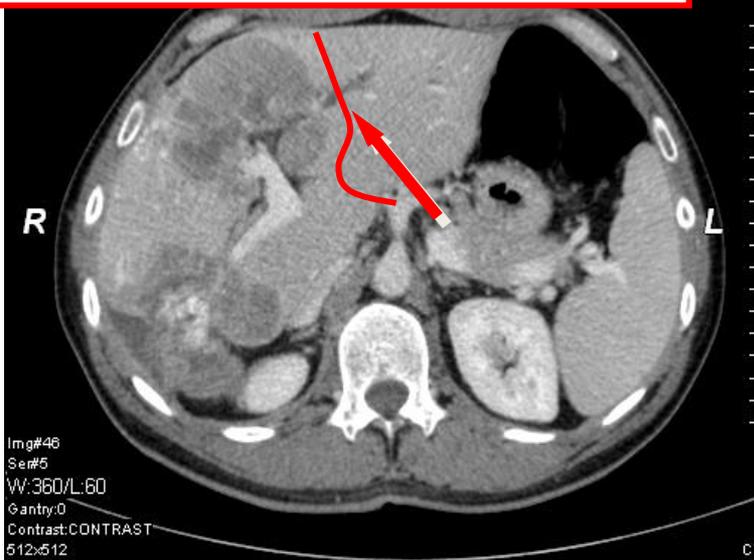
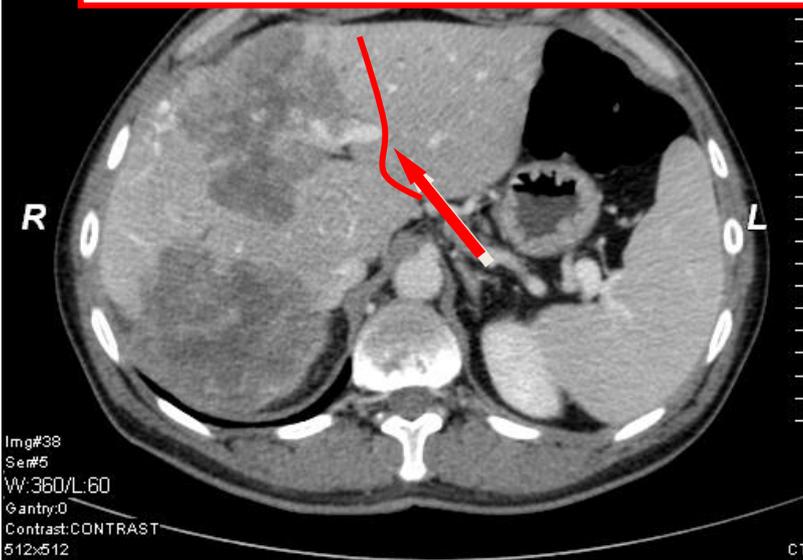


when tumor is crossing the border between segment II/III and IV and PV-reconstruction is required

where PVE and ALPPS don't not work



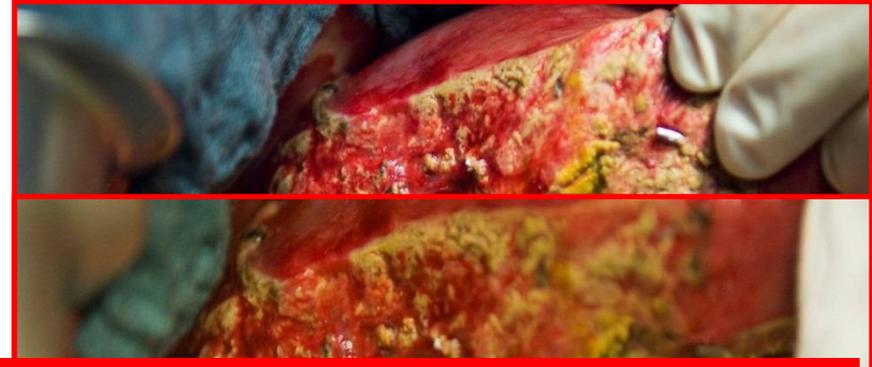
**Remnant volume = parts of Seg. II/III:
27% TLV**



where PVE and ALPPS don't not work

Operation (18.01.2011):

- **right trisectionectomy**
(Seg. I, IV-VIII, partial II and III)
- **portal vein resection** E-/E-anastomoses



Patient died of recurrent disease

33 months after resection

R0-resection



when ALPPS probably does not work



when ALPPS probably does not work



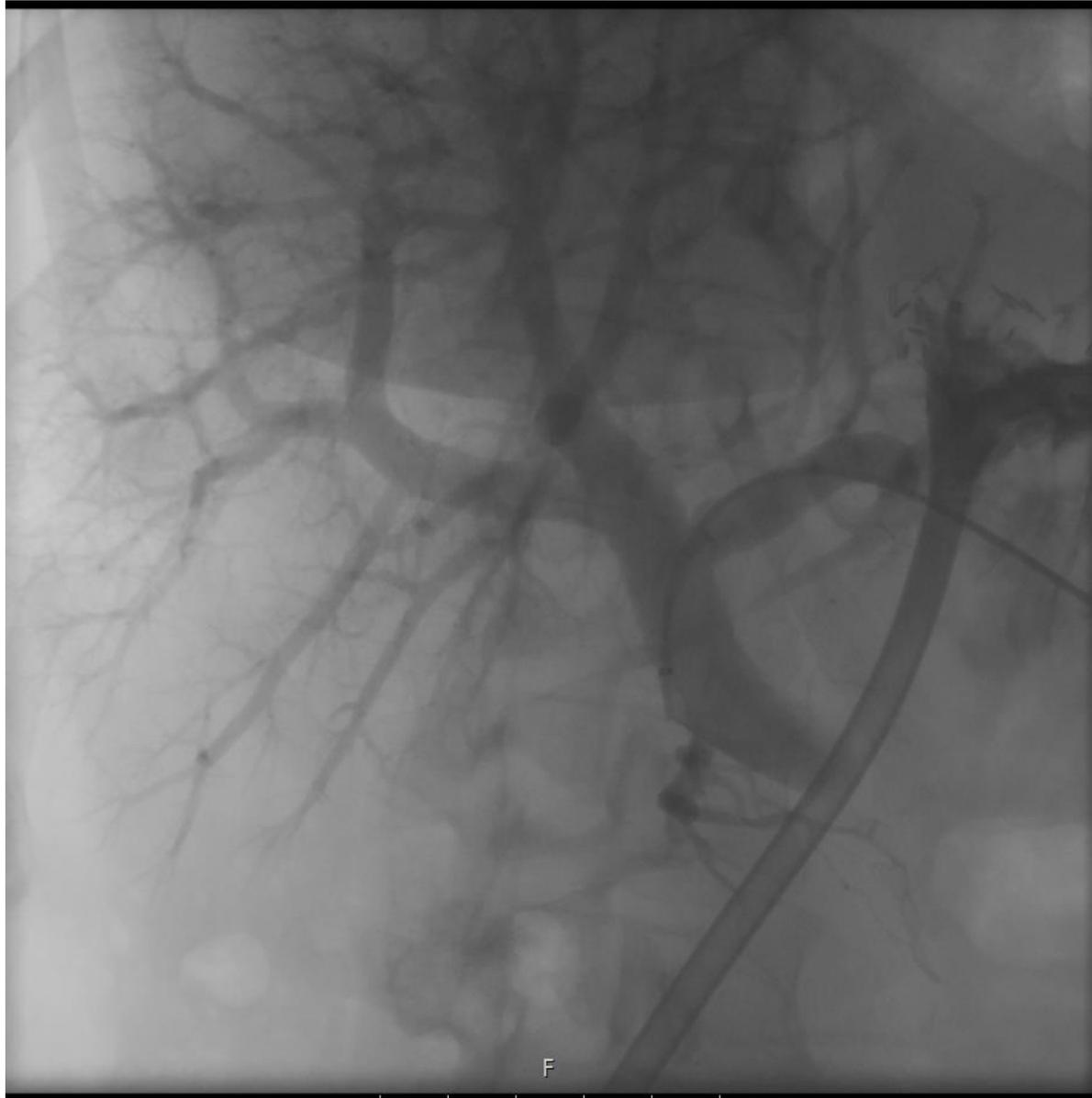
when perfusion of FLR is critically after step 1



when ALPPS probably does not work



when ALPPS probably does not work



PVE postop. day 8

Intended ALPPS – intraoperative change of strategy

- woman with synchronous CRLM
- Primary in the middle of rectum, non-obstructing



W: 375 / L: 60
Serie 8
Bild: 2
SD 5 mm
KM APPLIED

Abdomen axial

P



F

Intended ALPPS – intraoperative change of strategy

- woman with synchronous CRLM
- Primary in the middle of rectum, non-obstructing



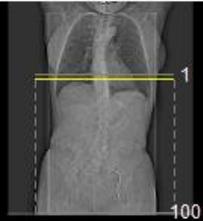
**Neoadjuvant Chemotherapy Folfiri
+ Targeted therapy (18 months)**



W: 300 / L: 40
Serie 9
Bild: 4
SD 5 mm
KM APPLIED

Abdomen 5.0 B30f

P



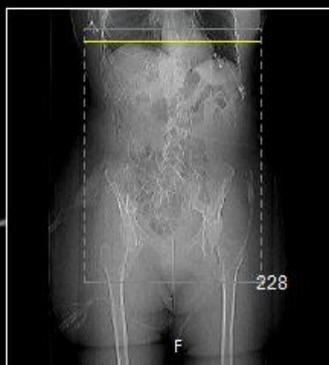
F



L

W: 360 / L: 60
Serie 5
Bild: 13
SD 3 mm
KM CONTRAST
venös

P



Intended ALPPS – intraoperative change of strategy

- postop. course uneventful
- Radiotherapy of primary tumor
- Resection of primary tumor 4 months after ALPPS



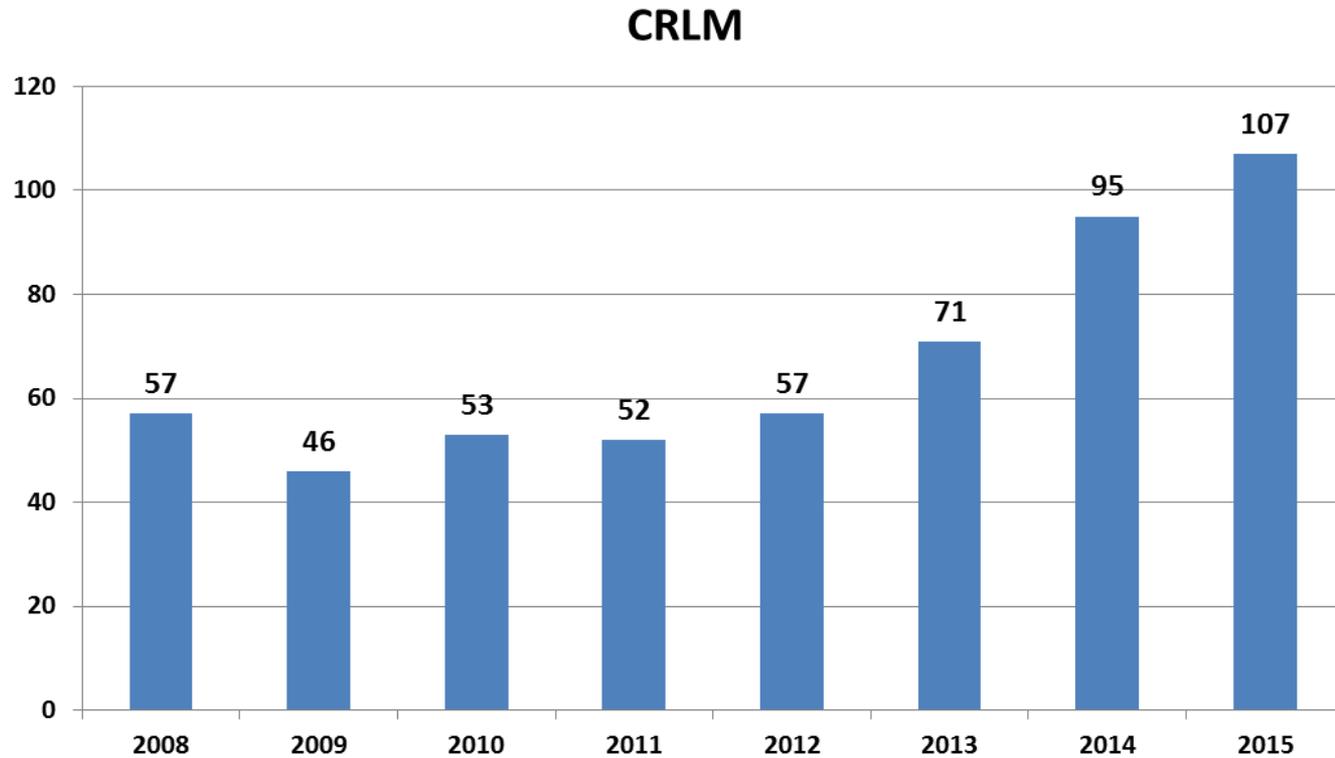
CT –Scan 6 months after liver operation: no recurrence

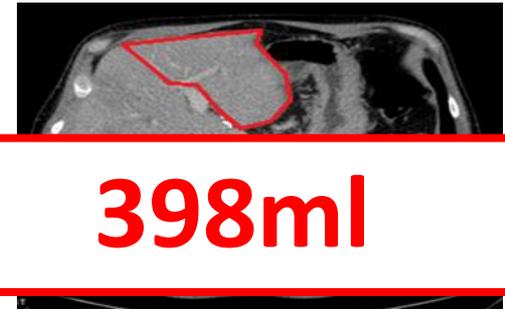
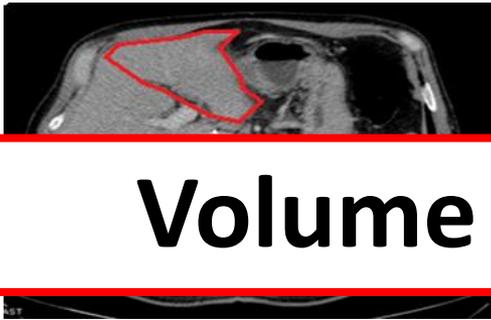
Liver resection in CRLM – Mainz data

ALPPS:

n = 6/553

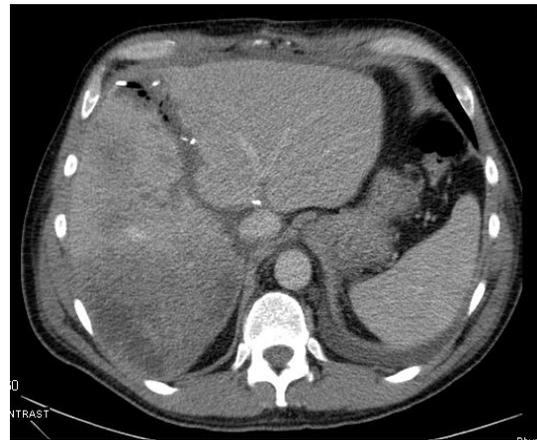
~ 1%



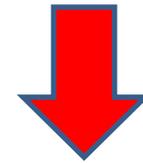


Volume Seg. II/III

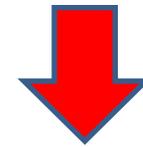
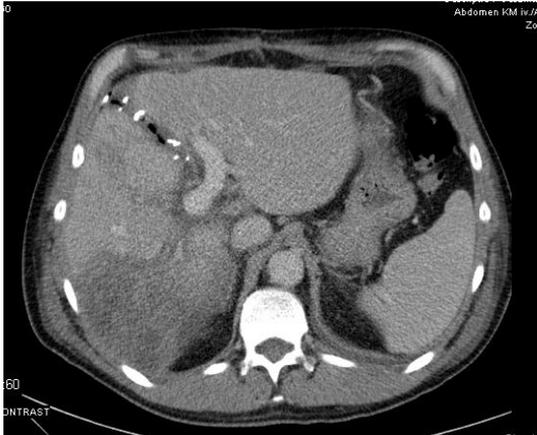
398ml



Volume Seg. II/III

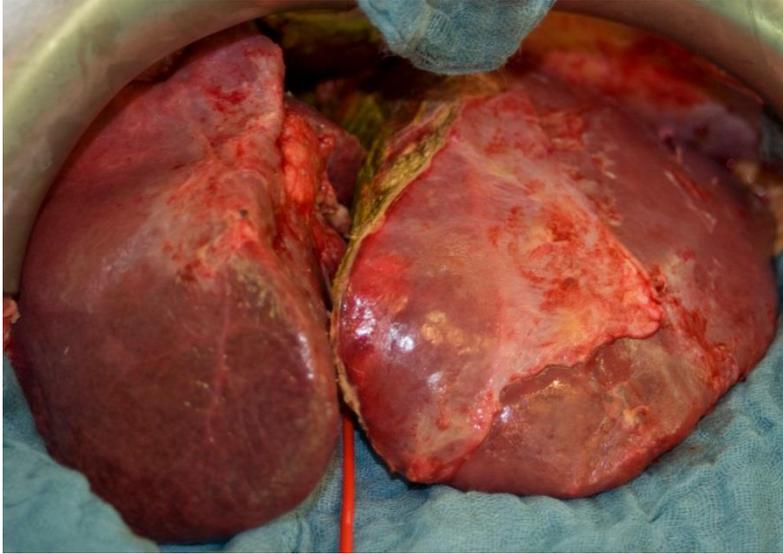


896ml



**Volume increase of
125%
within 6 days**

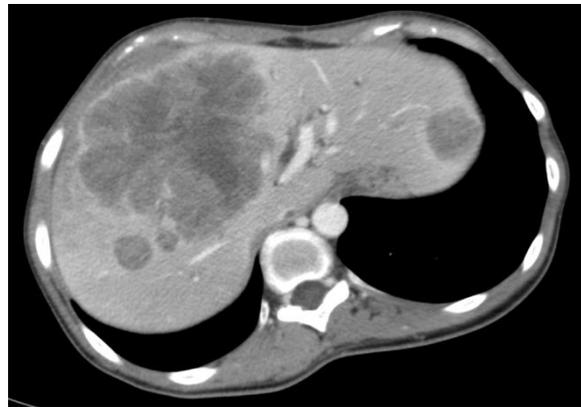
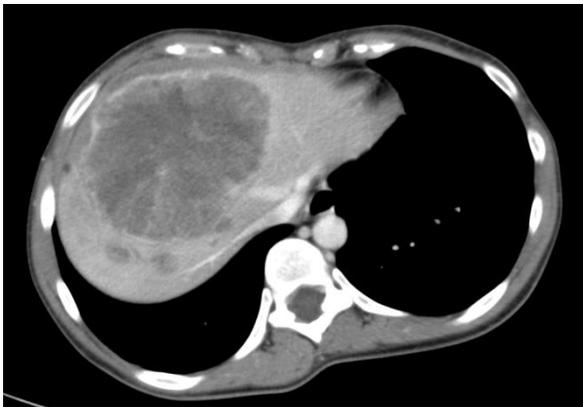
In-situ-Split – Colorectal Liver Metastases - Case report -



ALPPS – Colorectal Liver Metastases

- Case report -

- 46-year-old woman with synchronous colorectal liver metastases
- **Body weight 57kg**
- St. p. TARR (01/2012) (pT2, pN2a (4/31), cM1 (hep), G2-3, R0)

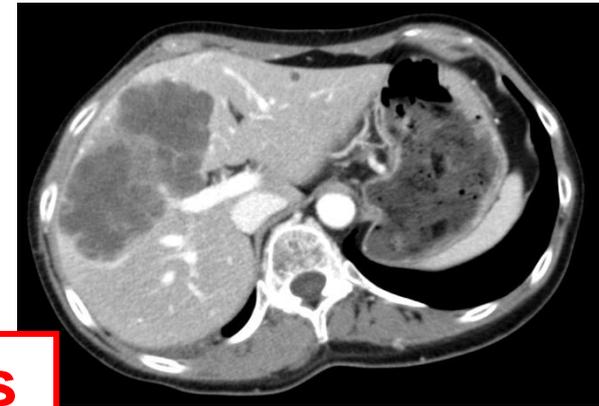
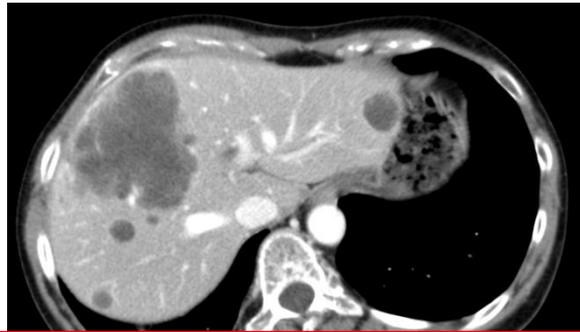


Neoadjuvant Chemotherapy Folfiri + Bevacizumab

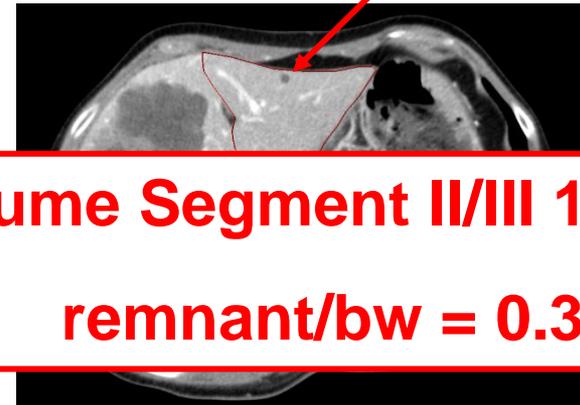
ALPPS – Colorectal Liver Metastases

- Case report -

CT scan after 12 cycles Folfiri + Bevacizumab



Regressive metastases

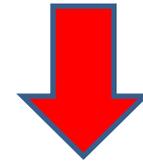


Volume Segment II/III 186 ml
remnant/bw = 0.3

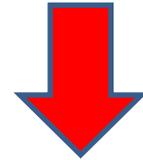
- ALPPS – case report -



Volumen Seg. II/III



369 ml



**98% increase of
volume within 8 days**

- ALPPS – case report -



ALPPS in CRLM

- Data University Mainz -

	Extent of liver resection	Treatment before	Body weight ratio		Time (d)	Tumor Recurrence	Following	Survival after diagnosis CRLM/ALPPS
1	Seg. IV-VIII	Cetuximab 10 months FOLFOX.	0,4	0,7	11	disseminated (3 months)	chemotherapy	† tumor recurrence (23/13 months)
2								recurrence (months)
3								recurrence (months)
4	Seg. IV-VIII	FOLFOX, Bevacicumab 10 months	0,3	0,6	8	hepatic (9 months)	-	† sepsis (8/2 months)

median DFS: 7 months

**median follow-up after ALPSS:
26 (2-49) months**

**median follow-up after diagnosis of CRLM:
34 (2-49) months**

- Summary -

- Liver volume \neq **function**
- After PVE/PVL dynamics of hypertrophy (KGR) seems to be more important than total volume increase
- PVE and PVL are standard techniques to induce hypertrophy of FLR
- TSH is the treatment of choice in functional irresectable bilateral CRLM
 - in TSH step 1 should be the smaller step
 - tendency to do PVE soon after step 1

- ALPPS in CRLM -

- ALPPS has broadened the surgical spectrum in CRLM
- Learning curve and technical refinements have led and will further lead to reduce M and M
- ALPPS should only be performed after state of the art therapy (neoadjuvant/downsizing chemotherapy) and only if PVE/PVL or TSH are not possible

Possible Indications for ALPPS

- need for extensive hypertrophy (> 60-80%) of FLR
- when technical or anatomical problems prevent PVE, i.e. when only one segment is to be preserved (monosegment ALPPS)
- after failure of PVE

ALPPS may offer the only chance for resection

Thank you!



12th Biennial E-AHPBA Congress 2017

European-African Hepato-Pancreato-Biliary Association

SAVE THE DATE

May, 23rd – 26th, 2017

Mainz, Germany

Congress chairman:

Professor Dr. med.

Hauke Lang, MA, FACS

University Medical Center, Mainz

Registration & Abstract Submission:

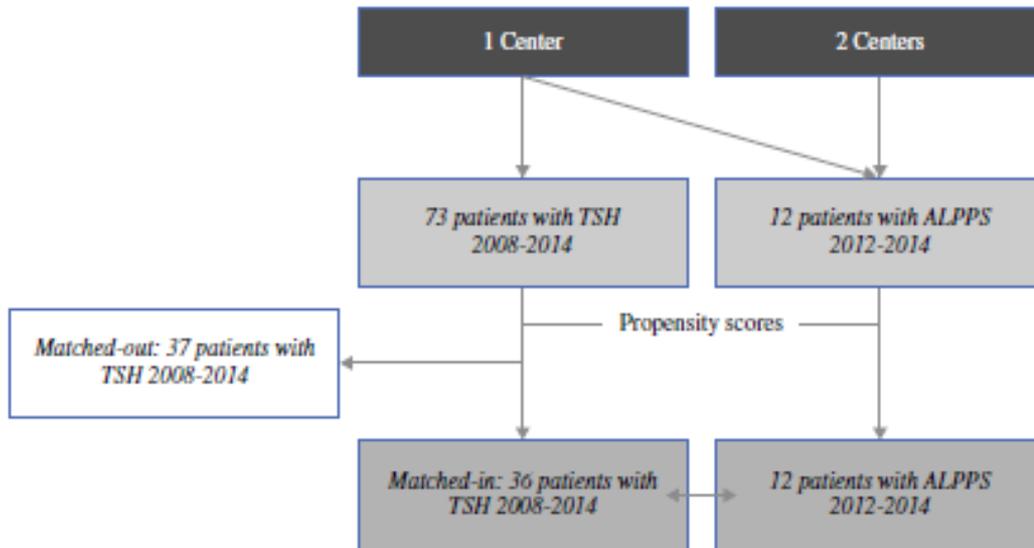
www.eahpba2017.com



Strategies to Increase the Resectability of Patients with Colorectal Liver Metastases: A Multi-center Case-Match Analysis of ALPPS and Conventional Two-Stage Hepatectomy

Francesca Ratti, MD¹, Erik Schadde, MD, FACS², Michele Masetti, MD³, Marco Massani, MD⁴, Matteo Zanella, MD³, Matteo Serenari, MD³, Federica Cipriani, MD¹, Luca Bonariol, MD⁴, Nicolò Bassi, MD⁴, Luca Aldrighetti, MD¹, and Elio Jovine, MD³

Ratti, Ann Surg Oncol 2015



Volume gain similar in ALPPS in PVE
47% vs 41%



but

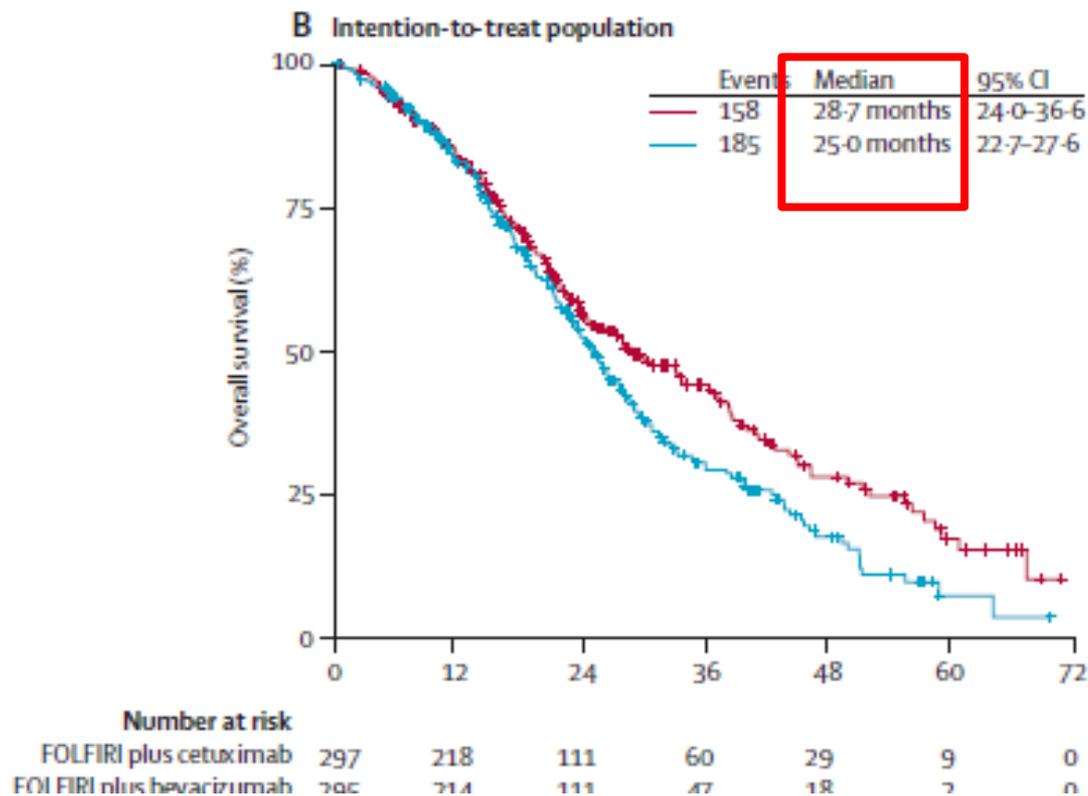
complication rate in ALPPS significantly higher

41% vs 17%

Results of CTx only in CRLM

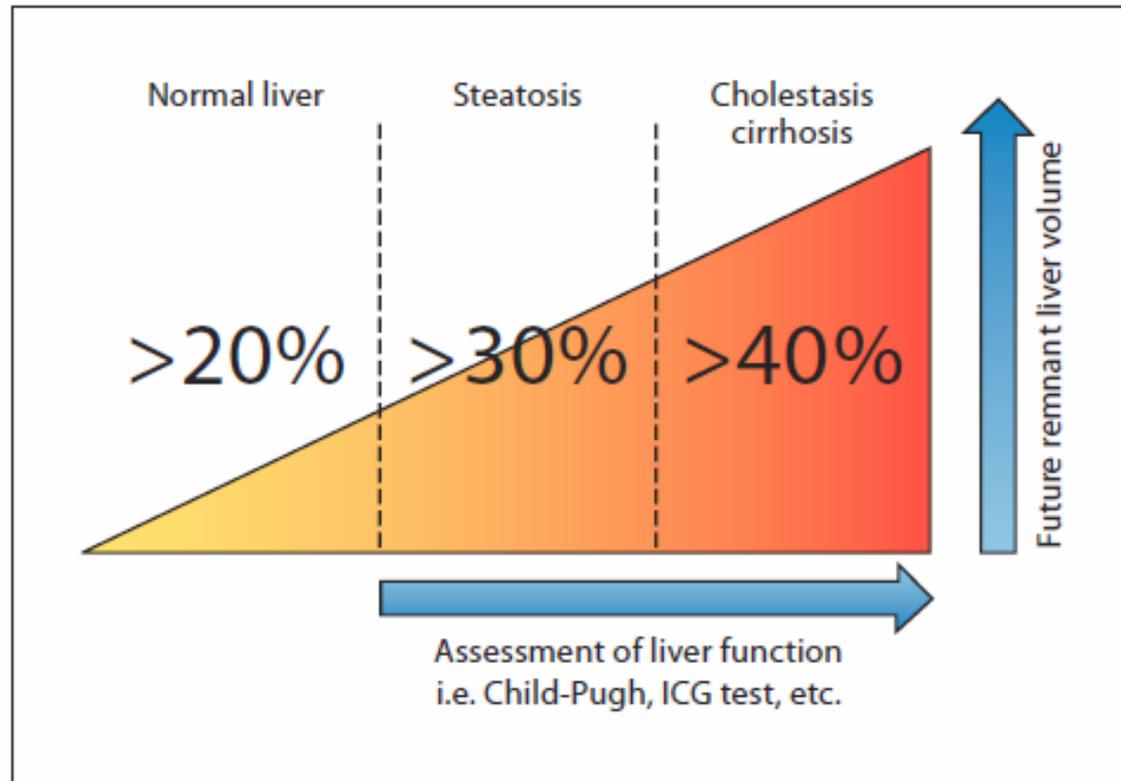
FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial

Heinemann et al., Lancet Oncol 2014



Remnant liver volume - How much is enough?

Limit for safe hepatic resection



Kinetic growth rate

sFRL = volume in CT / eTLV

DH = Degree of hypertrophy (%) sFRL2 – sFRL1

KGR = DH/time (weeks)

