Two-stage hepatectomy and ALPPS

Hauke Lang
Department of General, Visceral and Transplantation Surgery, Mainz
Functional Irresectability
Extended hepatectomy/right trisectionectomy

minimum of functional residual volume?
Volume/liver function

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

Liver \textit{volume} \neq \textit{Liver function}

Variations of liver anatomy

Liver remnant \textit{volume} \neq \textit{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

Radtke A et al., Am J Transpl 2008
# Trisectionectomy

<table>
<thead>
<tr>
<th>Author/year</th>
<th>right trisectionectomy</th>
<th>left trisectionectomy</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>mortality</td>
</tr>
<tr>
<td>Iwatsuki/1988</td>
<td>126</td>
<td>5.5%</td>
</tr>
<tr>
<td>Blumgart/1999</td>
<td>-</td>
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<tr>
<td>Melendez/2001</td>
<td>189</td>
<td>5.3%</td>
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<tr>
<td>Nishio/2005</td>
<td>-</td>
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</tr>
<tr>
<td>Lang/2006</td>
<td>121</td>
<td>5.8%</td>
</tr>
</tbody>
</table>

Lang H et al., J Am Coll Surg 2006
Required Volume of the liver remnant

normal quality

≥ 25% liver volume

≥ 20% eTLV (sFRL)

\[ eTLV = -794.41 + 1267.28 \times \text{body surface} \]

\[ S\ FRL = \frac{\text{remnant volume}}{\text{eTLV}} \]

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

\[ sFRL = \frac{\text{volume in CT}}{\text{eTLV}} \]

\[ DH = \text{Degree of hypertrophy (\%) \quad sFRL2 - sFRL1} \]

\[ KGR = \frac{DH}{\text{time (weeks)}} \]

<table>
<thead>
<tr>
<th>Best cut-off value</th>
<th>AUC (95% CI)</th>
<th>SE</th>
<th>P</th>
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<tbody>
<tr>
<td>KGR 2.0% per week</td>
<td>0.830 (0.736-0.923)</td>
<td>0.048</td>
<td>0.002</td>
</tr>
<tr>
<td>DH 7.5%</td>
<td>0.727 (0.539-0.915)</td>
<td>0.096</td>
<td>0.03</td>
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<tr>
<td>sFLR 29.6%</td>
<td>0.665 (0.486-0.845)</td>
<td>0.096</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Shindoe et al, J Am Coll Surg 2013
Volume of the liver remnant

Liver \textit{volume} \neq \textit{Liver function}

Clavien & al N Engl J Med 2007,
Portal vein embolization (PVE)  

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Two-Stage hepatectomy  

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Two-Stage hepatectomy + PVE  
*J Belghiti et al.* Hepatology 2008

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Hepatic Vein embolization  

---

History of hypertrophy induction

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

Feasibility = 81% / Morbidity = 76% / Mortality = 15%
• 33 patients with unresectable bilateral CR liver metastases

1\textsuperscript{st} Stage
Clean-up of FLR “easy side”

2\textsuperscript{nd} Stage
Resection of diseased side “difficult side”

Feasibility= 75% / Morbidity= 71% / Mortality= 0%
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.
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§

<table>
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<tr>
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<th>FLR Volume (mL)</th>
<th>FLR Volume/TLV (%)</th>
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<tbody>
<tr>
<td>Before PVE</td>
<td>561.1 ± 43.1</td>
<td>34.8 ± 1.6</td>
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<tr>
<td>1-2 wk after PVE</td>
<td>640.6 ± 53.5</td>
<td>39.7 ± 0.6</td>
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<tr>
<td>2 wk after HVE</td>
<td>714.8 ± 61.1</td>
<td>44.2 ± 1.1</td>
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<tr>
<td>1 wk after hepatectomy</td>
<td>1043.9 ± 149.5</td>
<td>64.5 ± 6.2</td>
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</tbody>
</table>
Hypertrophy induction

STAGE 1
Portal vein occlusion

60-70%

STAGE 2
Complete tumor removal

25-40%

Insufficient hypertrophy
Disease progression

NEVER UNDERGO 2\textsuperscript{nd} STAGE


**Kokudo N, et al.** *Hepatology* 2001


<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Patients (n)</th>
<th>PVE (n)</th>
<th>PVL (n)</th>
<th>Increase of liver volume (%)</th>
<th>Time interval (d)</th>
<th>Seg.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shindoh</td>
<td>2013</td>
<td>144</td>
<td>144</td>
<td>62 (0.3-379)</td>
<td>34 (12 – 385)</td>
<td>Seg. II/III</td>
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<tr>
<td>Capussotti</td>
<td>2008</td>
<td>48</td>
<td>31</td>
<td>53.4</td>
<td>29</td>
<td>Seg. II/III</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>17</td>
<td>43.1</td>
<td>40</td>
<td>Seg. II/III</td>
<td></td>
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<tr>
<td>Aussilhou</td>
<td>2007</td>
<td>35</td>
<td>18</td>
<td>35 ± 38</td>
<td>49 ± 3</td>
<td>Seg. II/III</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>17</td>
<td>38 ± 26</td>
<td>56 ± 3</td>
<td>Seg. II/III</td>
<td></td>
</tr>
<tr>
<td>Farges</td>
<td>2002</td>
<td>27</td>
<td>PVE normal hepatic function (n = 13)</td>
<td>44 ± 19</td>
<td>49 ± 13</td>
<td>Seg. I-IV</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PVE hepatic dysfunction (n = 14)</td>
<td>35 ± 28</td>
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</table>
8 weeks after PVL
ALPPS (In situ Splitting)

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 Goralcyk, 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*


- **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**

LR/BW = 0.48

400ml
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 transsection** 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
Patient had intrahepatic recurrence 2 years after ALPPS treated with repeated hepatectomy; the patient is alive now 80 months after ALPPS without recurrence

- 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

Schadde et al., World J Surg 2014

Swiss HPB Center, Zürich
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.


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)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Location before ALPPS</th>
<th>RFS¹ (months)</th>
<th>Location of Recurrence</th>
<th>OS² (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>13</td>
<td></td>
<td>Dead 25</td>
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<td></td>
<td></td>
<td></td>
<td>+ bone</td>
<td></td>
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<tr>
<td>2</td>
<td></td>
<td>7</td>
<td></td>
<td>Alive 20</td>
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<td></td>
<td></td>
<td></td>
<td>+ bone</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>+ peritoneum</td>
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<tr>
<td>3</td>
<td></td>
<td>8</td>
<td></td>
<td>Dead 8</td>
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<td></td>
<td></td>
<td></td>
<td>+ lymphnode</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>+ peritoneum</td>
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<tr>
<td>4</td>
<td></td>
<td>13</td>
<td></td>
<td>Alive 18</td>
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<td></td>
<td></td>
<td></td>
<td>+ lymphnode</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient</th>
<th>Location before ALPPS</th>
<th>RFS¹ (months)</th>
<th>Location of Recurrence</th>
<th>OS² (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td></td>
<td>6</td>
<td></td>
<td>Dead 11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+ lymphnode</td>
<td></td>
</tr>
<tr>
<td>6</td>
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<td>3</td>
<td></td>
<td>Alive 15</td>
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<tr>
<td>7</td>
<td></td>
<td>11</td>
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<td>Alive 12</td>
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<td></td>
<td></td>
<td></td>
<td>Increase in CEA</td>
<td></td>
</tr>
</tbody>
</table>

Oldhafer et al., World J Surg 2014
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%)

Schadde et al., Ann Surg 2014
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

Narita et al., Br J Surg 2011
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:

- Univariate
  - 3 or more CRLM in FLR at step 1
  - Age > 70 years
  - CEA > 200ng/ml

- Multivariate
  - 3 or more CRLM in FLR at 1 step
  - Age > 70 years

Narita et al., Br J Surg 2011
n = 141 PVE in CRLM

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

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

Resectability rate

- Unresectable: 46%
- Resectable: 75%

Survival

- Resected, stable
- Resected, progression
- Unresected, stable
- Unresected, progression

P = 0.001
Portal vein embolization and its effect on tumour progression for colorectal cancer liver metastases

E. Simoneau¹, M. Hassanain², M. Shaheen¹, M. Aljiffry⁵, N. Molla³, P. Chaudhury¹,², S. Anil⁴, A. Khashper³, D. Valenti³ and P. Metrakos¹

DFS

20 months
6 months
14 months
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

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

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

Schadde et al., Ann Surg 2014

Ann Surg 2012
Changing the paradigm in ALPPS

The current paradigm

1st Step

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

7-10 days, enough volume increase

2nd Step

- Less aggressive surgical procedure
- Goal: tumor resection
Changing the paradigm in ALPPS

The future paradigm! Mini ALPPS

1st Step

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

2nd Step

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

Patient in good condition, normal LF test, enough function increase
Inverting the ALPPS paradigm by minimizing first stage impact: the Mini-ALPPS technique

Eduardo de Santibañes¹ ² & Fernando A. Alvarez¹ & Victoria Ardiles¹ & Juan Pekolj¹ & Martin de Santibañes¹

Langenbecks Arch Surg 2016
Inverting the AL PPS paradigm by minimizing first stage impact: the Mini-AL PPS technique

Eduardo de Santibañes¹, Fernando A. Alvarez¹, Victoria Ardiles¹, Juan Pekolj¹, and Martín de Santibañes¹

Langenbecks Arch Surg 2016
Monosegment ALPPS hepatectomy: Extending resectability by rapid hypertrophy

- n = 12

- hypertrophy rate: 160 (93-250)%
- 90-day-mortality: 0%

1 Year SR 80%
1 Year DFS 50%

Schadde et al., Surgery 2015;157:676-689
• ALPPS in CRLM 23
• after failed PVE 10
• Solitary metastase 4 (size: 6-12 cm)
• 90-day-mortality 1 (4%)

OS: 2 year: 59%
DFS: 1 year 27%
median 6.4 months
Comparison Two-stage hepatectomy ALPPS

Björnsson et al., EJSO 2016

Resection rate: 100%
90-day mortality: 4%
OS: 2 year: 59%
DFS: 1 year 27%
median 6.4 months

Narita, BJ Surg 2011

Resection rate: 100%
90-day mortality: 4%
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%
Abdominal CT after multiple cycles of CTx and TACE with Irinotecan-loaded Beads 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.
Remnant volume = parts of Seg. II/III: 27% TLV

where PVE and ALPPS don’t not work
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
• woman with synchronous CRLM

• Primary in the middle of rectum, non-obstructing

**Intended ALPPS – intraoperative change of strategy**

Neoadjuvant Chemotherapy Folfiri + Targeted therapy (18 months)
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 -
- 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 -
<table>
<thead>
<tr>
<th>Extent of liver resection</th>
<th>Treatment before</th>
<th>Body weight ratio</th>
<th>Time (d)</th>
<th>Tumor Recurrence</th>
<th>Following</th>
<th>Survival after diagnosis CRLM/ALPPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seg. IV-VIII</td>
<td>Cetuximab 10 months</td>
<td>0.4 0.7</td>
<td>11</td>
<td>disseminated (3 months)</td>
<td>chemotherapy</td>
<td>† tumor recurrence (23/13 months)</td>
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<td>FOLFOX,</td>
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**median DFS:** 7 months

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

**median follow-up after diagnosis of CRLM:** 34 (2-49) months
- Liver volume ≠ 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!
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 Zanello, MD³, Matteo Serenari, MD³, Federica Cipriani, MD¹, Luca Bonariol, MD⁴, Nicolò Bassi, MD⁴, Luca Aldrighetti, MD¹, and Elio Jovine, MD³

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

Assessment of liver function i.e. Child-Pugh, ICG test, etc.

Guglielmi et al; Dig Surg 2012
Kinetic growth rate

sFRL = volume in CT / eTLV
DH = Degree of hypertrophy (%)  sFRL2 – sFRL1

KGR = DH/time (weeks)

Shindoe et al, J Am Coll Surg 2013