Come ottenere l’ipertrofia controlaterale prima della resezione.

Embolizzazione portale o TARE: le evidenze

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Come ottenere l’ipertrofia controlaterale prima della resezione.
Embollizzazione portale o TARE: le evidenze

Interdisciplinary Data Literature
- Interventional radiology
- Medical radiation oncology
- Nuclear medicine
- Medical physics
- Hepatologist - oncologist
- Surgical oncology
- Transplant surgery

No guidelines
No consensus
Come ottenere l’ipertrofia controlaterale prima della resezione. 

Embolizzazione portale o TARE: le evidenze

When evaluating patients for resection, two aspects can qualify the possible unresectability of the tumour.

[1] the presence of an inadequate future liver remnant (FLR) 
   strong independent predictor of post-operative complications 

[2] the close proximity of the tumour to vital hepatic structures that can make any type of intervention impossible
AIM:
Expanding the room for hepatic resection

RATIONALE
1. The liver has the ability to regenerate

1. The portal vein plays a central role in transporting trophic factors

Peter Paul Rubens, Prometheus Bound, 1611-18, Philadelphia Museum of Art
Liver Regeneration

George K. Michalopoulos
Department of Pathology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

Hepatocytes and Biliary Epithelial Cells

AIM:

Induce a liver “side effect”

As discussed above, hepatocytes, resting on the properties of facultative stem cells, fulfill functions (transport of bile). Under selective circumstances, however, they can become stem cells for hepatocytes. Clinical histologic observations have suggested that periportal hepatocytes may also be facultative stem cells for biliary cells, transforming into biliary cells when the latter cannot proliferate to repair biliary epithelium during chronic injury (e.g., primary biliary cirrhosis, primary sclerosing cholangitis) (Crosby et al., 1998). This phenomenon has now been demonstrated experimentally in rats with chomic liver (Lacombe et al., 1998). Periportal hepatocytes can transform into biliary epithelial cells when the latter now destroyed by DAPM and bile ducts are transmurally obstructed. Biliary obstruction is known to lead to bile ductule proliferation and, under the conditions described above, more than 50% of the newly emerging ductules carry markers unique to one of the two populations of the hepatocytes of the chionic liver (Michalopoulos et al., 2000). These findings clearly demonstrate that hepatocytes are also facultative stem cells for the biliary epithelium. As shown in Figure 4, the two types of epithelial cells of the liver (hepatocytes and biliary cells) constitute a bipolar system of facultative stem cells for each other, fully capable of repairing liver histology even when the classic regeneration fails.

Fig 4.
Cells from the biliary compartment (portal ductules and canals of Hering) transform into oval cells and these become hepatocytes when proliferation of hepatocytes is abolished during regeneration. Periportal hepatocytes can also convert to biliary cells when there is injury to biliary cells but their capacity for self repair is inhibited. Hepatocytes and biliary cells are facultative stem cells for each other.
AIM:
Expanding the room for hepatic resection

TOOLS:

• Portal vein embolization (PVE)

• Portal vein ligation (PVL)

• Associating liver partition with PVL for staged hepatectomy (ALPSS)

• Trans-arterial radioembolization (TARE)
AIM:
Expanding the room for hepatic resection

RATIONALE:
To induce a “side effect”

TOOLS

Portal vein embolization (PVE) as conversion therapy
Portal Vein Embolization: PVE

Makuuchi M et al Surgery 1990 first described PVE as a means of improving surgical outcomes by preventing peri-operative liver insufficiency.

3 approaches:
- transileocolic (surgical procedure)
- controlateral (via FLR)
- ipsilateral
PVE

The dark side of the guidelines

Table 1
Classification Systems for Hepatic Lobar and Segmental Anatomy

<table>
<thead>
<tr>
<th>Couinaud Classification System</th>
<th>Angio-Saxon Classification System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dorsal sector (segment I)</td>
<td>Caudate lobe</td>
</tr>
<tr>
<td>Left liver</td>
<td>Left lobe</td>
</tr>
<tr>
<td>Left paramedian sector</td>
<td>Anterior medial segment (quadrate lobe)</td>
</tr>
<tr>
<td>Segment IV</td>
<td>Anterior inferior subsegment (lateral segment)</td>
</tr>
<tr>
<td>Segment III</td>
<td>Posterior superior subsegment (lateral segment)</td>
</tr>
<tr>
<td>Left lateral sector</td>
<td>Right lobe</td>
</tr>
<tr>
<td>Segment II</td>
<td>Anterior segment</td>
</tr>
<tr>
<td>Right liver</td>
<td></td>
</tr>
<tr>
<td>Right paramedian sector</td>
<td>Anterior inferior subsegment</td>
</tr>
<tr>
<td>Segment V</td>
<td>Anterior superior subsegment</td>
</tr>
<tr>
<td>Segment VIII</td>
<td>Posterior segment</td>
</tr>
<tr>
<td>Right lateral sector</td>
<td>Posterior inferior subsegment</td>
</tr>
<tr>
<td>Segment VI</td>
<td>Posterior superior subsegment</td>
</tr>
<tr>
<td>Segment VII</td>
<td></td>
</tr>
</tbody>
</table>

#look at the anatomical variants#
#look at the surgical plan#
MDCT and/or MRI of the liver
- assessment of tumor and non tumor volume
- vascular assessment (portal vein patency; both tumour and hepatic arterial vascular bed)
- the extent of extrahepatic disease
**PVE**

**Update on Portal Vein Embolization: Evidence-based Outcomes, Controversies, and Novel Strategies**

Benjamin J. May, MD, Adam D. Talenfeld, MD, and David C. Madoff, MD

1. FLR future liver remnant (CT/MR volumetry)

1. TELV total estimated liver volume

\[ TELV = -794.41 + 1,267.28 \text{ (BSA)} \]

1. Body weight

---

**Vauthey JN et al. Liver Transplantation 2002**

Shah A. et al.

*Comparison of different methods to quantify future liver remnants after preoperative portal vein embolization to predict postoperative liver failure.*

*Hepatogastroenterology 2011*

#best method#: TELV

\[ p<0.005 \]
PVE

Update on Portal Vein Embolization: Evidence-based Outcomes, Controversies, and Novel Strategies

Benjamin J. May, MD, Adam D. Telenfeld, MD, and David C. Madoff, MD

J Vasc Interv Radiol 2013; 24:241–254
http://dx.doi.org/10.1016/j.jvir.2012.10.017

301 consecutive pts:

- pre-operative sFLR <20% had significantly higher rates of post-operative liver insufficiency and death for liver failure ($p<0.005$)

PVE

Update on Portal Vein Embolization: Evidence-based Outcomes, Controversies, and Novel Strategies
Benjamin J. May, MD, Adam D. Telenfeld, MD, and David C. Madoff, MD

In addition: Ribero D et al Br J Surg 2007

sFLR <20% and degree of sFLR hypertrophy after PVE <5%
predicted outcome after resection
PVE

Consensus Conference on the Multidisciplinary Treatment of Hepatocellular Cancer in 2010 recommended PVE for sFLR <20% of total estimated liver volume (TELV) in pts with preserved liver function.
PVE when sFLR <30% of total estimated liver volume (TELV) in pts with steatosis and hepatotoxic chemotherapy
And sFLR <40% of total estimated liver volume (TELV) in pts with well compensated cirrhosis (CPA)
# PVE: Complications

## Standards of Practice

**Quality Improvement Guidelines for Percutaneous Transcatheter Embolization**

Society of Interventional Radiology
Standards of Practice Committee

John F. Angle, MD, Nazir H. Siddiqi, MD, Michael J. Wallace, MD, Sanjoy Kandu, MD, LeAnn Stokes, MD, Joan C. Wojak, MD, and John F. Cardella, MD

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### Table 1. Complication Rates for Portal Vein Embolization Reviewed in Literature

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of Patients; Complication Rate</th>
<th>Complication Type</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kodama et al (2002) (38)</td>
<td>47 patients; 7 (15%) complications</td>
<td>Pneumothorax</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subcapsular hematoma</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arterial puncture</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pseudoaneurysm</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hemobilia</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Portal vein thrombus</td>
<td>1</td>
</tr>
<tr>
<td>Di Stefano et al (2005)</td>
<td>188 patients; 24 (12.8%) adverse events</td>
<td>Migration of embolic material to FLR</td>
<td>10</td>
</tr>
<tr>
<td>(37)</td>
<td></td>
<td>Transient liver failure</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Occlusion of portal vein</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subcapsular hematoma</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hemobilia</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hemoperitoneum</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rupture of gallbladder metastasis</td>
<td>1</td>
</tr>
<tr>
<td>Abulkhir et al (2006)</td>
<td>Meta-analysis of 37 studies involving 1,088 patients; reported morbidity 2.2%</td>
<td>Liver abscess</td>
<td>3</td>
</tr>
<tr>
<td>(36)</td>
<td></td>
<td>Cholangitis</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Left or main portal vein thrombus</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subcapsular hematoma</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Portal hypertension</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Septic necrosis</td>
<td>1</td>
</tr>
</tbody>
</table>

*FLR = future liver remnant.*
**PVE**

*Combination Therapy in the setting of HCC*


D01 10.1246/aos.0454-010-1125-3

ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Sequential Transcatheter Arterial Chemoembolization and Portal Vein Embolization versus Portal Vein Embolization Only before Major Hepatectomy for Patients with Hepatocellular Carcinoma

Hyunkyung Yeo, MD1, Jin Hyoong Kim, MD1, Gi-Young Ko, MD1, Kyung Won Kim, MD1, Dong Il Gwos, MD1, Sung-Gyu Lee, MD1, and Shila Hwang, MD1

1Department of Radiology and Research Institute of Radiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; 2Department of Surgery, Division of Hepatobiliary Surgery and Liver Transplantation, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

**RATIONALE:**

Trans-arterial chemoembolization before PVE induces a greater inflammatory response, which is known to contribute to liver regeneration

71 pts: TACE plus PVE

135 pts

64 pts: PVE
Sequential Transcatheter Arterial Chemoembolization and Portal Vein Embolization versus Portal Vein Embolization Only before Major Hepatectomy for Patients with Hepatocellular Carcinoma

Hyeokyoung You, MD, Jin Hyung Kim, MD, Gi-Young Ko, MD, Kyung Won Kim, MD, Dong Hwan, MD, Sung-Gyu Lee, MD, and Shin Hwang, MD

Sequential arterial and PVE is effective and safe

PVE
Combination Therapy in the setting of HCC

PVE only
TACE + PVE

Overall survival rate

Disease-free survival rate

Patients at risk
TACE + PVE 71 61 43 30 16 10 7 3
PVE-alone 64 46 25 14 10 8 2 1

Patients at risk
TACE + PVE 71 51 32 22 12 8 6 3
PVE-alone 64 20 12 7 5 4 1 1

135 pts

p = .035
p = .028
p = .001
PVE
CONTROVERSIES
Combined right (RPVE) and segment IV (4PVE)

13 pts (RPVE)  
13 pts (RPVE plus 4PVE)

No difference volume increase \((p=0.20)\)
No difference IIs, IIIIs rate of increase \((p=0.40)\)

58 pts (RPVE)  
15 pts (RPVE plus 4PVE)

Statistically significant difference
RPVE plus 4PVE better: volume increase \((p=0.044)\)
IIs, IIIIs rate of increase \((p=0.021)\)

Different in technical experience and sample size
PORTAL VEIN LIGATION (PVL)
Definition

First emphasized by Cantlie in 1897, later by Ros in 1920
Clinical implementation in 1975 by Honjo

✓ Manipulation of the portal blood flow

✓ Two-stage procedure:
1) “cleansing” of the FLR from tumour is performed along with PVL
2) when adequate hypertrophy of the FLR reached, resection of the diseased liver part
PVL and PVE in comparison

Mixed results
- Aussilhou B et al. Right portal vein ligation is as efficient as portal vein embolization to induce hypertrophy of the left liver remnant. J Gastrointest Surg 2008; 12: 297–303

Portal occlusion (PVE or PVL) increase volume FLR up to 40% within 3 to 8 weeks

BUT

MAJOR ISSUE:
drop-out up to 35% of pts of either insufficient liver hypertrophy of the FLR or tumor progression within 3-8 weeks interval between portal vein occlusion and resection

WE MUST BE MORE RAPID TO GET THE HYPERTROPHY OF THE FLR
Associating liver partition with PVL for staged hepatectomy

ALPSS

PVL and transection of the liver

First emphasized by Dr Hans Schlitt in Regensburg, Germany 2007
Data reported by Schnitzbauer et al 2012 (Ann Surg 2012)

1. After PVL portal-portal shunts, which can lead to recanalization of the ligated right portal vein, develop

2. Liver transection, reduces portal-portal shunts
   AND
   releases circulatory cytokines and growth factors not ONLY liver – specific (similar effects by injuring other organs)

International ALPSS registry (http://www.alpss.net/)
May 2016: 553 cases from 84 centers around the world
Conventional è il A:

**Stage 1.** surgical exploration, right PVL, in situ splitting (ISS) of the liver parenchyma along the right rim of the round ligament, divided and are either clipped with metal clips or oversewn. Biliary and arterial structures and venous drainage of the right liver are retained

**Stage 2.** remove the right extended lobe and ligating the right hepatic artery, right bile duct and hepatic vein
## ALPSS: Advantages

### 1. rapid hypertrophy

<table>
<thead>
<tr>
<th>Surgical approach (study type)</th>
<th>Tumor type(s)</th>
<th>Evidence level</th>
<th>Patients (n)</th>
<th>Age (y)</th>
<th>Volume increase (%)</th>
<th>Internal (days)</th>
<th>Preop sample (%)</th>
<th>Completion (%)</th>
<th>R0 resection (%)</th>
<th>Overall mortality (%)</th>
<th>In-hospital mortality (%)</th>
<th>OS (%)</th>
<th>Recurrence (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional ALPPS (multicenter)</td>
<td>CRLM (14), HCC (3), Hilar CC (2), ICC (2), GBC (2), NLRM (2)</td>
<td>4</td>
<td>25</td>
<td>63</td>
<td>74</td>
<td>9</td>
<td>48</td>
<td>100</td>
<td>96</td>
<td>64</td>
<td>12</td>
<td>6-months (90)</td>
<td>NR</td>
<td>Schild et al. (86)</td>
</tr>
<tr>
<td>Conventional ALPPS (single-center)</td>
<td>CRLM (7), HCC (1), Hilar CC (1), NLRM (1)</td>
<td>4</td>
<td>10</td>
<td>52</td>
<td>82</td>
<td>7</td>
<td>60</td>
<td>100</td>
<td>100</td>
<td>40</td>
<td>0</td>
<td>NR</td>
<td>20</td>
<td>Saha et al. (84)</td>
</tr>
<tr>
<td>Conventional ALPPS (multicenter)</td>
<td>CRLM (2), HCC (1), Hilar CC (3), Bcl (1), NLRM (2)</td>
<td>4</td>
<td>39</td>
<td>57</td>
<td>83</td>
<td>14</td>
<td>NR</td>
<td>96</td>
<td>100</td>
<td>59</td>
<td>13</td>
<td>NR</td>
<td>NR</td>
<td>Tomes et al. (87)</td>
</tr>
<tr>
<td>Conventional ALPPS (single-center)</td>
<td>CRLM (7)</td>
<td>4</td>
<td>7</td>
<td>66</td>
<td>66</td>
<td>13</td>
<td>29</td>
<td>100</td>
<td>100</td>
<td>86</td>
<td>0</td>
<td>1 year (71)</td>
<td>86</td>
<td>Oda et al. (89)</td>
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<tr>
<td>Conventional ALPPS (single-center)</td>
<td>CRLM (7), ICC (1), Hilar CC (3)</td>
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<td>9</td>
<td>67</td>
<td>87</td>
<td>13</td>
<td>30</td>
<td>100</td>
<td>100</td>
<td>66</td>
<td>22</td>
<td>NR</td>
<td>NR</td>
<td>Liu et al. (90)</td>
</tr>
<tr>
<td>Conventional ALPPS (single-center)</td>
<td>CRLM (6), HCC (5), Hilar CC (6), ICC (4)</td>
<td>4</td>
<td>16</td>
<td>67</td>
<td>87</td>
<td>13</td>
<td>33</td>
<td>100</td>
<td>97</td>
<td>67</td>
<td>29</td>
<td>NR</td>
<td>40</td>
<td>Nadel et al. (91)</td>
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<tr>
<td>ALPPS (single-center)</td>
<td>CRLM (17), HCC (1), NLRM (18)</td>
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<td>22</td>
<td>65</td>
<td>61</td>
<td>7</td>
<td>68</td>
<td>100</td>
<td>100</td>
<td>63</td>
<td>9</td>
<td>1 year (91)</td>
<td>5</td>
<td>Rubes et al. (92)</td>
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<td>CRLM (28), HCC (3), Hilar CC (4), ICC (8), NLRM (2)</td>
<td>3s</td>
<td>48</td>
<td>57</td>
<td>77</td>
<td>7</td>
<td>58</td>
<td>100</td>
<td>93</td>
<td>73</td>
<td>15</td>
<td>NR</td>
<td>NR</td>
<td>Schadde et al. (81)</td>
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<td>CRLM (14), HCC (7), Hilar CC (11), ICC (8), GBC (8), NLRM (19)</td>
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<td>60</td>
<td>86</td>
<td>10</td>
<td>NR</td>
<td>98</td>
<td>91</td>
<td>IIB (40)</td>
<td>9</td>
<td>1 year (73)</td>
<td>9</td>
<td>Schadde et al. (91)</td>
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<td>Conventional ALPPS (single-center)</td>
<td>CRLM (14)</td>
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<td>14</td>
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<td>90</td>
<td>8</td>
<td>100</td>
<td>100</td>
<td>86</td>
<td>38</td>
<td>0</td>
<td>9-months (100)</td>
<td>14</td>
<td>Hernandez-Alejandro et al. (93)</td>
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<td>12</td>
<td>59</td>
<td>47</td>
<td>11</td>
<td>75</td>
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<td>100</td>
<td>83</td>
<td>83</td>
<td>1 year (82)</td>
<td>27</td>
<td>Raddi et al. (94)</td>
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<td>Conventional ALPPS (multicenter)</td>
<td>CRLM (10), NLRM (1)</td>
<td>3s</td>
<td>62</td>
<td>59</td>
<td>48</td>
<td>8</td>
<td>82.3</td>
<td>95</td>
<td>NR</td>
<td>89.8</td>
<td>12.9</td>
<td>NR</td>
<td>NR</td>
<td>Truant et al. (95)</td>
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<tr>
<td>Conventional ALPPS or partial ALPPS (single-center)</td>
<td>CRLM (18), HCC (3), Hilar CC (1), ICC (1), NLRM (8)</td>
<td>4</td>
<td>11</td>
<td>68</td>
<td>54</td>
<td>7</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>First (18), Second (46)</td>
<td>9</td>
<td>NR</td>
<td>NR</td>
<td>Tanaka et al. (96)</td>
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<td>Conventional ALPPS or partial ALPPS (single-center)</td>
<td>CRLM (9), HCC (1), Hilar CC (1), ICC (2), NLRM (3)</td>
<td>4</td>
<td>16</td>
<td>61</td>
<td>86</td>
<td>9</td>
<td>43.7</td>
<td>100</td>
<td>100</td>
<td>64</td>
<td>12.5</td>
<td>1 year (28)</td>
<td>40</td>
<td>Akerkar et al. (97)</td>
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<tr>
<td>Anterior approach for ALPPS (single-center)</td>
<td>HCC (13)</td>
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<td>53</td>
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<td>15.3</td>
<td>7.7</td>
<td>NR</td>
<td>NR</td>
<td>Chan et al. (98)</td>
</tr>
</tbody>
</table>

### 2. feasibility (97%) and R0 resection (83-100%)

**47-93% increase in FLR within 7-14 days**

**Reasons:**

1. after partial hepatectomy, a STRESS SIGNAL is generated due to the increase of energy demand per unit liver volume (ISS)

2. Altered hemodynamic factors (PVL)
ALPSS: Disadvantages

1. High mortality and morbidity
   - Complications: 36%
   - Morbidity rate: 68%
   - In-hospital mortality rate: 12%

2. Early tumor recurrence
   - ALPSS may promote tumor growth

Volume: 317 ml vs 475 ml

SUV: 4.3 vs 6.3

Ki-67 labeling index for tumor cells: 60% vs 80%
PVE vs PVL vs ALPSS in comparison
Which is the best????

Systematic review

Meta-analysis of associating liver partition with portal vein ligation and portal vein occlusion for two-stage hepatectomy

D. Eshkamin2, D. A. Bagnoli1, M. Lurie1, A. Wirzschilling1, M. Lessner1,2 and E. A. Glöeren1

BJS 2016; 103: 1768–1782

2796 publications

3670 pts after PVE
290 pts after PVL
367 pts after ALPSS

90 publications

179 pts after PVE
123 pts after PVL
55 pts after ALPSS
## PVE vs PVL vs ALPSS

### Speed of FLR hypertrophy before resection

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Random, 95% CI</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ausilhou 2008</td>
<td>35</td>
<td>18</td>
<td>38</td>
<td>26</td>
<td>17</td>
<td>36.6%</td>
<td>-3.00 [-24.47, 18.47]</td>
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<td></td>
</tr>
<tr>
<td>Rolles 2012</td>
<td>41.5</td>
<td>18</td>
<td>35.2</td>
<td>3.7</td>
<td>20</td>
<td>42.9%</td>
<td>6.30 [-0.33, 12.93]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schadde 2014</td>
<td>37.5</td>
<td>29.4</td>
<td>29.8</td>
<td>30</td>
<td>26.2%</td>
<td>8.10</td>
<td>[-7.04, 23.24]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>van Lienden 2012</td>
<td>67.4</td>
<td>21.8</td>
<td>31.9</td>
<td>7</td>
<td>13.3%</td>
<td>37.90</td>
<td>[11.65, 64.15]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>99</td>
<td></td>
<td>74</td>
<td></td>
<td></td>
<td>93.4</td>
<td>[-1.81, 20.48]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau^2 = 63.88; Chi^2 = 6.20; df = 3 (P = 0.10); I^2 = 52%

Test for overall effect: Z = 1.64 (P = 0.10)

---

### Comparison Results

- **PVE vs PVL**: 46% vs 35%  \( p=0.10 \)
- **ALPSS vs PVE**: 76% vs 37%  \( p<0.001 \)
- **ALPSS vs PVL** (only 1 study): 87% vs 29%  \( p<0.001 \)

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**Infusion of CD133” Bone Marrow-Derived Stem Cells After Selective Portal Vein Embolization Enhances Functional Hepatic Remnant After Extended Right Hepatectomy: A Retrospective Single-Center Study**

Ann Surg 2012;255:70-85

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**2nd Interventional Radiologist under 40 Meeting**

**Interventional Oncology**
### PVE vs PVL vs ALPSS

**Forest plots comparing morbidity and mortality between strategies**

**Morbidity PVE vs PVL**
- PVE: 7 of 12 (58.3%)
- PVL: 5 of 14 (35.7%)
- Risk ratio: 1.63 (95% CI: 0.70, 3.82)

**Mortality PVE vs PVL**
- PVE: 2 of 12 (16.7%)
- PVL: 3 of 14 (21.4%)
- Risk ratio: 0.79 (95% CI: 0.22, 2.79)

**ALPSS vs PVL (only 1 study):**
- Morbidity: 73% vs 62%
- Mortality: 15% vs 8%

**Mortality ALPSS vs PVE**
- ALPSS: 1 of 7 (14.3%)
- PVE: 0 of 12
- Risk ratio: 4.00 (95% CI: 0.41, 38.00)

**Mortality ALPSS vs PVE**
- ALPSS: 1 of 7 (14.3%)
- PVE: 0 of 12
- Risk ratio: 1.00 (95% CI: 0.00, 10.00)

---

**Inclusion of CD133+ Bone Marrow Derived Stem Cells After Selective Portal Ven Embolization Enhances Functional Hepatic Reserves After Extended Right Hepatectomy**

**A Retrospective Single-Center Study**

A. Schmiedeck, MD; J. B. Schenk, MD; J. K. Petz, MD; T. B. V. Hoffmann, MD; T. M. J. van der Made, MD; J. M. K. van der Made, MD; B. M. M. van der Made, MD; M. J. van der Made, MD; K. van der Made, MD


---

**ALPSS vs PVL (only 1 study):**
- Morbidity 73% vs 62%
- Mortality 15% vs 8%

**Mortality ALPSS vs PVE**
- ALPSS: 1 of 7 (14.3%)
- PVE: 0 of 12
- Risk ratio: 4.00 (95% CI: 0.41, 38.00)

**Mortality ALPSS vs PVE**
- ALPSS: 1 of 7 (14.3%)
- PVE: 0 of 12
- Risk ratio: 1.00 (95% CI: 0.00, 10.00)
ALPSS: BETTER hypertrophy of the FLR in a SHORTER time

BUT

ALPSS International Registry (http://www.alpss.net/) showed

1. 93% of deaths after 2 stage for post-hepatectomy liver failure (PHLF)

2. 16-31% PHLF even when sufficient FLR volumes achieve

3. 75% pts 90-day mortality liver-related (peak of bilirubin >5mg/dL or a MELD score>10)

4. Early tumor recurrence
Preliminary results from small series suggest that

1. FLR volumetric increase **PRECEDES** its functional improvement

2. ALPSS might promote tumor growth

ALPSS Registry’s data suggest FLR sufficiency defined by classical volumetric criteria **IS NOT ENOUGH** in this scenario

**Shortening times is not the main factor to improve the post-operative outcomes**
Key question:

Not HOW LARGE

BUT

HOW GOOD

the FLR function has to be to avoid PHLF?

Need to evaluate liver function using Hepatobiliary Scintigraphy (HBS)
Hepatobiliary scintigraphy (HBS)


Scintigraphic criteria for the diagnosis of obstructive hepatobiliary diseases with Tc-99m IDA. Krishnamurthy S, Krishnamurthy CT, Lieberman D, Keeffe EB.

- Iminodiacetic acid derivate ($^{99m}$Tc-mebrofenin) (IDA)
- High liver uptake and directly excreted into the biliary system

![Scintigraphy Images](image_url)
Hepatobiliary scintigraphy (HBS) and SPECT

Anterior View

Posterior View

\[ \% \text{ FLR-C} = \frac{\text{counts FLR}}{\text{counts TLV}} \times 100 \]
Volume vs Function

Functional assessment versus conventional volumetric assessment in the prediction of operative outcomes after major hepatectomy

Hiromitsu Hayashi, MD, PhD, Toru Beppu, MD, PhD, FACS, Hirohisa Okabe, MD, PhD, Hideyuki Kuroki, MD, Shigeki Nakagawa, MD, PhD, Katsunori Imai, MD, PhD, Hidetoshi Nitta, MD, PhD, Akira Chikamoto, MD, PhD, FACS, Takatoshi Ishiko, MD, PhD, FACS, and Hideo Baba, MD, PhD, FACS. Kumamoto, Japan

Conventional volumetric assessment

- Safe FR volume and function: 76%
- Marginal FR volume and function: 24%

Functional assessment

- Safe FR volume and function: 76%
- Marginal FR volume but safe in FR function: 16%

133 pts

32 pts

11 pts

21 pts
Hepatobiliary scintigraphy (HBS)

Assessment of Future Remnant Liver Function Using Hepatobiliary Scintigraphy in Patients Undergoing Major Liver Resection

Wilmar de Graaf, Krijn P. van Lienden, Sander Dinant, Joris J. T. H. Roelofs, Olivier R. C. Busch, Dirk J. Gouma, Roelof J. Bennink, Thomas M. van Gulik

55 pts

FLR cut-off: 2.69%/min/m² BSA
Identifies pts with a significant risk of developing PHLF
Hepatobiliary scintigraphy (HBS) after PVE

PVE in 24 pts

FLR cut-off: 2.69%/min/m²

Conclusions: 3 pts would not have needed pre-operative PVE
7 pts did not achieve a sufficient increase in FLR function to allow a safe resection 3 weeks after PVE, compared with 12 pts and 9 pts based on FLR volume and sFRL
Primary Aim:
PHLF and 90-day mortality using HBS con 99mTc-mebrofenina e SPECT-TC

Secondary Aims:
- Best method (formula) to evaluate the liver function
- Compare SPECT/TC vs CT or MR volumetric criteria
- Morbidity and mortality rate
ISSUE
SHORTENING TIMES IS OUR MAIN GOAL?

ISSUE
LOCAL TUMOR CONTROL then RESECT?

"Alice: “Per quanto tempo è per sempre?”
Bianconiglio: “A volte, solo un secondo”.

Lewis Carrol

NOT
AIM:
Expanding the room for hepatic resection

RATIONALE:
To induce a “side effect”

TOOLS

Trans-arterial radioembolization (TARE) as conversion therapy
Radioembolization (TARE) as conversion therapy

HCC

Given that TARE is effective....

clinical practice guidelines

Hepatocellular carcinoma: ESMO–ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

C. Verslype1,2, O. Rosmorduc3 & P. Rougier4, on behalf of the ESMO Guidelines Working Group*

1. Department of Gastroenterology and Oncology, University Hospitals Leuven, Leuven, Belgium; 2. European Society of Digestive Oncology; 3. Department of Gastroenterology and Hepatology, Saint-Anne Hospital, Paris, France; 4. Department of Digestive Oncology, European Georges-Pompidou Hospital, Paris, France

5. Management of locally advanced/metastatic disease: palliative treatments

- TACE is recommended for patients with HCC BCLC stage B, or those with an excellent liver function and multinodular asymptomatic tumors without macroscopic vascular invasion or extra-hepatic spread [I, A].
- The combination of TACE with sorafenib—either sequential or concomitant—cannot be recommended outside clinical trials.
- Sorafenib is the standard systemic therapy for patients with advanced HCC and well-preserved liver function (BCLC stage C) and those with intermediate stage HCC who progress following TACE [I, A].
- In case of progression or intolerance to sorafenib, best supportive care is preferred or patients should be included in clinical trials.
- Systemic chemotherapy, tamoxifen, immunotherapy, anti-androgen or somatostatin analogues are not recommended for the clinical management of HCC patients [I–II, A–B].

- The role of radioembolization with glass or resin Y–90 spheres may be competitive with sorafenib or TACE in subsets of patients, such as those with prior TACE failure, excellent liver function, macrovascular invasion and the absence of extra-hepatic disease [III, C].
- External beam radiotherapy can be used to control pain in patients with bone metastases [II, B].
- For patients with end-stage disease with heavily impaired liver function or a poor performance status (both due to the tumor involvement of the liver) only symptomatic treatment is advocated [III, B].
Radioembolization (TARE) as conversion therapy: mets

Given that TARE is effective....

ESMO consensus guidelines for the management of patients with metastatic colorectal cancer

Recommendation 16: Embolisation

- For patients with liver-limited disease failing the available chemotherapeutic options
  - Radioembolisation with yttrium-90 microspheres should be considered [II, B]
  - Chemoembolisation may also be considered as a treatment option [IV, B]
  - Radioembolisation (and chemoembolisation) of CLM in earlier treatment lines may be interesting as ‘consolidation treatment’ but should be limited to clinical trials
Given that TARE can downstage pts....

1) If MELD ≤9 and no ascites
2) At best, in study protocols, but also in clinical practice

Intermediate HCC
Child-Pugh A-B
PST 0-1
Large / multinodular

Child-Pugh
A-B 7

Child-Pugh
B 8-9

Down-stage with ablation

1 nodule
>5 cm
RES

1st line
TACE (±Abl)
or RES

1
Alternative
TACE or TARE (±Abl)
Sorafenib

TARE² (±Abl)
Sorafenib

≥4 nodules
≥4 nodules
TACE or Sorafenib

≥4 nodules
TARE²

2-3 nodules
>3 cm
TACE or TARE (±Abl)

2-3 nodules
>3 cm

No

OLT

BSC

Down-staged
Radioembolization (TARE) as conversion therapy

Hepatic radioembolization as a bridge to liver surgery

Arthur J. A. T. Braat1*, Julia E. Huijbregts1, I. Quintus Molenaar2, Inne H. M. Borel Rinkes2, Maurice A. A. J. van den Bosch1 and Marnix G. E. H. Lam1

1 Department of Radiology and Nuclear Medicine, University Medical Center Utrecht, Utrecht, Netherlands
2 Department of Surgery, University Medical Center Utrecht, Utrecht, Netherlands

Table 4 | Hypertrophy after RE.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients</th>
<th>Follow-up period</th>
<th>Volume measurement</th>
<th>Degree of hypertrophy contralateral lobe (%)</th>
<th>Degree of atrophy treated lobe (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jekobs et al. (83)</td>
<td>32</td>
<td>139 days</td>
<td>CT/MRI</td>
<td>8.9</td>
<td>21.2</td>
</tr>
<tr>
<td>Cobo et al. (84)</td>
<td>20</td>
<td>3 months</td>
<td>CT/MRI</td>
<td>40</td>
<td>62</td>
</tr>
<tr>
<td>Ahmadzadehfar et al. (85)</td>
<td>24</td>
<td>44–66 days</td>
<td>MRI</td>
<td>57</td>
<td>6</td>
</tr>
<tr>
<td>Edeline et al. (86)</td>
<td>34</td>
<td>3 months</td>
<td>CT</td>
<td>29</td>
<td>23</td>
</tr>
<tr>
<td>Vouche et al. (87)</td>
<td>83</td>
<td>1 month</td>
<td>CT/MRI</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3–6 months</td>
<td>MRI</td>
<td>35</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 9 months</td>
<td>MRI</td>
<td>45</td>
<td>37</td>
</tr>
<tr>
<td>Garlipp et al. (88)*</td>
<td>35</td>
<td>48 days</td>
<td>MRI</td>
<td>29</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>141†</td>
<td>33 days†</td>
<td></td>
<td>61.5†</td>
<td></td>
</tr>
</tbody>
</table>

NA, data not available.
*Only prospective study.
†RE vs. PVE, PVE results are marked.
Radioembolization (TARE) as conversion therapy

Downstaging Hepatocellular Carcinoma: A Systematic Review and Pooled Analysis

Neehar D. Parikh, Akbar K. Waljee, and Amit G. Singal

1 Division of Gastroenterology, University of Michigan Health System, University of Michigan, Ann Arbor, MI; 2 VA Ann Arbor Health Services Research and Development Center of Clinical Management Research, Ann Arbor, MI; and 3 Division of Digestive and Liver Diseases, University of Texas South Western Medical Center, Dallas, TX

Figure 5. Pooled post-LT HCC recurrence stratified by treatment modality (TACE versus TARE).

P = 0.40
Radioembolization (TARE) as conversion therapy

Given that TARE is effective and can downstage pts....

We suppose to EXPLOIT

Not only
1. to obtain R0 (local tumor control)

But also
2. to increase functional FLR ("side effect" of TARE)
ISSUE
*SHORTENING TIMES IS NOT OUR MAIN GOAL*

ISSUE
*LOCAL TUMOR CONTROL then RESECT*

ISSUE
We need to obtain COMPLETE RESPONSE before RESECT????
Radioembolization (TARE) as conversion therapy

It can be hypothesized, in the best clinical scenario, that a PR/OR can be sufficient to induce the disengagement of the tumor from vital hepatic structures which would otherwise represent the main surgical contra indication.

50-75% necrosis to downstage pts
Radioembolization (TARE) as conversion therapy

Increase in FLR 3 months: 21-32%
TARE vs PVE: mets

Left-Liver Hypertrophy After Therapeutic Right-Liver Radioembolization Is Substantial but Less Than After Portal Vein Embolization

Benjamin Garlipp,
Thierry de Baere,
Robert Damm,
Romy Irmscher,
Mark van Buskirk,
Patrick Stuibs,
Frederic Deschamps,
Frank Meyer,
Ricarda Seidensticker,
Konrad Mohrnie,
Maciej Pech,
Holger Annbauer,
Hans Lippert,
Jens Reker,
and Max Seidensticker

(Hepatology 2014;59:1864-1873)

Liver Mets PVE: 141 pts
TARE: 35 pts

In the full analysis set of RE patients entered into our study (n = 35), 9 of the 18 individuals who had a baseline FLR ratio <25% had an FLR ratio >25% at follow-up, indicating that volume gain induced by RE may be sufficient to achieve resectability in a substantial proportion of patients. Given the fact that PVE

<table>
<thead>
<tr>
<th>Variable</th>
<th>RE</th>
<th>PVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (median)</td>
<td>SD</td>
<td>Median (median)</td>
</tr>
<tr>
<td>FLR baseline (mL)</td>
<td>369.7 (339)</td>
<td>142.2</td>
</tr>
<tr>
<td>FLR post treatment (mL)</td>
<td>470.6 (435)</td>
<td>203.6</td>
</tr>
<tr>
<td>Change from baseline (mL)</td>
<td>101.9 (80)</td>
<td>106.5</td>
</tr>
<tr>
<td>Change from baseline (%)</td>
<td>29 (25.3)</td>
<td>22.9</td>
</tr>
<tr>
<td>P value (change from baseline within treatment, both mL and %)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
TARE vs PVE: mets

Left-Liver Hypertrophy After Therapeutic Right-Liver Radioembolization Is Substantial but Less Than After Portal Vein Embolization

Benjamin Garlipp,1 Thierry de Baere,2 Robert Damm,3 Romy Immscher,4 Mark van Buskirk,4 Patrick Stuibs,1 Frederic Deshamps,5 Frank Meyer,1 Ricardo Seidensticker,5 Konrad Molnär,3 Maciej Pech,3 Holger Andlbauer,5 Hans Lippert,4 Jens Reckers,1 and Max Seidensticker5

(HEPATOLOGY 2014;59:1864-1873)

development. Conclusion: PVE induces significantly more contralateral hypertrophy than RE with therapeutic (nonlobectomy) doses. However, contralateral hypertrophy induced by RE is substantial and RE minimizes the risk of tumor progression in the treated lobe, possibly making it a suitable modality for selected patients. (HEPATOLOGY 2014;59:1864-1873)

portal vein embolization (Fig. 1). The inherent benefit of the prolonged waiting period is the possibility to assess previously undetected contralateral metastases or synchronous HCC, since the occurrence of tumor progression in the non-treated lobe after RE is comparable to PVE (Table 4).
Radioembolization (TARE) as conversion therapy

In the induction of FRL hypertrophy, the underlying mechanism of liver hypertrophy remains a mystery (82). Since the embolic effect of RE is less substantial than in PVE, remnant hypertrophy after RE might largely be based on an irradiation induced effect in the treated liver lobe. This causes fibrosis, leading to increased portal pressure and eventually to shunting of portal venous blood away from the irradiated fibrotic lobe to the untreated contralateral lobe by preferential flow (83, 84, 86). This effect and its results do not arise as rapidly as in PVE, as described by Vouche et al. and Corrêa et al. (87, 90). After PVE, a more macroscopic occlusion creates a sudden shunt of portal venous blood to the untreated lobe. In some cases, repeated RE resulting in a higher cumulative dose led to an increase in hypertrophy of the untreated lobe (50). Only Edeline et al. found no correlation between the absorbed dose and hypertrophy in their study (86). That study was soon followed by a multivariate analysis of Vouche et al., in which the absorbed dose was no significant variable (87). Nonetheless, no studies have been performed solely to investigate this phenomenon and its relation to dose.
Radioembolization (TARE) as conversion therapy: DOSE

Volumetric Changes after \(^{90}\text{Y}\) Radioembolization for Hepatocellular Carcinoma in Cirrhosis: An Option to Portal Vein Embolization in a Preoperative Setting?

Jaileen Edeline, MD,*,**, Laurence Lessi, MD,***, Karim Boudjema, MD, PhD,†‡, Yan Rolland, MD,§,** Anne Beulle, Faxry Le Pa, Marc Poulet, MD,●, Jean-Luc Rassat MD, PhD,‖ Bruno Chinnici, PhD,§, Etienne Garin, MD, PhD,***, and Evelyne Boucher, MD

| TABLE 3 Maximal increase of contralateral volume in different subgroups of patients |
|-----------------------------------------------|-----------------------------|-----------------------------|
| Characteristic                                | Maximal increase, mean (95% CI) | p |
| Overall (n = 34)                              | 42% (+16 to +67%)            | 0.50 |
| Portal vein thrombosis                        | 51% (+9 to +94%)             | 0.05 |
| Any portal vein thrombosis (n = 14)          | 28% (+10 to +46%)            | 0.30 |
| Branch portal vein thrombosis (n = 9)         | 28% (−1 to +57%)             | 0.01 |
| Main portal vein thrombosis (n = 5)           | 28% (−3 to +59%)             | 0.01 |
| Treatment site                                | 21% (+2 to +39%)             | 0.01 |
| Left hepatic artery (n = 11)                  |                            |    |
| Right hepatic artery (n = 22)                 |                            |    |
| Type of spheres                               |                            |    |
| Glass microspheres (n = 30)                   | 43% (+14 to +72%)            | 0.81 |
| Resin microspheres (n = 4)                    | 32% (−23 to +87%)            | 0.01 |
| Patients with biopsy-proven cirrhosis (n = 18)| 62% (+14 to +109%)           | 0.12 |
| Child-Pugh score                              |                            |    |
| A5 (n = 25)                                   | 50% (+16 to +85%)            | 0.12 |
| A6 (n = 7)                                    | 23% (−2 to +47%)             | 0.12 |
| B7 (n = 2)                                    | −1% (−83 to +75%)            | 0.12 |
| Portal hypertension                           |                            |    |
| Yes (n = 19)                                  | 20% (+11 to +30%)            | 0.10 |
| No (n = 15)                                   | 69% (+12 to +126%)           | 0.10 |

CT confidence interval
TAKE HOME MESSAGES

✓ Liver has the ability to regenerate if damaged

✓ Timing of liver regeneration is variable

✓ Time is not the main factor of resectability.

Elegibility to surgery
IS NOT ONLY A DECISION
of the Surgeon
BUT ALSO
of the Interventional Radiologist

✓ Local tumor control is our main goal to switch pt from unresectable to resectable
Thank you for the attention

*alberta.cappelli@aosp.bo.it*