The dark side of the guidelines
2nd Interventional Radiologist under 40 Meeting
Interventional Oncology
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Società Medica Chirurgica - Palazzo dell'Archiginnasio

Come ottenere l'ipertrofia controlaterale prima della resezione. Embolizzazione portale o TARE: le evidenze

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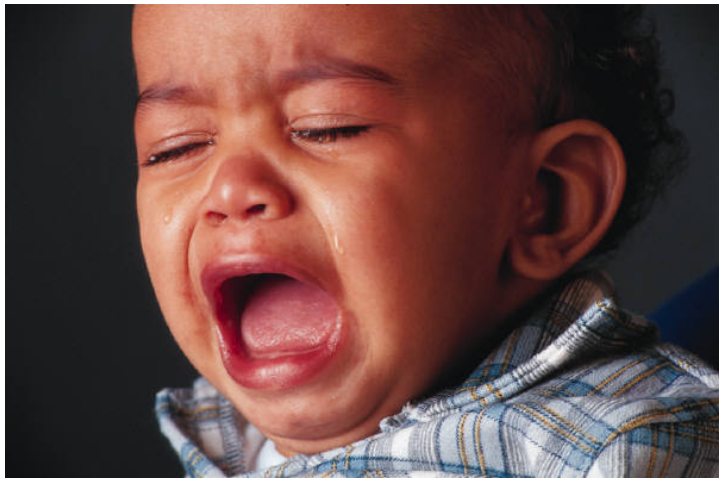
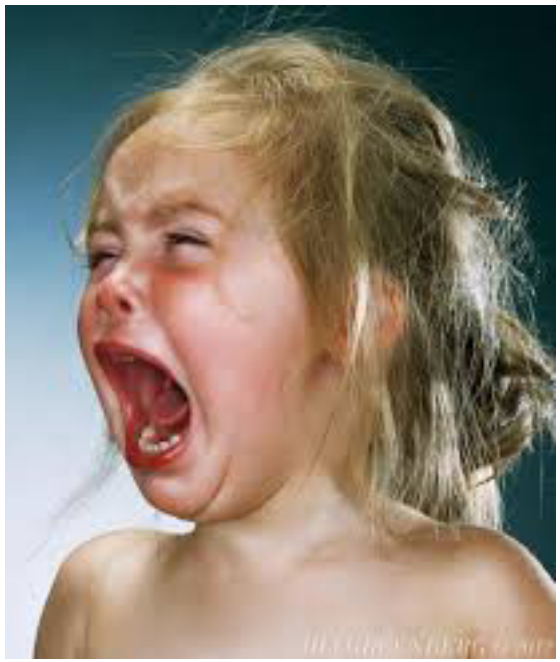


No guidelines
No consensus

Interdisciplinary Data

Literature

- **Interventional radiology**
- **Medical radiation oncology**
- **Nuclear medicine**
- **Medical physics**
- **Hepatologist - oncologist**
- **Surgical oncology**
- **Transplant surgery**



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 indipendent predictor of post-operative complications

[Shoup M et al J Gastrointestinal Surg 2003; Ribero D et al. Br J Surg 2007]

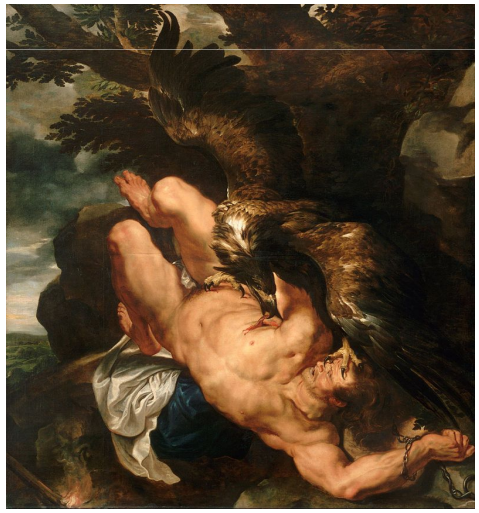
[2] the close proximity of the tumour to vital hepatic structures that can make any type of intervention impossible

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 trasporting trophic factors**



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

J Cell Physiol. 2007 November ; 213(2): 286–300. doi:10.1002/jcp.21172.

Liver Regeneration

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

Hepatocytes and Biliary E

Other

As discussed above. hepatocytes, restorin properties of *faculta* term "facultative" in 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 chimeric livers (Laconi et al., 1998). Periportal hepatocytes can transform into biliary epithelial cells when the latter are destroyed by DAPM and bile ducts are simultaneously 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 chimeric liver (Michalopoulos et al., 2005a). 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.

AIM:
Induce a liver " side effect"

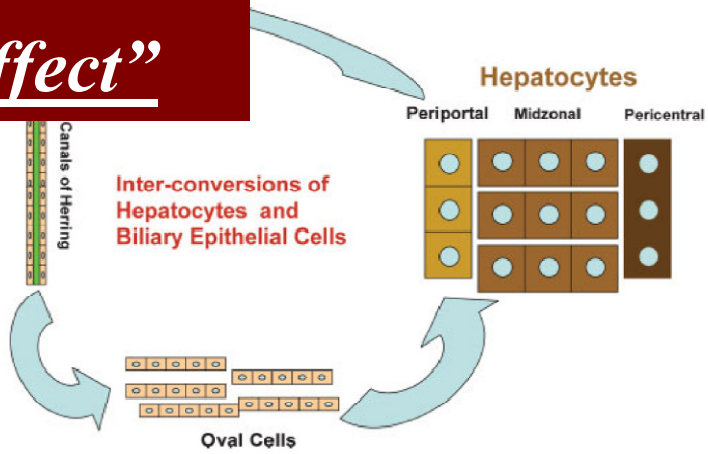


Fig. 4.
Cells from the biliary compartment (portal ductules and canals of Herring) transform into oval cells and these become hepatocytes when proliferation of hepatocytes is inhibited during regeneration. Periportal hepatocytes can also convert to biliary cells when there is injury to biliary cells 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:

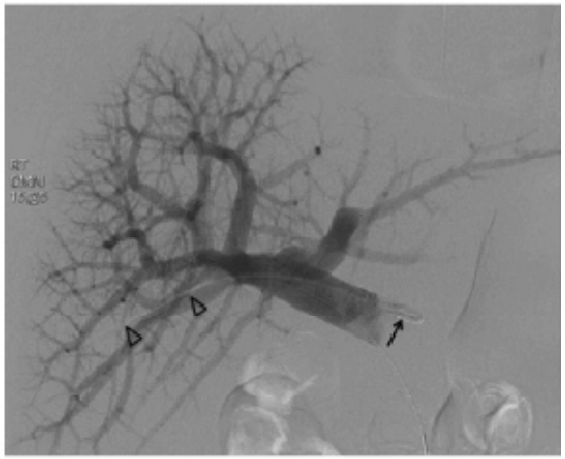
- Portal vein embolization (PVE)
- Portal vein ligation (PVL)
- Associating liver partition with PVL for staged hepatectomy (ALPSS)
- Trans-arterial radioembolization (TARE)

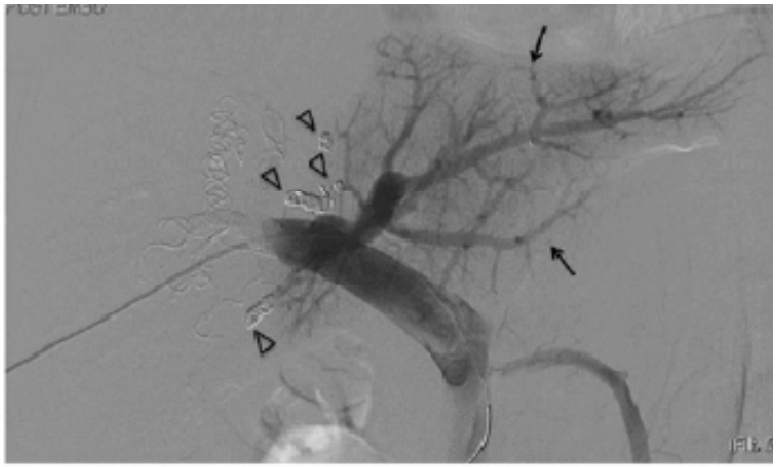
AIM:
Expanding the room for hepatic resection

RATIONALE:
To induce a " side effect"

TOOLS

Portal vein embolization (PVE)
as *conversion therapy*



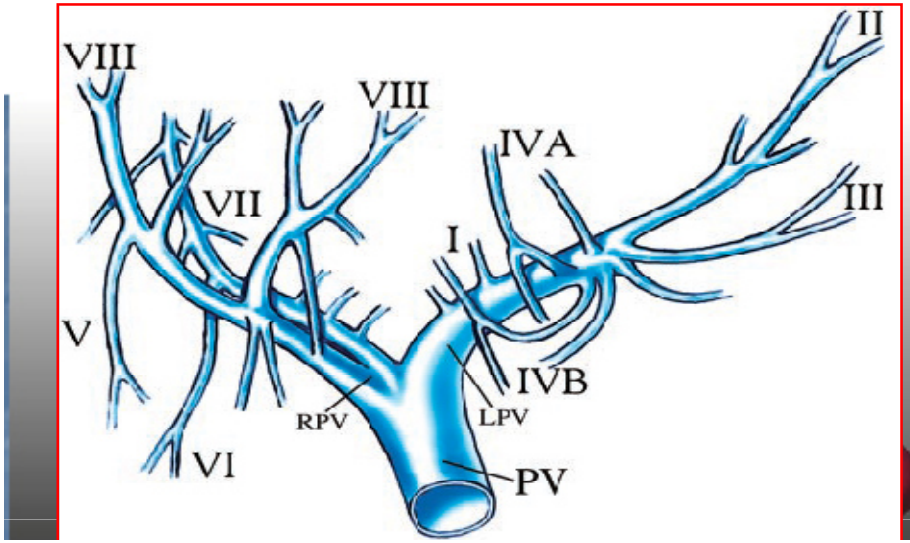


Portal Vein Embolization: PVE

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



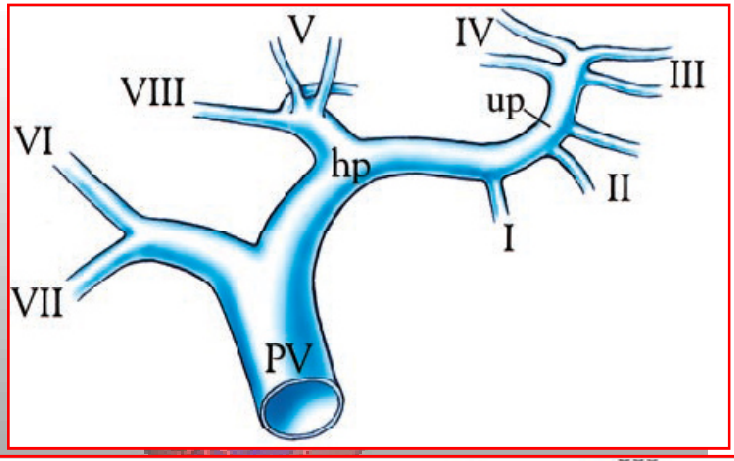
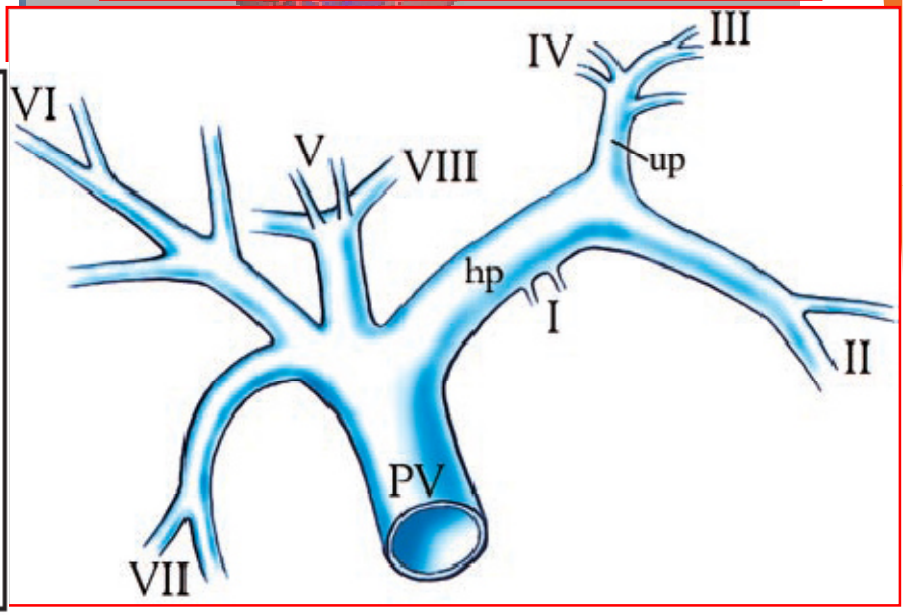


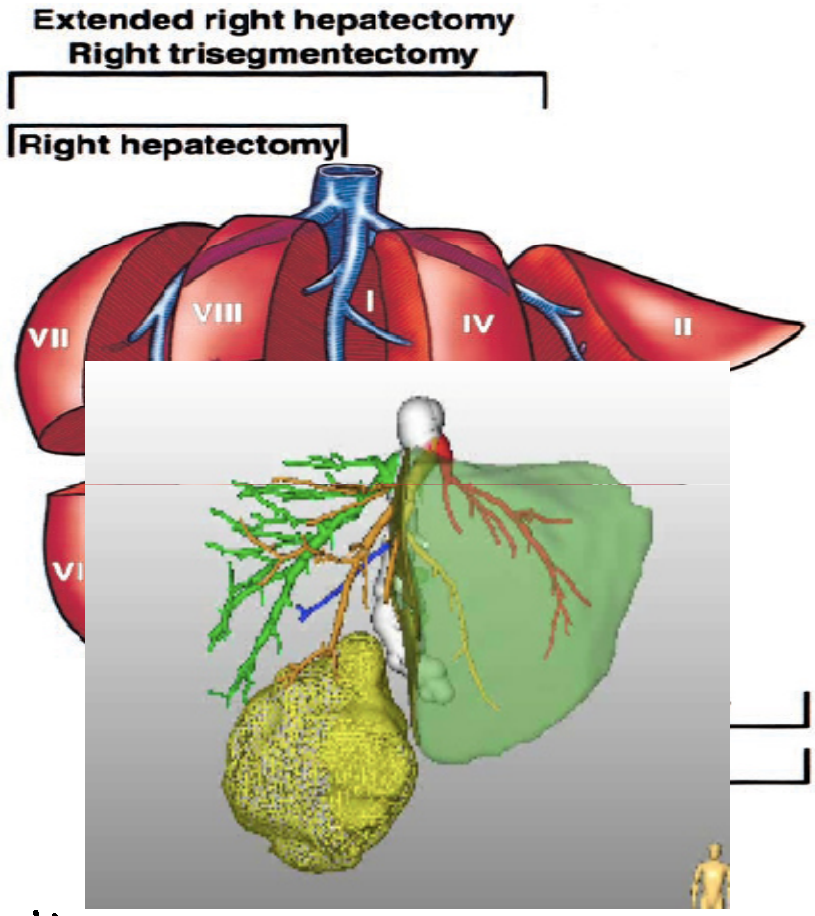
Table 1
Classification Systems for Hepatic Lobar and Segmental Anatomy

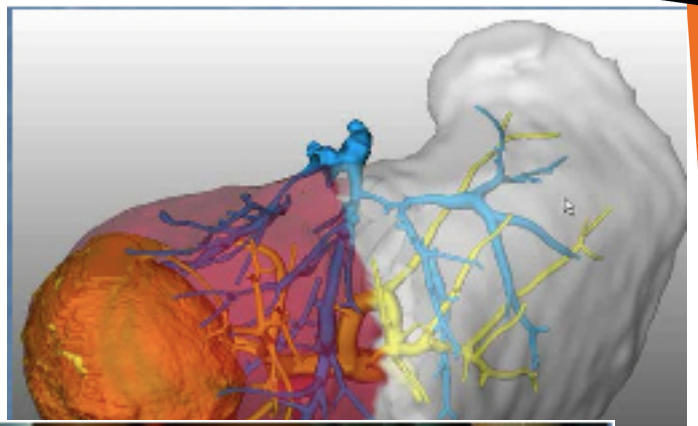
Couinaud Classification System	Anglo-Saxon Classification System
Dorsal sector (segment I)	Caudate lobe
Left liver	Left lobe
Left paramedian sector	
Segment IV	Anterior medial segment (quadrate lobe)
Segment III	Anterior inferior subsegment (lateral segment)
Left lateral sector	
Segment II	Posterior superior subsegment (lateral segment)
Right liver	Right lobe
Right paramedian sector	Anterior segment
Segment V	Anterior inferior subsegment
Segment VIII	Anterior superior subsegment
Right lateral sector	Posterior segment
Segment VI	Posterior inferior subsegment
Segment VII	Posterior superior subsegment

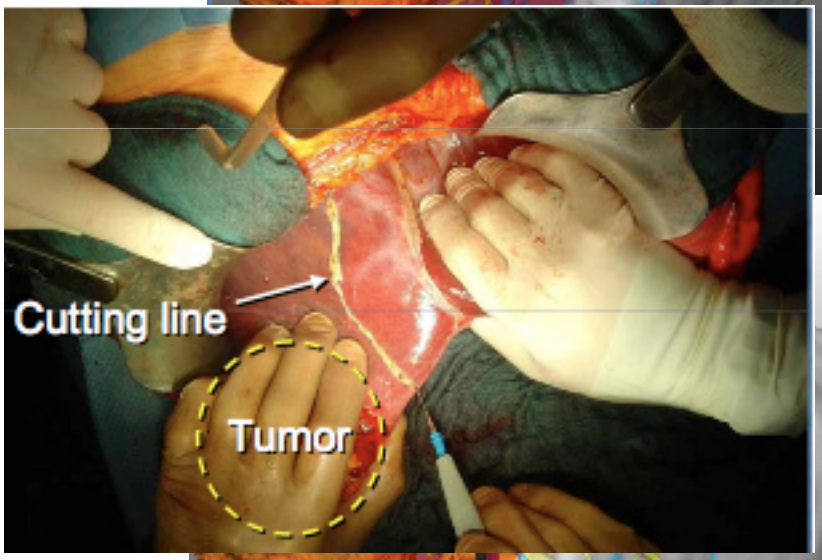


#look at the anatomical variants#

PVE





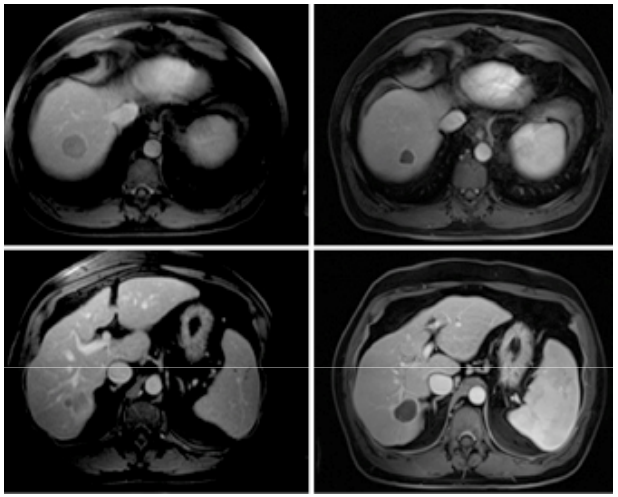


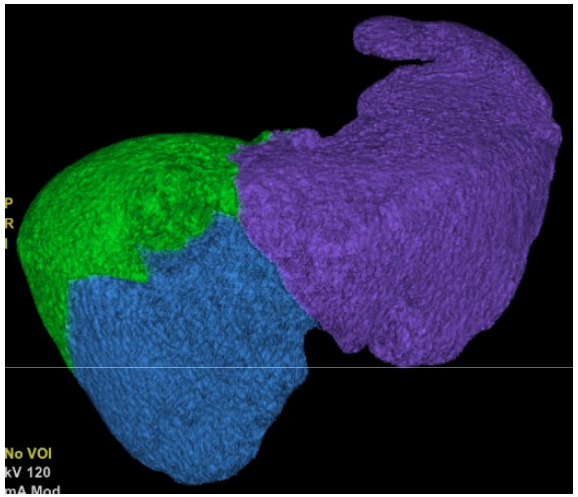
#look at the surgical plan#

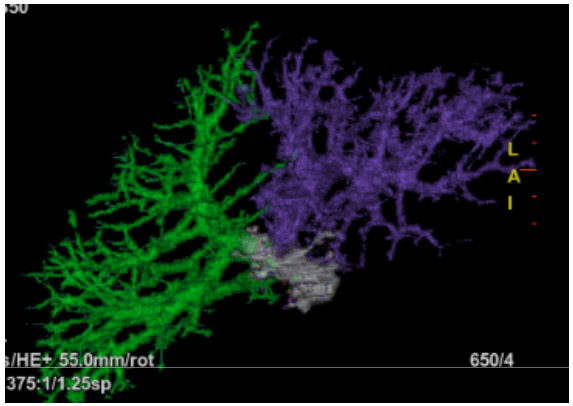
PVE

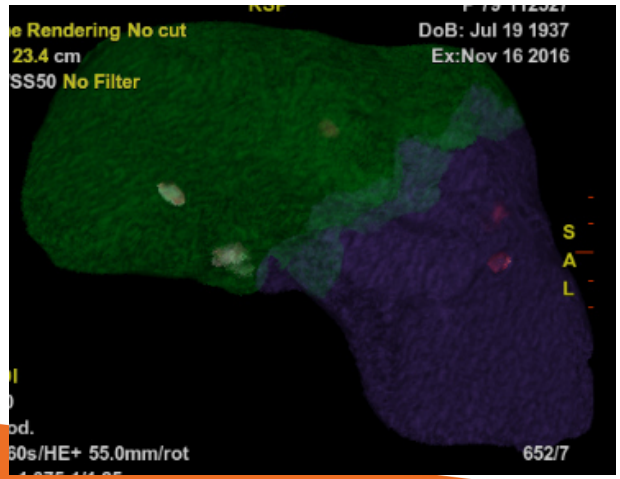
MDCT and/or MRI of the liver

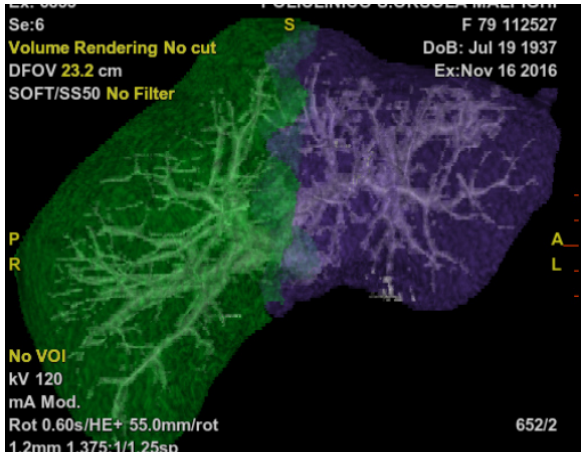
- assessment of tumor and non tumor volume
- vascular assessment (portal vein patency; both tumour and hepatic arterial vascular bed)
- the extent of extrahepatic disease

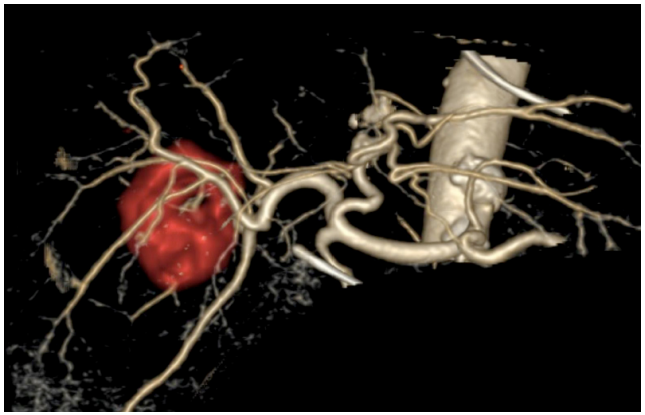












PVE

REVIEW ARTICLE

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

J Vasc Interv Radiol 2013; 24:241–254

http://dx.doi.org/10.1016/j.jvir.2012.10.017

Vauthey JN et al Liver Transplantation 2002

1. FLR future liver remnant (CT/MR volumetry)
1. TELV total estimated liver volume → $TELV = -794.41 + 1{,}267.28\ (BSA)$
1. Body weight

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

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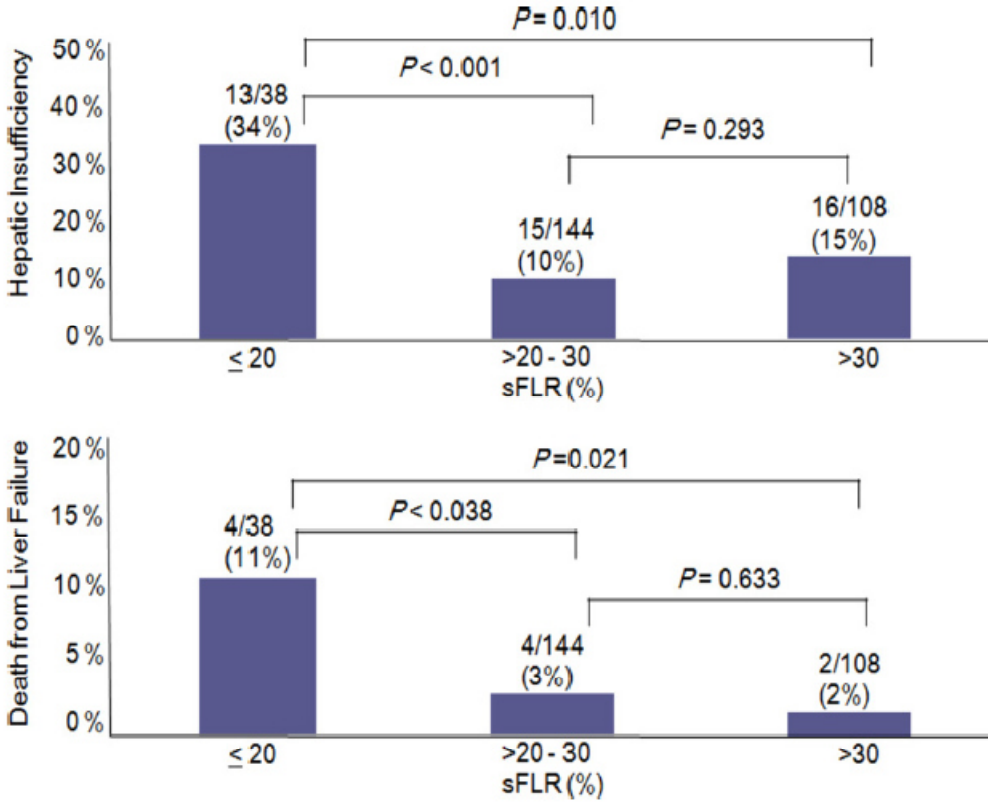

301 consecutive pts:

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

Kishi Y et al. Ann Surg 2009

PVE

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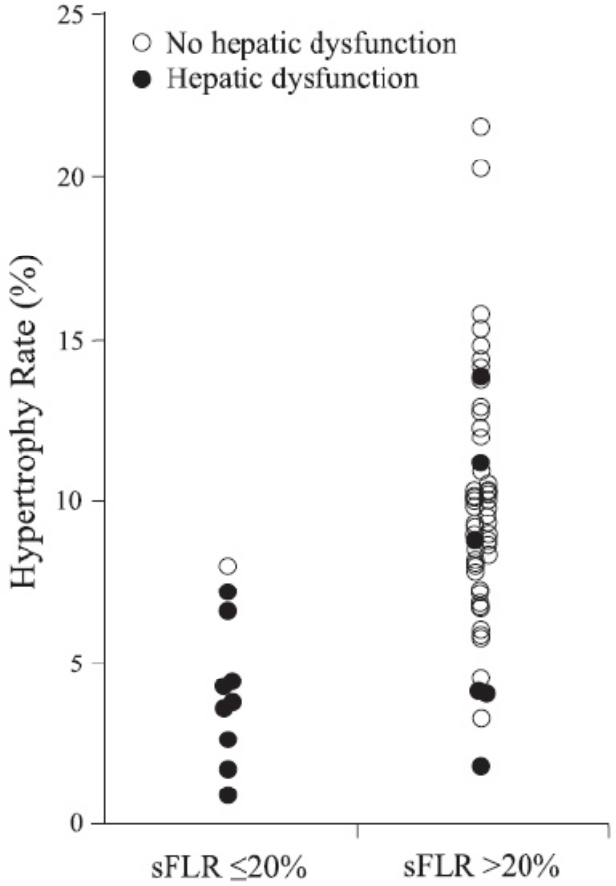

In addition: ***Ribero D et al Br J Surg 2007***

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

PVE

DOI:10.1111/j.1477-2574.2010.00184.x

HPB

EDITORIAL

AHPBA/SSO/SSAT Sponsored Consensus Conference on Multidisciplinary Treatment of Hepatocellular Carcinoma

Elijah Dixon[1], Eddie Abdalla[2], Roderich E. Schwarz[3] & Jean-Nicolas Vauthey[2]

[1]Division of Surgical Oncology, Department of Surgery, University of Calgary, Calgary, Alberta, Canada. [2]Department of Surgical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX; and [3]Division of Surgical Oncology, UT Southwestern Medical Center, Dallas, TX, USA.

HPB 2010, 12, 287–288

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

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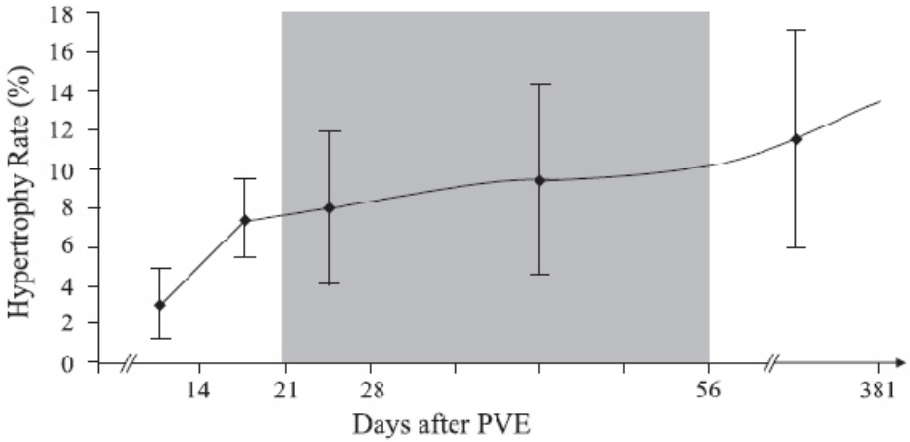
J Vasc Interv Radiol 2013; 24:241–254
http://dx.doi.org/10.1016/j.jvir.2012.10.017

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

However: ***Ribero D et al Br J Surg 2007***

ISSUE: Timing of regeneration is variable!!!

- **Steatosis**
- **Hepatotoxic chemotherapy**
- **Cirrhosis**



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, Nasir H. Siddiqi, MD, Michael J. Wallace, MD, Sanjoy Kundu, MD, LeAnn Stokes, MD, Joan C. Wojak, MD, and John F. Cardella, MD

DOI: 10.1016/j.jvir.2010.06.014

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

Reference	Number of Patients; Complication Rate	Complication Type	Number
Kodama et al (2002) (38)	47 patients; 7 (15%) complications	Pneumothorax	2
		Subcapsular hematoma	2
		Arterial puncture	1
		Pseudoaneurysm	1
		Hemobilia	1
		Portal vein thrombus	1
Di Stefano et al (2005) (37)	188 patients; 24 (12.8%) adverse events	Migration of embolic material to FLR	10
		Transient liver failure	6
		Occlusion of portal vein	3
		Subcapsular hematoma	2
		Hemobilia	1
		Hemoperitoneum	1
		Rupture of gallbladder metastasis	1
Abulkhir et al (2008) (36)	Meta-analysis of 37 studies involving 1,088 patients; reported morbidity 2.2%	Liver abscess	3
		Cholangitis	2
		Left or main portal vein thrombus	2
		Subcapsular hematoma	2
		Portal hypertension	1
		Septic necrosis	1

FLR = future liver remnant.

PVE
Combination Therapy in the setting of HCC

Ann Surg Oncol (2011) 18:1251–1257
DOI 10.1245/s10434-010-1423-3

Annals of SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

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 Yoo, MD[1], Jin Hyoung Kim, MD[1], Gi-Young Ko, MD[1], Kyoung Won Kim, MD[1], Dong Il Gwon, MD[1], Sung-Gyu Lee, MD[2], and Shin Hwang, MD[2]

[1]Department of Radiology and Research Institute of Radiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; [2]Department 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

135 pts

71 pts: TACE plus PVE

64 pts: PVE

PVE
Combination Therapy in the setting of HCC

Ann Surg Oncol (2011) 18:1251–1257
DOI 10.1245/s10434-010-1423-3

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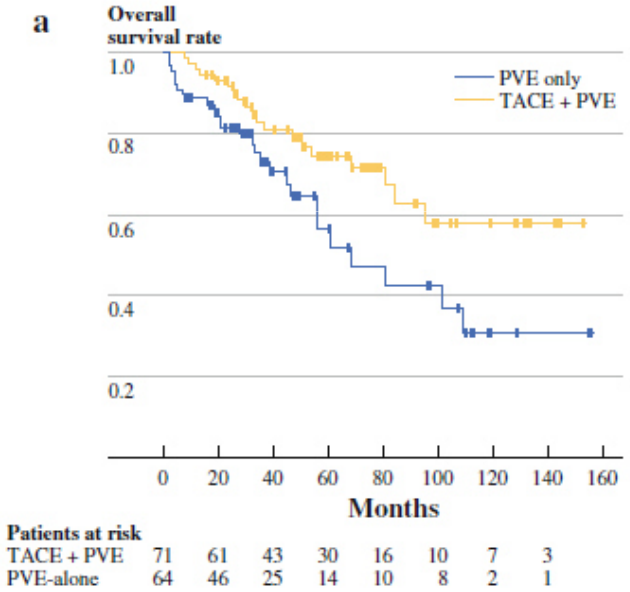
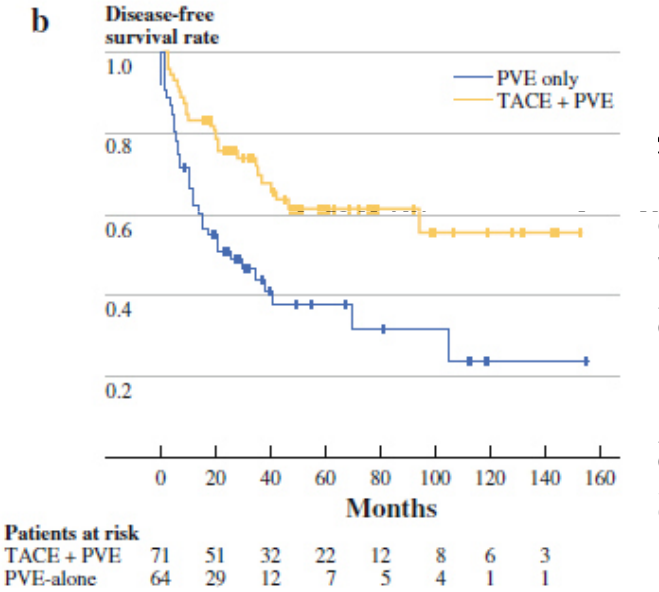




135 pts

e-free survival

3%
0%
1%
56%
2%
1%
8%
24%

Sequential arterial and PVE is effective and safe

p=.035 ***p=.028*** ***p=.001***

PVE CONTROVERSIES
Combined right (RPVE) and segment IV (4PVE)

Extension of Right Portal Vein Embolization to Segment IV Portal Branches

Lorenzo Capussotti, MD; Andrea Muratore, MD; Alessandro Ferrero, MD; Giovanni Carlo Anselmetti, MD; Andrea Corgnier, MD; Daniele Regge, MD

Arch Surg. 2005;140:1100-1103

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

No difference volume increase *(p=0.20)*
No difference IIs, IIIs rate of increase *(p=0.40)*

Is embolization of segment 4 portal veins before extended right hepatectomy justified?

Yoji Kishi, MD,[a] David C. Madoff, MD,[b] Eddie K. Abdalla, MD,[a] Martin Palavecino, MD,[a] Dario Ribero, MD,[a] Yun Shin Chun, MD,[a] *and* Jean-Nicolas Vauthey, MD,[a] *Houston, Tex*

(Surgery 2008;144:744-51.)

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

Statistically significant difference

RPVE plus 4PVE better: volume increase *(p=0.044)*
IIs, IIIs 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*
- *Robles R et al. Comparative study of right portal vein ligation versus embolisation for induction of hypertrophy in two-stage hepatectomy for multiple bilateral colorectal liver metastases. Eur J Surg Oncol 2012; 38: 586–593*
- *Van Lienden KP et al. Intrahepatic left to right portoportal venous collateral vascular formation in patients undergoing right portal vein ligation. Cardiovasc Intervent Radiol 2013; 36: 1572–1579*

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

Associating liver partition with PVL for staged hepatectomy
ALPSS

Systematic Review and Meta-Analysis

Medicine®

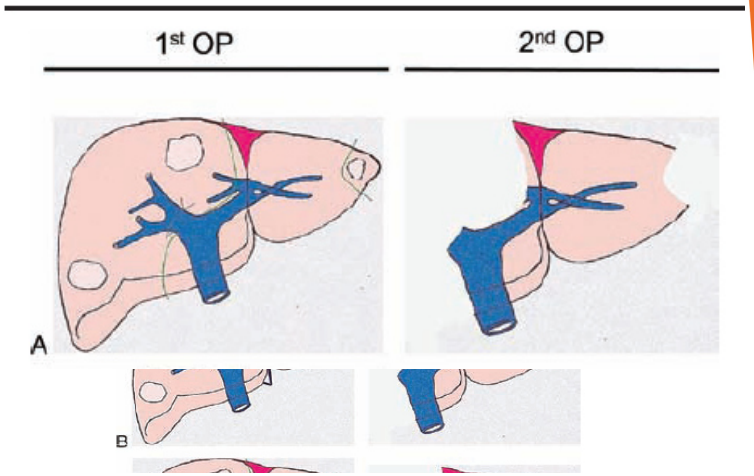
OPEN

An updated systematic review of the evolution of ALPPS and evaluation of its advantages and disadvantages in accordance with current evidence

Yu-Long Cai (MD)[a], Pei-Pei Song (PhD)[b], Wei Tang (MD, PhD)[a], Nan-Sheng Cheng (MD)[a,*]

Published online 1 May 2016

http://dx.doi.org/10.1097/MD.0000000000003941



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

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

Summary of reported outcomes of ALPPS.

Surgical approach (study type)	Tumor type (n)	Evidence level	Patients (n)	Age (yr)	Volume increase (%)	Interval (days)	Preop chemo (%)	Completion (%)	R0 resection (%)	Overall morbidity (%)	In-hospital mortality (%)	OS (%)	Recurrent (%)	Ref.
Conventional ALPPS (multicenter)	CRLM (14), HCC (3), Hilar CC (2), ICC (2), GBC (1), MEH (1), NCRLM (2)	4	25	63	74	9	48	100	96	64	12	6-months (86)	NR	Schnitzbauer et al[19]
Conventional ALPPS (single-center)	CRLM (7), HCC (1), Hilar CC (1), NCRLM (1)	4	10	52	82	7	60	100	100	40	0	NR	20	Sala et al[26]
Conventional ALPPS (multicenter)	CRLM (32), HCC (1), Hilar CC (3), Benign (1), SA (2)	4	39	57	83	14	NR	95	100	59	13	NR	NR	Torres et al[27]
Conventional ALPPS (single-center)	CRLM (7)	4	7	66	65	13	29	100	100	86	0	1 year (71)	86	Oldhafer et al[28]
Conventional ALPPS (single-center)	CRLM (7), ICC (3), Hilar CC (3)	4	9	67	87	13	30	100	100	66	22	NR	NR	Li et al[29]
Conventional ALPPS (single-center)	CRLM (5), HCC (1), Hilar CC (5), ICC (4)	4	15	67	87	13	33	100	87	67	29	NR	40	Nadalin et al[30]
ALTPS (single-center)	CRLM (17), HCC (1) NCRLM (4)	4	22	65	61	7	68	100	100	63	9	1 year (91)	5	Robles et al 2014[25]
Conventional ALPPS (multi-center)	CRLM (26), HCC (3), Hilar CC (4), ICC (8), NCRLM (7)	3b	48	57	77	7	58	100	83	73	15	NR	NR	Schadde et al[31]
Conventional ALPPS (multicenter)	CRLM (141), HCC (17), Hilar CC (11), ICC (8), GBC (6), NCRLM (19)	3a	202	60	86	10	NR	98	91	IIIA (40) IIIB (28)†	9	1 year (73) 2 years (59)	NR	Schadde et al 2014[32]
Conventional ALPPS (single-center)*	CRLM (14)	4	14	57	93	8	100	100	86	36	0	9-months (100)	14	Hernandez-Alejandro et al[33]
Conventional ALPPS (multicenter)	CRLM (12)	4	12	59	47	11	75	100	100	83	8.3	1 year (92)	27	Ratti et al[34]
Conventional ALPPS (multicenter)	CRLM (50), HCC (3), Hilar CC (3), GBC (4), NCRLM (4)	3b	62	59	48	8	82.3	95	NR	80.6	12.9	NR	NR	Truant et al[35]
Conventional ALPPS (single-center)	CRLM (10), NCRLM (1)	4	11	68	54	7	100	100	0	First (18), Second (46)‡	9	NR	NR	Tanaka et al[36]
Conventional ALPPS or partial ALPPS (single-center)	CRLM (19), HCC (3), Hilar CC (1), ICC (1), NCRLM (6)	4	30	57	90	6	60	97	93.1	53	6.6	1 year (78) 2 years (63)	40	Alvarez et al[37]
Conventional ALPPS (single-center)	CRLM (9), HCC (1), Hilar CC (1), ICC (2), NCRLM (3),	4	16	61	86	9	43.7	100	100	64	12.5	3 years (49)	56	Lang et al[38]
Anterior approach for ALPPS (single-center)	HCC (13)	4	13	62	53	8	NR	100	100	15.3	7.7	NR	NR	Chan et al[39]

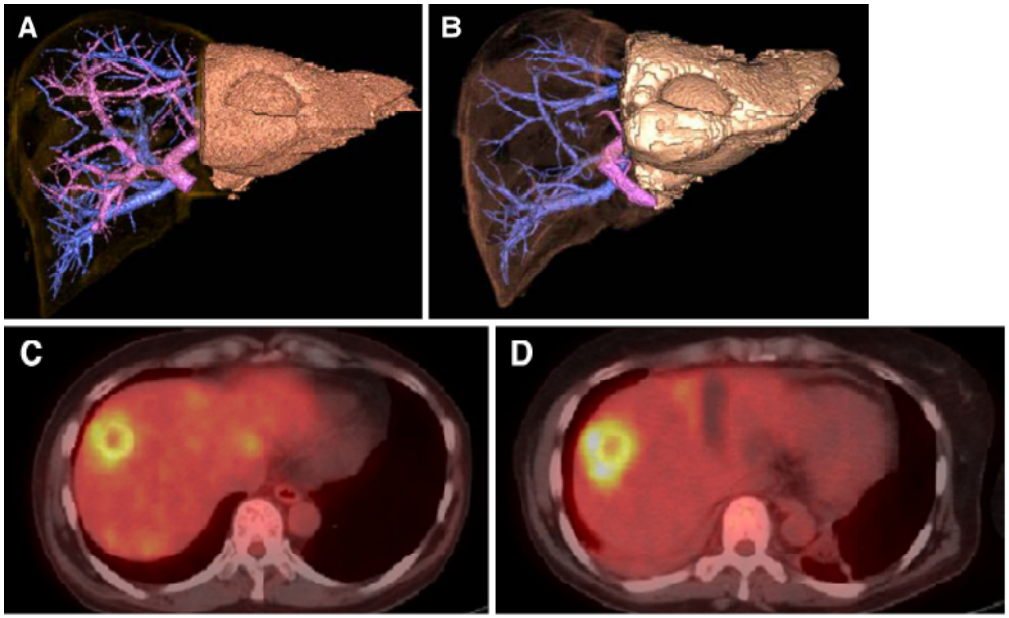
47-93% increase in FLR within 7-14 days

Reasons:

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

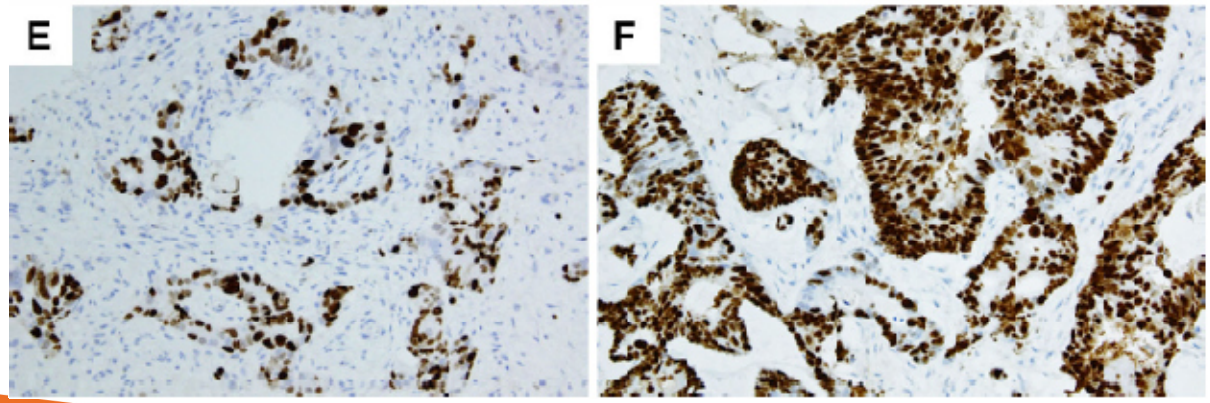
2. Altered hemodynamic factors (PVL)

ALPSS: Disadvantages



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

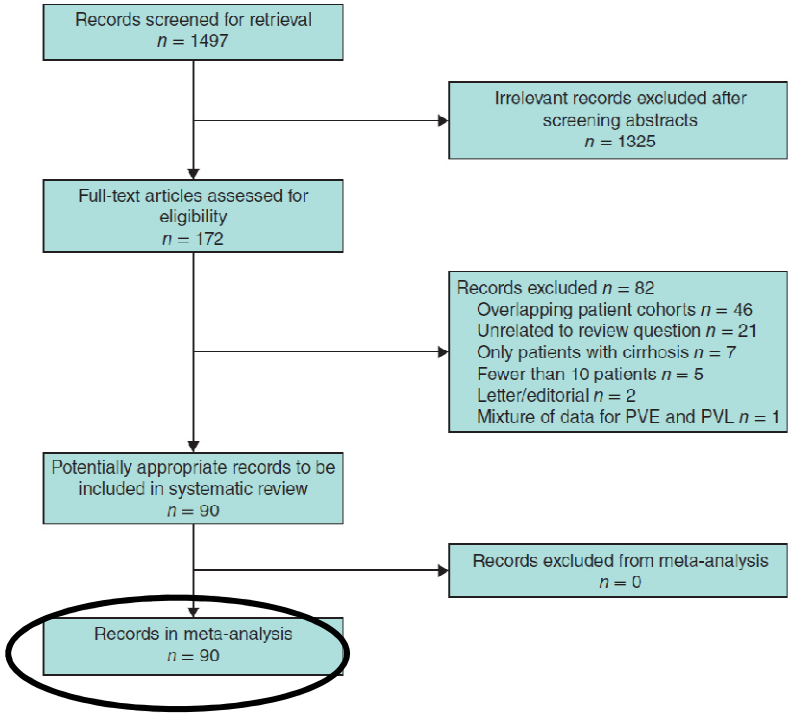
Meta-analysis of associating liver partition with portal vein ligation and portal vein occlusion for two-stage hepatectomy

D. Eshmuminov[1], D. A. Raptis[1], M. Linecker[1], A. Wirsching[1], M. Lesurtel[1,2] and P.-A. Clavien[1]

BJS 2016; **103**: 1768–1782

2796 publications

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

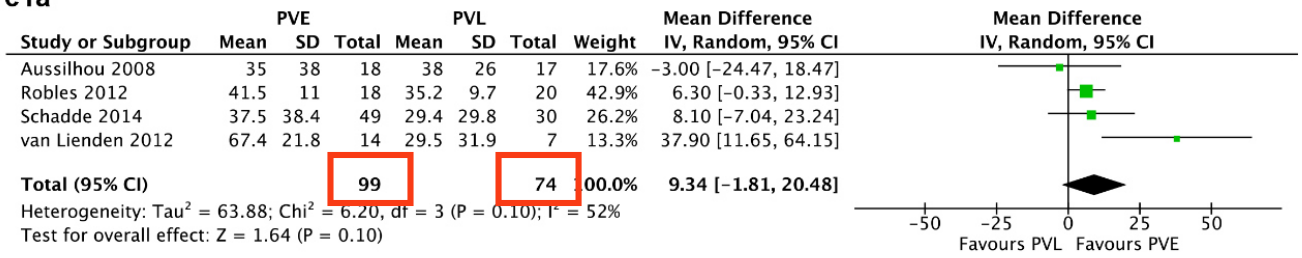


90 publications

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

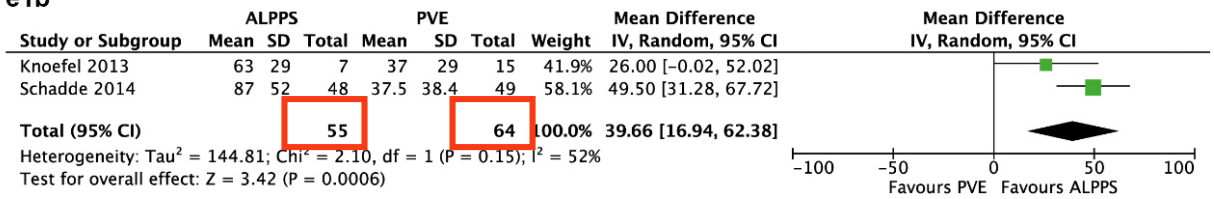
PVE vs PVL vs ALPSS
Speed of FLR hypertrophy before resection

e1a



PVE vs PVL : 46% vs 35% ***p=0.10***

e1b



ALPSS vs PVE: 76% vs 37% ***p<0.001***

Infusion of CD133⁺ Bone Marrow–Derived Stem Cells After Selective Portal Vein Embolization Enhances Functional Hepatic Reserves After Extended Right Hepatectomy

A Retrospective Single-Center Study

Jan Schulte am Esch, MD,* Moritz Schmelzle, MD,*† Günther Fürst, MD,† Simon C. Robson, MD,† Andreas Krieg, MD,* Constanze Dohme, MD,* Roy Y. Tustas, MD,* Andrea Alexander, MD,* Hans M. Klein, MD,§ Stefan A. Topp, MD,* Johannes G. Bode, MD,¶ Dieter Häussinger, MD,¶ Claus F Eisenberger, MD,* and Wolfram Trudo Knoefel, MD*

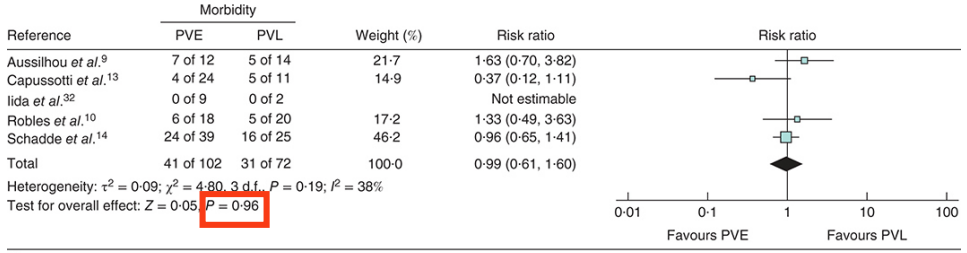
(*Ann Surg* 2012;255:79–85)

ALPSS vs PVL (only 1 study): 87% vs 29%
p<0.001

PVE vs PVL vs ALPSS

Forest plots comparing morbidity and mortality between strategies

Morbidity PVE vs PVL
p=0.96



a PVE *versus* PVL: morbidity after stage 2

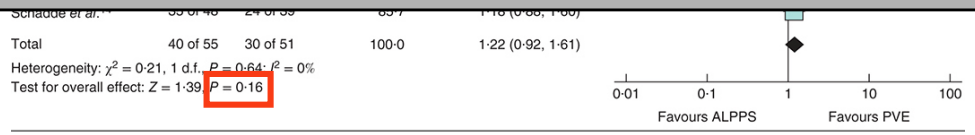
Infusion of CD133+ Bone Marrow–Derived Stem Cells After Selective Portal Vein Embolization Enhances Functional Hepatic Reserves After Extended Right Hepatectomy

A Retrospective Single-Center Study

Jan Schulte am Esch, MD, Moritz Schmelzle, MD,*† Günther Fürst, MD,‡ Simon C. Robson, MD,† Andreas Krieg, MD,* Constanze Duhme, MD,* Roy Y. Tustas, MD,* Andrea Alexander, MD,* Hans M. Klein, MD,§ Stefan A. Topp, MD,* Johannes G. Bode, MD,¶ Dieter Häussinger, MD,¶ Claus F. Eisenberger, MD,* and Wolfram Trudo Knoefel, MD**

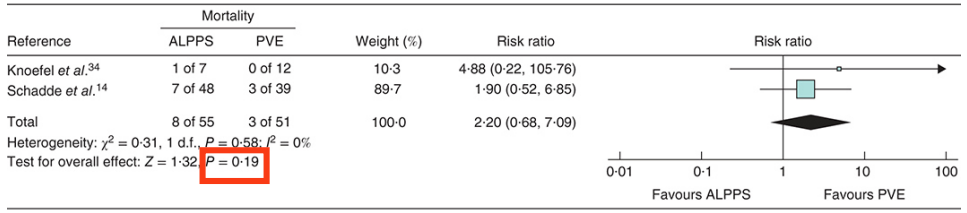
(*Ann Surg* 2012;255:79–85)

ALPSS vs PVL (only 1 study):
morbidity 73% vs 62%
mortality 15 vs 8%
p= ns



Morbidity ALPSS vs PVE
p=0.16

c ALPPS *versus* PVE: morbidity



Mortality ALPSS vs PVE
p=0.19

d ALPPS *versus* PVE: mortality

British Journal of Surgery
Volume 103, Issue 13, pages 1768-1782, 16 SEP 2016 DOI: 10.1002/bjs.10290
http://onlinelibrary.wiley.com/doi/10.1002/bjs.10290/full#bjs10290-fig-0002

Associating liver partition with PVL for staged hepatectomy
ALPSS

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**

Volume vs Function

ALPPS—Where Do We Stand, Where Do We Go?

Eight Recommendations From the First International Expert Meeting

Karl J. Oldhafer, MD, Gregor A. Stavrou, MD,* and Thomas M. van Gulik, MD†; on behalf of the Core Group*

(*Ann Surg* 2016;263:839–841)

February 2015 ALPSS Consensus Conference in Hamburg

Preliminary results from small series suggest that

1. FLR volumetric increase <u>PRECEDES</u> 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

<u>Shortening times is not the main factor to improve the post-operative outcomes</u>

Volume vs Function

Interstage Assessment of Remnant Liver Function in ALPPS Using Hepatobiliary Scintigraphy

Prediction of Posthepatectomy Liver Failure and Introduction of the HIBA Index

Victo

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ALP
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)% of

Key question:

Not HOW LARGE

BUT

HOW GOOD

the FLR function has to be to avoid PHLF?

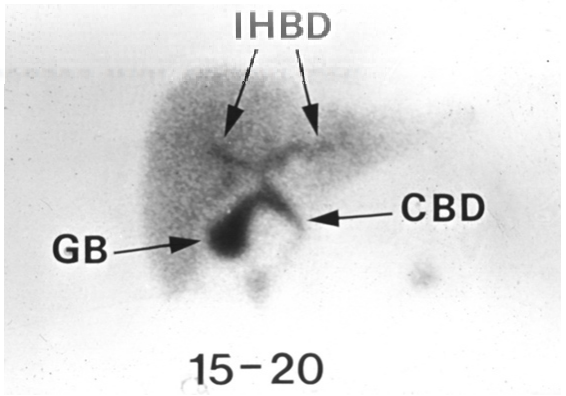
Need to evaluate liver function using Hepatobiliary Scintigraphy (HBS)

Hepatobiliary scintigraphy (HBS)

Clin Nucl Med. 1988 Oct;13(10):704-9.

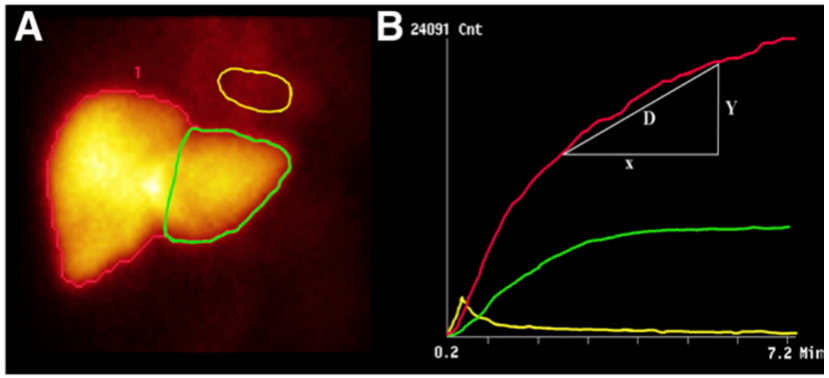
Scintigraphic criteria for the diagnosis of obstructive hepatobiliary diseases with Tc-99m IDA.

Krishnamurthy S[1], Krishnamurthy GT, Lieberman D, Keeffe EB.



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

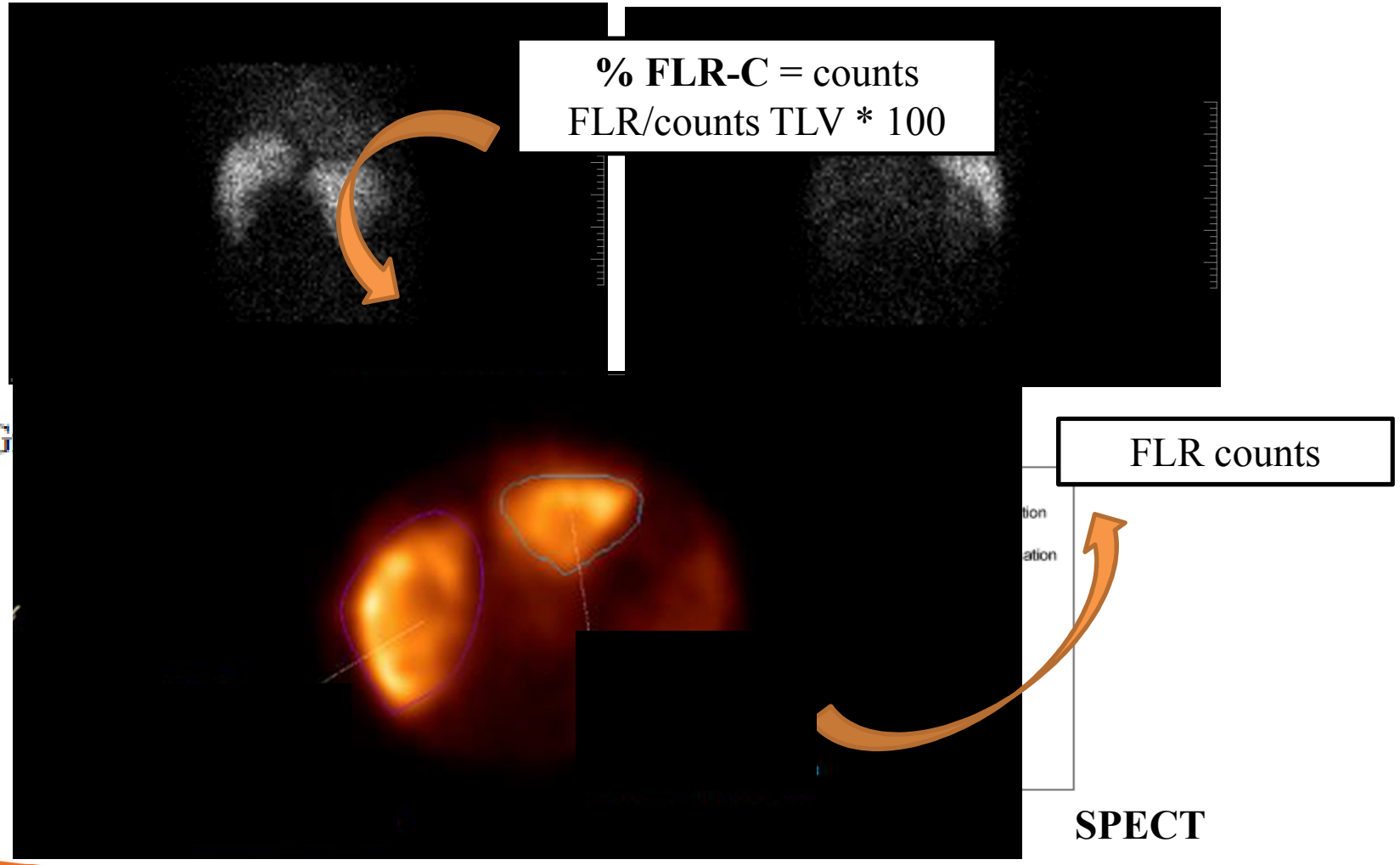
Fig. 1.4. Clinical SPECT(/CT) systems. (*Courtesy*: Philips and GE.)



Hepatobiliary scintigraphy (HBS) and SPECT

Anterior View

Posterior View



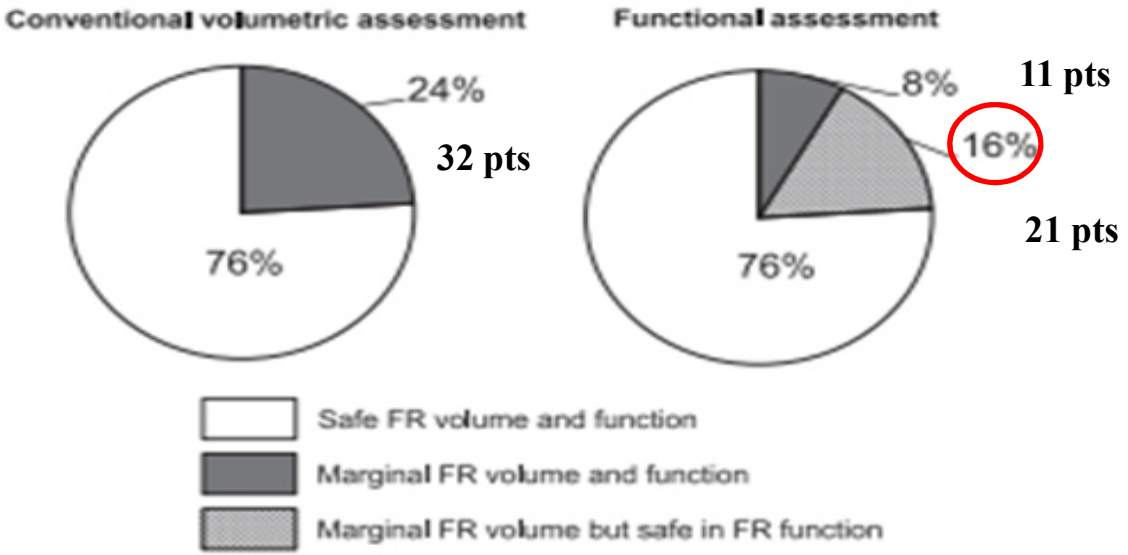
Volume vs Function

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

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

Surgery 2015

133 pts



Hepatobiliary scintigraphy (HBS)

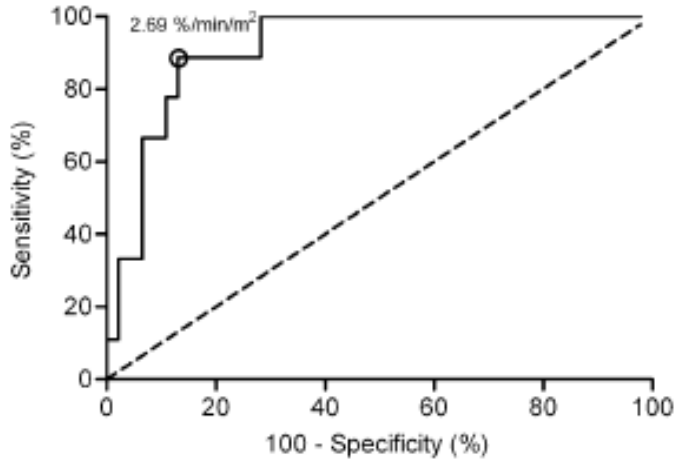
J Gastrointest Surg (2010) 14:369–378
DOI 10.1007/s11605-009-1085-2

ORIGINAL ARTICLE

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

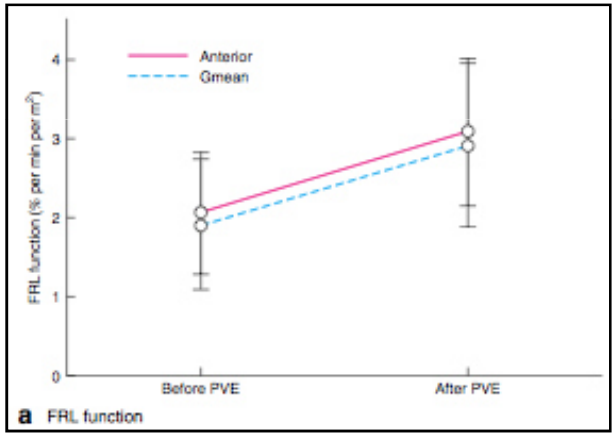
Original article

Increase in future remnant liver function after preoperative portal vein embolization

W. de Graaf[1], K. P. van Lienden[2], J. W. van den Esschert[1], R. J. Bennink[3] and T. M. van Gulik[1]

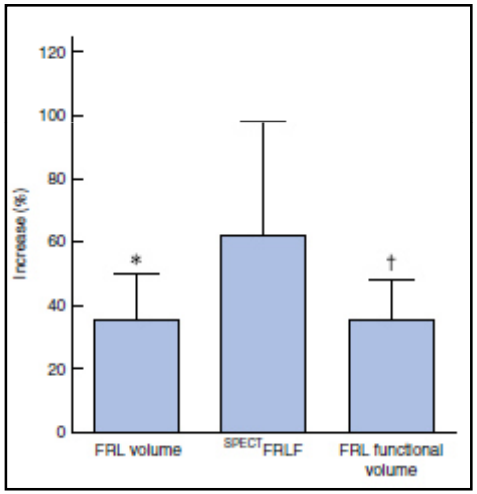
Departments of [1]Surgery, [2]Radiology and [3]Nuclear Medicine, Academic Medical Centre, Amsterdam, The Netherlands
Correspondence to: Dr T. M. van Gulik, Department of Surgery, Academic Medical Centre, IWO-1, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands
(e-mail: t.m.vangulik@amc.uva.nl)

British Journal of Surgery 2011; 98: 825–834



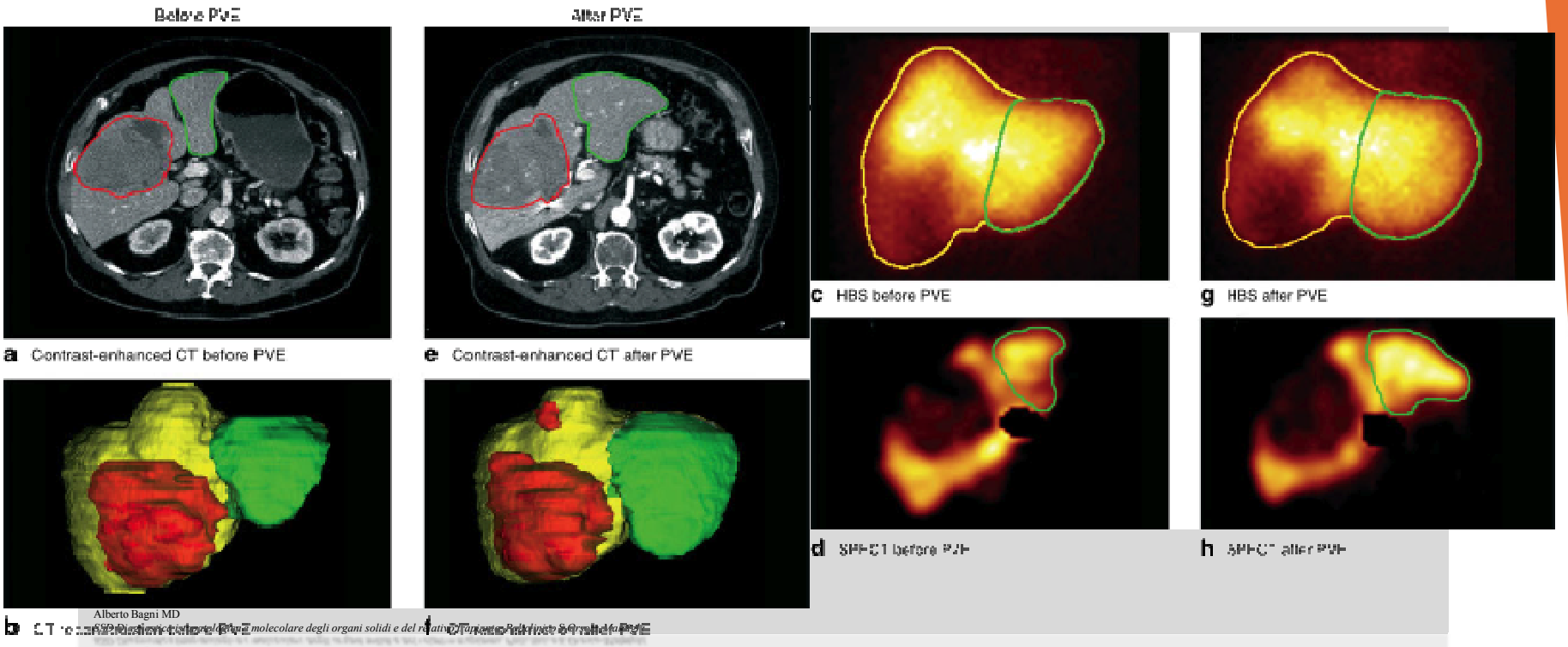
PVE in 24 pts

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

SPECT-HBS in Bologna



Alberto Bagni MD

Valutazione volumetrica e molecolare degli organi solidi e del relativo tumore addominale

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?

"Alice: "Per quanto tempo è per sempre?"

Bianconiglio: "A volte, solo un secondo"."

Lewis Carrol

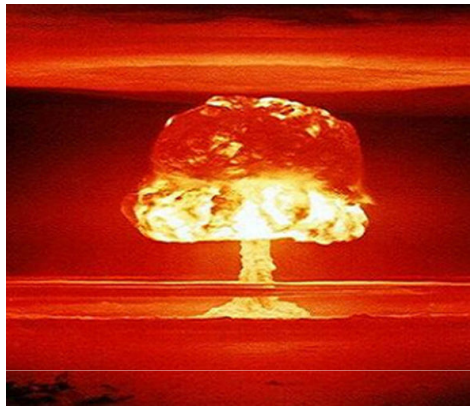
NOT

ISSUE

LOCAL TUMOR CONTROL then RESECT??????

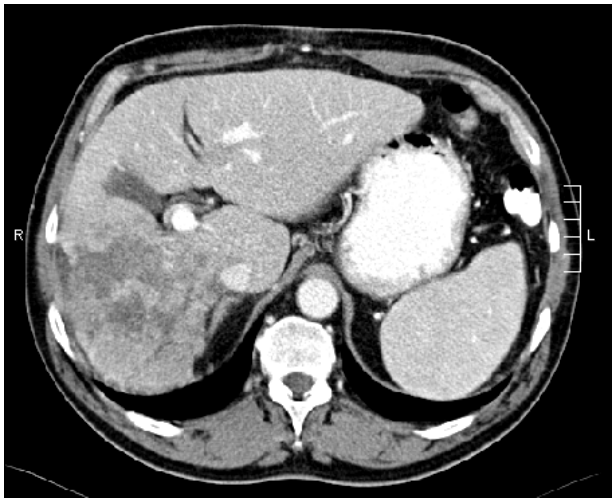
AIM:
Expanding the room for hepatic resection

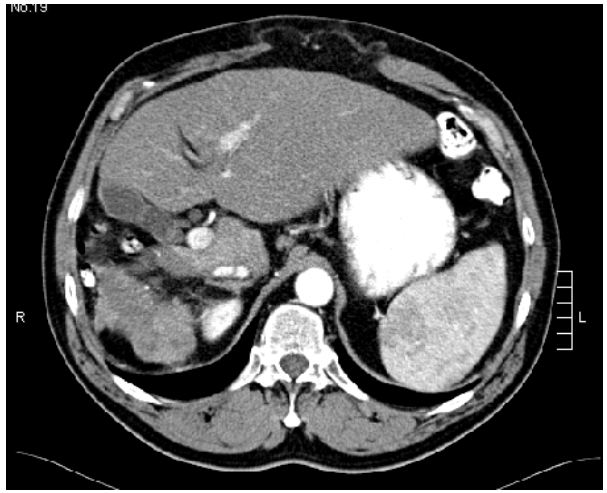
RATIONALE:
To induce a " side effect"



TOOLS

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





Radioembolization (TARE) as conversion therapy HCC

Given that TARE is effective….

clinical practice guidelines

Annals of Oncology 23 (Supplement 7): vii41–vii48, 2012
doi:10.1093/annonc/mds225

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

C. Verslype[1,2], O. Rosmorduc[3] & P. Rougier[4], on behalf of the ESMO Guidelines Working Group*

ESDO, European Society of Digestive Oncology

Departments of [1]Hepatology; [2]Digestive Oncology, University Hospitals Leuven, Leuven, Belgium; [3]Department of Gastroenterology and Hepatology, Saint-Antoine 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].
- TACE with selective administration with doxorubicin-eluting beads is recommended to minimize systemic side effects of chemotherapy [II, 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….

Annals of Oncology 27: 1386–1422, 2016
doi:10.1093/annonc/mdw235
Published online 5 July 2016

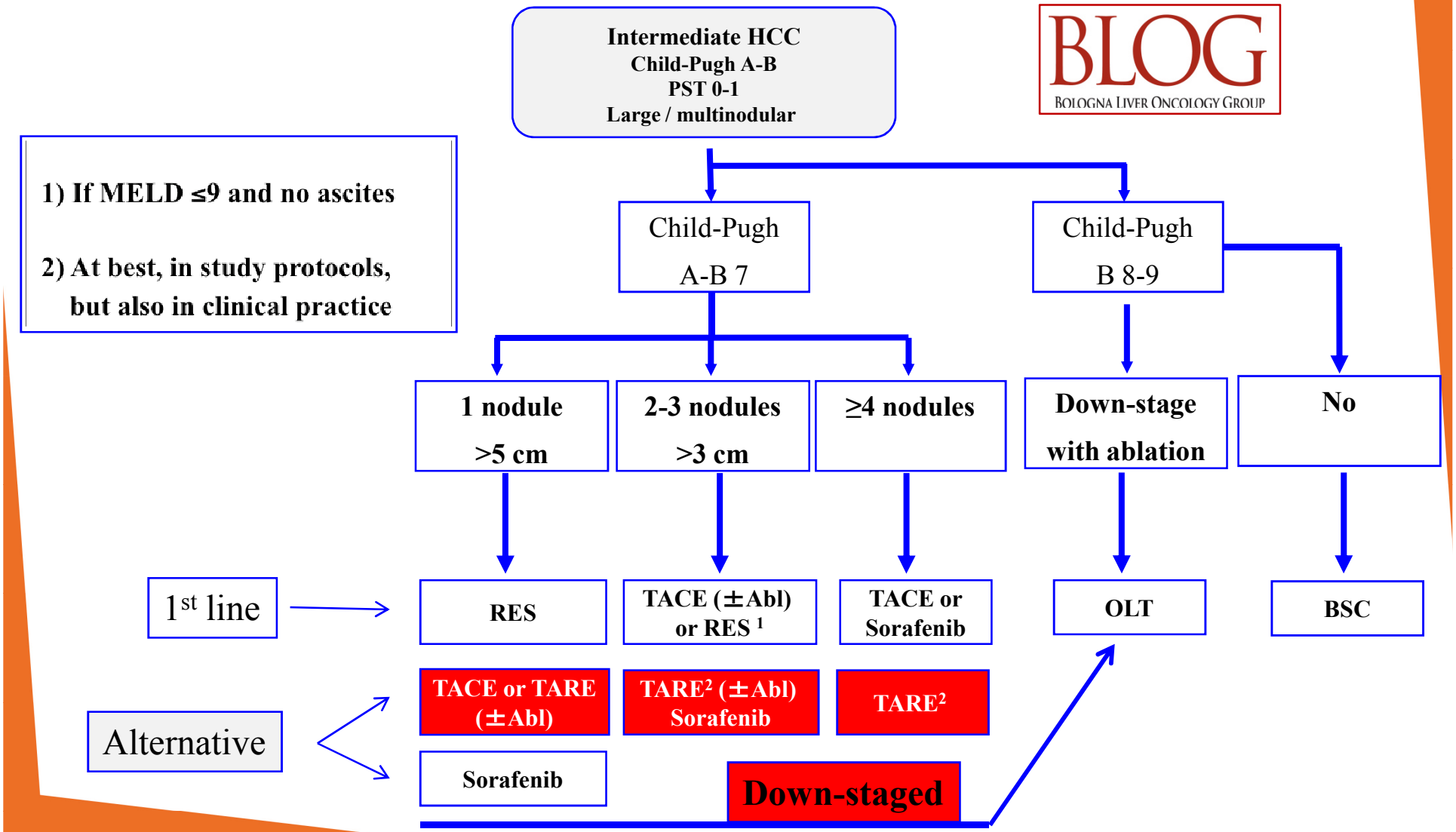
ESMO consensus guidelines for the management of patients with metastatic colorectal cancer

E. Van Cutsem[1*], A. Cervantes[2], R. Adam[3], A. Sobrero[4], J. H. Van Krieken[5], D. Aderka[6], E. Aranda Aguilar[7], A. Bardelli[8], A. Benson[9], G. Bodoky[10], F. Ciardiello[11], A. D'Hoore[12], E. Diaz-Rubio[13], J.-Y. Douillard[14], M. Ducreux[15], A. Falcone[16,17], A. Grothey[18], T. Gruenberger[19], K. Haustermans[20], V. Heinemann[21], P. Hoff[22], C.-H. Köhne[23], R. Labianca[24], P. Laurent-Puig[25], B. Ma[26], T. Maughan[27], K. Muro[28], N. Normanno[29], P. Österlund[30,31], W. J. G. Oyen[32], D. Papamichael[33], G. Pentheroudakis[34], P. Pfeiffer[35], T. J. Price[36], C. Punt[37], J. Ricke[38], A. Roth[39], R. Salazar[40], W. Scheithauer[41], H. J. Schmoll[42], J. Tabernero[43], J. Taïeb[25], S. Tejpar[1], H. Wasan[44], T. Yoshino[45], A. Zaanan[25] & D. Arnold[46]

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 be also 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….



Radioembolization (TARE) as conversion therapy

REVIEW ARTICLE
published: 30 July 2014
doi: 10.3389/fonc.2014.00199

Hepatic radioembolization as a bridge to liver surgery

Arthur J. A. T. Braat[1], Julia E. Huijbregts[1], I. Quintus Molenaar[2], Inne H. M. Borel Rinkes[2], Maurice A. A. J. van den Bosch[1] and Marnix G. E. H. Lam[1]*

[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.

Reference	Patients	Follow-up period	Volume measurement	Degree of hypertrophy contralateral lobe (%)	Degree of atrophy treated lobe (%)
Jakobs et al. (83)	32	139 days	CT/MRI	8.9	21.2
Gaba et al. (84)	20	3 months	CT/MRI	40	52
Ahmadzadehfar et al. (85)	24	44–66 days	MRI	57	6
Edeline et al. (86)	34	3 months	CT	29	23
Vouche et al. (87)	83	1 month	CT/MRI	7	2
		3–6 months		35	21
		>9 months		45	32
Garlipp et al. (88)[a]	35	46 days	MRI	29	NA
	141[†]	33 days[†]		61.5[†]	

NA, data not available.
[a] Only prospective study.
[†] RE vs. PVE, PVE results are marked.

Radioembolization (TARE) as conversion therapy

LIVER TRANSPLANTATION 21:1142–1152, 2015

ORIGINAL ARTICLE

Downstaging Hepatocellular Carcinoma: A Systematic Review and Pooled Analysis

Neehar D. Parikh,[1] Akbar K. Waljee,[1] and Amit G. Singal[2]

[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

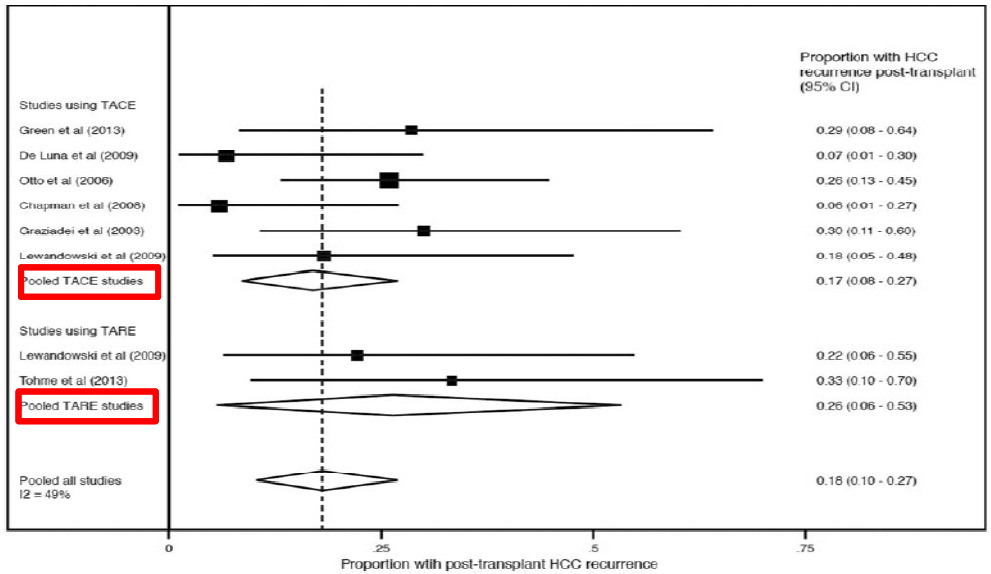


Figure 5. Pooled post-LT HCC recurrence stratified by treatment modality (TACE versus TARE).

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

Liver Cancer

Liver Cancer 2016;5:303–311

Review

Selective Internal Radiation Therapy

CCC
PR 25-82.3%

It can be hypotesized, 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 controindication

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50-75% necrosis to downstage pts

Table 1. Summary of literature reporting response rates of HCC/CCC after SIRT

Author (year)	Patients n°	SIRT modality	Tumor response criteria	Tumor Response rate	Median OS (mo)
Cholangiocarcinoma					
Soydal (2015) [11]	16	Resin	RECIST	PR: 30%	9.8
Filippi (2015) [12]	18	Resin	RECIST	PR: 82.3%	14.8
Camacho (20				PR: 4.7% PR: 62% PR: 9.5%	16.3
Rafi (2013) [				PR: 11%	11.5
Mouli (2013)				PR: 25%	14.6 (solitary) 5.7 (multifocal)
Hoffmann (2012) [16]	33	Resin	RECIST	PR: 36%	22
Haug (2011) [17]	26	Resin	RECIST	PR: 22%	11.7
Saxena (2010) [18]	25	Resin	RECIST	PR: 26%	9.3
Ibrahim (2008) [19]	24	Glass	WHO	PR: 27%	14.9
					7.7 (Child-Pugh B)
Kooby (2010) [25]	27	Resin	WHO/RECIST	PR: 11%	6
Carr (2010) [26]	99	Glass	WHO/RECIST	OR: 41% (CR 3%; PR 38%)	11.5
Lewandowski (2009) [27]	43	Glass	WHO/RECIST EASL	PR: 61% (CR 0%) OR: 86% (CR 47%; PR 39%)	35.7
Kulik (2008) [28]	108	Glass	WHO/RECIST EASL	PR: 42% RR: 70%	NR
Sangro (2006) [29]	24	Resin	WHO/RECIST	DC: 100% RR: 23.8%	7
Salem (2005) [30]	43	Glass	WHO/RECIST EASL	PR: 47% PR: 79%	24 (Okuda I) 13 (Okuda II)
Carr (2004) [31]	65	Glass	WHO/RECIST	PR: 38.4%	21 (Okuda I) 10 (Okuda II)

OS=overall survival; OR (PR+CR)=objective response; DC=disease control; RR=reduction rate; WHO=World Health Organization; mRECIST=modified RECIST; EASL=European Association for the Study of the Liver; PVTT=portal vein tumor thrombosis.

Liver Cancer

Review

Selective Internal Radiation Therapy (SIRT) as Conversion Therapy for Unresectable Primary Liver Malignancies

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Radioembolization (TARE) as conversion therapy

Increase in FLR 3 months: **21-32%**

Table 2. Summary of literature reporting volumetric changes

Author (year)	Patients n°	Tumor types	Area of Y90 treatment	Hypertrophy of non-treated liver
Bishay (Abstract; 2015) [32]	15	HCC: 33.3% CCC: 26.7% Other: 40%	Right lobe: 100%	Maximal increase of 30.7% at 6 months; 3-month: 29.1%.
Theysohn (2014) [33]	45	HCC: 100%	Right lobe: 100%	Maximal increase of 50.5% at 6 months; 3-month: 45.4%
Teo (2014) [34]	17	HCC: 100%	Right lobe: 100%	Mean FLR increase of 42.3% at a median of 5 months of follow-up
Fernández-Ros (2014) [35]	83	HCC: 62.7% CCC: 4.8% Other: 32.5%	Right hemi-liver: 72.3% Left hemi-liver: 16.9%	Maximal increase of 45.0% at 6.5 months; 3-month: 18.0%
Vouche (2013) [36]	83	HCC: 80.7% CCC: 9.6% Other: 9.7%	Right lobe: 100%	Maximal increase of 45% after 9 months from SIRT; 3-month: 24%

TARE results in both good local tumor control and an increase of the FLR

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 Irmscher,[3] Mark van Buskirk,[4] Patrick Stübs,[1] Frederic Deschamps,[2] Frank Meyer,[1] Ricarda Seidensticker,[3] Konrad Mohnike,[3] Maciej Pech,[3] Holger Amthauer,[3] Hans Lippert,[1] Jens Ricke,[3] and Max Seidensticker[3]

(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 3. Group Comparison: Absolute an

	RE		PVE		
Variable	Mean (median)	SD	Median (median)	SD	*P* Value
FLR baseline (mL)	368.7 (339)	142.2	381.7 (323)	166.0	0.763
FLR post treatment (mL)	470.6 (435)	203.6	589.5 (535)	221.9	
Change from baseline (mL)	101.9 (80)	106.5	207.9 (176)	114.7	<0.001
Change from baseline (%)	29 (25.3)	22.9	61.5 (50.6)	37.3	<0.001
P value (change from baseline within treatment, both mL and %)	<0.001		<0.001		

TARE vs PVE: mets

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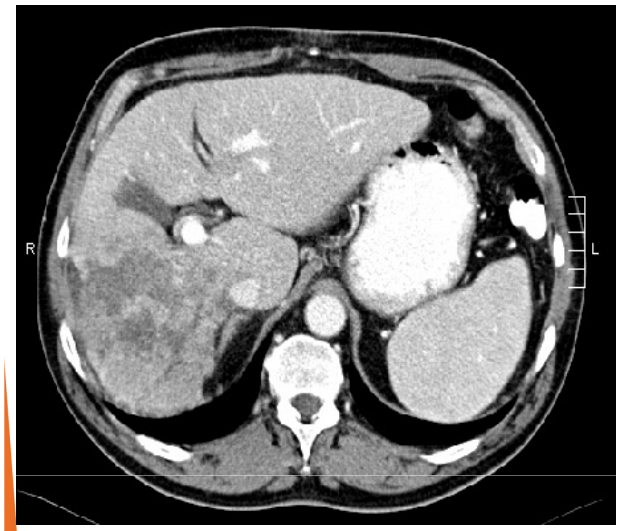
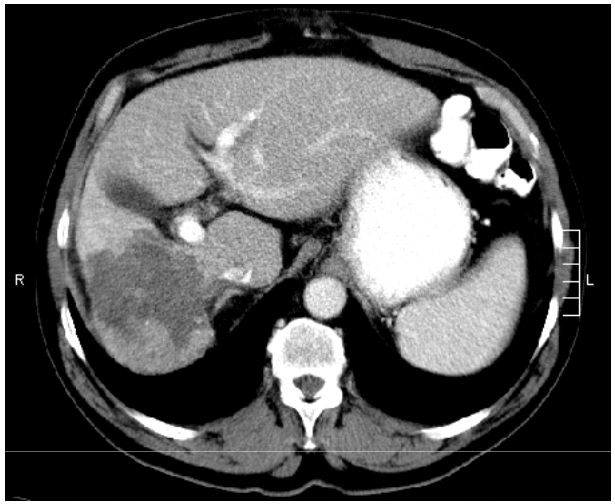
(HEPATOLOGY 2014;59:1864-1873)

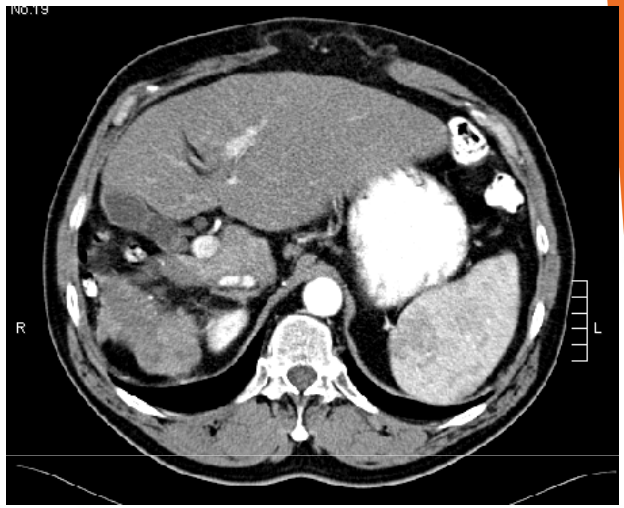
development. *Conclusion:* PVE induces significantly more contralateral hypertrophy than RE with therapeutic (nonlobectomy) doses. However, contralateral hypertrophy induced by RE is substantial and RE minimizes the risk of tumor progression in the treated lobe, possibly making it a suitable modality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

develop hypertrophy (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

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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

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

Julien Edeline, MD[1,2,3], Laurence Lenoir, MD[2,3,4], Karim Boudjema, MD, PhD[3,5], Yan Rolland, MD[2,6], Anne Boulic[7], Fanny Le Du[1], Marc Pracht, MD[1,2], Jean-Luc Raoul, MD, PhD[8], Bruno Clément, PhD[2], Etienne Garin, MD, PhD[2,3,4], and Eveline Boucher, MD[1]

TABLE 3 Maximal increase of contralateral volume in different subgroups of patients

Characteristic	Variable	Maximal increase, mean (95 % CI)	*p*
Overall ($n = 34$)		+42 % (+16 to +67 %)	
Portal vein thrombosis	No portal vein thrombosis ($n = 20$)	+51 % (+9 to +94 %)	0.50
	Any portal vein thrombosis ($n = 14$)	+28 % (+10 to +46 %)	
	Branch portal vein thrombosis ($n = 9$)	+28 % (−1 to +57 %)	
	Main portal vein thrombosis ($n = 5$)	+28 % (−3 to +59 %)	
Treatment site	Left hepatic artery ($n = 11$)	+21 % (+2 to +39 %)	0.20
	Right hepatic artery ($n = 23$)	+52 % (+15 to +89 %)	
Type of spheres	Glass microspheres ($n = 30$)	+43 % (+14 to +72 %)	0.81
	Resin microspheres ($n = 4$)	+32 % (−23 to +87 %)	
Patients with biopsy-proven cirrhosis ($n = 18$)		+62 % (+14 to +109 %)	
Child-Pugh score	A5 ($n = 25$)	+50 % (+16 to +85 %)	0.12
	A6 ($n = 7$)	+23 % (−2 to +47 %)	
	B7 ($n = 2$)	−1 % (−83 to +75 %)	
Portal hypertension	Yes ($n = 19$)	+ 20 % (+11 to +30 %)	0.10
	No ($n = 15$)	+69 % (+12 to +126 %)	

CI 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***

Opera di Mario Lupo (1986).
Monumento al Gabbiano Jonathan Livingston, protagonista del libro di Richard Bach (Molo Sud SBT)

...."guardare l'orizzonte da un altro punto di vista eleva la conoscenza".....

Thank you for the attention

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