



Synchronous liver metastases
Oncosurgical Strategy

How to resect the unresectable?

Epidemiology

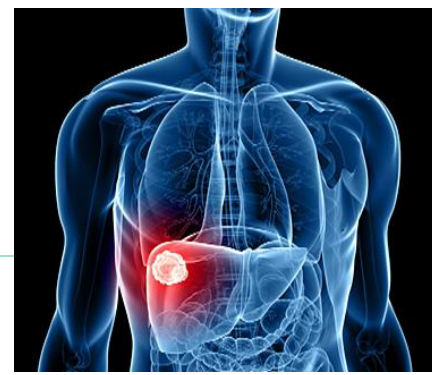


Portugal

- 7129 new cases of Colorectal Cancer *
- 1/3 are rectal cancers
- 3797 mortality cases*

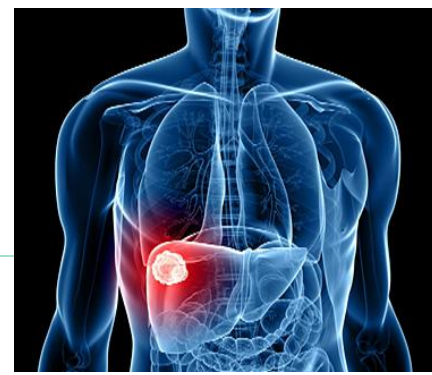


Epidemiology



- ✓ 25% of patients have metastatic disease at presentation
- ✓ 30% develop metastases during the course of their disease
- ✓ The liver is the most common site of metastatic disease,
 - Involved in 80 % of cases
 - Liver-only mets (40 %)

Median survival – hepatic metastases



Untreated – survival 6 and 12 months

Systemic chemotherapy - median survival of 2-year

Resected R0 - 5 year survival ranges between 27% to 74%
- 10 Y survival 9- 50%




Results of hepatic resection for mets CCR

	n	Survival at 5 Years %	median survival , M
Hughes, KS; 1986	607	33	NR
Scheele, J; 1995	434	33	40
Nordlinger, B; 1996	1568	28	NR
Jamison, RL; 1997	280	27	33
Fong, Y; 1999	1001	37	42
Iwatsuki, S; 1999	305	32	NR
Choti, M; 2002	133	58	NR
Abdalla, E; 2004	190	58	NR
Fernandez, FG; 2004	100	58	NR
Wei, AC; 2006	423	47	NR
Aloia TA; 2006	150	71	
Rees, M; 2008	929	36	42.5
de Jong, M; 2009	1669	47	36
Morris, EJ; 2010	3116	44	NR

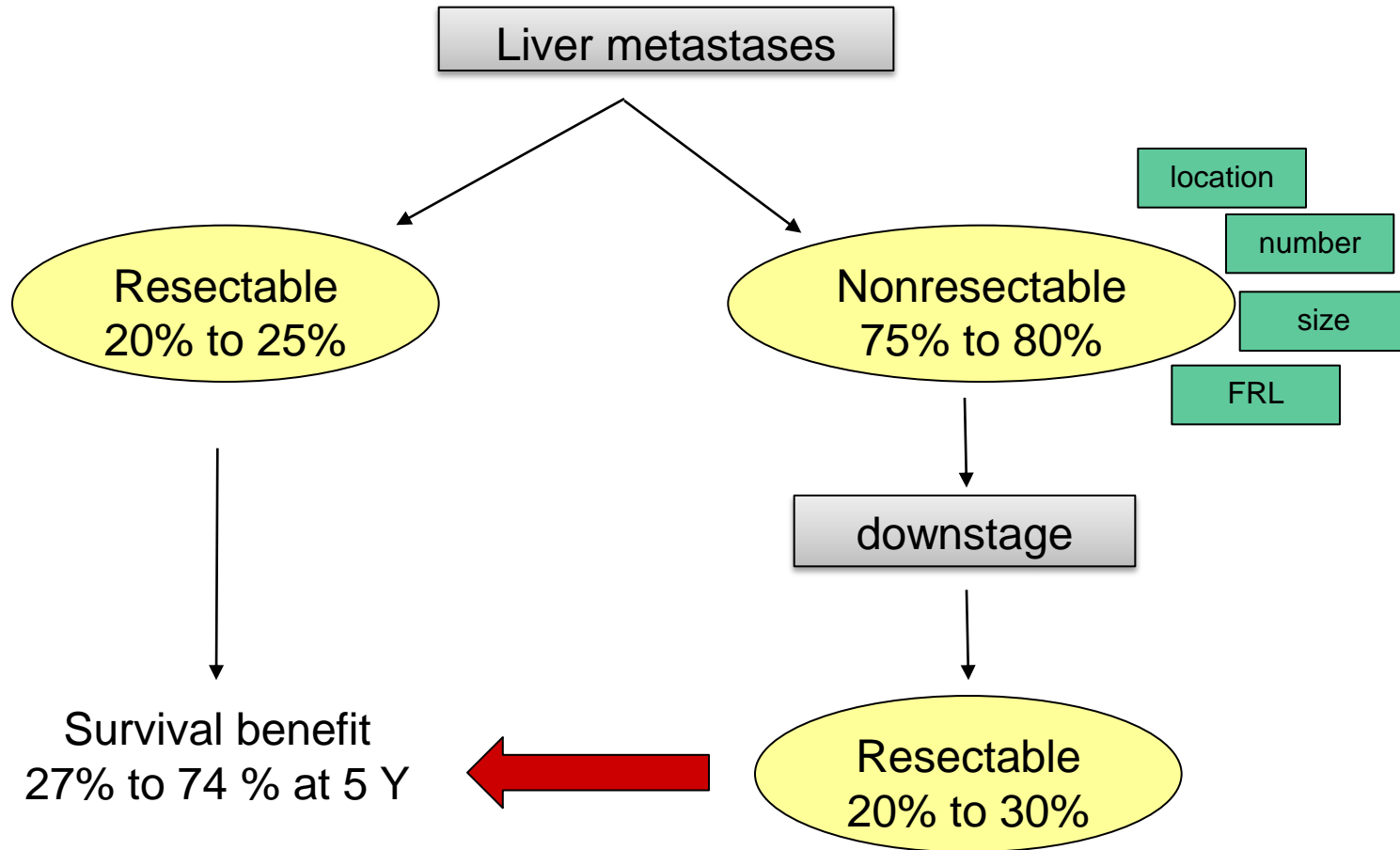
Resected R0 - 5 year survival ranges between 27% to 74%
- 10 Y survival 9- 50%

Resection is the only chance of long-term survival / cure



-
- ✓ Only a minority of patients are suitable for upfront surgery 20% – 25%
 - ✓ When patients with unresectable disease are **downstaged to complete resection**, long-term data support 5 and 10-year survival are similar to upfront resectable patients
-
- 

Liver metastases in colorectal cancer



Liver metastases in colorectal cancer

How to resect the unresectable?



“Resectable”

1. Appropriate medical candidate for surgery

Patient

2. The metastatic liver tumor can be completely resected.

Tumor

3. Sufficient future remnant liver

Liver



Patient selection and Preoperative assessment

- ✓ **CT** - scan of the abdomen and chest
- ✓ **MRI** - if small lesions, a fatty liver or preop CT
- ✓ **PET** - in case of tumor recurrence
 - in patients with a previous liver resection
 - suspected distant metastasis.

Tumor evaluation

- ✓ Child Pugh,
- ✓ ICGRI5

liver function evaluation



Two management strategies (to improve resectability.)

Tumor

- **Shrink tumors**

- ✓ Conversion chemotherapy,
- ✓ Hepatic Arterial Infusion Pump Therapy

Liver

- **Optimize the FLR**

- ✓ parenchymal-sparing liver surgery
- ✓ PVE
- ✓ two-stage hepatectomy
- ✓ (ALPPS)
- ✓ local ablation techniques



Strategies to Shrink Tumor Burden

- ✓ Systemic Chemotherapy
- ✓ Hepatic Arterial Infusion Pump Therapy



Systemic Chemotherapy

- In the 5-FU era - **response rates** approximately 20 %

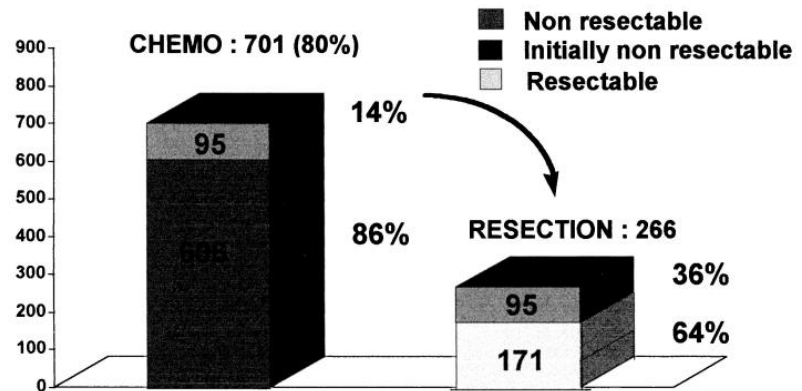
- Modern chemotherapeutic agents
(Oxaliplatin, Irinotecan ... and new regimens FOLFOX, FOLFIRI ...)
 - tumor response rates of >50%
 - 6-month stable disease 90–95 %
 - long **median survival** (30 months).



Five-Year Survival Following Hepatic Resection After Neoadjuvant Therapy for Nonresectable Colorectal [Liver] Metastases

R. Adam, MD, PhD, E. Avisar, MD, A. Ariche, MD, S. Giachetti, MD, D. Azoulay, MD, PhD, D. Castaing, MD, F. Kunstlinger, MD, F. Levi, MD, and F. Bismuth, MD

- N= 872
- 701 patients with unresectable CRLM (80%)
- FOLFOX
- 14 % resectable

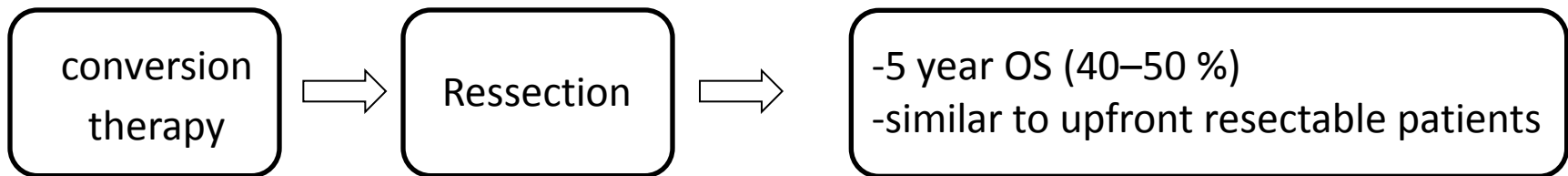


5-year survival 39 %

Tumor response rate -patients with unresectable CRLM

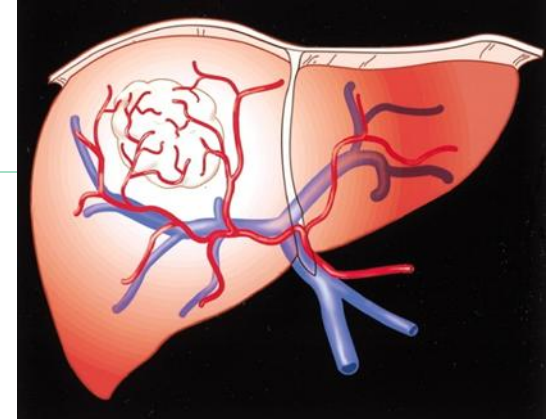
Study	Year	No. of patients	Regimen	Response rate (%)	Conversion rate (%)	Overall R0 resection rate (%)
Tournigand et al. [9]	2004	109	FOLFIRI → FOLFOX	56	9	7.3
			FOLFOX → FOLFIRI	54	22	12.5
Hurwitz et al. [10]	2004	813	Irinotecan + bolus 5-FU	35	<2	?
			Irinotecan + bolus 5-FU + bevacizumab	45	<2	?
Ho et al. [11]	2005	40	FOLFIRI	55	10	?
Alberts et al. [12]	2005	42	FOLFOX	60	40	33
Masi et al. [13]	2006	74	FOLFOXIRI	26 (19 patients)		26
Barone et al. [14]	2007	40	FOLFIRI	48	33	?
Ychou [15]	2008	34	FOLFOXIRI	71	82	27
Masi et al. [16]	2009	196	FOLFOXIRI	21 (42 patients)		18.8
Saltz et al. [17]	2008	1,401	FOLFOX + bevacizumab	47	8.4	?
			Capecitabine + oxaliplatin + bevacizumab	49	6.1	?
Folprecht et al. [18]	2010	67	FOLFOX + cetuximab	70	60	38
			FOLFIRI + cetuximab	70	60	30
Bokemeyer et al. [19]	2009	134	FOLFOX	34	3	?
			FOLFOX + cetuximab	57	12	?
Masi et al. [20]	2010	57	FOLFOXIRI + bevacizumab	77	26	26
Douillard et al. [21]	2010	656	FOLFOX	48	9.4	7.0
			FOLFOX + panitumumab	55	10.5	8.3
Kopetz et al. [22]	2010	43	FOLFIRI + bevacizumab	65	9	
Peeters et al. [23]	2010	1,186	FOLFIRI + panitumumab	35		
			FOLFIRI	10		
Van Cutsem et al. [24]	2011	666	FOLFIRI	40	4.6	2.0
			FOLFIRI + cetuximab	57	5.7	5.1
Ye et al. [25]	2013	138	FOLFIRI/FOLFOX	29.4	13.2	7.4
			FOLFIRI/FOLFOX + cetuximab	57.1	28.6	25.7
Leone et al. [26]	2013	49	Oxaliplatin + capecitabine + panitumumab	54	30.6	10

-
- Modern preop CT allows complete resection in 12-35% of patients
 - A strong correlation between the **response rates and the resection rates** of patients with initially unresectable CLRM



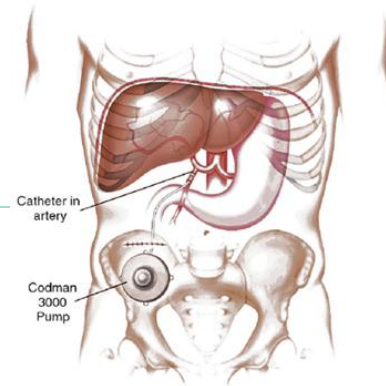
Hepatic Arterial Infusion Pump Therapy

The concept



- Liver mets larger than 3 mm over 80% of their blood irrigation is by hepatic artery
- Normal hepatocytes derive their blood supply from the PV (75%)
- The tip of the catheter is positioned at the gastroduodenal-hepatic artery junction

Hepatic Arterial Infusion Pump Therapy



- This directed therapy allows an increased amount of cytotoxic drugs without increasing the systemic side effects
- HAIP increased the possibility of tumor response and might improve liver function
- This therapy can be used in combination with systemic chemotherapy





Hepatic arterial infusion pump chemotherapy in the management of colorectal liver metastases: expert consensus statement

P.J. Karanicolas MD, P. Metrakos MD,† K. Chan MD,* T. Asmis MD,* E. Chen MD,* T.P. Kingham MD,‡ N. Kemeny MD,‡ G. Porter MD,§ R.C. Fields MD,|| J. Pingpank MD,# E. Dixon MD,** A. Wei MD,* S. Cleary MD,* G. Zogopoulos MD,† C. Dey MD,* M. D'Angelica MD,‡ Y. Fong MD,‡ S. Dowden MD,** and Y.J. Ko MD**

TABLE 1 Summary of consensus statements

HAIPI chemotherapy should be given in combination with systemic chemotherapy.

HAIPI chemotherapy should be offered in the context of a multidisciplinary program that includes expertise in hepatobiliary surgery, medical oncology, interventional radiology, nursing, and nuclear medicine.

HAIPI chemotherapy in combination with systemic therapy should be considered in patients with unresectable colorectal liver metastases who have progressed on first-line systemic treatment. In addition, HAIPI chemotherapy is acceptable as first-line treatment in patients with unresectable colorectal liver metastases.

HAIPI chemotherapy is not recommended in the setting of extrahepatic disease outside the context of a clinical trial.

HAIPI chemotherapy in combination with systemic therapy is an option for select patients with resected colorectal liver metastases.



Phase II trial of hepatic artery infusional and systemic chemotherapy for patients with unresectable hepatic metastases from colorectal cancer: Conversion to resection and long-term outcomes

Michael I. D'Angelica, MD¹, Camilo Correa-Gallego, MD¹, Philip B. Paty, MD¹, Andrea Cercek, MD², Alexandra N. Gewirtz, BA², Joanne F. Chou, MPH³, Marinella Capanu, PhD³, T. Peter Kingham, MD¹, Yuman Fong, MD¹, Ronald P. DeMatteo, MD¹, Peter J. Allen, MD¹, William R. Jarnagin, MD¹, and Nancy Kemeny, MD.²

¹Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY

- 49 patients with unresectable CRLM
- combined HAIP and systemic CT including bevacizumab
- **47% achieved conversion to resection** at a median of 6 months from treatment initiation
- 3-year OS – resected patients 80% / not resection 26%

Two management strategies (to improve resectability.)

Tumor

- Shrink tumors

- ✓ Conversion chemotherapy,
- ✓ Hepatic Arterial Infusion Pump Therapy

Liver

- Optimize the FLR


- ✓ parenchymal-sparing liver surgery
- ✓ PVE
- ✓ two-stage hepatectomy
- ✓ (ALPPS)
- ✓ local ablation techniques



Strategies to optimize FRL

The objective

Resection of all detectable lesions with tumor-free margins

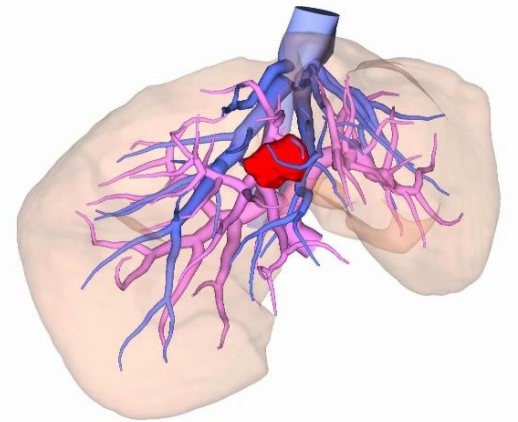
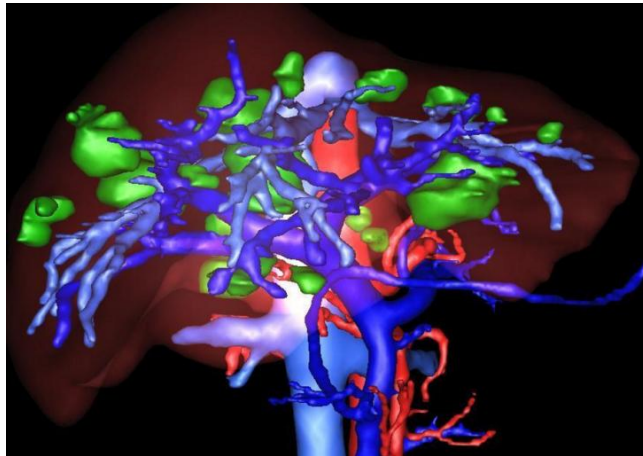
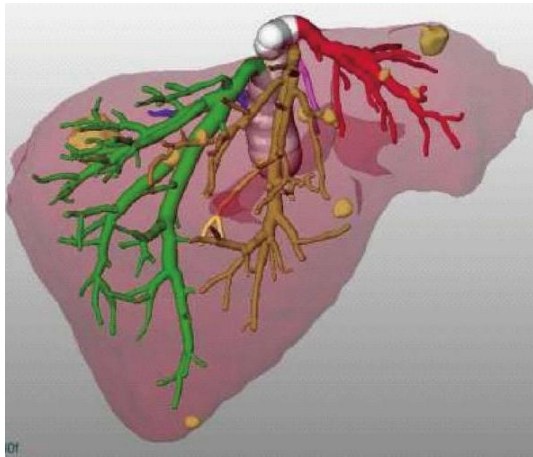
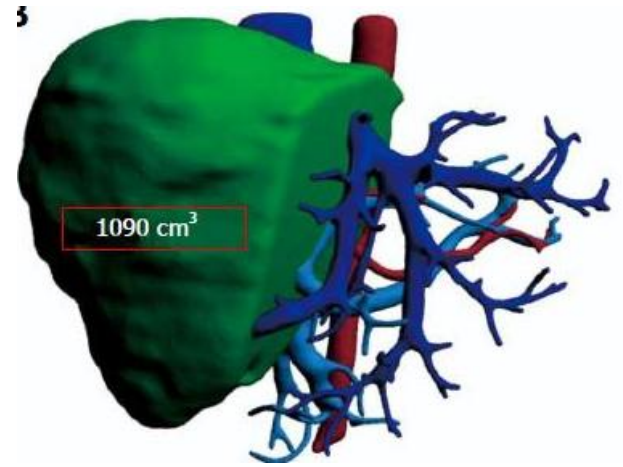
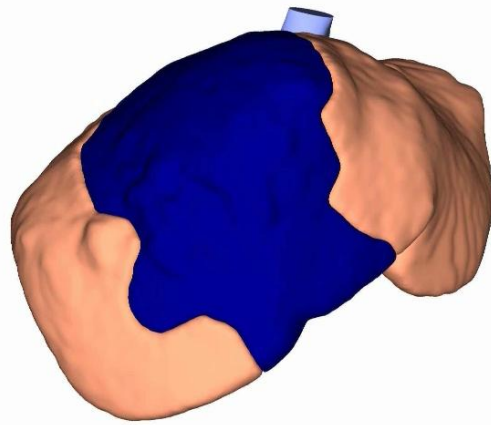
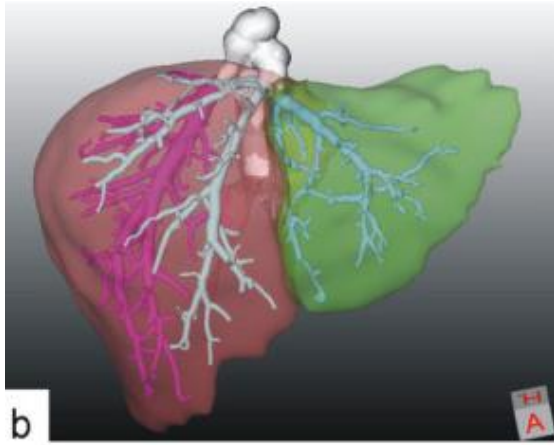
- ✓ parenchymal-sparing liver surgery
 - ✓ PVE
 - ✓ two-stage hepatectomy
 - ✓ (ALPPS)
 - ✓ local ablation techniques
-
- 

Preoperative Planning and Volumetric Assessment

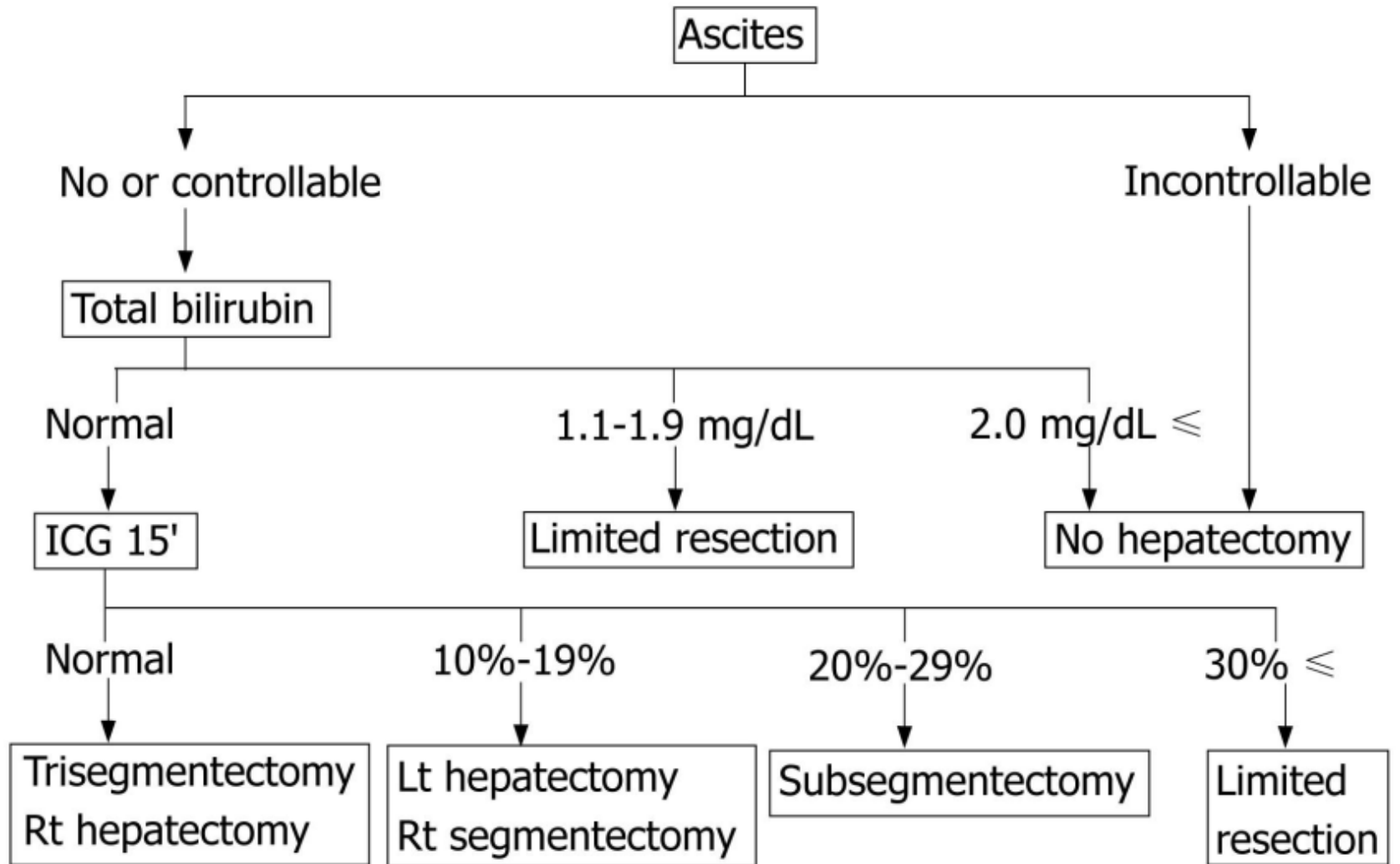
To achieve a safe hepatic resection with an adequate FLR

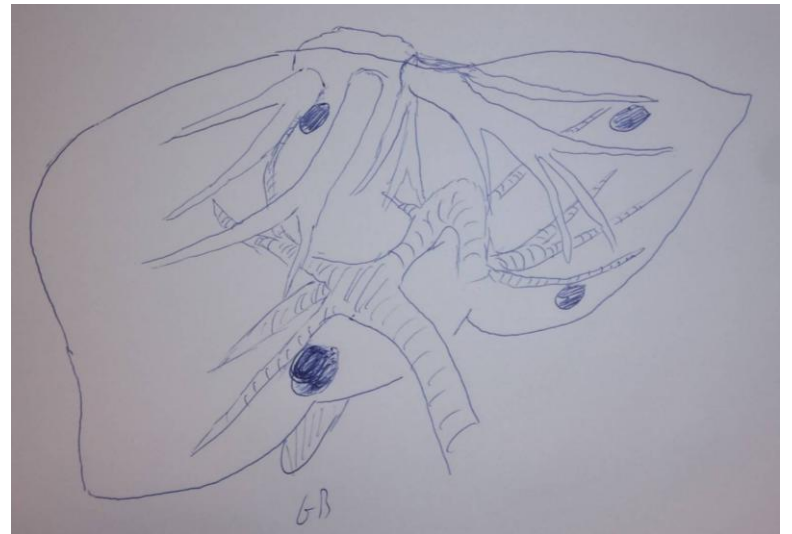
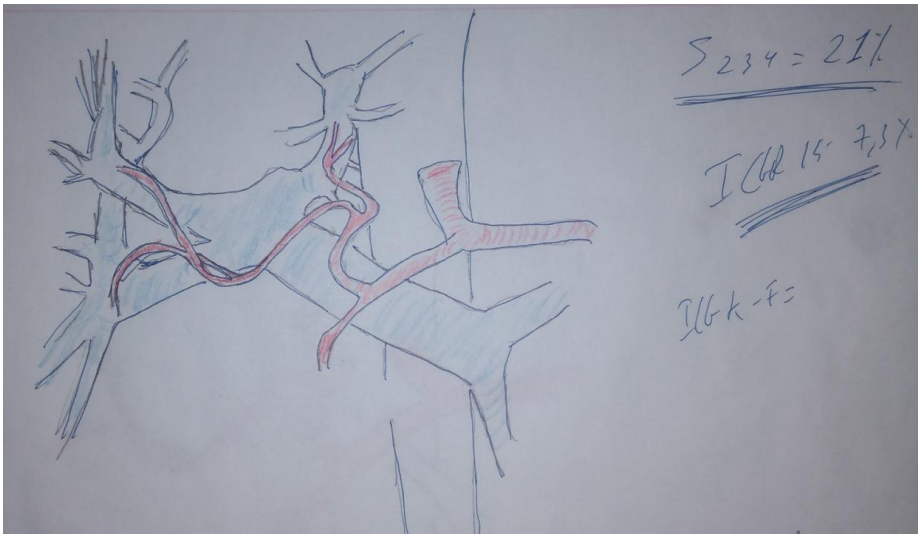
- Evaluation of the underlying parenchymal status and **function**
- Evaluation of liver **tumors** (the proximity to critical structures)
- Evaluation of liver **volumes** (FRL)





Makuuchi's criteria





A	B	C	D	E	F	G	H	I	J	K	L	M	N
28		3995	17977,5		494	2223		2330	10485				
31		7426	33417		2184	9828		4615	20767,5				
34		11281	50764,5		3825	17212,5		6698	30141				
37		14528	65376		4963	22333,5		8450	38025				
40		17086	76887		6152	27684		9997	44986,5				
43		19362	87129		5989	26950,5		10632	47844				
46		21007	94531,5		6152	27684		11503	51763,5				
49		21546	96957		5564	25038		10341	46534,5				
52		22328	133968		5926	26667		9977	59862				
56		22893	103018,5		5756	25902		9407	42331,5				
59		22185	99832,5		5688	25596		8773	39478,5				
62		21914	98613		5116	30696		8758	39411				
65		21002	94509		5052	22734		7934	35703				
68		20099	90445,5		5153	23188,5		7939	35725,5				
71		18532	83394		4864	21888		8179	36805,5				
74		16561	74524,5		4444	19998		7863	35383,5				
77		14401	64804,5		3876	17442		7325	32962,5				
80		12627	56821,5		3944	17748		6466	29097				
83		11401	51304,5		3615	16267,5		6654	29943				
86		9006	40527		3057	13756,5		5012	22554				
89		7404	33318		2687	12091,5		4070	18315				
92		5832	26244		1982	8919		3165	14242,5				
95		4652	20934		1439	6475,5		2200	9900				
98		3688	16596		1073	4828,5		1524	6858				
101		2358	10611		803	3613,5		910	4095				
104		1481	6664,5		399	1795,5		399	1795,5				
107		762	3429		108	486		108	486				
110		456	2052										
113		200	900										
116		108	486										
											total		
											0		
									Total				
			Volume total						785496				
			1640163			459046,5							
			S 234						47,89133:				

Volume total = 1,533
volume 234 = 33,4%
Volume 23 = 18,9%

Parenchymal-sparing liver surgery

(One-Stage Ultrasonically Guided Liver Resection)

- A profound knowledge of liver patient's anatomy
- Expert IOUS skills

- This technique allow **radical but conservative** liver resections
- Avoiding the unnecessary sacrifice of functional parenchyma
- Reducing the risk of developing **postoperative liver failure**
- Avoiding the necessity of **PVE / two stage hepatectomy**

with equal or better perioperative and long-term outcomes than non-PSLS

Impact of the Degree of Liver Resection on Survival for Patients with Multiple Liver Metastases from Colorectal Cancer

Kuniya Tanaka · Hiroshi Shimada · Chizuru Matsumoto · Kenichi Matsuo · Kazuhisa Takada · Yasuhiko Nagano · Shinji Tago



ELSEVIER

The American Journal of Surgery 181 (2001) 153–159
Scientific papers

The American
Journal of Surgery

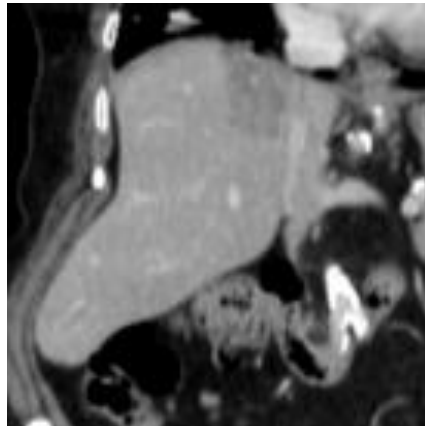
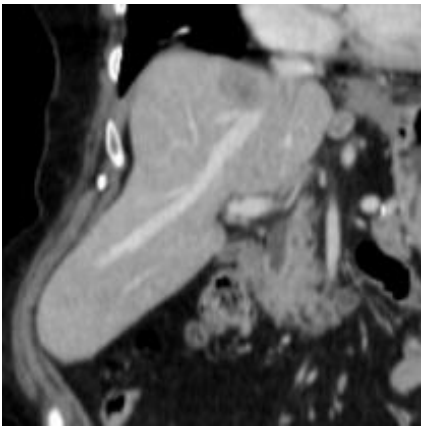
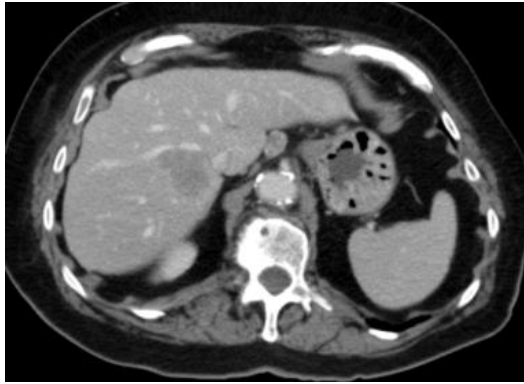
Anatomical major resection versus nonanatomical limited resection for liver metastases from colorectal carcinoma

Norihiro Kokudo, M.D.*, Keiichiro Tada, M.D., Makoto Seki, M.D., Hirotohi Ohta, M.D.,
Kaoru Azekura, M.D., Masashi Ueno, M.D., Toshiki Matsubara, M.D.,
Takashi Takahashi, M.D., Toshifusa Nakajima, M.D., Tetsuichiro Muto, M.D.

□ “Prophylactic” large resections were useless in preventing intra or extra-hepatic recurrence

- increased patient risk
- less chances of future repeated resection
- poorer prognosis after major resection than after multiple minor resections

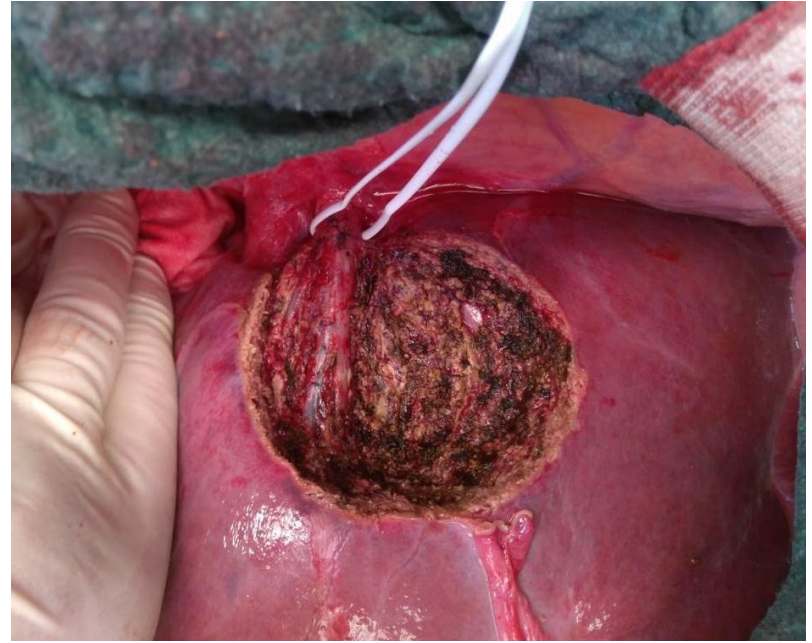
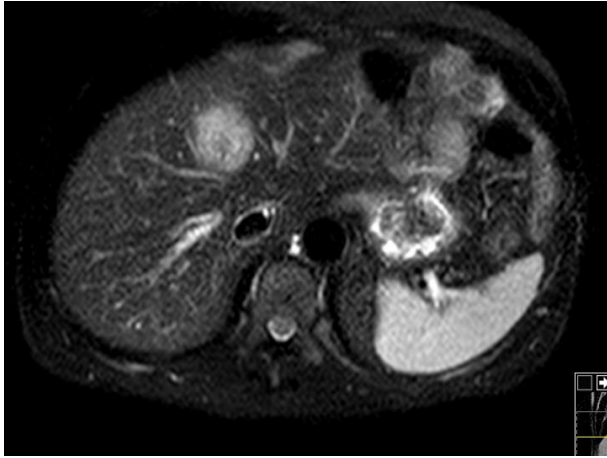
S7 resection



S7
partial resection of RHV
reconstruction by running suture



S4a



PVE (portal vein embolization)

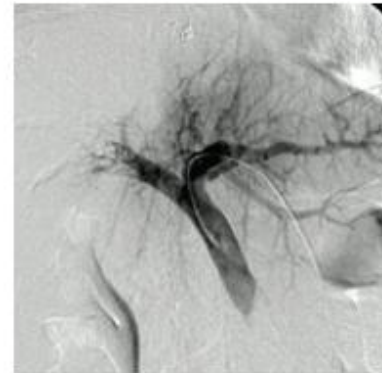


- ❑ Introduced in the 1980s by Makuuchi
- ❑ Tumor is technically resectable but the **FRL is too small**
- ❑ Is embolized the PV supplying the portion of liver to be resected
- ❑ Induce ipsilateral atrophy and contralateral compensatory hypertrophy of the FRL up to 40% over a median period of approximately 4 weeks*

PVE



Surgery



- ✓ Surgery 2 to 6 weeks after PVE

- ✓ Resectability 60% to 82%
 - progression of hepatic or extrahepatic disease

 - Insufficient hypertrophy 9%



Impact of portal vein embolization on long-term survival of patients with primarily unresectable colorectal liver metastases

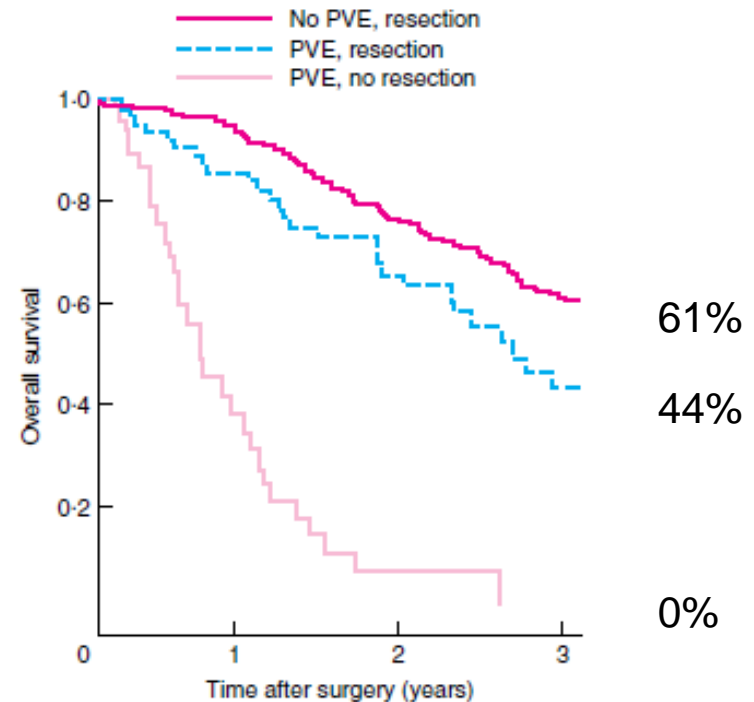
D. A. Wicherts^{1,4}, R. J. de Haas^{1,4}, P. Andreani¹, D. Sotirov¹, C. Salloum¹, D. Castaing^{1,2,3}, R. Adam^{1,2,3} and D. Azoulay¹

¹Centre Hépatobiliaire, Assistance Publique-Hôpitaux de Paris, Hôpital Paul Brousse, ²Institut National de la Santé et de la Recherche Médicale, Unité 785, and ³Université Paris-Sud, Unité Mixte de Recherche-S 785, Villejuif, France, and ⁴Department of Surgery, University Medical Centre Utrecht, Utrecht, The Netherlands

n = 364 hepatectomias major

PVE = 67 (18%)

Morbilidade: 41 % não PVE / 55% PVE



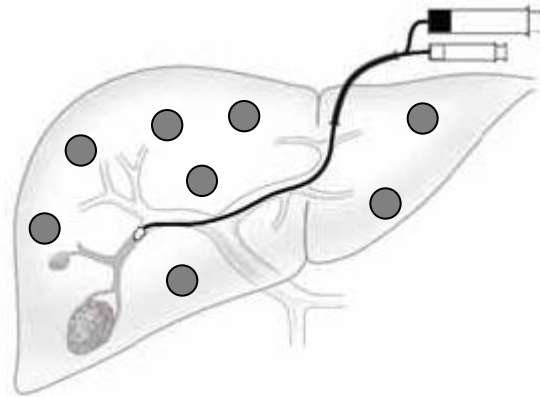
PVE



PVE in bilobar disease

PVE may increase tumor growth rate

Kokudo N et al, Hepatology, 2001;34:267-72.

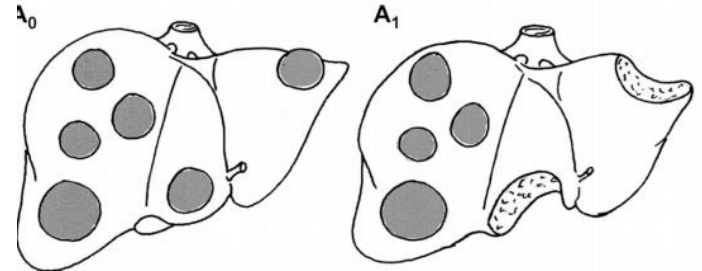


Two stage hepatectomy



Two stage hepatectomy

In patients with bilobar, multinodular tumor

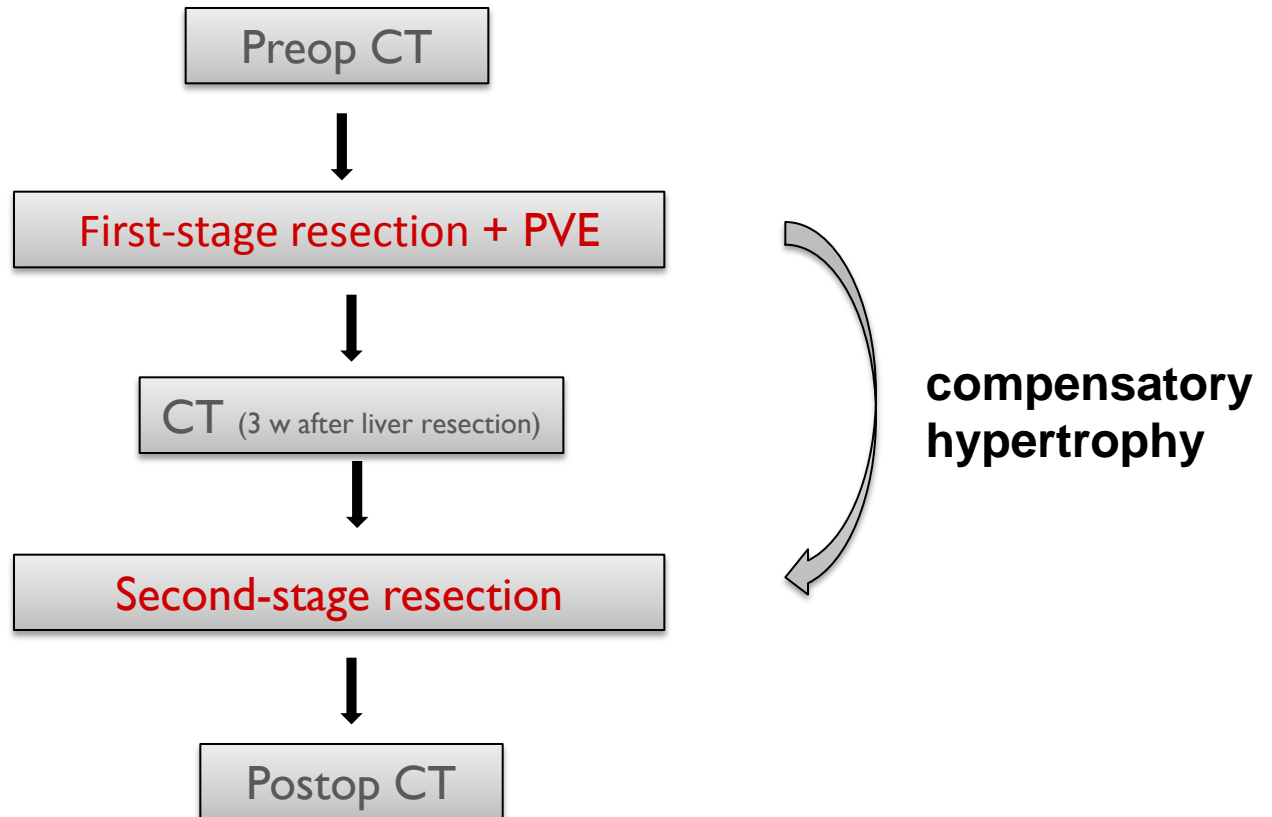


- **the first stage** - clearing the FLR
- PVE to increase the volume of the tumor-free FLR.
- **second stage** - resection of the remaining disease

The second stage resection is completed in 69-77% of patients **

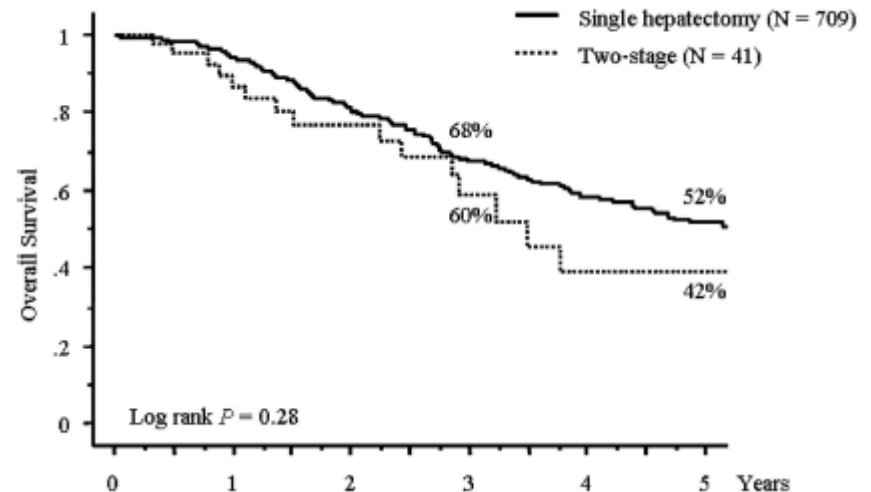
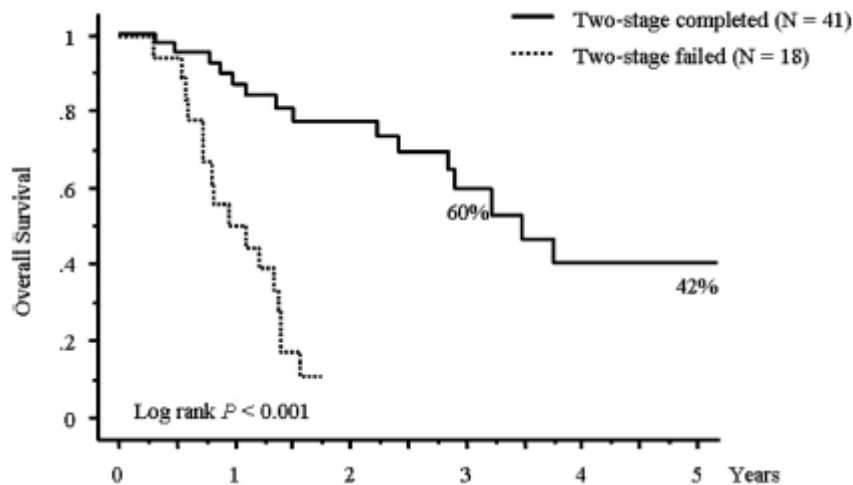
Patients who complete two-stage procedure had an overall 5 Y survival of 42%

Two stage hepatectomy-strategy



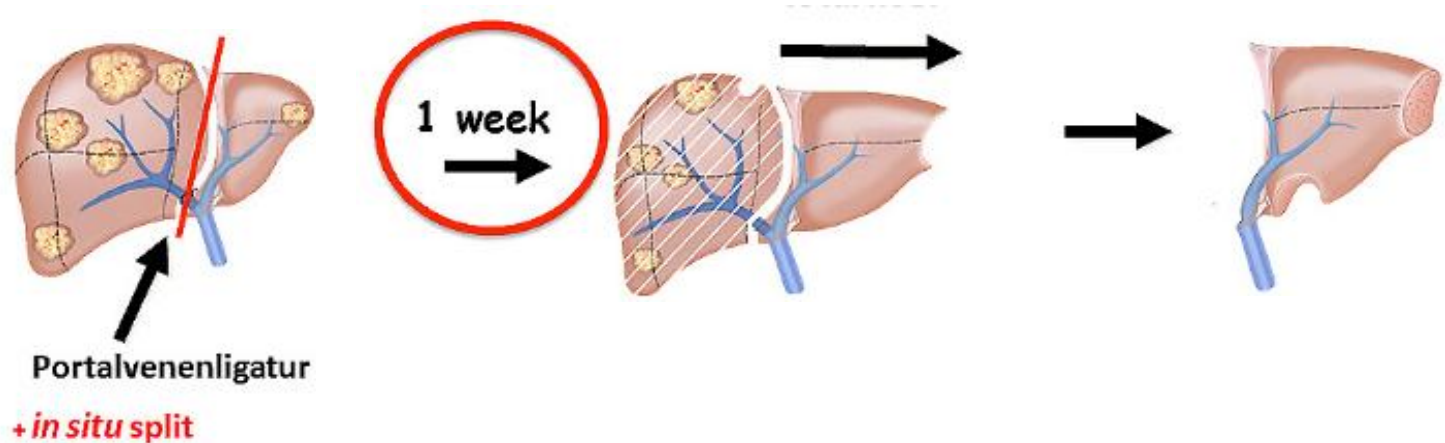
Long-Term Results of Two-Stage Hepatectomy for Irresectable Colorectal Cancer Liver Metastases

Dennis A. Wicherts, MD,† Rafael Miller, MD,*‡ Robbert J. de Haas, MD,*†
Georgia Bitsakou, MD,* Eric Vibert, MD,* Luc-Antoine Veilhan, MD,* Daniel Azoulay, MD, PhD,
Henri Bismuth, MD, FACS(Hon).* Denis Castaing, MD.*§¶ and René Adam, MD, PhD*§¶*



Conclusions: Two-stage hepatectomy provides a 5-year survival of 42% and a hope of long-term survival for selected patients with extensive bilobar CLM, irresectable by any other means.

ALPPS - Associated Liver Partition and Portal vein ligation for Staged hepatectomy



- Is a novel two-stage technique for optimizing FLR
- **First stage** -Portal vein ligation is combined with an in situ liver transection
- Results in a pronounced short-term parenchymal hypertrophy over approximately 1 week
- **Second stage** (1 week), a second laparotomy to remove the pre-divided liver



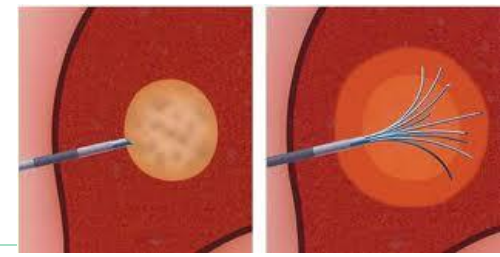
ALPPS - Associated Liver Partition and Portal vein ligation for Staged hepatectomy

- The increase in FLR with ALPPS ranges from 63-87%
- Advantage of ALPPS over PVE is the short interval to completion surgery
 - hypertrophy of the FLR
 - in less than 10 days (ALPPS)
 - compared to over 3 weeks for PVE

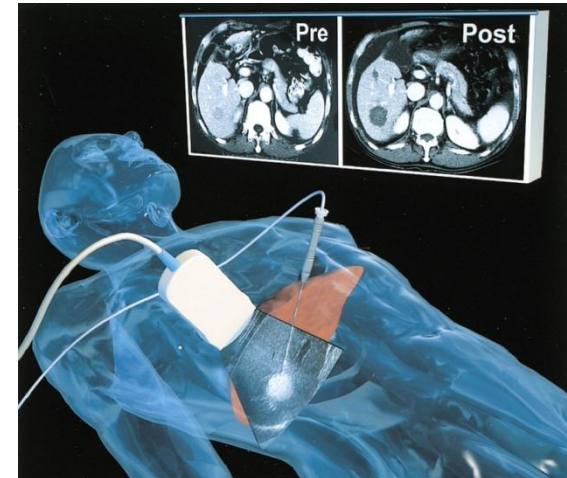
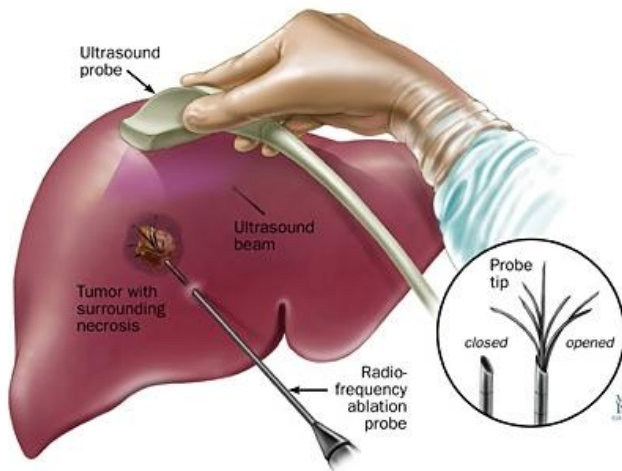
Morbidity 53-71% / mortality of 0-22%

The benefit of ALPPS over conventional PVE is heavily debated

Locoregional Therapies - RFA



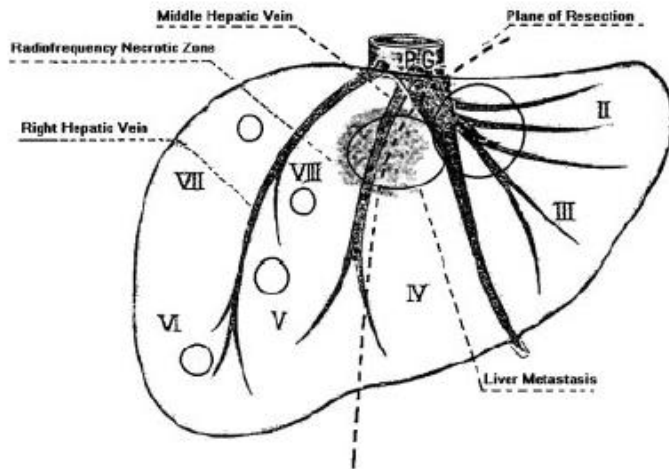
- ✓ RFA thermally ablate tumors
- ✓ Can be performed percutaneously, laparoscopically, or during laparotomy



Locoregional Therapies - RFA

Indications:

- ✓ Patients who are not candidates for surgical resection (co-morbidities)
- ✓ May be used in combination with resection in order to optimize FLR



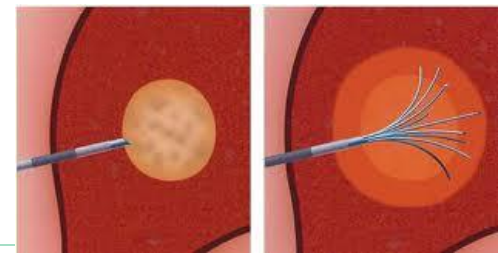
The Trans-Metastasis Hepatectomy (Through Metastases Previously Ablated With Radiofrequency): Results of a 13-Case Study of Colorectal Cancer

DOMINIQUE ELIAS, MD, PhD,^{1*} DIMITRI MANGANAS, MD,¹ EMMANUEL BENIZRI, MD,¹ FANNY DUFOUR, MD,¹
PAOLA MENEGON, MD,¹ TIJANI EL HARROUDI, MD,¹ AND THIERRY de BAERE, MD²

¹Department of Surgical Oncology, Institut Gustave Roussy, Cancer Center, Villejuif, cedex, France

²Unit of Interventional Radiology, Institut Gustave Roussy, Cancer Center, Villejuif, cedex, France

Locoregional Therapies - RFA



Disadvantage / limits

- ✓ Tumors greater than 30 mm (high recurrence rate)
- ✓ Contact with major biliary structures (risk for bile duct stricture and fistula)
- ✓ Contact with major vascular structures (risk of an inadequate ablation)



Original Investigation

Long-term Outcomes Following Tumor Ablation for Treatment of Bilateral Colorectal Liver Metastases

Paul J. Karanicolas, MD, PhD; William R. Jarnagin, MD; Mithat Gonen, PhD; Scott Tuorto, BA; Peter J. Allen, MD; Ronald P. DeMatteo, MD; Michael I. D'Angelica, MD; Yuman Fong, MD

- 141 patients treated with multiple resections
- 95 patients treated with ablation + resection techniques
- 5-year OS was statistically similar
 - ablation-resection (56 %)
 - multiple resection (49 %)

Conclusions and Relevance Treatment of bilateral, multiple hepatic metastases with **combined resection and ablation was associated with improved perioperative outcomes without compromising long-term survival compared with bilateral resection.** Ablative therapies extend the capability of delivering potentially curative treatment for bilateral hepatic colorectal metastases.

Nonresectable
liver-only metastases

Standard treatment option



Palliative chemotherapy

What about liver transplantation?



Chemotherapy or Liver Transplantation for Nonresectable Liver Metastases From Colorectal Cancer?

Svein Dueland, MD, PhD, Tormod K. Guren, MD, PhD,* Morten Hagness, MD, PhD,†‡
Bengt Glimelius, MD, PhD,§ Pål-Dag Line, MD, PhD,† Per Pfeiffer, MD, PhD,¶ Aksel Foss, MD, PhD,†‡
and Kjell M. Tveit, MD, PhD*‡*

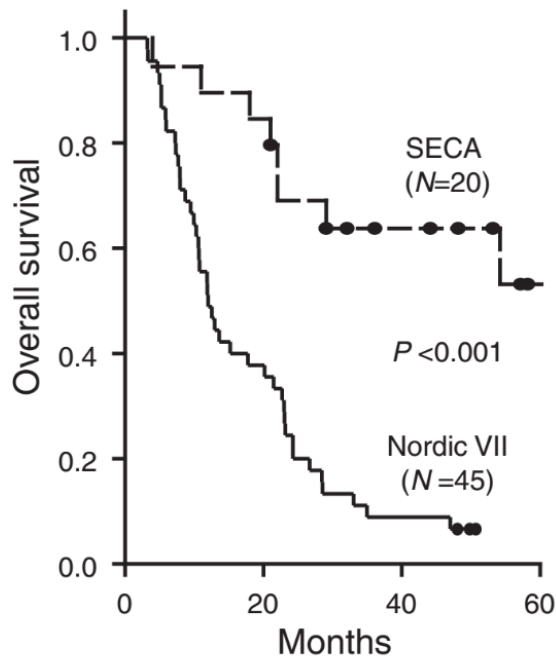
- ❑ comparison of results in 2 prospective studies SECA / NORDIC VII
 - CRC nonresectable metastases
 - liver-only metastases

- ✓ SECA study - patients undergoing liver transplantation

- ✓ NORDIC VII study - patients receiving chemotherapy
 - Nordic FLOX with or without cetuximab

Chemotherapy or Liver Transplantation for Nonresectable Liver Metastases From Colorectal Cancer?

Svein Dueland, MD, PhD,* Tormod K. Guren, MD, PhD,* Morten Hagness, MD, PhD,††
Bengt Glimelius, MD, PhD,§ Pål-Dag Line, MD, PhD,† Per Pfeiffer, MD, PhD,¶ Aksel Foss, MD, PhD,††
and Kjell M. Tveit, MD, PhD*‡



5-year OS

-56% in patients undergoing liver transplantation

-9% in patients starting firstline chemotherapy

Chemotherapy or Liver Transplantation for Nonresectable Liver Metastases From Colorectal Cancer?

Svein Dueland, MD, PhD, Tormod K. Guren, MD, PhD,* Morten Hagness, MD, PhD,†‡
Bengt Glimelius, MD, PhD,§ Pål-Dag Line, MD, PhD,† Per Pfeiffer, MD, PhD,¶ Aksel Foss, MD, PhD,†‡
and Kjell M. Tveit, MD, PhD*‡*

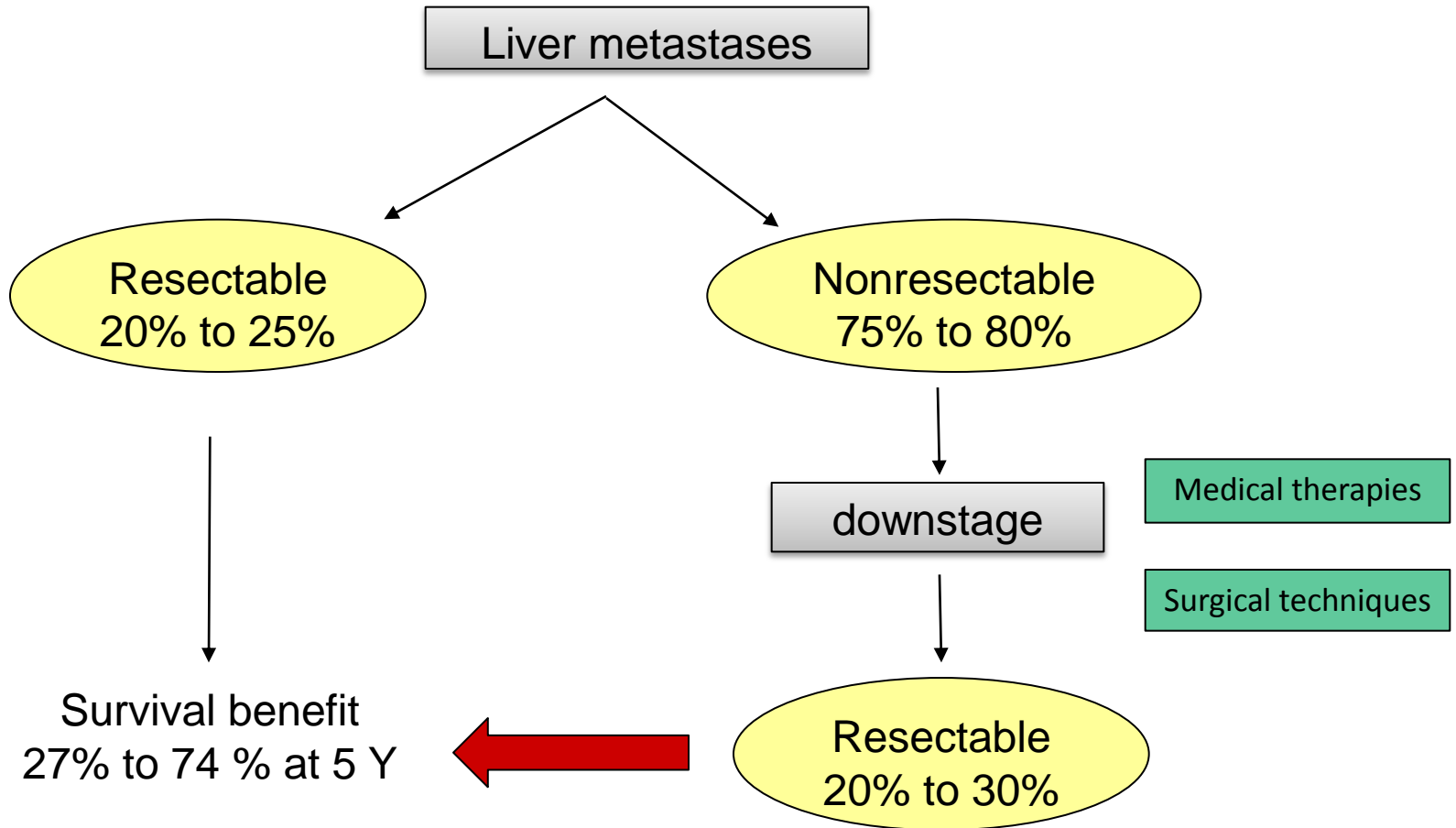
Author recommendations

- ❑ Selecting patients for liver transplantation based on
 - CEA <80 µg/L
 - metastases < 5.5 cm
 - no progressive disease at the time of transplantation
 - more than 2 years from diagnosis of CRC

May be obtained a 5-year OS rate of 75%



Liver metastases in colorectal cancer



Conclusion



- Surgical resection remains the treatment of choice for resectable CLM
- Surgical techniques and medical therapies, are currently utilized in to improve resectability.
- Treating hepatic metastases requires a knowledge of all treatment options
- Patients with unresectable disease are **downstaged to complete resection**, long-term data support 5 and 10-year survival are similar to upfront resectable patients
- Liver Transplantation for Unresectable CRCLM? ...

Will the paradigm change in the future?



XI JORNADAS DE
CIRURGIA DE BRAGA
CONTROVÉRSIAS
NO CANCRO DO RETO



7 de outubro de 2016
Auditório do Hospital de Braga



Obrigado



► Diretor do Serviço de Cirurgia Geral:
Dr. Mesquita Rodrigues

Humberto Cristino