Management of colorectal cancer liver metastases

How far should we go?

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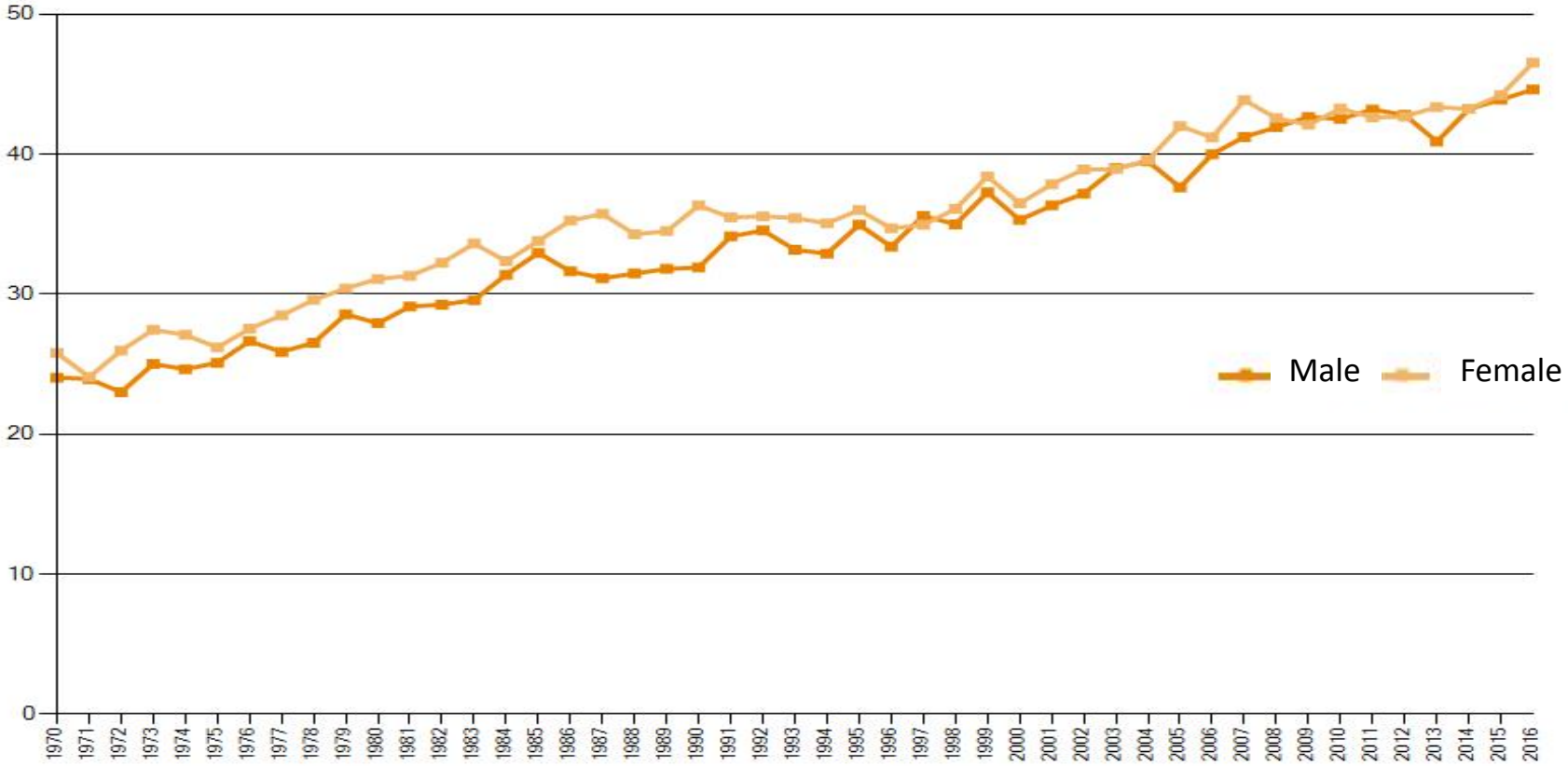
Colorectal cancer (CRC)

- Third most commonly diagnosed cancer
- Fourth most common cause of cancer death
- Anually 1.4 million new cases and 694 000 deaths (2012)



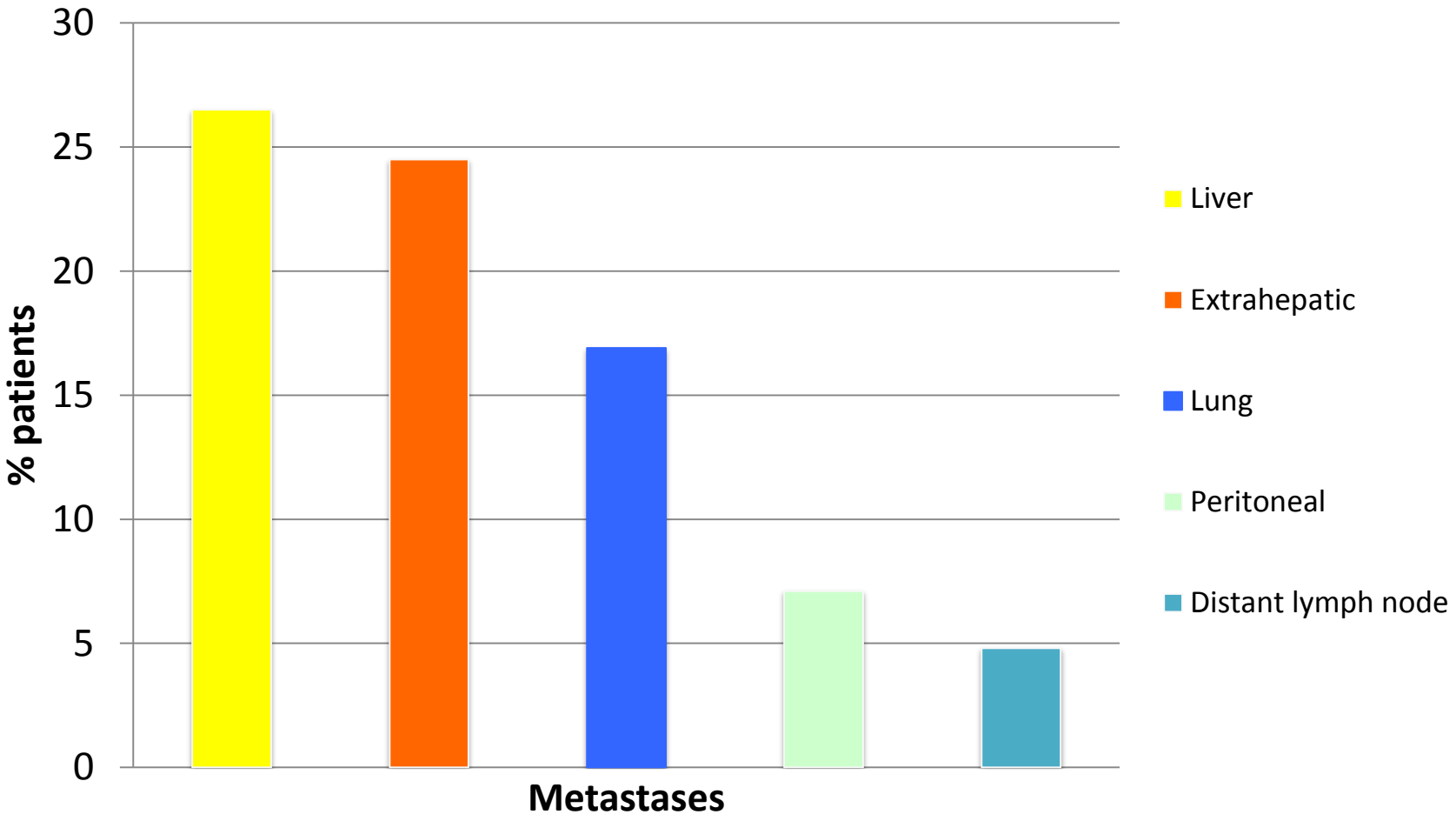
The incidence of colorectal cancer liver metastases (CRCLM)

- Frequently reported as 40-50% of patients with CRC

- True incidence – population-based studies
  - 24.7% – 27.3%

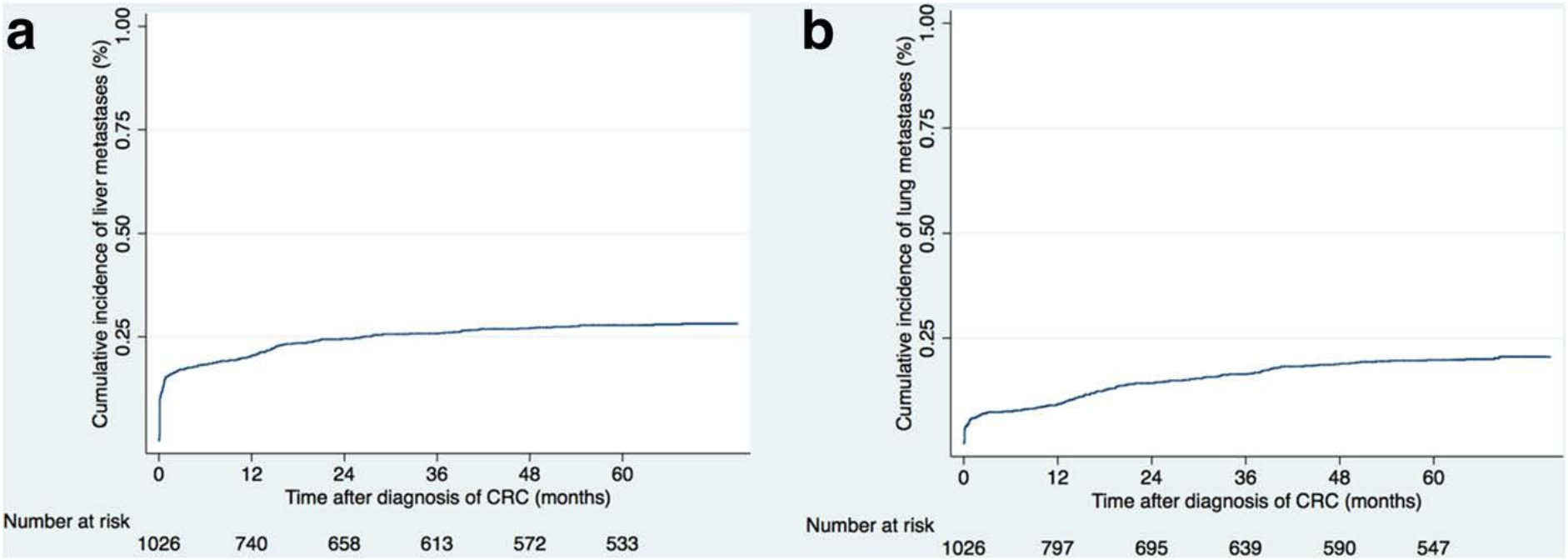
Manfredi S, et al. Ann Surg. 2006;244:254–259
Hackl C, et al. BMC Cancer. 2014;14:810
Engstrand J, Jonas E, et al. BMC Cancer. 2018;18:78

Metastatic patterns



Engstrand J, Jonas E, et al. BMC Cancer. 2018;18:78
Engstrand J, Jonas E, et al. Oncologist. 2017;22:1067-1074

Cumulative incidence (a) liver and (b) lung metastases*



*related to the time of diagnosis of the primary tumour

Engstrand J, Jonas E, et al. BMC Cancer. 2018;18:78

All liver metastases are present and potentially detectable at the diagnosis and/or operation of the primary tumour

- It **is not** about:
  - development
  - presentation
- It **is** about
  - detection

Strongest quality parameter for pre- and peri-operative liver imaging

Gd-EOB-DTPA (Primovist® /Eovist®)
Gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid

	Pre-contrast	Arterial phase	Portovenous phase	Delayed phase	Hepatobiliary phase
CE-MDCT	✓	✓	✓	✓	X
ECCM-MRI	✓	✓	✓	✓	X
Gd-EOB-DTPA-MRI	✓	✓	✓	✓	✓

CE-MDCT	contrast-enhanced multi-detector computed tomography
ECCM-MRI	MRI with extracellular contrast media
Gd-EOB-DTPA-MRI	gadoxetic acid-enhanced MRI

Curative intervention for CRCLM - the 1900's paradigm

Decisions based on ***what is taken away***

- Number of metastases
- Size of metastases
- Segmental distribution
- Macroscopic surgical margins
- Extrahepatic disease

Resectable → Operation

Unresectable → Palliation

from the colon in 51 (71 per cent) patients. It was well differentiated in 7 (10 per cent) patients, moderately in 57 (79 per cent) and poorly in 8 (11 per cent). In 3 (4 per cent) patients the tumour was classified as Dukes' A, in 19 (26 per cent) as Dukes' B and in 50 (69 per cent) as Dukes' C. The hepatic tumours were well differentiated in 3 (4 per cent) patients, moderately in 64 (89 per cent) and poorly in 5 (7 per cent). All histological slides were reviewed.

Altogether twelve (17 per cent) patients had extrahepatic disease, which involved two extrahepatic sites in four of them. Dissection of the hepatoduodenal ligament, with removal of lymph glands for microscopic examination, was performed in 31 (43 per cent) patients, and revealed lymph node metastases in the liver hilum in six and around the coeliac axis in two. The remaining extrahepatic intra-abdominal manifestations consisted of overgrowth to the diaphragm (2) or the vena

- Retrospective analysis 1971-1984
- 72 resections

- Recommendations
  - <4 liver tumours
  - no extrahepatic disease
  - a resection margin of at least I0 mm

Liver resection should not be performed unless all of these requirements are met

Ekberg, et al. Br J Surg. 1986;73:727-31

Curative intervention for CRCLM - the 2000's paradigm

Decisions based on ***what is left behind***

- Absolute contra-indications
  - Inability to achieve a R_0 situation in the liver
  - Inability to leave a sufficient future liver remnant (FLR)

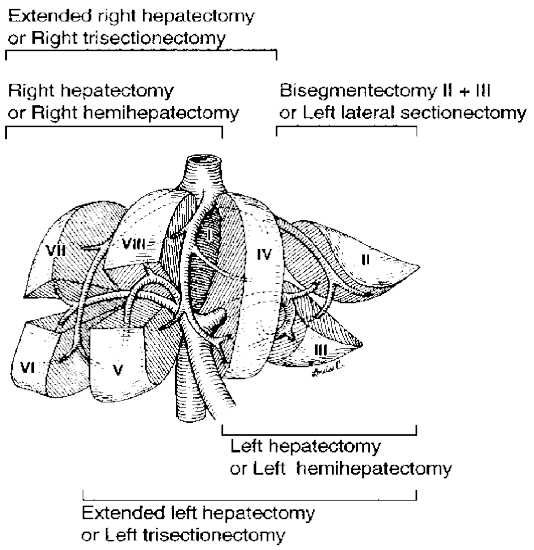
- Relative contra-indications
  - extrahepatic disease
  - progress on chemotherapy
  - and more……

Pawlik T, et al. The Oncologist 2008;13:51-64

The future liver remnant

Liver failure is the biggest cause of post-operative mortality after liver resection

- Sufficient volume and quality
  - to sustain immediate post-operative function
  - to allow sufficient post-resection regeneration
- Intact arterial and portal supply and biliary and venous drainage
- Tumour free



Belghiti J, et al. J Am Coll Surg. 2000;191:38-46
Jarnagin W, et al. Ann Surg. 2002;236:397-407

What is a sufficient future liver remnant?

World Journal of Surgery

"State of the Art" in Liver Resection and Living Donor Liver Transplantation: A Worldwide Survey of 100 Liver Centers

Stefan Breitenstein · Carlos Apestegui · Henrik Petrowsky · Pierre Alain Clavien

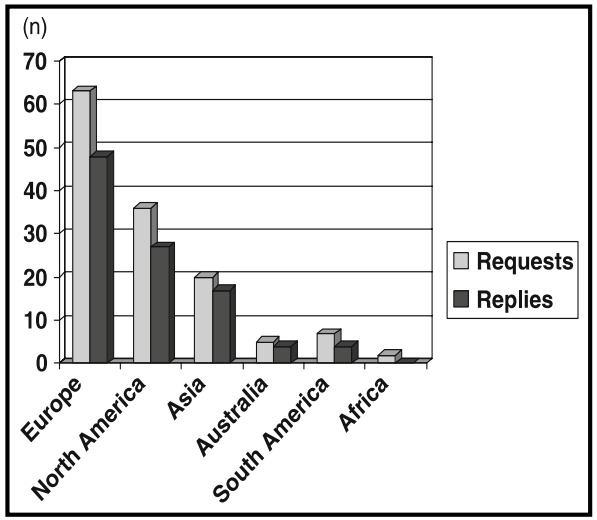
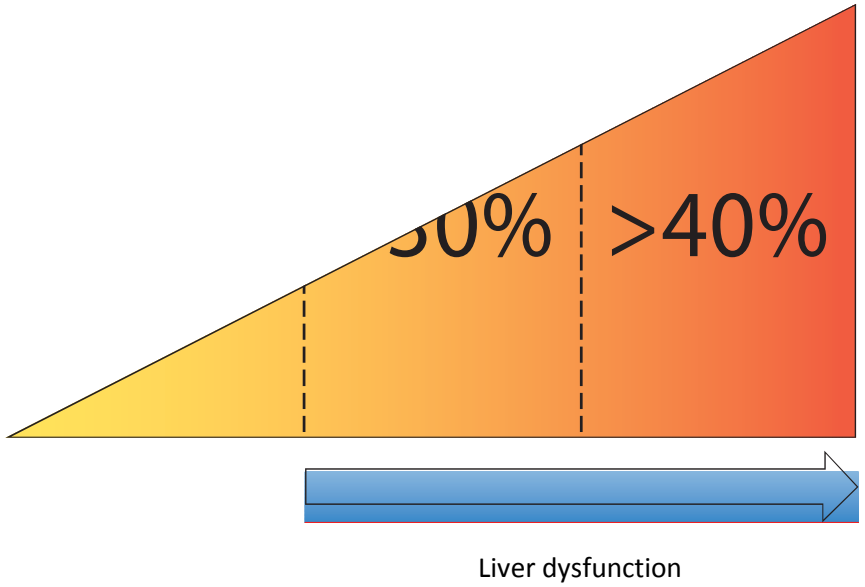


Table 1 Critical liver mass for liver resection and partial liver transplantation

	Normal liver (%)	Cirrhotic liver (%)	Donor volume in LRLT (%)	Graft-body-weight-ratio
Europe	28 (15–40)	50 (30–80)	35 (30–50)	0.8 (0.6–1.2)
North America	25 (15–30)	50 (25–90)	35 (30–45)	0.8 (0.8–1)
Asia	30 (20–40)	50 (30–80)	35 (30–45)	0.8 (0.6–0.8)
Australia	28 (25–30)	50 (40–50)	35	–
South America	28 (25–40)	45 (40–80)	38 (35–40)	0.8 (0.8–1.2)
Overall	25 (15–40)	50 (25–90)	40 (30–50)	0.8 (0.6–1.2)

Data are expressed as medians and ranges unless otherwise indicated

Breitenstein S, et al. World J Surg. 2009;33:797-803



Guglielmi A, et al. Dig Surg 2012;29:6–17

Conversion strategies

Group 1

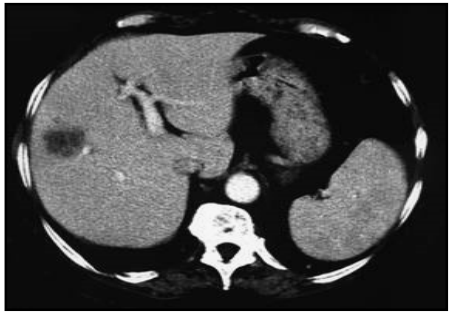
Readily resectable with a single intervention (15-25%)

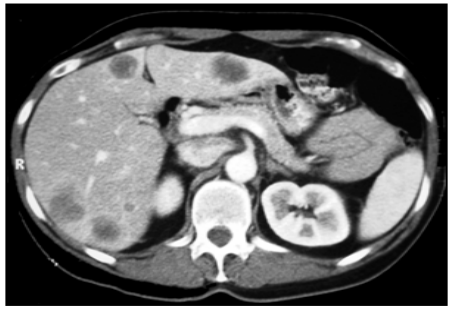
Group 2

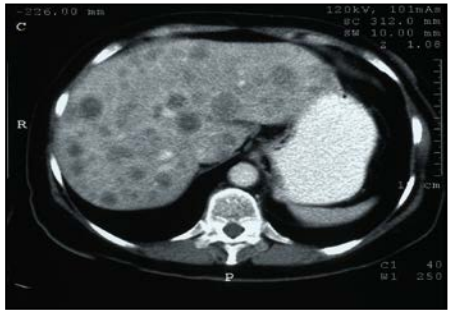
Unresectable but potentially resectable with multimodality conversion (15-20%)

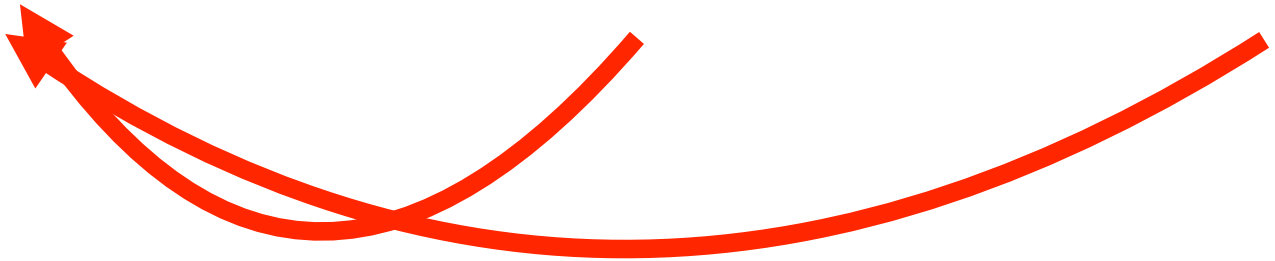
Group 3

Unresectable and unlikely to become resectable (60-70%)









Conversion strategies

Resection is precluded by combinations of

- Segmental distribution of disease
- Too small FLR
- Engagement of vital FLR-related structures

Conversion strategies

Tumour-targeting

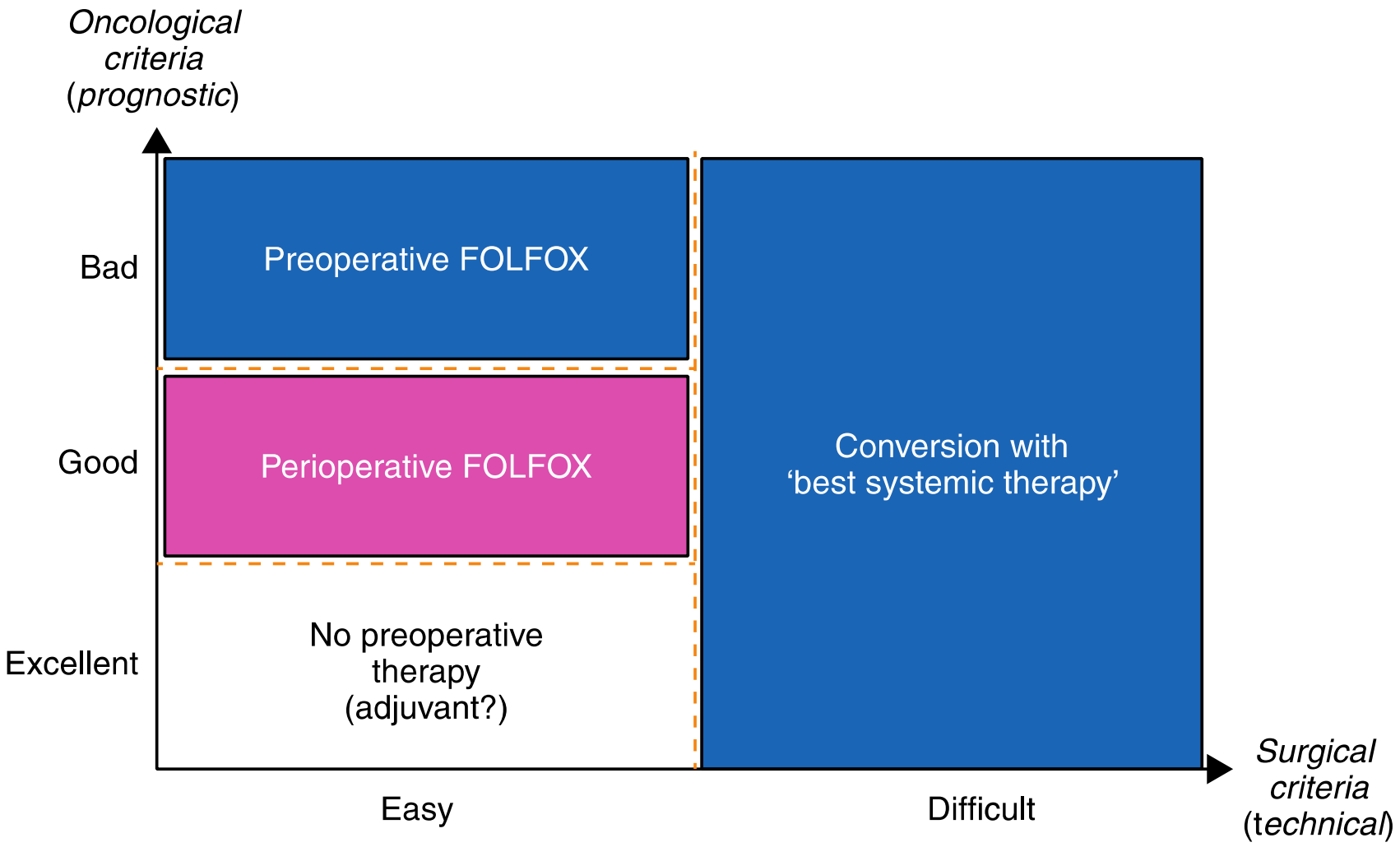
- Conversion chemotherapy
- Local ablation techniques

FLR-targeting

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

Combination

- Staged surgery
- In situ liver split (ALPPS)
- Liver transplant


Oncological criteria (prognostic)
Bad
Good
Excellent
Preoperative FOLFOX
Perioperative FOLFOX
No preoperative therapy (adjuvant?)
Conversion with 'best systemic therapy'
Easy
Difficult
Surgical criteria (technical)

Complete response in CRCLM

- Complete radiological response – 9-37% of patients
- Complete pathological response – 20-100% of lesions
- Complete clinical response – 26-62% of lesions

Elias et al. , D. et al. J Surg Oncol 2004;86:4-9
Benoist, S. et al. J. Clin. Oncol 2006;24:3939-3945
Elias, D. et al.. Ann. Surg Oncol 2007;14:3188-3194
Fiorentini, G. et al. Tumori 2008;94:489-492
Tanaka, K. et al.. Ann. Surg 2009;250:935-942
Auer, R. C. et al. Cancer 2010;16:1502-1509
van Vledder, M. G. et al. J Gastrointest Surg 2010;14:1691-1700
Ferrero, A. et al. J Gastrointest Surg 2012;16:806-14

Local ablation

Radiofrequency ablation (RFA)

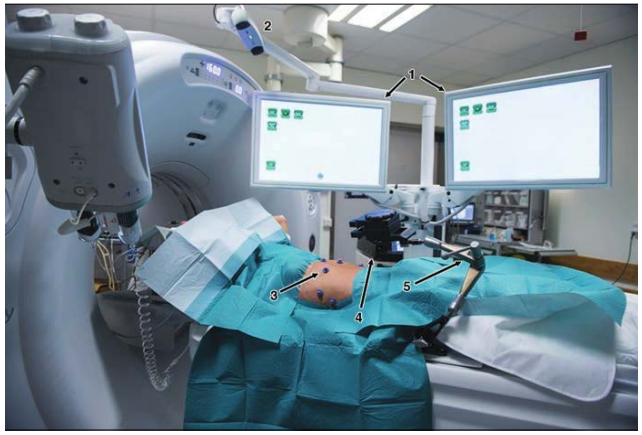
- energy delivered as current
- oscillations in the RF range polarizes molecules (water)
- creates a wobble that induces heat by friction that is conducted

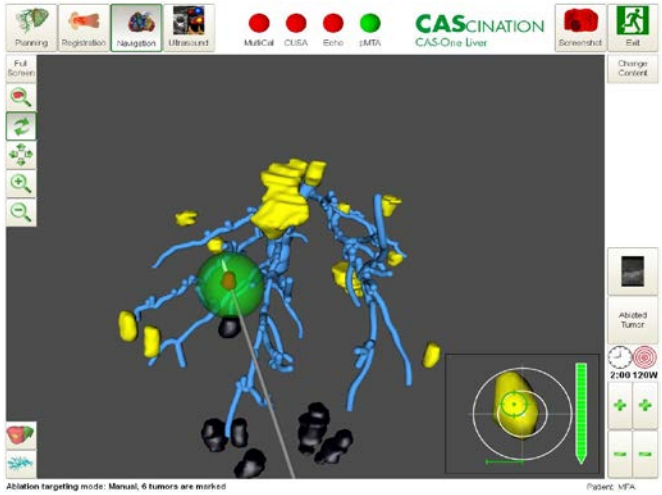
Microwave ablation (MWA)

- direct application of an electromagnetic field
- oscillation in MW frequency range (0.915 or 2.45 GHz)
- water molecules oscillate and cause frictional heat

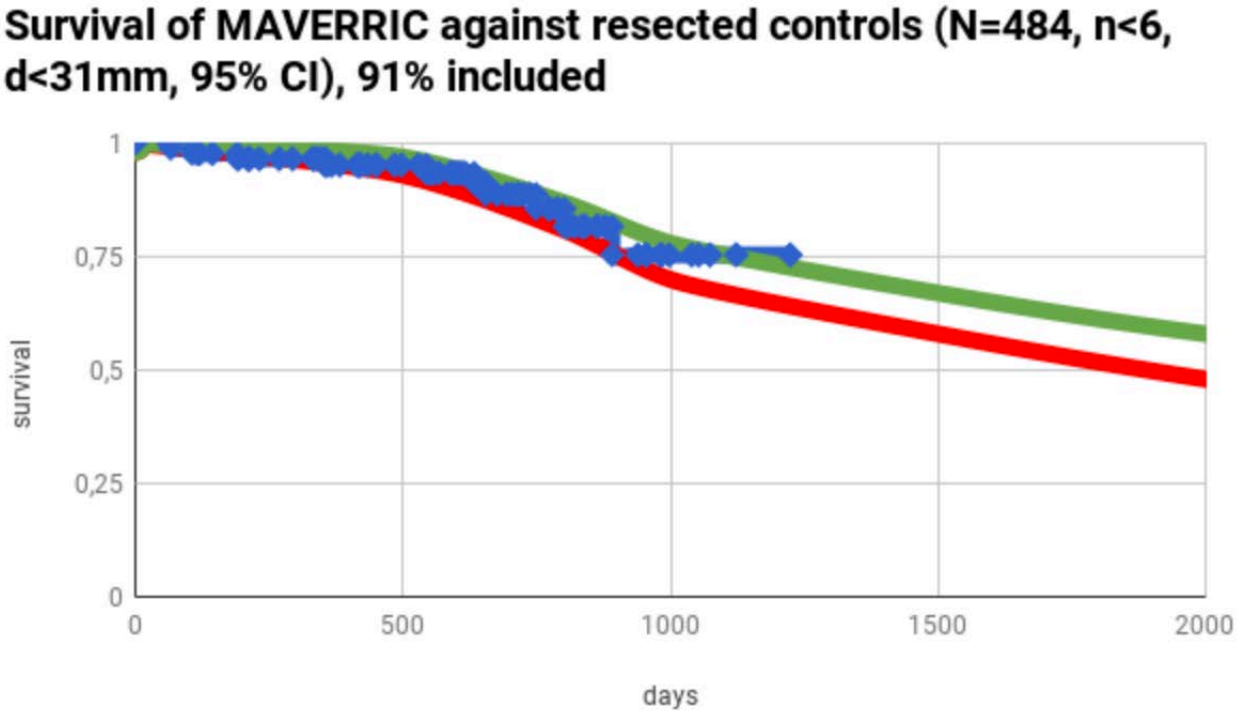
Irreversible electroporation (IRE)

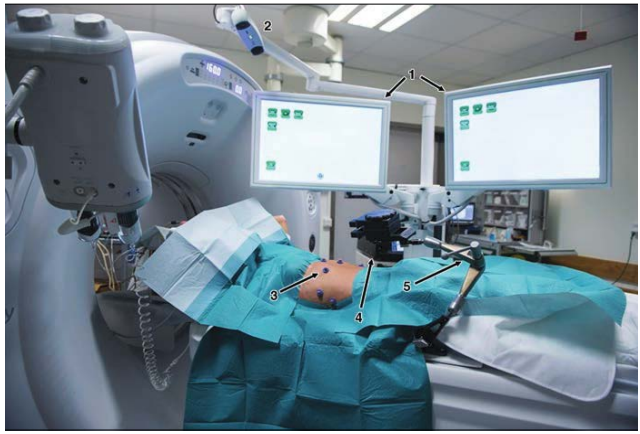
- short bursts of 3000–5000 volts at 20–50 ampere
- delivered between a lattice of electrodes surrounding the tumour
- disruption of cell membranes (apoptosis, cell death with minimal heat)
- surrounding connective tissue is preserved (vessels, bile ducts, nerve sheaths)

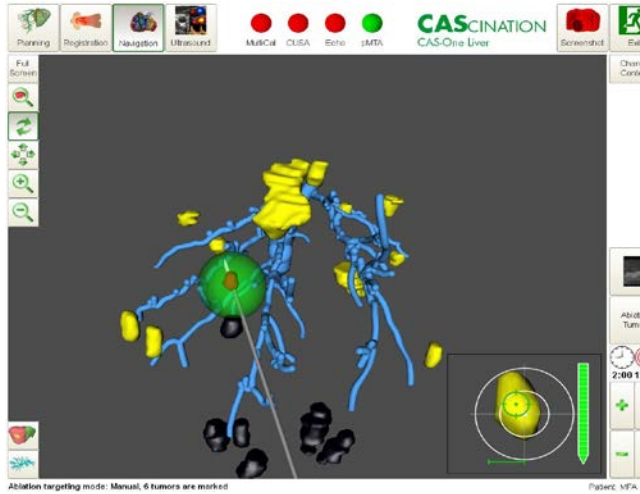


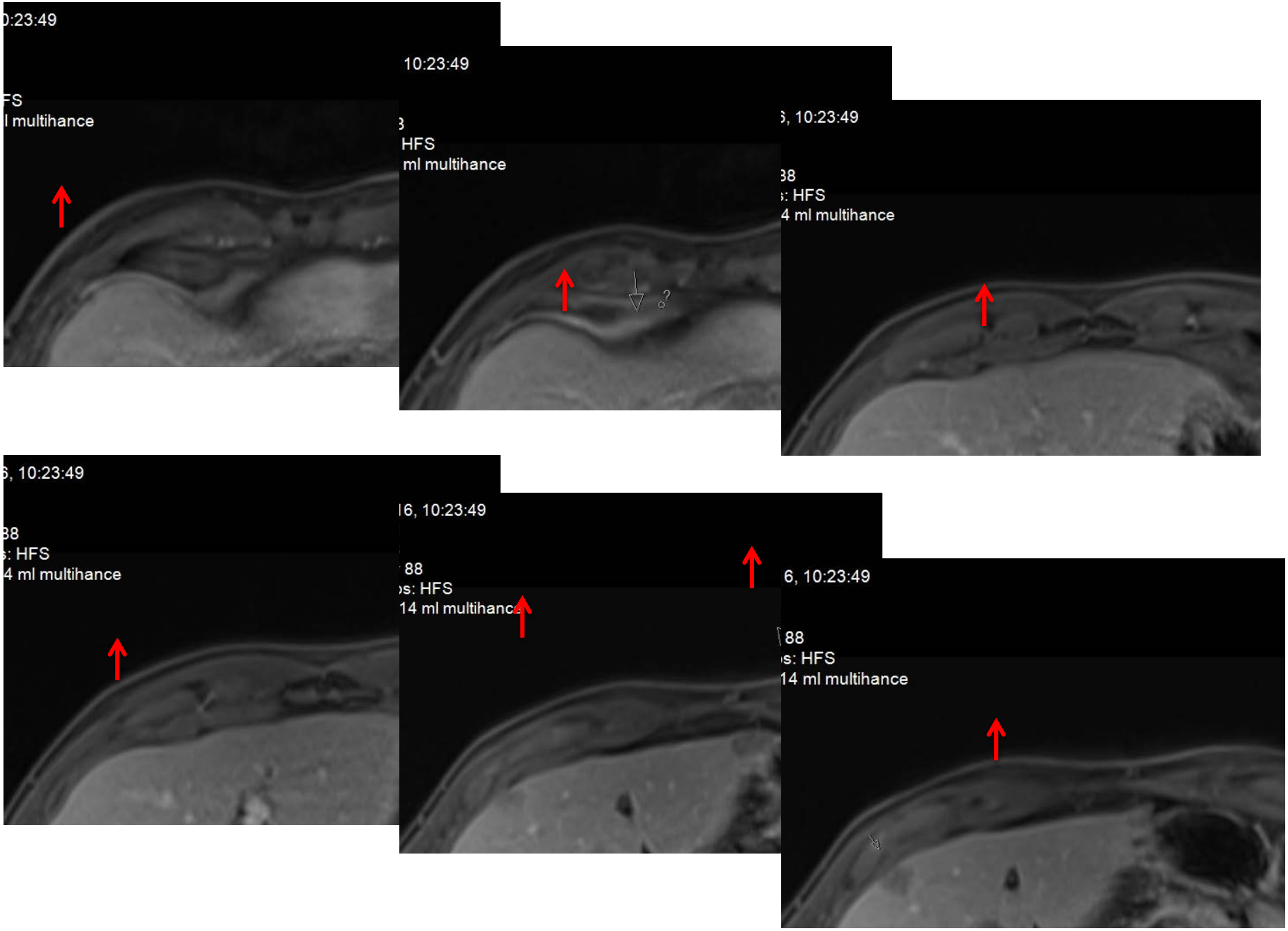


LA versus resection








0:23:49
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l multihance
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38
: HFS
4 ml multihance
, 10:23:49
38
s: HFS
4 ml multihance
16, 10:23:49
88
s: HFS
14 ml multihance
6, 10:23:49
88
s: HFS
14 ml multihance

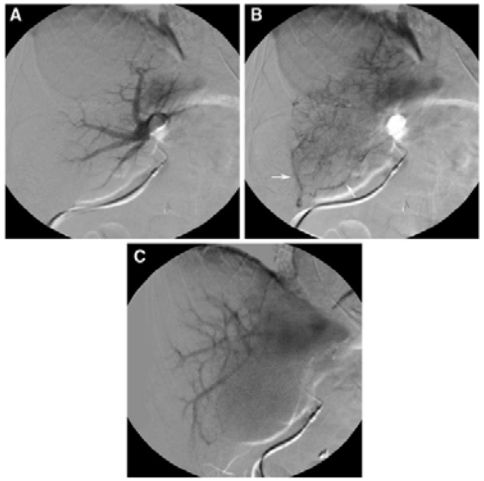
PVE versus PVL

Clinical studies with intraoperative portal vein ligation to hypertrophy the remnant volume, either alone or compared with percutaneous portal vein embolisation.

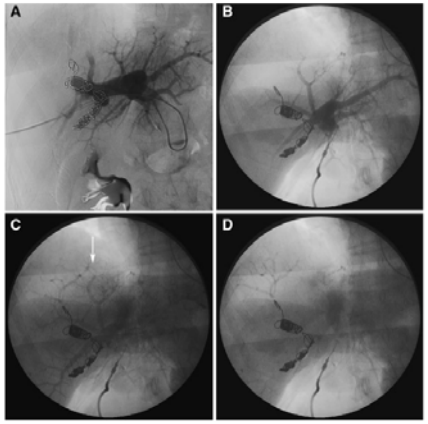
	Type of study (*n*)	Indications (*n*)	POT	One-stage vs TSH	Volume increase after PVL and/or PVE	*p*<
Denys, 1999[26]	Clinical case	LMCRC	PVL: firstly PVE: after failure of PVL	One-stage: yes TSH: no	PVL: failure PVE: After failure 256%	
Broering, 2002[12]	Prospective (34 cases)	LMCRC (17) HCC (2), CC (13), Others (2)	PVL: 17 PVE: 17 (10 percutaneous and 7 transileocolic)	One-stage: all cases TSH: no	PVL: from 287 ml to 411 ml (123 ml) PVE: from 271 to 459 ml (188 ml)	0.012
Selzner, 2006[34]	Retrospective (11 cases)	All LMCRC	PVL: 11 (10 right portal vein and 1 left portal vein) PVE: no	One-stage: all cases TSH: no	PVL: from 42 to 52% (10%) PVE: no	0.001
Aussilhou, 2008[13]	Retrospective (35 cases)	NETLM (10) LMCRC (25)	PVL: 17 PVE: 18	One-stage: 18 cases of PVE TSH: 17 cases of PVL	PVL: from 477 to 638 ml (38%) PVE: from 509 ml to 641 (35%)	n.s.
Capussotti, 2008[15]	Retrospective (2 hospitals) (48 cases)	All LMCRC	PVL: 17 PVE: 31	One-stage: 37 cases TSH: 11 cases	PVL: from 17.7 to 26.9% PVE: from 17.5% to 24.7%	n.s.
Are, 2008[27]	Laparoscopy (9 cases)	LMCRC (5) ChC (3) HCC (1)	PVL: 9 PVE: no	One-stage: 2 cases TSH: 7 cases	PVL: from 209 ml to 495 ml (2 needed subsequent PVE) PVE: no	–
Homayounfar, 2009[16]	Retrospective (24 cases)	All LMCRC	PVL: 24 (23 right portal vein and 1 left portal vein) PVE: no	One-stage: no cases TSH: 24 cases	PVL: from 350.5 ml to 475 ml (35.7%) PVE: no	–
Szijarto, 2009[17]	Retrospective (14 cases)	All LMCRC	PVL: 14 PVE: no	One-stage: no cases TSH: 14 cases	PVL: Increase in 28.9% PVE: no	–
Karoui, 2010[28]	Retrospective (2 hospitals) (33 cases)	LMCRC (11 cases without portal occlusion)	PVL: 17 PVE: 5	One-stage: no cases TSH: 33 cases (in first operation only resected CRC)	PVL: 22% (9–30%). Increase in all cases PVE: 22% (9–30%). Increase in all	–
Sturensson, 2010[31]	Retrospective (26 cases)	All LMCRC	PVL: 4 PVE: 22	One-stage: 26 cases TSH: excluded of the study	PVL: 4 after PVL hypertrophy PVE: 12 cases after PVE needed other PVE	–

POT: portal occlusion technique; PVL: portal vein ligation; PVE: portal vein embolisation; LMCRC: liver metastases of colorectal cancer; NETLM: neuroendocrine tumour liver metastases, TSH: two-stage liver resection; CHT: chemotherapy; HCC: hepatocarcinoma; CC: cholangiocarcinoma; IAC: intra-arterial chemotherapy.

PVL



PVL

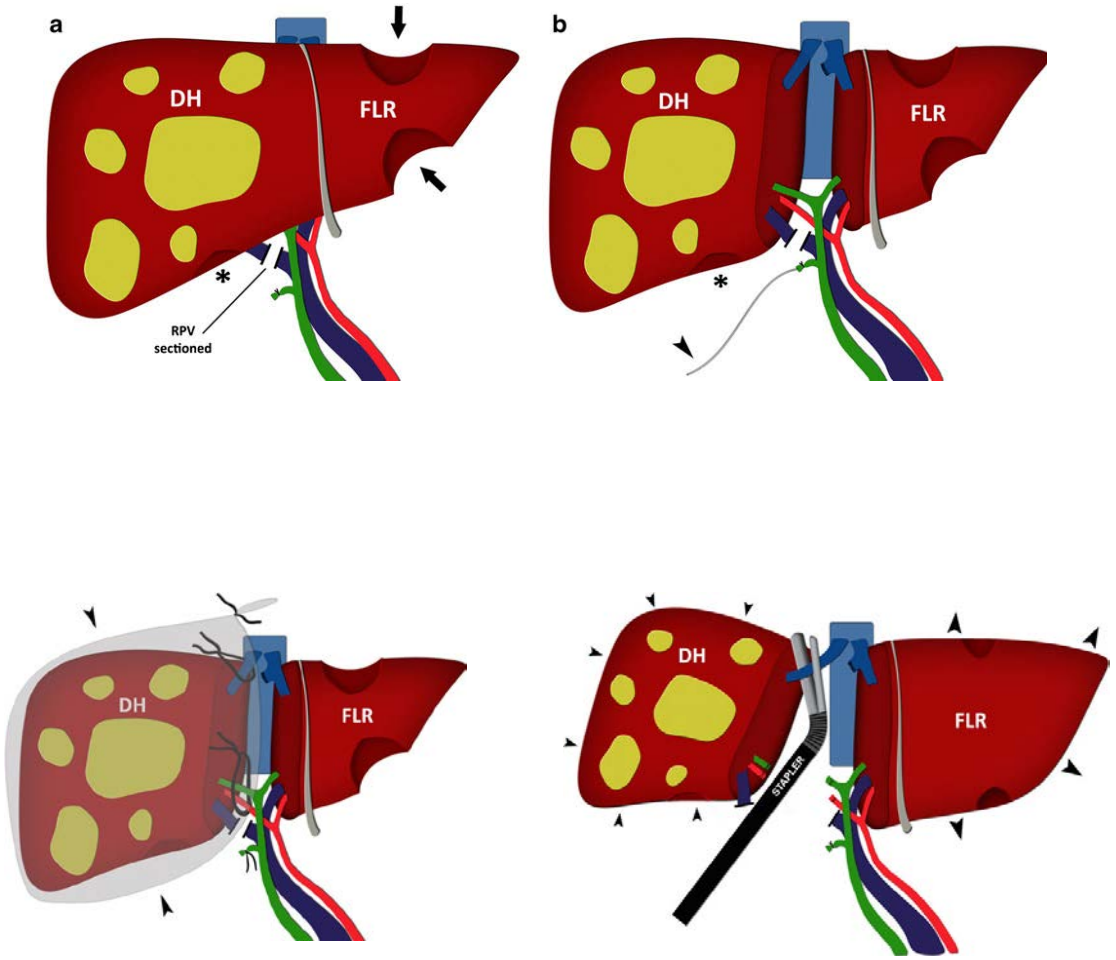


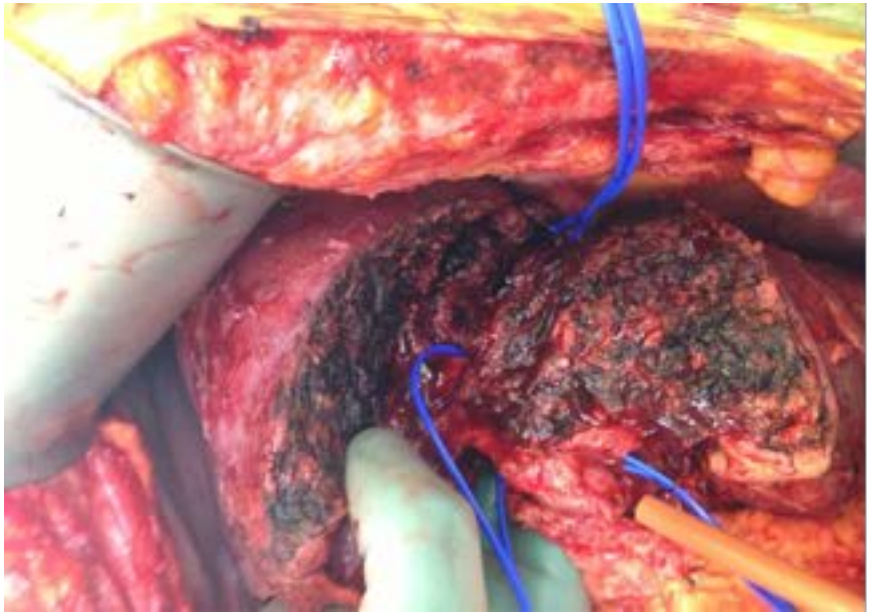
Robles R, et al. Eur J Surg Oncol. 2012;38:586-93

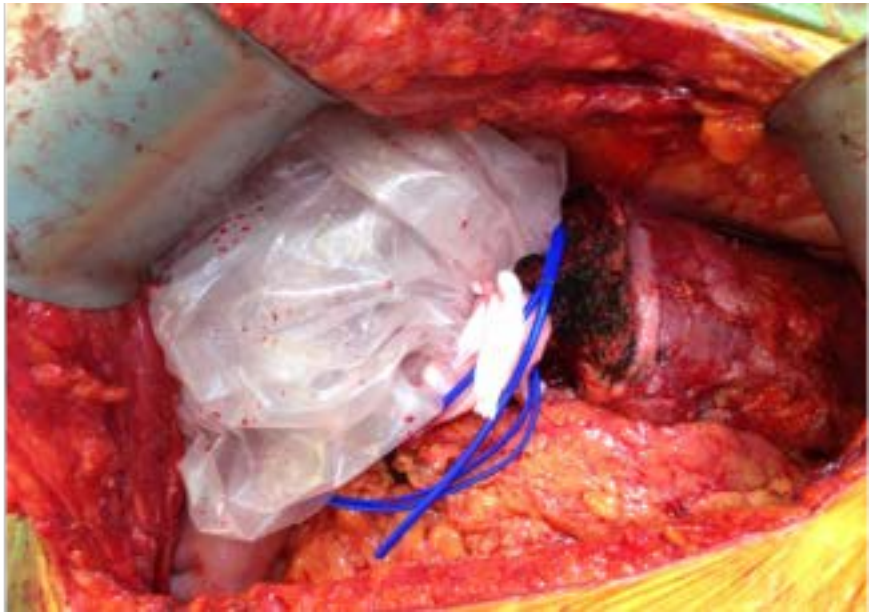
Van Lienden KP, et al. Cardiovasc Intervent Radiol. 2013 Mar 13. [Epub ahead of print]

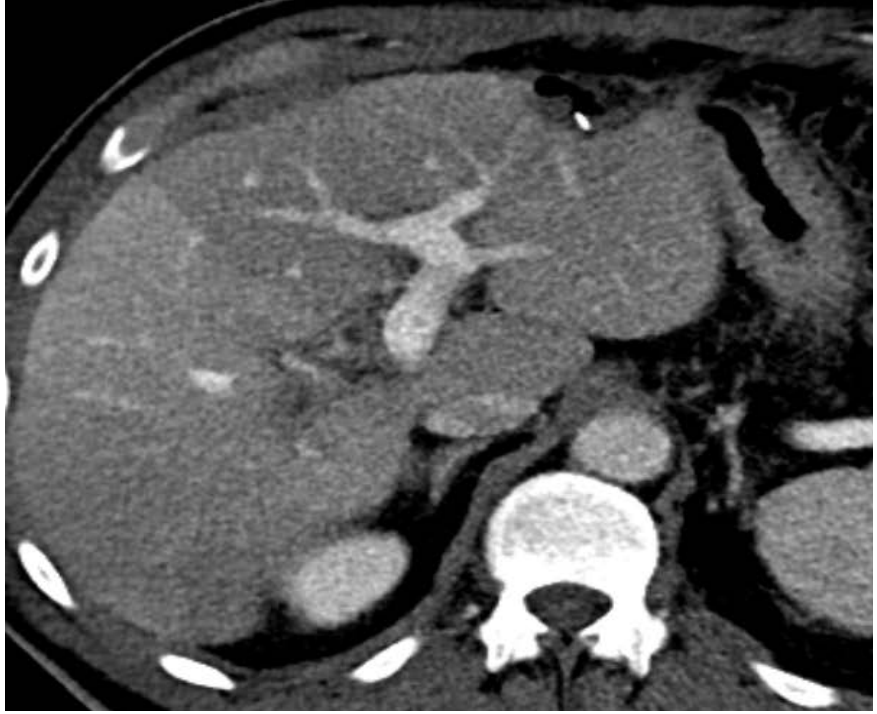
In situ split (ALPPS)

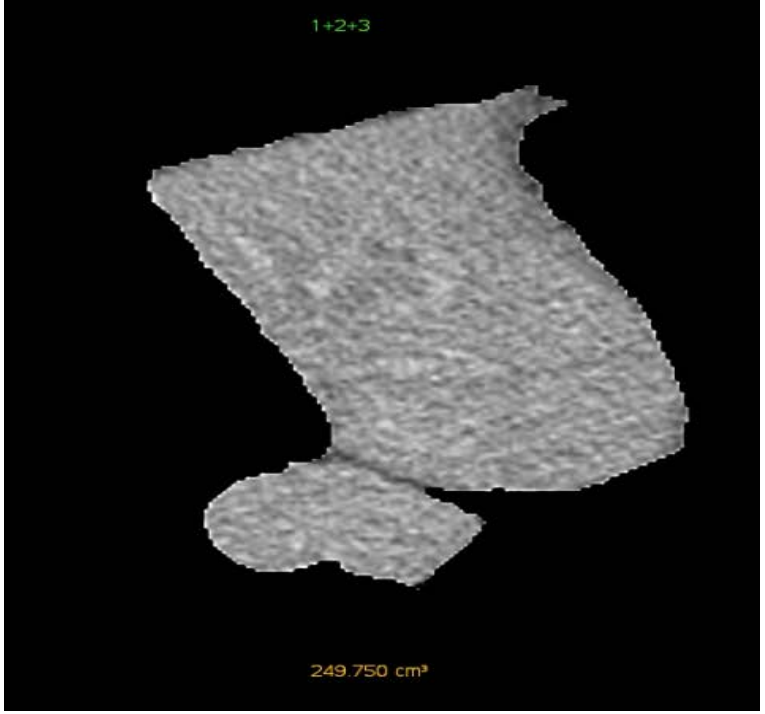
- Operation 1:
  - division of liver parenchyma
  - FLR - preservation of vascularity and biliary drainage
  - Resectate - portal vein ligation, preservation of arterial supply and biliary/venous drainage
- Operation 2:
  - Resection

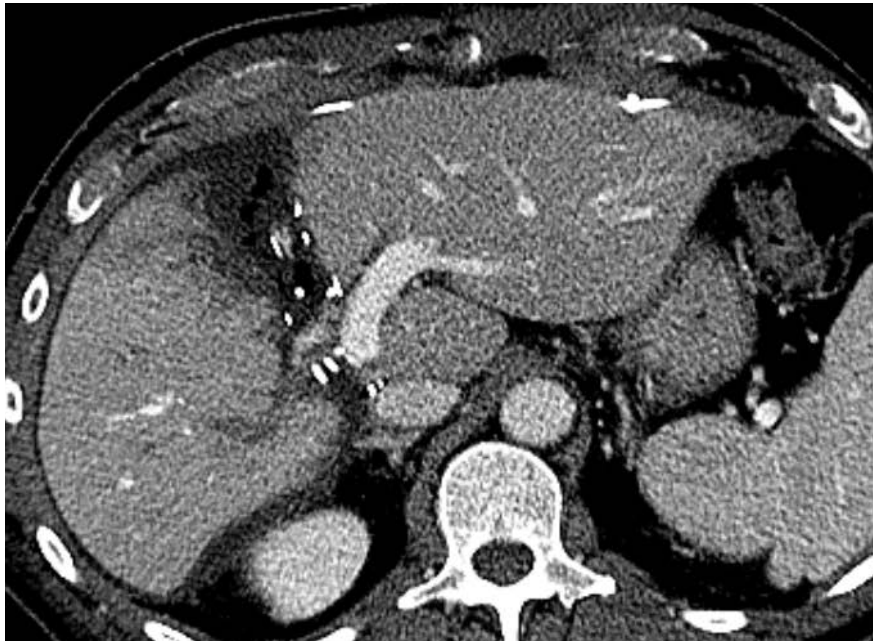


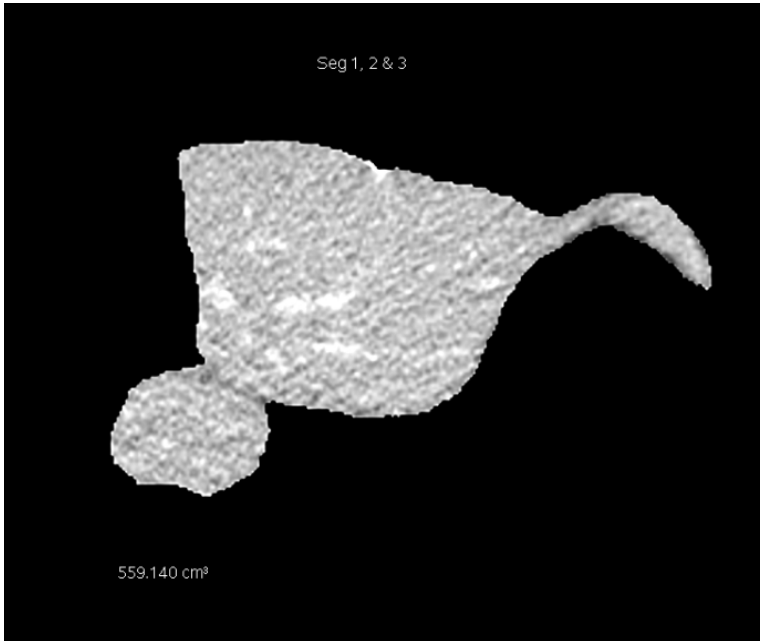


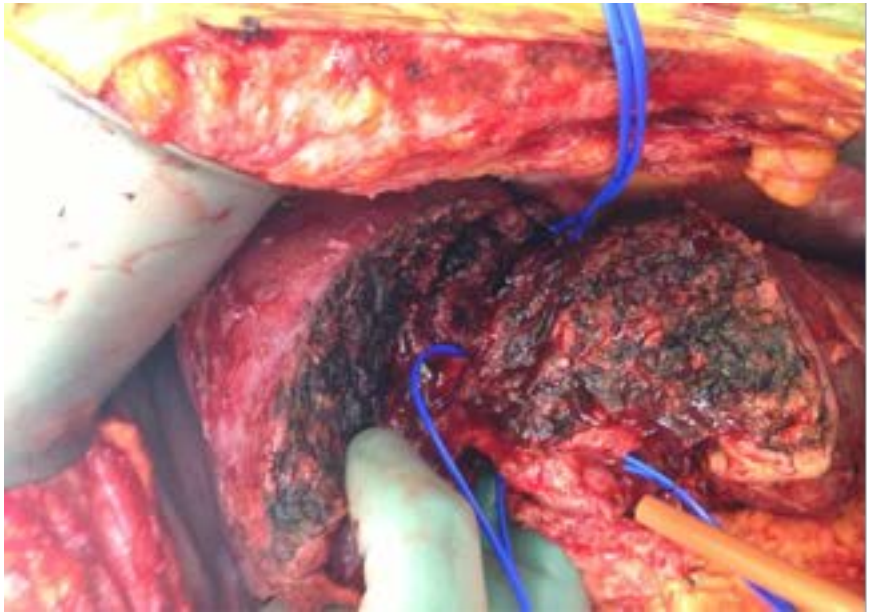


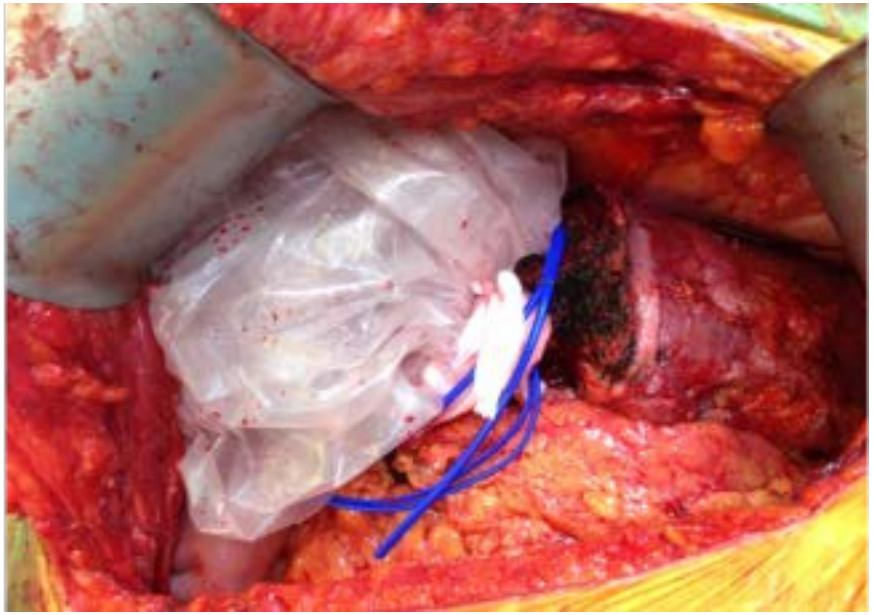


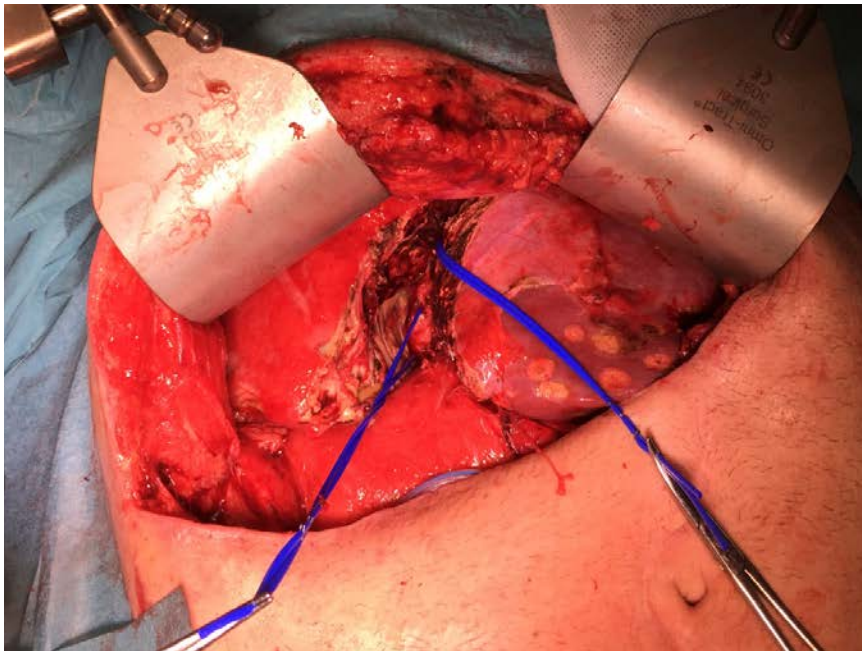

1+2+3
249.750 cm³

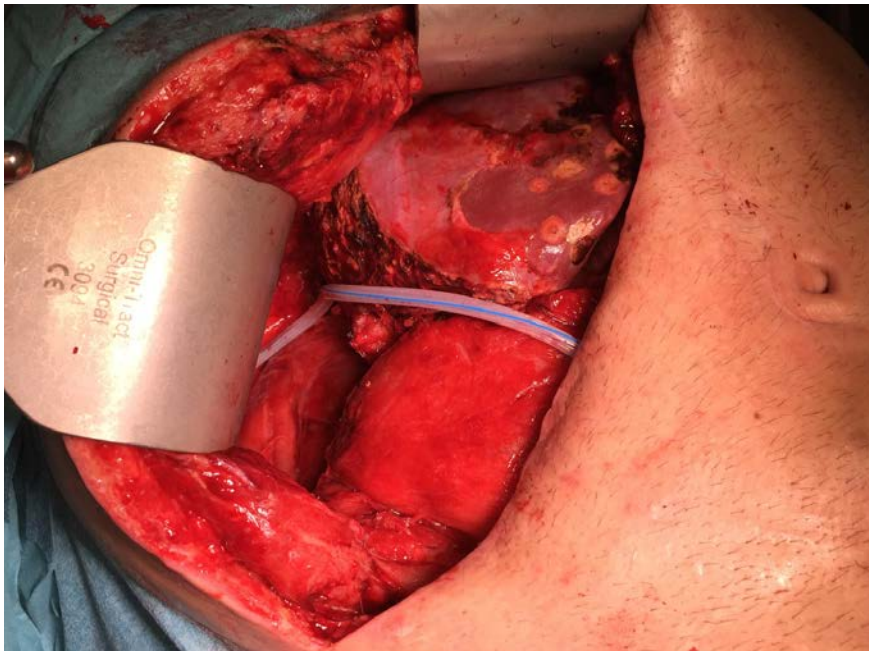



Seg 1, 2 & 3
559.140 cm³



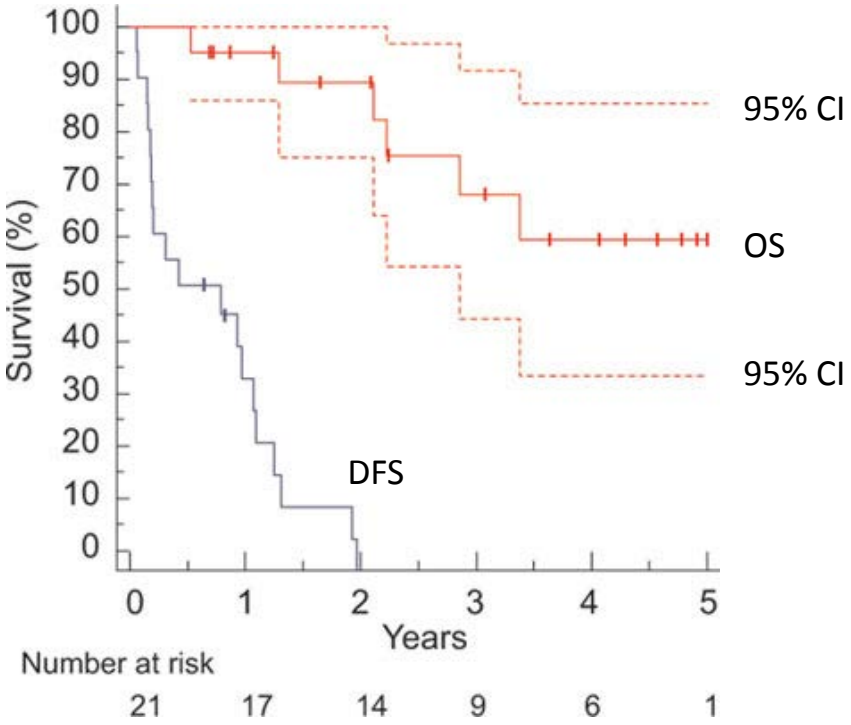






Liver Transplantation for Nonresectable Liver Metastases From Colorectal Cancer

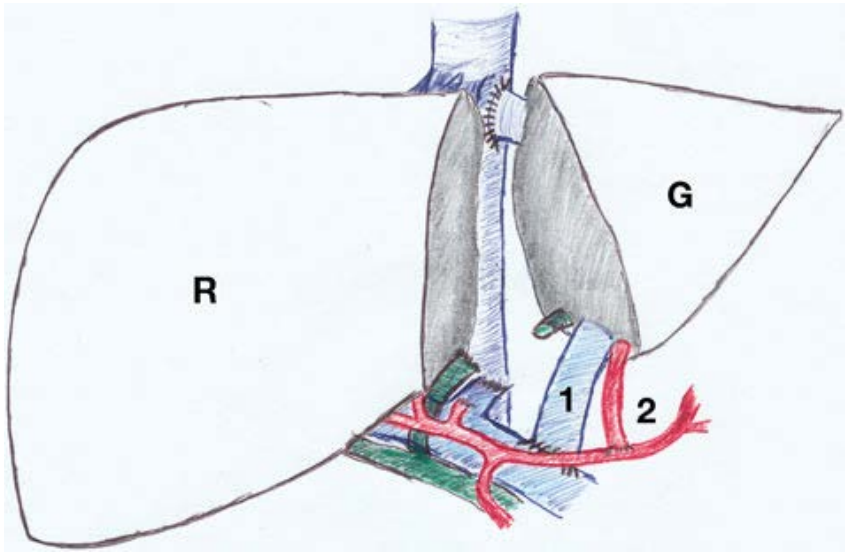
Morten Hagness, MD,† Aksel Foss, MD, PhD,*† Pål-Dag Line, MD, PhD,* Tim Scholz, MD, PhD,* Pål Foyn Jørgensen, MD, PhD,* Bjarte Fosby, MD,*† Kirsten Muri Boberg, MD, PhD,‡ Øystein Mathisen, MD, PhD,§ Ivar P. Gladhaug, MD, PhD,†§ Tor Skatvedt Egge, MD,¶ Steinar Solberg, MD, PhD,‖ John Hausken, MD,** and Svein Dueland, MD, PhD††*



A Novel Concept for Partial Liver Transplantation in Nonresectable Colorectal Liver Metastases

The RAPID Concept

Pål-Dag Line, MD, PhD, Morten Hagness, MD, PhD,* Audun Elnaes Berstad, MD, PhD,† Aksel Foss, MD, PhD,*§ and Svein Dueland, MD, PhD‡*



Hagness M, et al. Ann Surg 2013;257:800–806
Line P, et al. Ann Surg 2015,262:e5–e9

Resectability alone is a bad predictor of survival after liver resection for CRCLM

Predictors of recurrence

- Nordlinger
- Fong
- Nagashima
- Konopke
- Sofocleous
- Basingstoke

- Age
- T-stage
- N-stage
- Primary tumor differentiation
- Size of largest metastasis
- Number of metastasis
- Disease-free interval to LM
- CEA level at time of hepatectomy
- Extra-hepatic metastasis

Dupré A, et al. J Surg Oncol. 2018;117:1330-1336

Curative intervention for CRC metastases – the post 2010 paradigm

OMD – oligometastatic disease

- metastases at 2-3 sites, n ≤ 5 (or sometimes more)
- predominantly visceral (liver, primary, lung, peritoneum, nodes and ovary)
- lesions in bones and brain are excluded

Van Cutsem E, et al. Annals of Oncology 2016;27:1386-1422

Curative intervention for CRC metastases – the post 2010 paradigm

OMD

- potentially curative approach

Non-OMD

- long-term disease control, potentially contributing to OS (although unlikely, potentially cure)

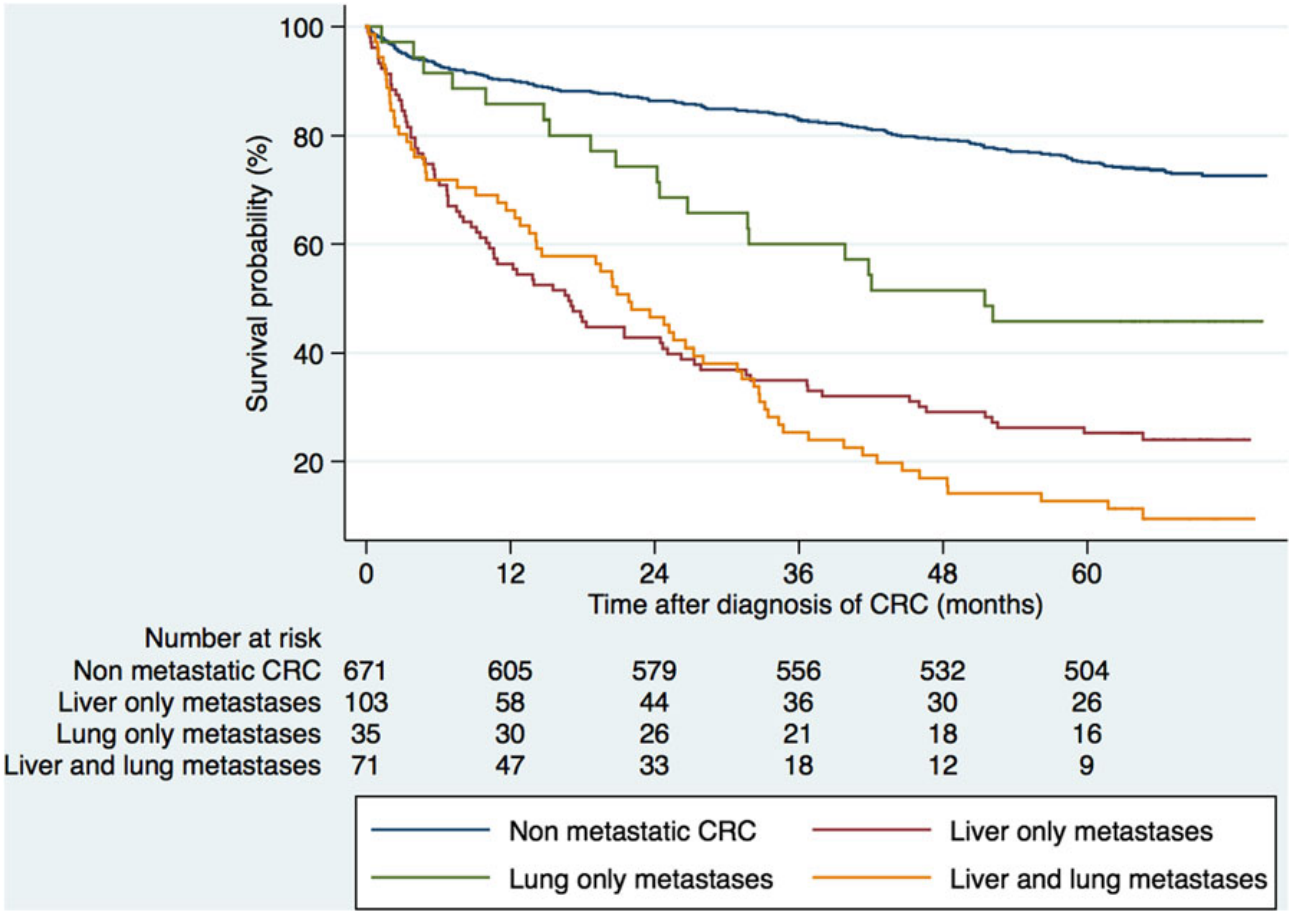
Van Cutsem E, et al. Annals of Oncology 2016;27:1386-1422

Survival (OS) liver metastases

BSC vs. palliative chemotherapy, median survival 0.24 versus 1.2 years, $p < 0.001$
Palliative chemotherapy vs. curative intended interventions, median survival 1.2 vs. 4.7 years, $p < 0.001$

Engstrand J, Jonas E, et al. BMC Cancer. 2018;18:78

Survival (OS) liver and lung metastases



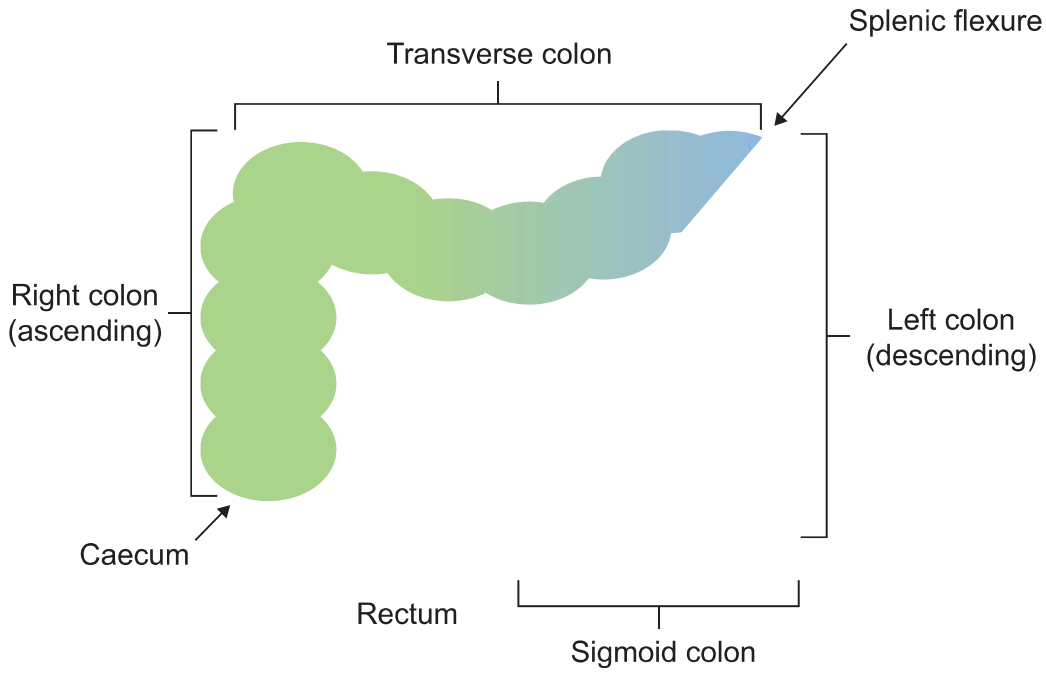
Liver and lung vs. liver-only metastases, median survival 1.8 and 1.4 years, p = 0.204
Liver-only vs. lung-only metastases, median survival 1.4 and 4.3 years, p = 0.006
Lung-only metastases vs. non-metastatic CRC p < 0.001

Engstrand J, Jonas E, et al. BMC Cancer. 2018;18:78

Midgut versus hindgut CRC

Differences

- microbiome
- clinical
- chromosomal
- molecular

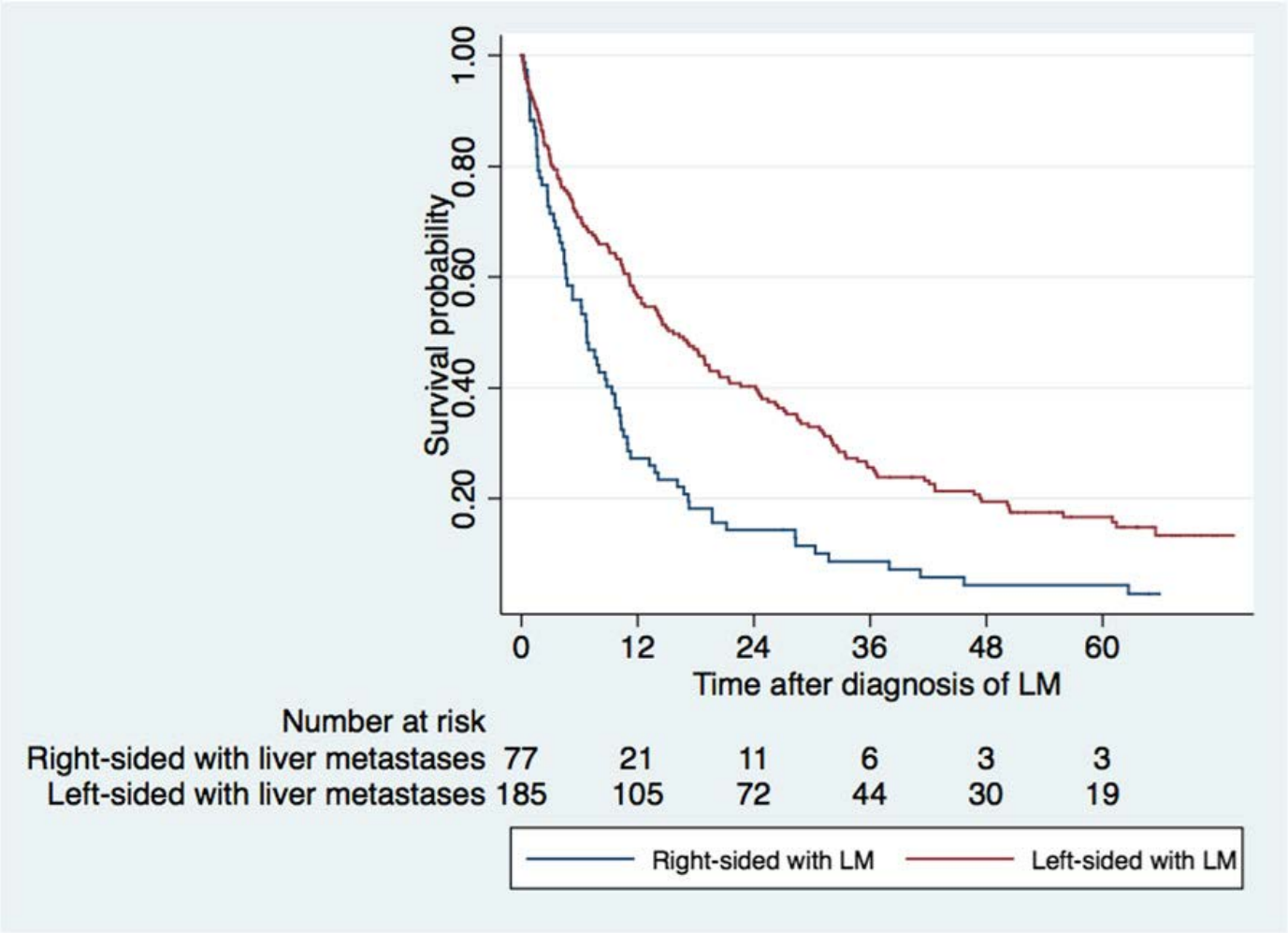


Midgut versus hindgut CRC

- Liver metastases were more frequent in hindgut cancers (28.4% versus 22.1%, p = 0.029)
- Lung metastases were more frequent in hindgut cancers (19.7% versus 13.2%, p = 0.010)
- Peritoneal metastases were more frequent in midgut cancers (10.6% versus 5.5%, p = 0.003)
- Patients with liver metastatic hindgut cancer were more often resected, compared to patients with liver metastatic midgut cancer (30.8% versus 14.2%, p = 0.005)

Engstrand J, Jonas E, et al. BMC Cancer. 2018;18:78

Survival (OS) midgut versus hindcut CRC + LM

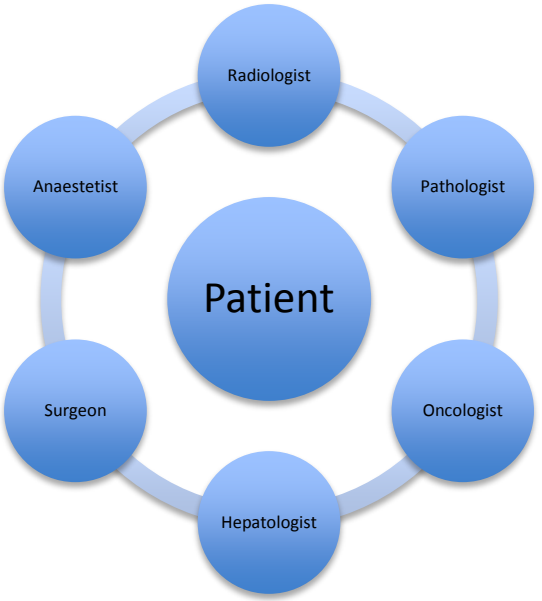


Midgut versus hindgut cancer with liver metastases (median survival 17.7 versus 6.7 months) ($p < 0.001$)

Survival (OS) midgut versus hindcut CRCLM

Resected liver metastatic hindgut versus midgut cancer (p = 0.012)
Non-resected liver metastatic hindgut versus midgut cancer (p = 0.007)

MDT assessment



In a patient with synchronously detected bi-lobar CRCLM there are more than 2 000 000 treatment options

Conclusions

- New indications for curative intervention for CRCLM
- Think technical, but also oncological
- Centralization and centres of excellence
- No treatment of M1 patients before MDT assessment

Thank you