Management of synchronous colorectal cancer liver metastases

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- Definition and terminology
- Prevalence of synchronous CRCLM
- Detection and work-up
- Treatment

Incidence of colorectal cancer liver metastases (CRCLM)

Incidence of synchronous colorectal cancer liver metastases (CRCLM)

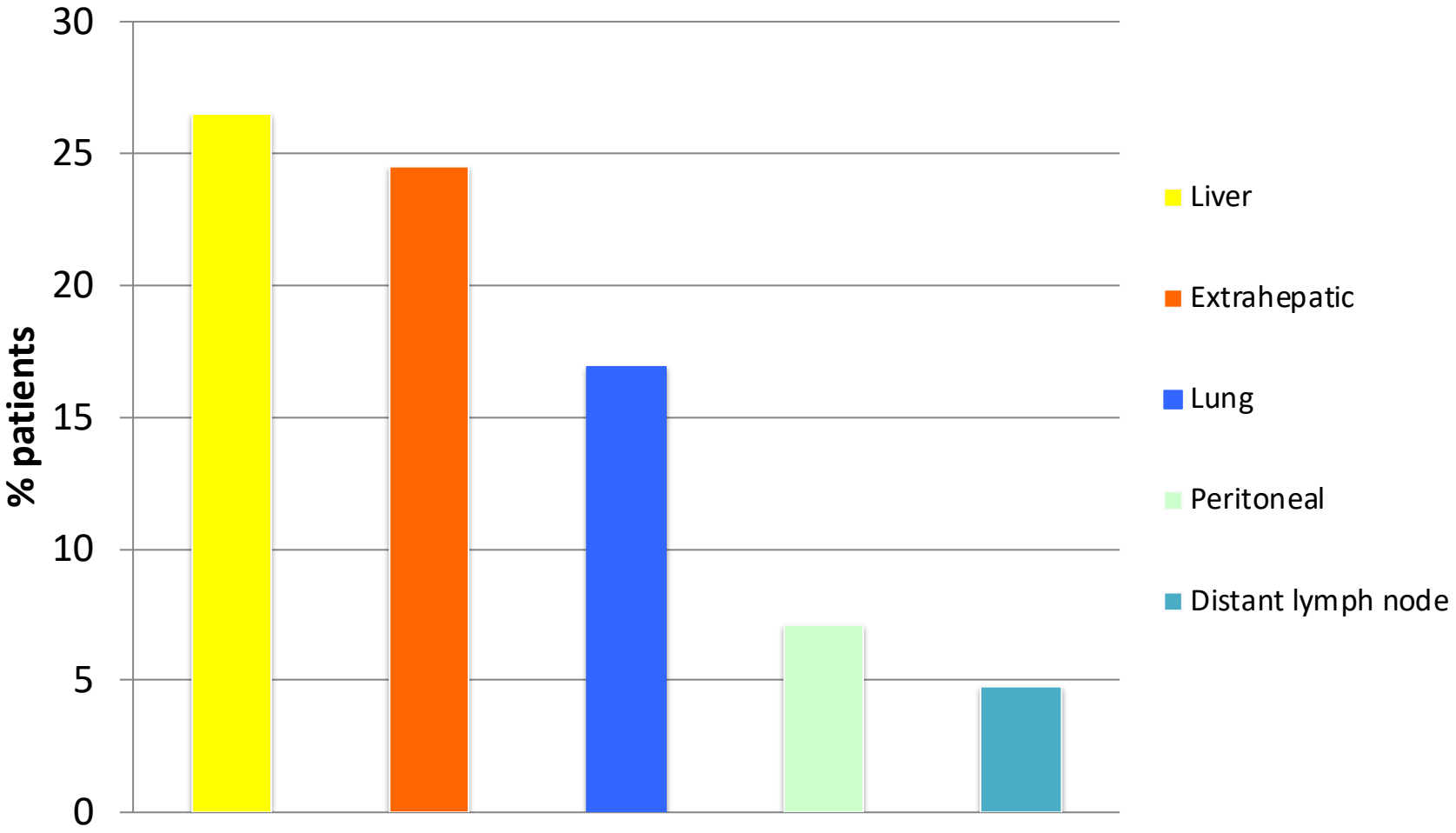
Incidence of colorectal cancer liver metastases (CRCLM)

- Frequently reported as 40-50% of patients with colorectal cancer (CRC)

- True incidence – population-based studies
  - Manfredi et al. – 27.3% (5-year follow-up)
  - Hackl et al. – 24.7% (5-year follow-up)
  - Engstrand J et al. – 26.5% (5-year follow-up)

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

Definition – synchronous vs. metachronous

Definition

There is no consensus on the definition of synchronous vs. metachronous metastases

- At diagnosis of the primary tumour
- 3 months afterwards
- 6 months afterwards
- 12 months afterwards

Synchronous and metachronous liver metastases in patients with colorectal cancer—towards a clinically relevant definition

Jennie Engstrand[1*], Cecilia Strömberg[2], Henrik Nilsson[1], Jacob Freedman[1] and Eduard Jonas[2,3]

Table 4 Summary of time points for defining synchronous vs. metachronous and prognostic significance as measured by OS and DFS in publications in 2005–2018

Defining time point	Studies (*n*)	Prognostic value			
		OS significant	OS non-significant	DFS significant	DFS non-significant
Primary tumour diagnosis/surgery	18	9	9	4	8
Three months post-primary tumour diagnosis/surgery	4	2	2	0	1
Six months post-primary tumour diagnosis/surgery	12	4	8	0	5
Twelve months post-primary tumour diagnosis/surgery	7	0	7	0	1
Total	41	15	26	4	15

OS overall survival, *DFS* disease-free survival

Engstrand J, Jonas E. et al. World J Surg Oncol. 2019 Dec 26;17(1):228. doi: 10.1186/s12957-019-1771-9

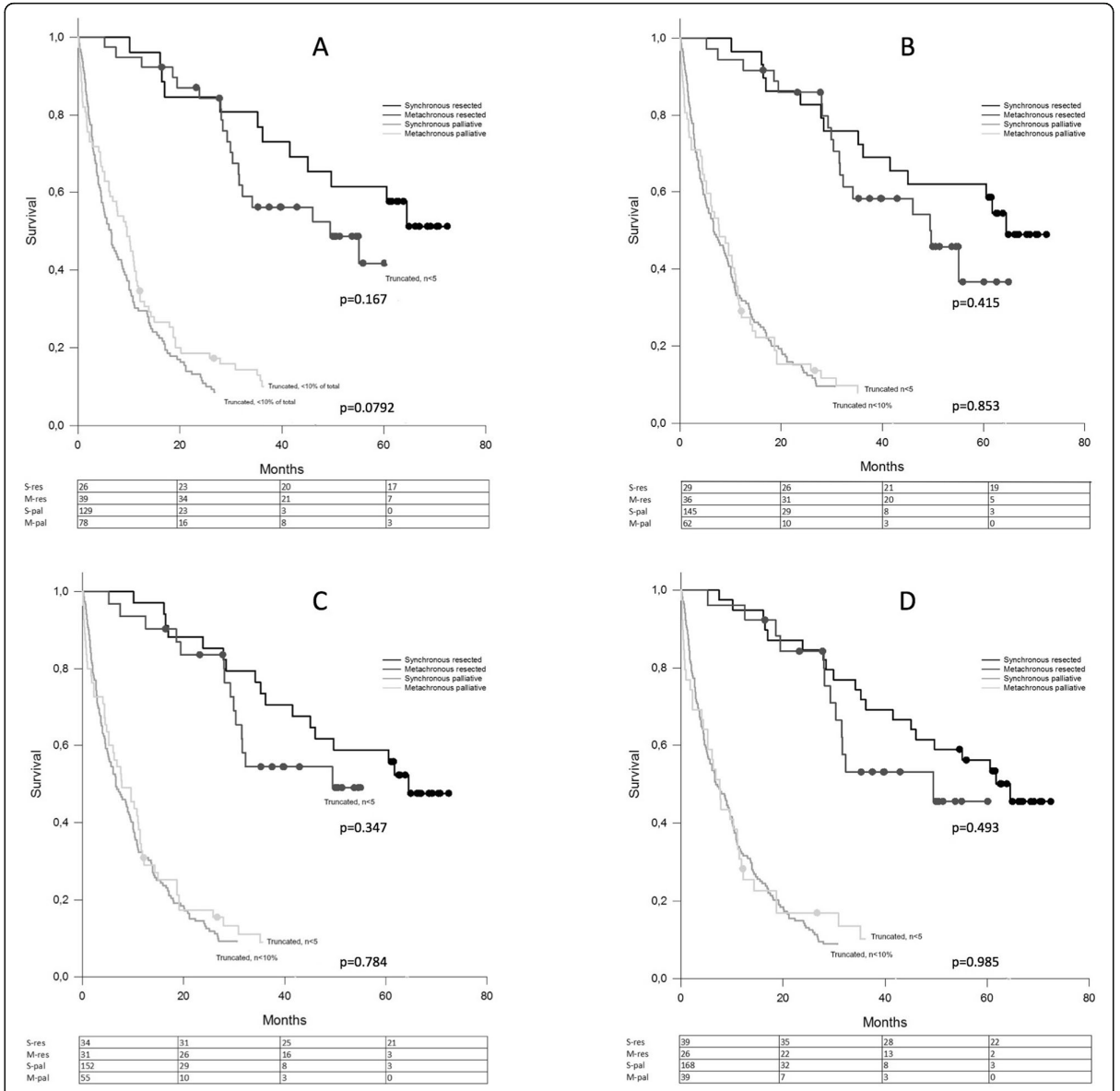


Fig. 2 a–**d** Overall survival curves for synchronous and metachronous detected metastases. Operated and non-operated patients shown for the different synchronous/metachronous cut-off points at **a**, detection of the primary tumour (non-operated, palliative)/operation for the primary tumour (resected) and **b**, 3 months, **c**, 6 months and **d**, 12 months after detection/resection of the primary tumour

Engstrand J, Jonas E. et al. World J Surg Oncol. 2019 Dec 26;17(1):228. doi: 10.1186/s12957-019-1771-9

Terminology

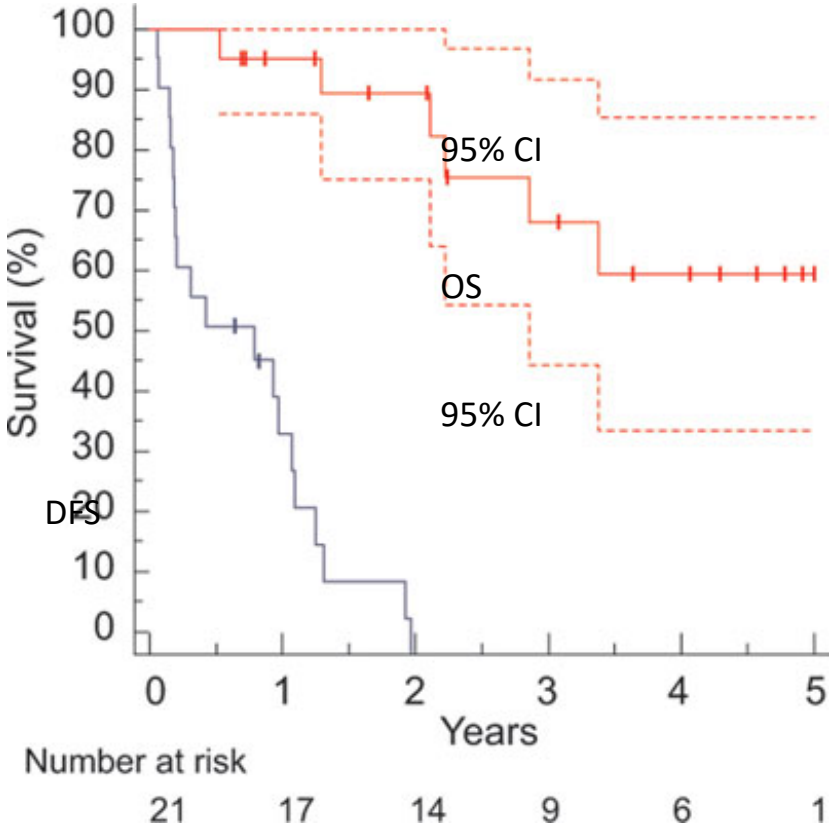
- CRCLMs are always synchronous
- Detection is synchronous or metachronous

CRCLMs are always synchronous

- After CRC removal no new LMs can form
- Are detectable at CRC presentation

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††*



Hagness M, et al. Ann Surg 2013;257:800–806

Detection is synchronous or metachronous

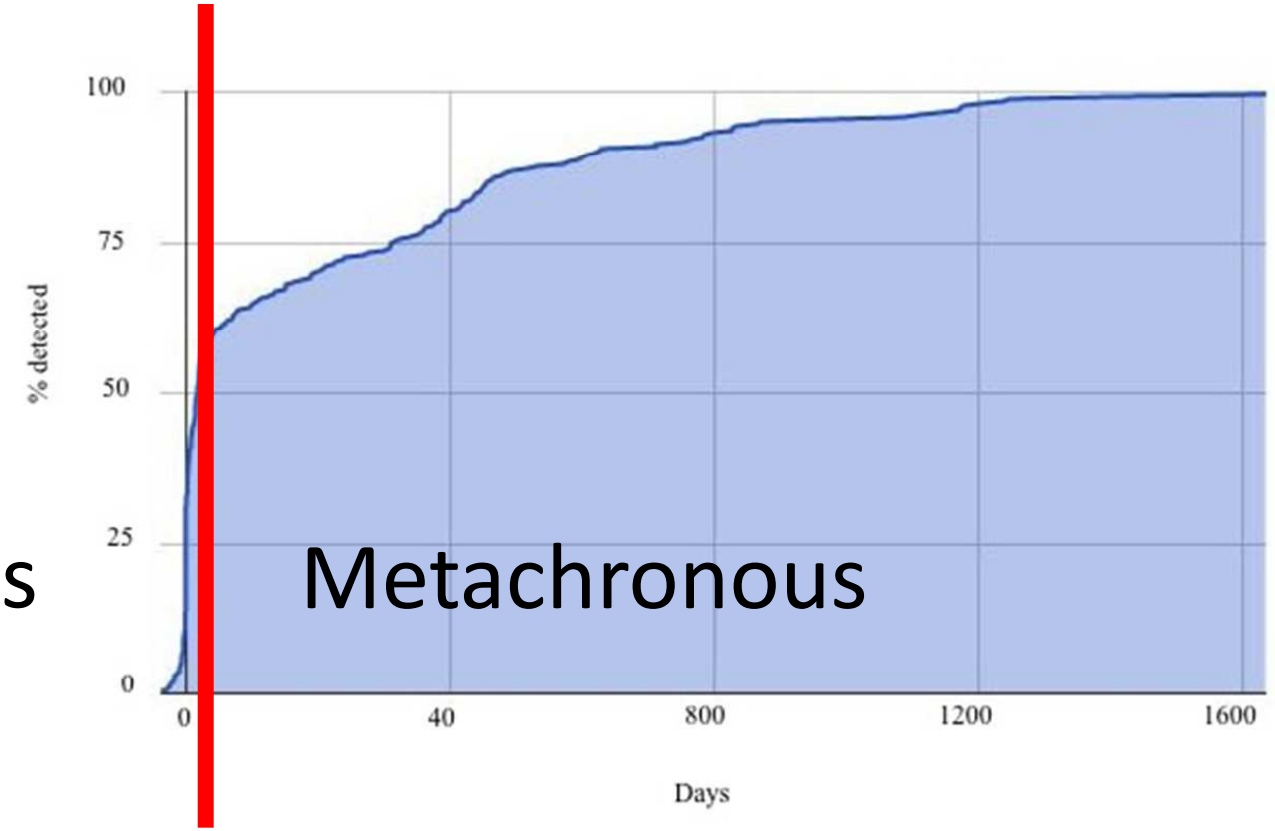
Definition

Metastases diagnosed at the time of diagnosis of the primary tumour and in patients operated for CRC at the time of operation

- Semantically correct – the primary tumour and metastases have to be present at the same time
- Diagnosing metastatic disease at the time of diagnosis of the primary tumour has got important therapeutic implications

Prevalence

Synchronous

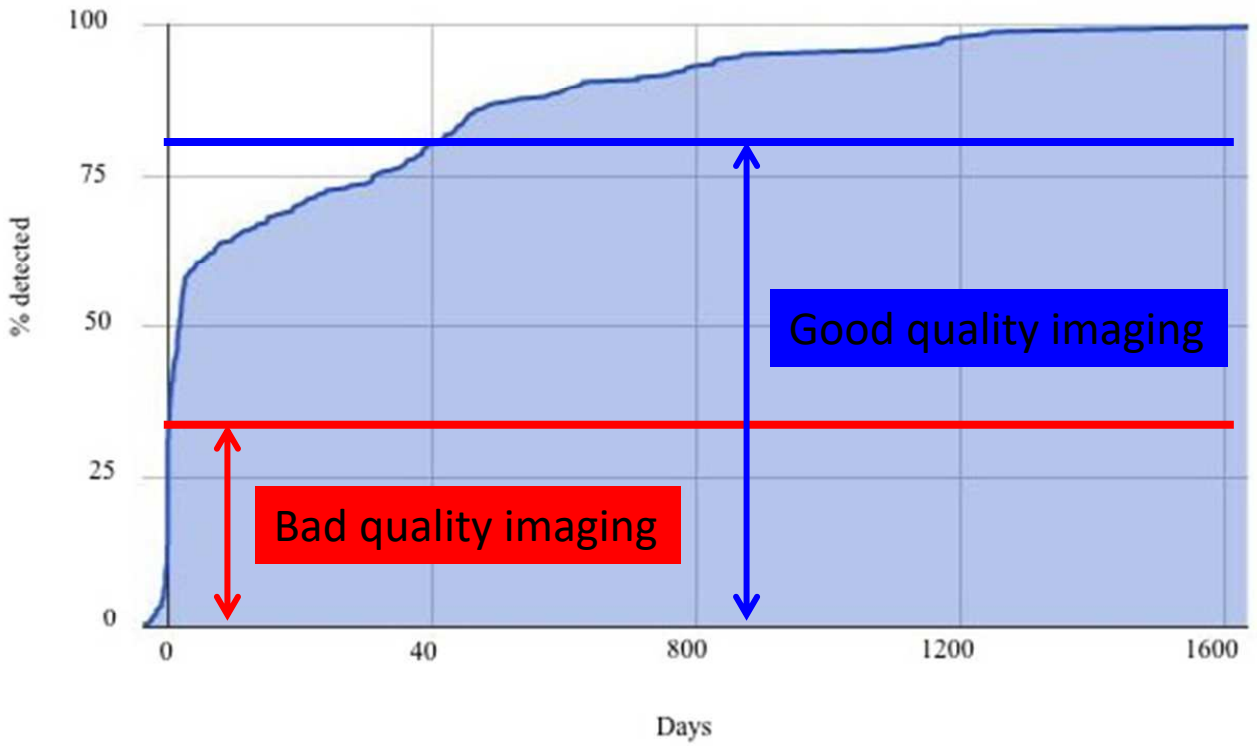


Metachronous

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

CRCLMs are synchronous in all patients! The detection varies!

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



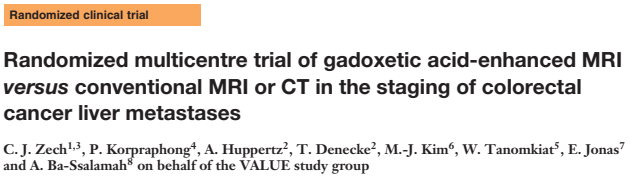
% synchronous detection is the strongest quality parameter for pre- and peri-operative liver imaging

Detection and work-up for CRCLM

- Ultrasound (US))
  - Sonovue
  - Sonazoid
- CE multidetector CT (CE-MDCT) 4-phase
  - Iodine-based contrast
- Magnetic resonance imaging (MRI)
  - Extracellular contrast
  - Hepato-cellular contrast

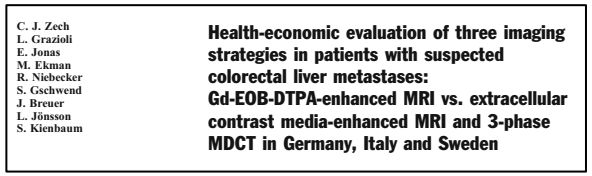
MRI is still widely regarded as a problem-solving modality in unclear cases, rather than a first-line imaging modality

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

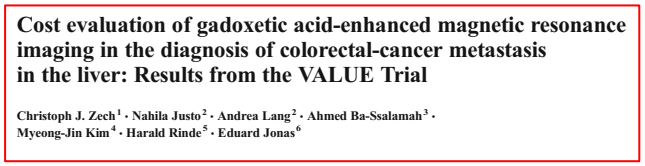

Randomized clinical trial

Randomized multicentre trial of gadoxetic acid-enhanced MRI *versus* conventional MRI or CT in the staging of colorectal cancer liver metastases

C. J. Zech[1,3], P. Korpraphong[4], A. Huppertz[2], T. Denecke[2], M.-J. Kim[6], W. Tanomkiat[5], E. Jonas[7] and A. Ba-Ssalamah[8] on behalf of the VALUE study group


C. J. Zech
L. Grazioli
E. Jonas
M. Ekman
R. Niebecker
S. Gschwend
J. Breuer
L. Jönsson
S. Kienbaum

Health-economic evaluation of three imaging strategies in patients with suspected colorectal liver metastases: Gd-EOB-DTPA-enhanced MRI vs. extracellular contrast media-enhanced MRI and 3-phase MDCT in Germany, Italy and Sweden


Cost evaluation of gadoxetic acid-enhanced magnetic resonance imaging in the diagnosis of colorectal-cancer metastasis in the liver: Results from the VALUE Trial

Christoph J. Zech[1] · Nahila Justo[2] · Andrea Lang[2] · Ahmed Ba-Ssalamah[3] · Myeong-Jin Kim[4] · Harald Rinde[5] · Eduard Jonas[6]

MRI with Primovist

- More sensitive - detect more
- Surgery more often performed
- If used as primary modality – no further imaging required
- Less often change pre-operative plan
- Generally a more economic strategy

Zech C, Jonas E, et al. Eur Radiol. 2009;19:S753–S763
Zech C, Jonas E, et al. Br J Surg. 2014;101:613-21
Zech C, Jonas E, et al. Eur Radiol. 2016;26:4121-4130

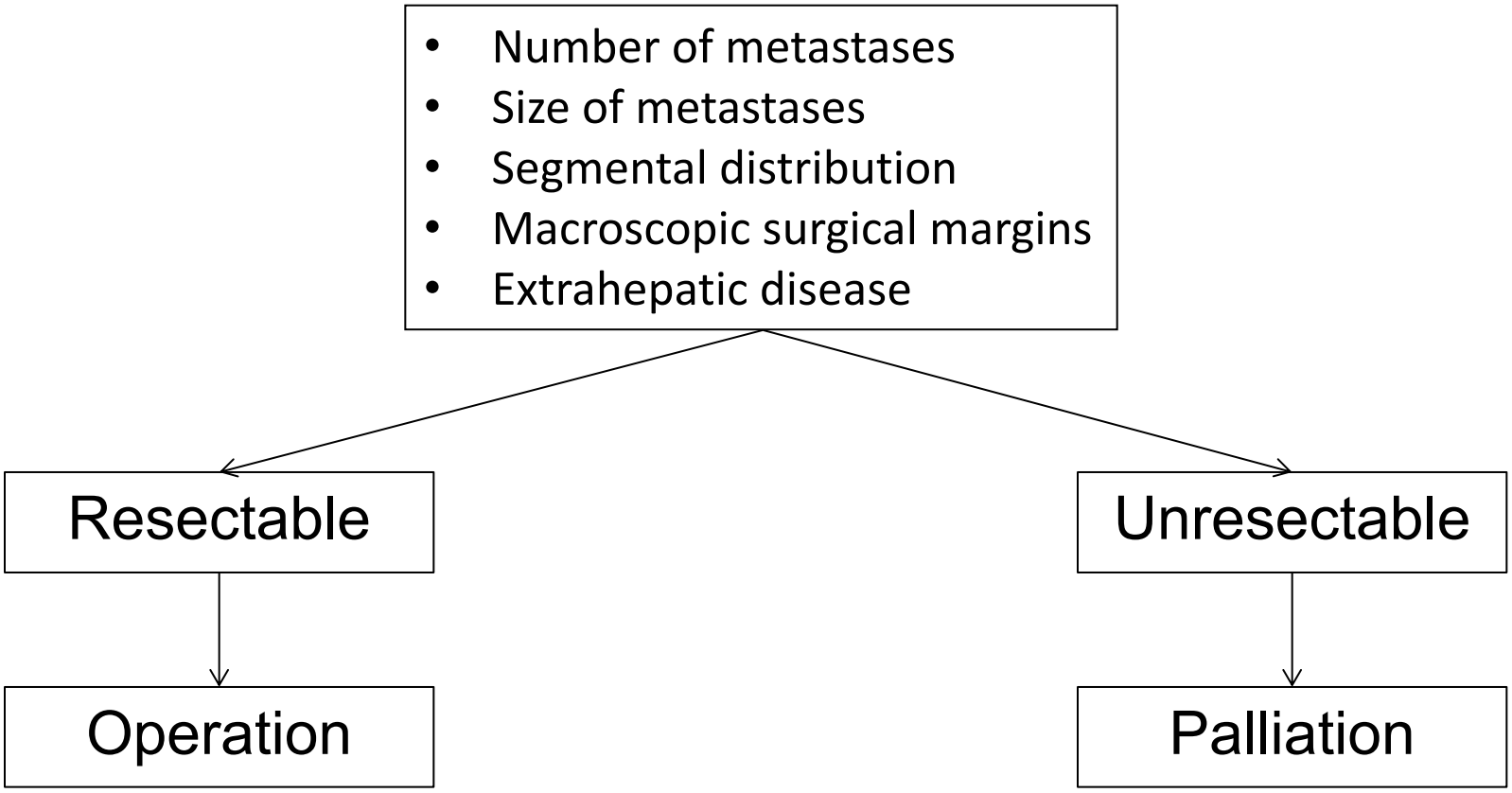
Treatment

All the permutations of modern CRCLM treatment apply but influenced by timing of the liver intervention

- Before CRC operation
- Simultaneous to CRC operation
- After CRC operation

Curative intervention for CRCLM - the 1900's paradigm

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



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

Curative intervention for CRCLM – 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

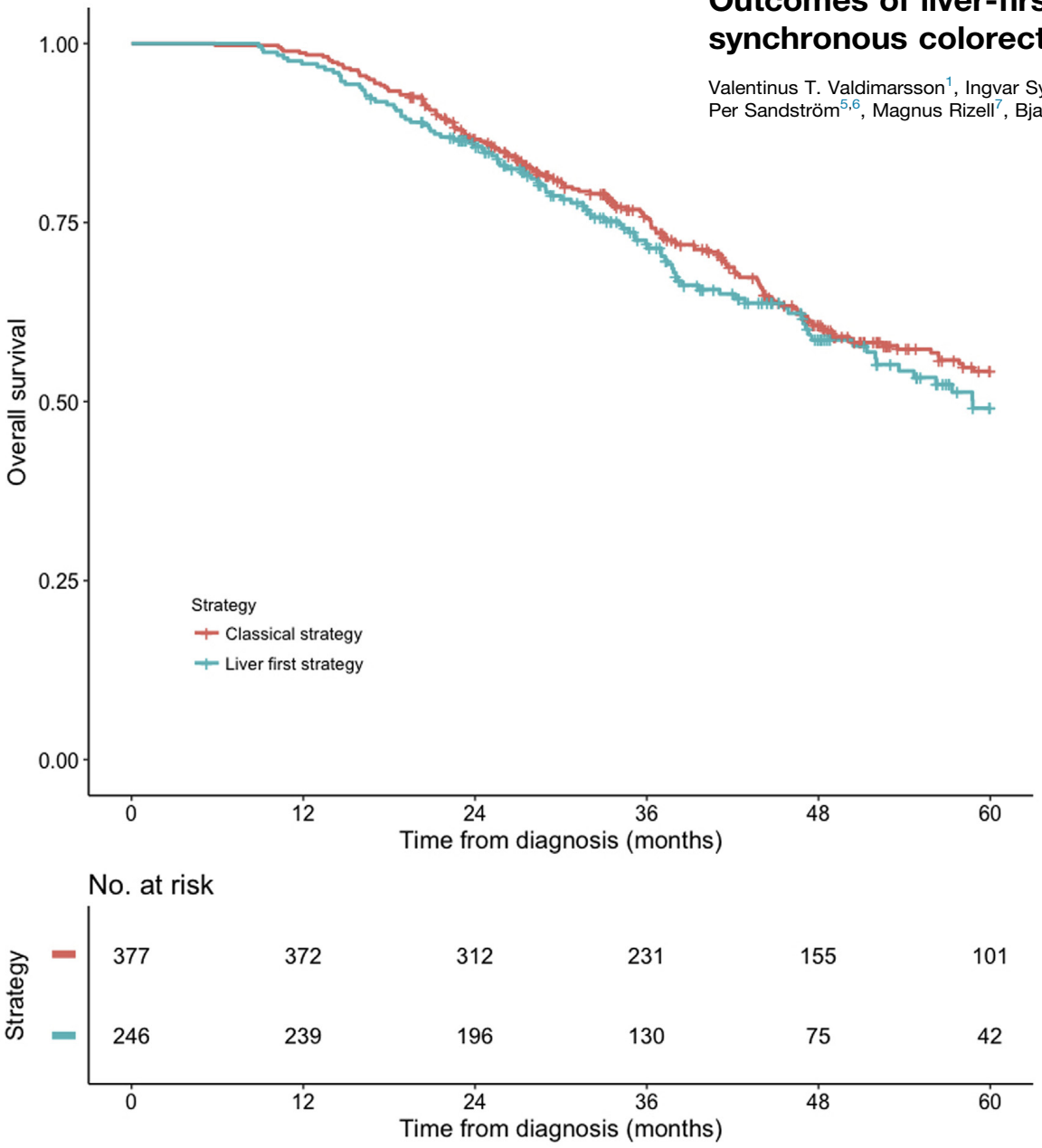
Liver first operation for synchronous CRCLM

- Indications:
  - extensive liver disease /borderline resectability
  - rectal cancer
- Advantages:
  - avoids risk of progression beyond resectability
  - rectal cancer – liver resection in post-radiation pause
- Results:
  - similar survival to colon first strategy

ORIGINAL ARTICLE

Outcomes of liver-first strategy and classical strategy for synchronous colorectal liver metastases in Sweden

Valentinus T. Valdimarsson[1], Ingvar Syk[2], Gert Lindell[1], Agneta Norén[3], Bengt Isaksson[3,4], Per Sandström[5,6], Magnus Rizell[7], Bjarne Ardnor[8] & Christian Sturesson[1,4]



Valdimarsson VT, et al. HPB. 2018;20:441-447

Simultaneous vs. delayed operation for synchronous CRCLM

- Indication – easy colon and easy liver

- Results:
  - shorter hospital stay for simultaneous
  - similar perioperative morbidity
  - similar long-term survival

Guo Y, et al. Am Surg. 2018 Feb 1;84:192-200

Simultaneous vs. delayed operation for synchronous CRCLM

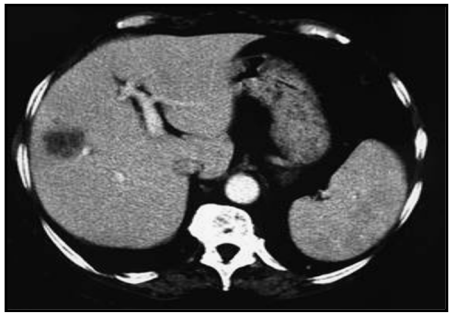
- Indication – high-risk colon and high-risk liver

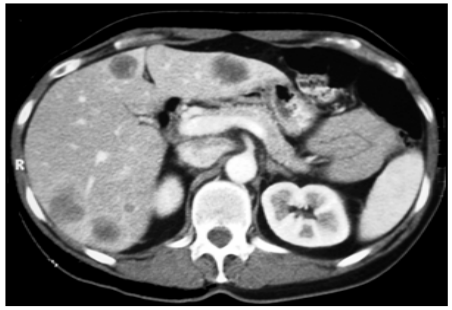
- Results:
  - shorter hospital stay for simultaneous
  - similar perioperative morbidity
  - similar long-term survival

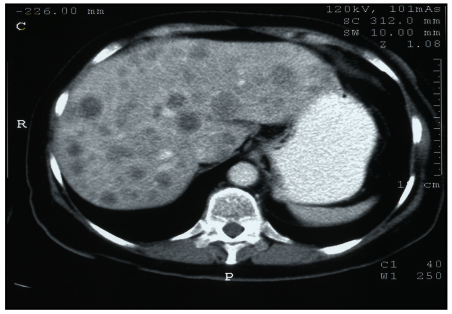
Guo Y, et al. Am Surg. 2018 Feb 1;84:192-200

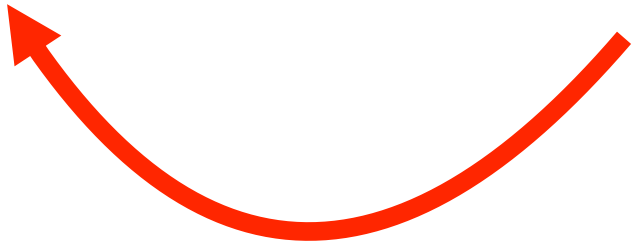
Resectable vs. unresectable

Group 1	Group 2	Group 3
Readily resectable with a single intervention (15-25%)	Unresectable but potentially resectable with multimodality conversion (15-20%)	Unresectable and unlikely to become resectable (60-70%)









Conversion strategies

Tumour-targeting

- Conversion chemotherapy
- Staged surgery
- Local ablation techniques

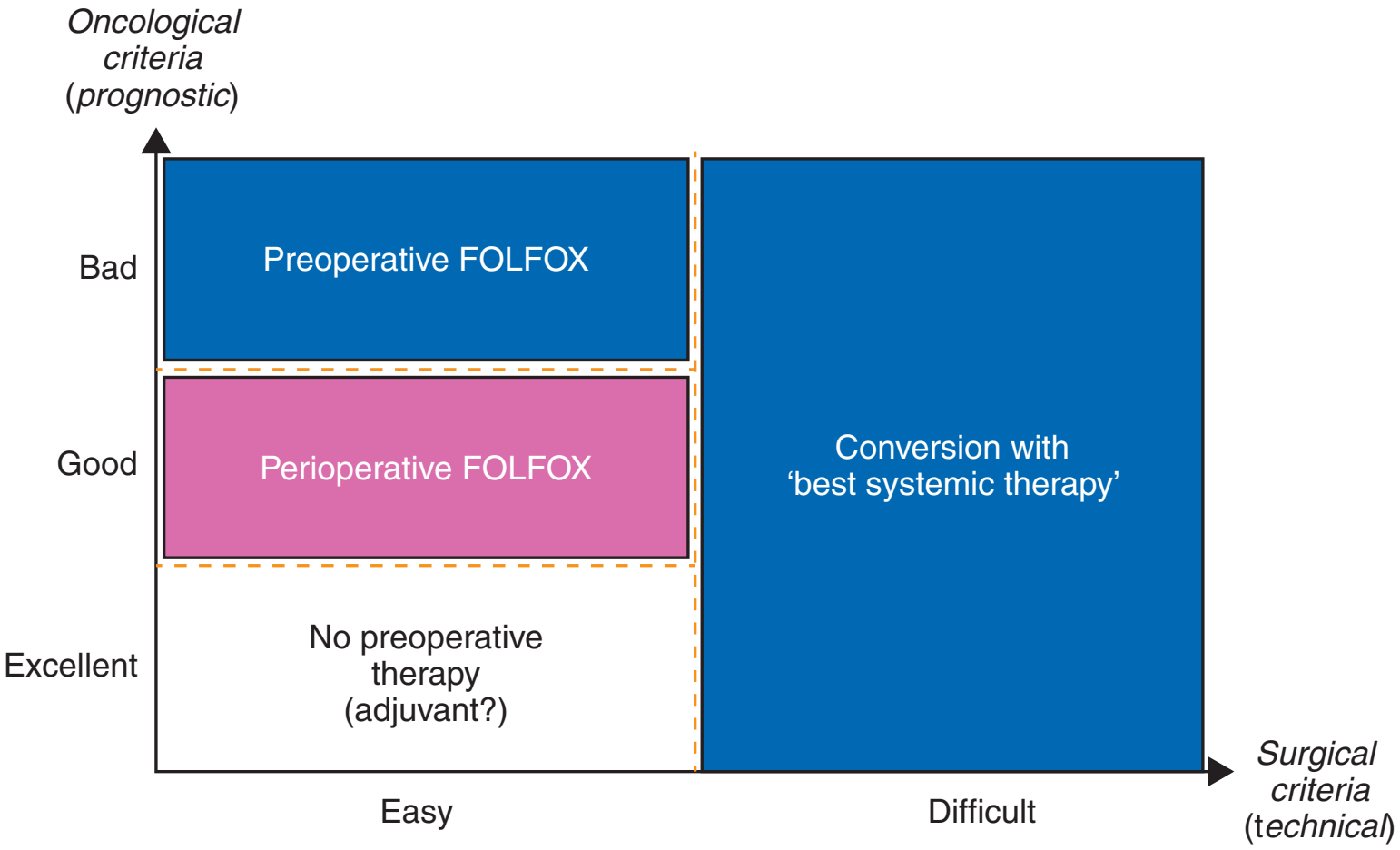
FLR-targeting

- Portal vein embolization
- Portal vein ligation

Combination

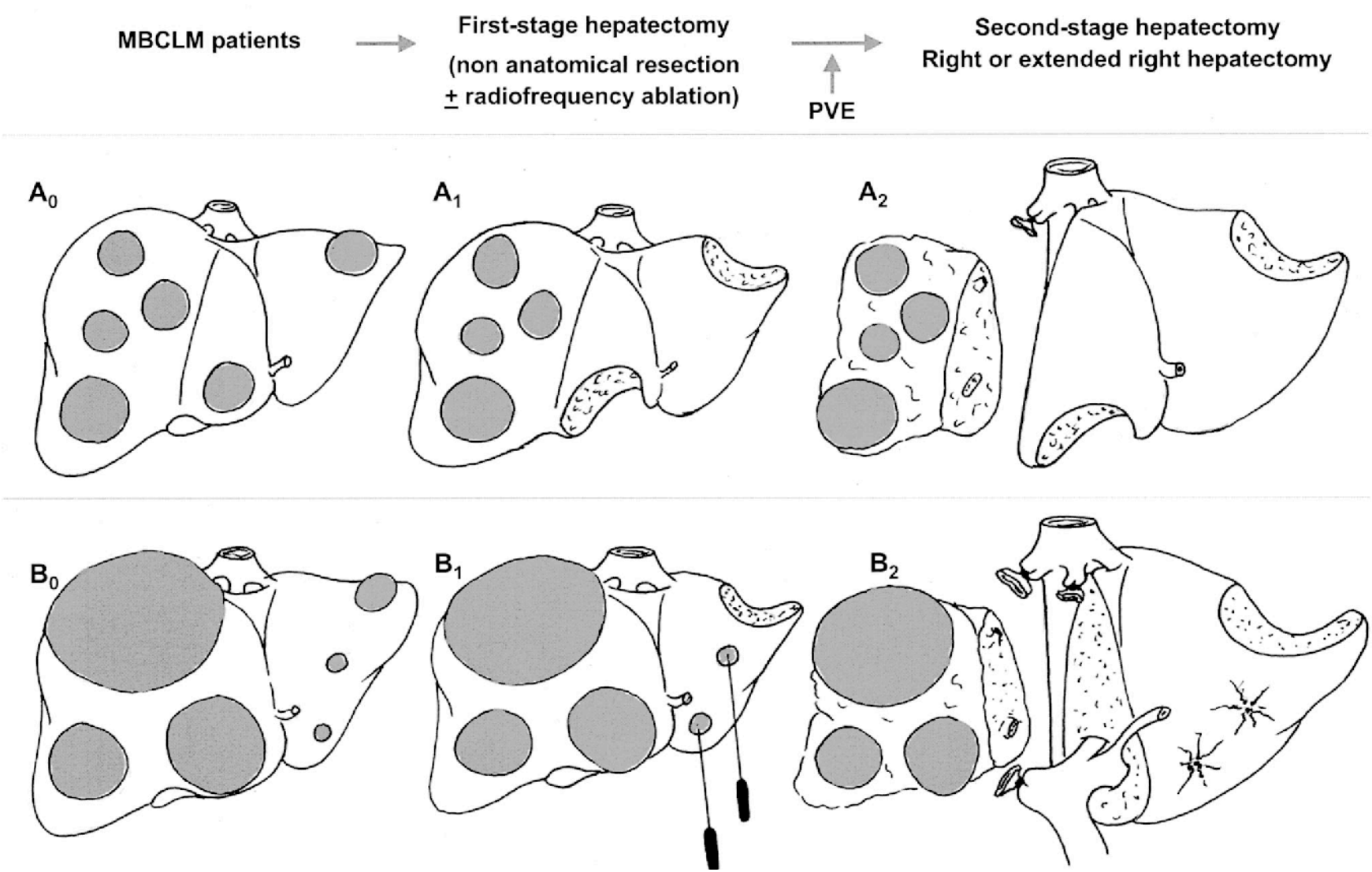
- In situ liver split (ALPPS)
- Liver transplant

Chemotherapy



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

Two-stage liver resection

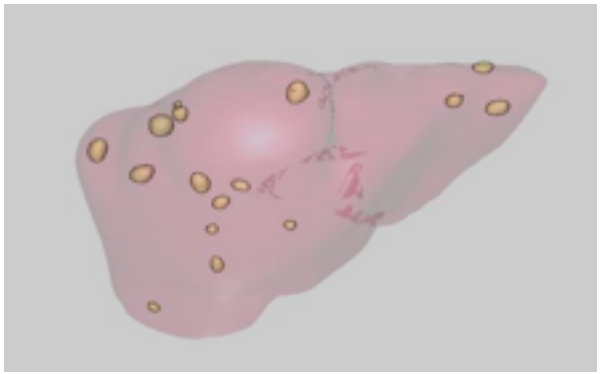


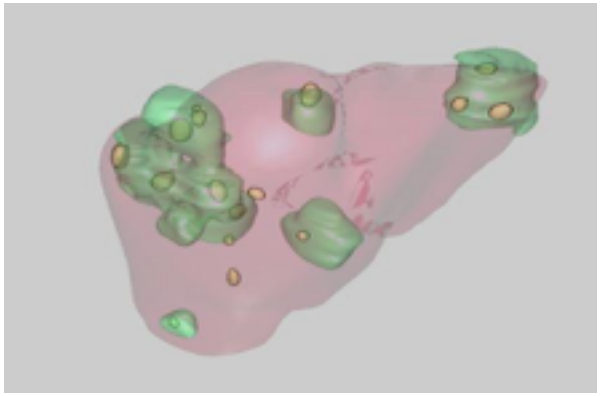
A multiple microwave ablation strategy in patients with initially unresectable colorectal cancer liver metastases – A safety and feasibility study of a new concept

J. Engstrand [a], H. Nilsson [a], A. Jansson [b], B. Isaksson [b], J. Freedman [a], L. Lundell [b], E. Jonas [a,*]

[a] *Karolinska Institutet, Department of Clinical Sciences, Danderyd Hospital, Division of Surgery, Stockholm, Sweden*

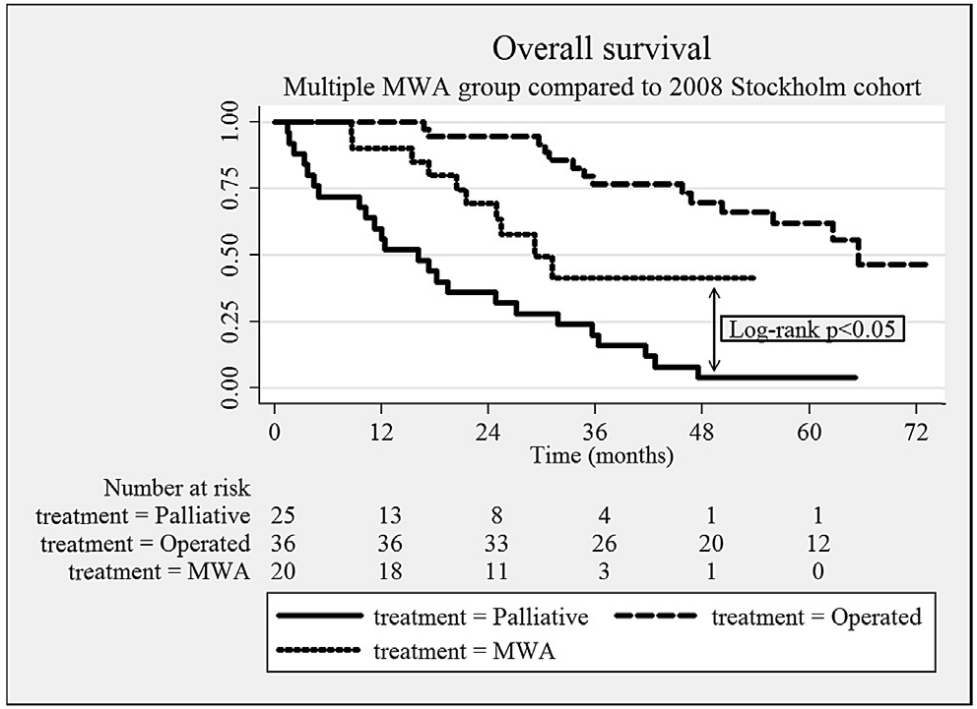
[b] *Division of Surgery, Department of Clinical Sciences, Intervention and Technology (CLINTEC), Karolinska Institutet at Karolinska University Hospital, Huddinge, Sweden*





Treatment-related parameters in the MWA group.

	Median (min–max)
Number of ablations	7 (4–22)
Operation time (min)	235 (112–475)
Length of hospital stay (days)	10 (2–24)
Relation of ablation to colorectal surgery	***n***
Before	3
Simultaneously	12
After	5
Navigation	***n***
Ultrasound	13
Computer-assisted	7



Engstrand J, Jonas E, et al. Eur J Surg Oncol. 2014 May 20. [Epub ahead of print]

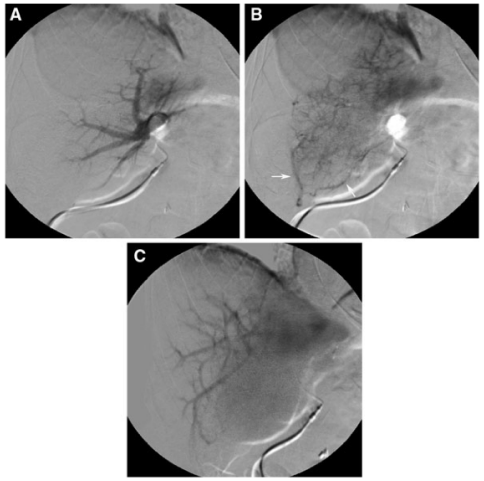
PVE versus PVL

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

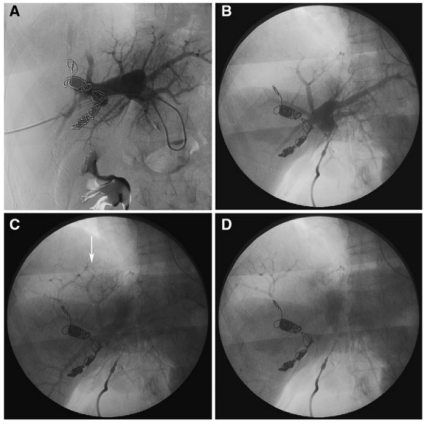
	Type of study (*n*)	Indications (*n*)	POT	One-stage vs TSH	Volume increase after PVL and/or PVE	*p*<
Denys, 1999[26]	Clinical case	LMCRC	PVL: firstly PVE: after failure of PVL	One-stage: yes TSH: no	PVL: failure PVE: After failure 256%	
Broering, 2002[12]	Prospective (34 cases)	LMCRC (17) HCC (2), CC (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

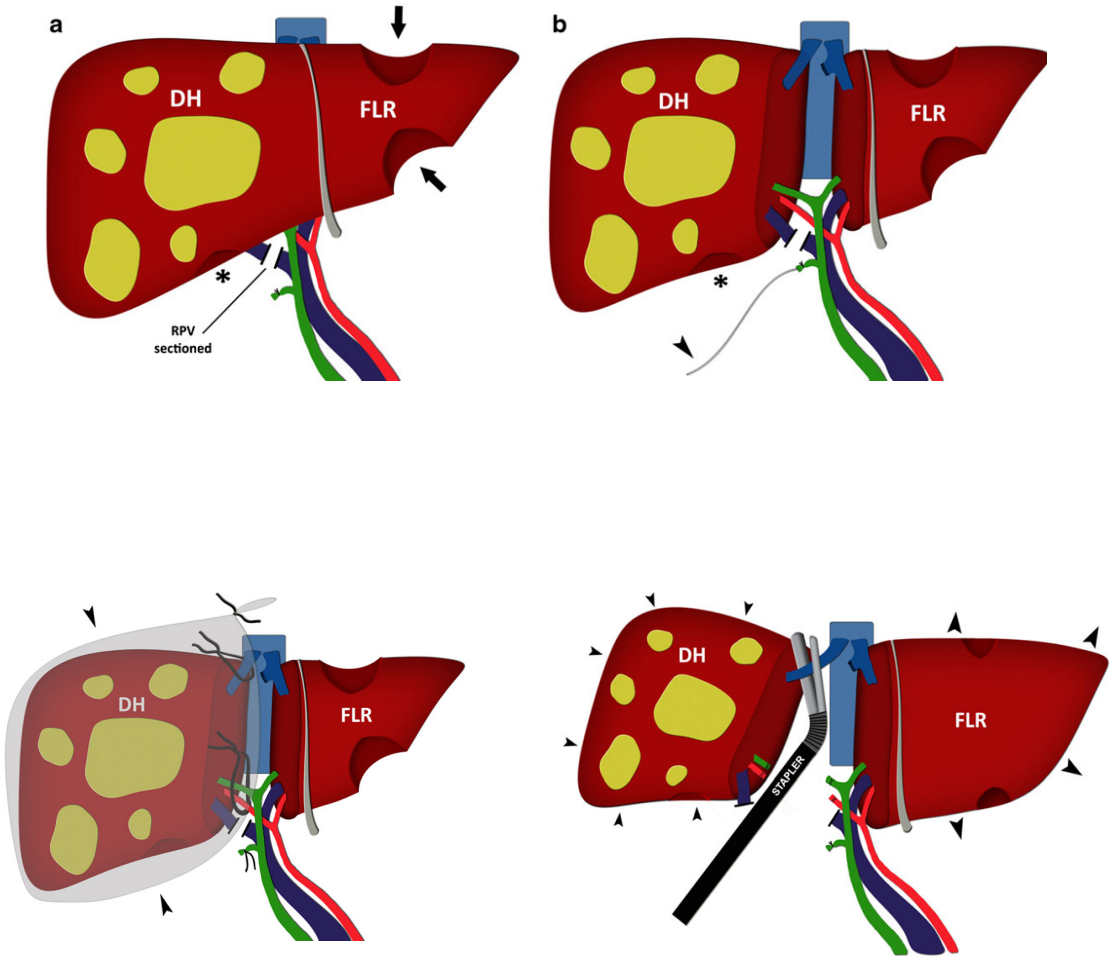


Robles R, et al. Eur J Surg Oncol. 2012;38:586-93

Van Lienden KP, et al. Cardiovasc Intervent Radiol. 2013 Mar 13.]

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



Liver Transplantation for Nonresectable Liver Metastases From Colorectal Cancer

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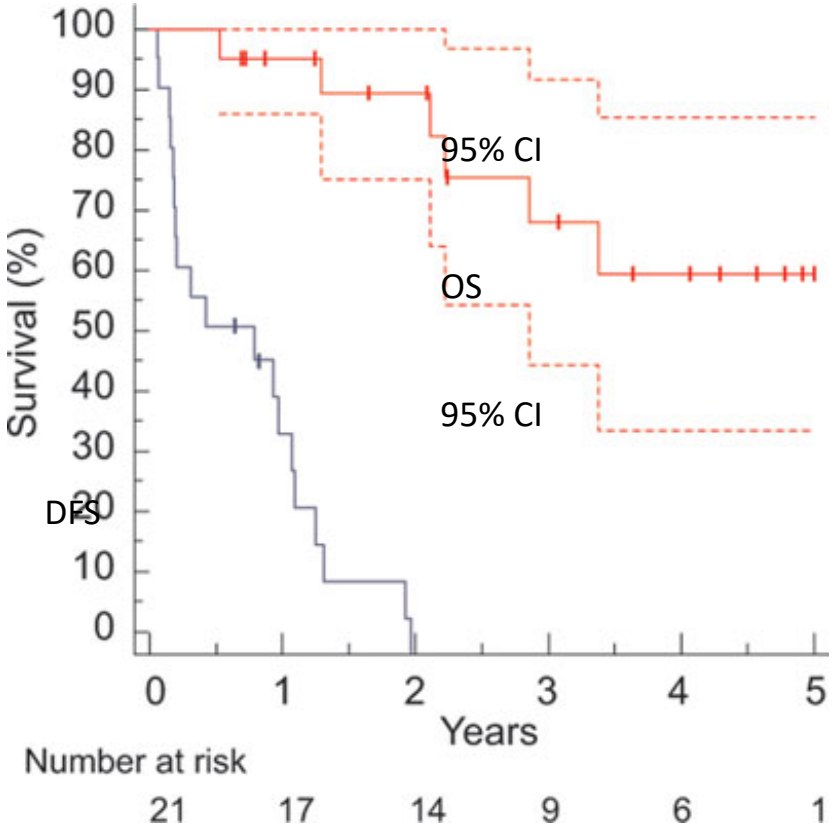
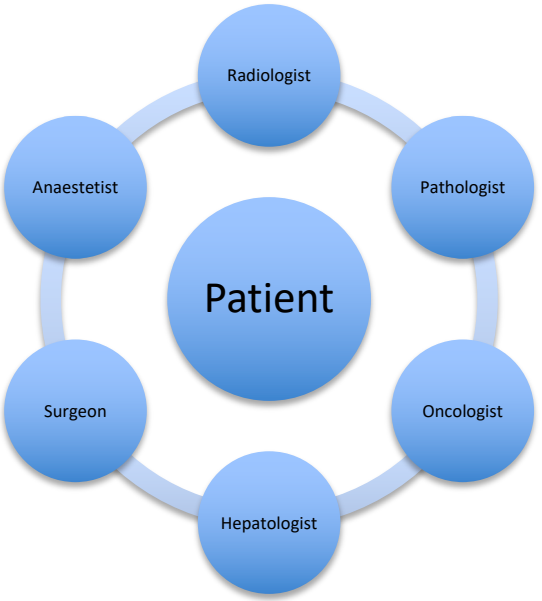


Hagness M, et al. Ann Surg 2013;257:800–806

MDT assessment



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

Thank you