Kontroverze léčby synchronních metastáz karcinomů tlustého střeva a konečníku
Pohled chirurga

Miroslav Ryska

10. pražské mezioborové onkologické kolokvium 23.-25.1.2019

Prague 10. ONCO ONCOLOGY COOPERATION

Treatment controversion in patients with synchronous colorectal liver metastases View of surgeon

Miroslav Ryska

10. pražské mezioborové onkologické kolokvium 23.-25.1.2019

CRLM - colorectal liver metastases

5-year survival of CRLM patients receiving **surgery** and neoadjuvant therapy has increased to up to 50 %

but:

more than about 70 % patients after liver resection develop recurrence in the remnant liver

⟹ surgical resection for resectable CRLM is still a controversial

Hof J et al, Br J Surg 2016; 103: 1055-1062
Omichi K et al, Eur J Surg Oncol 2018; 44: 122-129

CRLM - colorectal liver metastases

Management is complex - colorectal and liver resection, chemotherapy, radiotherapy
- many approaches

Levels of evidence for synchronous metastases is poor
- few recent prospective series
- several retrospective analyses
- number of patients is very limited

evidence-based medicine → experience-based medicine

Viganó L, World J Hepatol 2012; 4: 237-241

CRLM - colorectal liver metastases

Management is complex - colorectal and liver resection, chemotherapy, radiotherapy
- many approaches

Levels of evidence for synchronous metastases is poor
- few recent prospective series
- several retrospective analyses
- number of patients is very limited

evidence-based medicine → **experience-based medicine**

Viganó L, World J Hepatol 2012; 4: 237-241

CRLM - colorectal liver metastases

Management is complex - colorectal and liver resection, chemotherapy, radiotherapy
- many approaches

Levels of evidence for synchronous metastases is poor
- few recent prospective series
- several retrospective analyses
- number of patients is very limited

EBM → **EBM**

Viganó L, World J Hepatol 2012; 4: 237-241

Development of liver resectability definition for CRLM

Ekberg H 1986: < 4 mets, no extrahepatic metastatic disease, resection margin > 1 cm
van Dam RM 2014: > 4 mets in both lobes, centrally located, resectable extrahepatic disease
Viganó L 2015: > 8 mets, no risk factors including extrahepatic disease, no response to chemotherapy
Allard MA 2017: > 10 mets

Ekberg H et al, Br J Surg 1986; 73: 727-731
van Dam RM et al, HPB (Oxford) 2014; 16: 550-559
Viganó L et al, Br J Surg 2015; 102: 92-101
Allard MA et al, Br J Cancer 2017; 117: 604-611

Complications and survival

van Dam RM – extended liver resection vs. traditional indication group		
	major complications	33.1 % vs 19.5 %
	OS	41.4 mo vs. 68.8 mo
	DFS rates	10.2 mo vs. 22.0 mo
	10-year DFS rates	15.8 % vs. 35.5 %
Viganó L –	OS	20.1 % vs. 44.2 %
	RFS rates	13.6 % vs. 28.7 %
Allard MA –	5-year OS	30 %
	R0/R1 3 and 5-year	61 % vs. 39 %

Ekberg H et al, Br J Surg 1986; 73: 727-731
van Dam RM et al, HPB (Oxford) 2014; 16: 550-559
Viganó L et al, Br J Surg 2015; 102: 92-101
Allard MA et al, Br J Cancer 2017; 117: 604-611

Current criteria for resectability of CRLM

- any tumor number
- any tumor distribution in the liver
- stable or resectable extrahepatic disease
  (excl. portal lymphadenopathy)
- functional liver remnant > 20 % of total liver volume
  > 30 - 40 % for severe chemotherapy associated liver dysfunction
- venous involvement amenable to venous resection or reconstruction
- tumor-free margin (1 mm)

Chakedis J et al, Curr Probl Surg 2017; 54: 554-602

Current criteria for resectability of CRLM

Determination of CRLM resectability should be based on oncological principles and technical feasibility as outlined in Hepato-Pancreato-Biliary Expert Consensus Statement 2012

→

extended liver resection: 1 - tumor size < 40 mm
2 - preoperative MRI
3 - adjuvant chemotherapy
4 - negative resection margin +
sufficient liver remnant

no liver resection: 1 - no response to chemotherapy
2 - no resectable extrah. disease

Adams RB et al, HPB (Oxford) 2013; 15: 91-103

Current criteria for resectability of CRLM

Determination of CRLM resectability should be based on oncological principles and technical feasibility as outlined in Hepato-Pancreato-Biliary **Expert Consensus Statement 2012**

extended liver resection: 1 - tumor size < 40 mm
2 - preoperative MRI
3 - adjuvant chemotherapy
4 - negative resection margin + sufficient liver remnant

no liver resection: 1 - no response to chemotherapy
2 - no resectable extrah. disease

Adams RB et al, HPB (Oxford) 2013; 15: 91-103

Synchronous CRLM resectable

Optimal surgical management is still controversial: 3 types

1 – **classic – bowel first** (2 stages)
resection of primary – chemotherapy – after 3 – 6 mo LM
2 – **synchronous resection**
resection of primary and LM in the same surgical procedures
3 – **liver first** (2 stages)
LM – chemo(radio)therapy – resection of primary

Avallance AE et al, Colorectal Dis 2018; 20: 486-495

Synchronous CRLM resectable

Optimal surgical management is still controversial: 3 types

1 – **classic – bowel first** (2 stages)
resection of primary – chemotherapy – after 3 – 6 mo LM
2 – **synchronous resection**
resection of primary and LM in the same surgical procedures
3 – **liver first** (2 stages)
LM – chemo(radio)therapy – resection of primary

In UK 2018: **71.1 % : 14.8 % : 14.2 %** (n = 1.830 pts.)

Avallance AE et al, Colorectal Dis 2018; 20: 486-495

Synchronous CRLM resectable

Ad 1 – **classic – bowel first** (2 stages)

Pro: avoidance of - bowel-related complications
- primary progression

Cons: resectable CRLM become unresectable
liver toxicity of chemotherapy

Ad 3 – **liver first** (2 stages)

Pro: avoidance - LM unresectable
- liver toxicity of chemotherapy
(less FLR is required, less liver- related complications)

Synchronous CRLM resectable

Ad 1 – **classic – bowel first** (2 stages)

Pro: avoidance of - bowel-related complications
- primary progression

Cons: resectable CRLM become unresectable
liver toxicity of chemotherapy

Ad 3 – **liver first** (2 stages)

Pro: avoidance - LM unresectable
- liver toxicity of chemotherapy
(less FLR is required, less liver- related complications)

But: no difference in 5-year OS (54 % vs. 49 %)

Valdimarsson VT et al, HPB (Oxford) 2018; 20: 441-447

Synchronous CRLM resectable

1 and 3: **staged surgical treatment**

- need of second surgery (median time 4.7 – 7.0, 2.0 – 9.0 mo resp.)
- increasing the lenght of hospital stay

- 16.3 – 35 % of liver first and bowel first fail to proceed to the second operation (!!) … disease progression, complications

But: progression means agressive tumor biology ➡ avoids extensive resection

Welah FK et al, Br J Surg 2016; 103: 600-603

Synchronous CRLM resectable

Ad 2 - **one stage operation** in selected pts.

- simultaneous operation is safe
- number is increasing from 26.8 % (2010) to 35.6 % (2015)

But: no difference in OS a DFS compare to 2 stage operations:

1-year survival 90.5 % vs. 92.6 %

5-year survival 38.5 % vs. 38.9 %

Criteria for one stage operation: age < 70 years, LR of no more 3 segments colonic resection (esp. right-sided), excl. other factors

Vallance AE et al, Colorectal Dis. 2018; 20: 486-495
Silberhumer GR et al, Surgery 2016; 160: 67-73

Synchronous CRLM resectable

Neoadjuvant chemotherapy (neoCTx) – is controversial

Pro: control systemic disease, eliminate micro-metastatic disease, downsize LM and primary
3-year DFS 34.2 % vs. 16.8 % (Kim CW 2017)
partial response means better results
better results in R1 resection (esp. K-ras mutation)

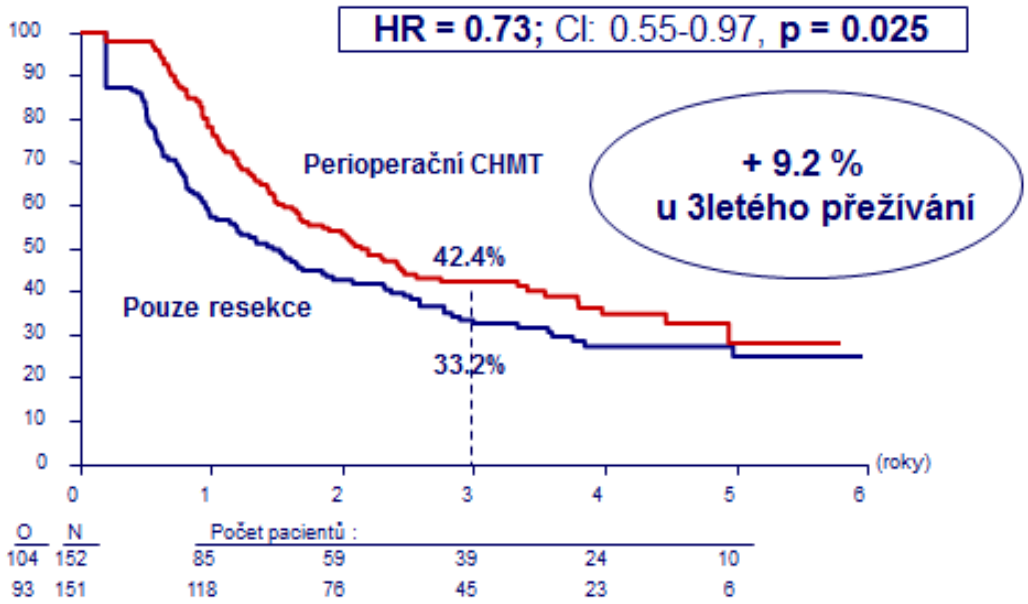
But: results are very controversial, esp. target therapy

Kim CW et al, Medicine (Baltimore) 2017; 96: e6174

Synchronous CRLM resectable

„Progres – free survival“ u resekovaných

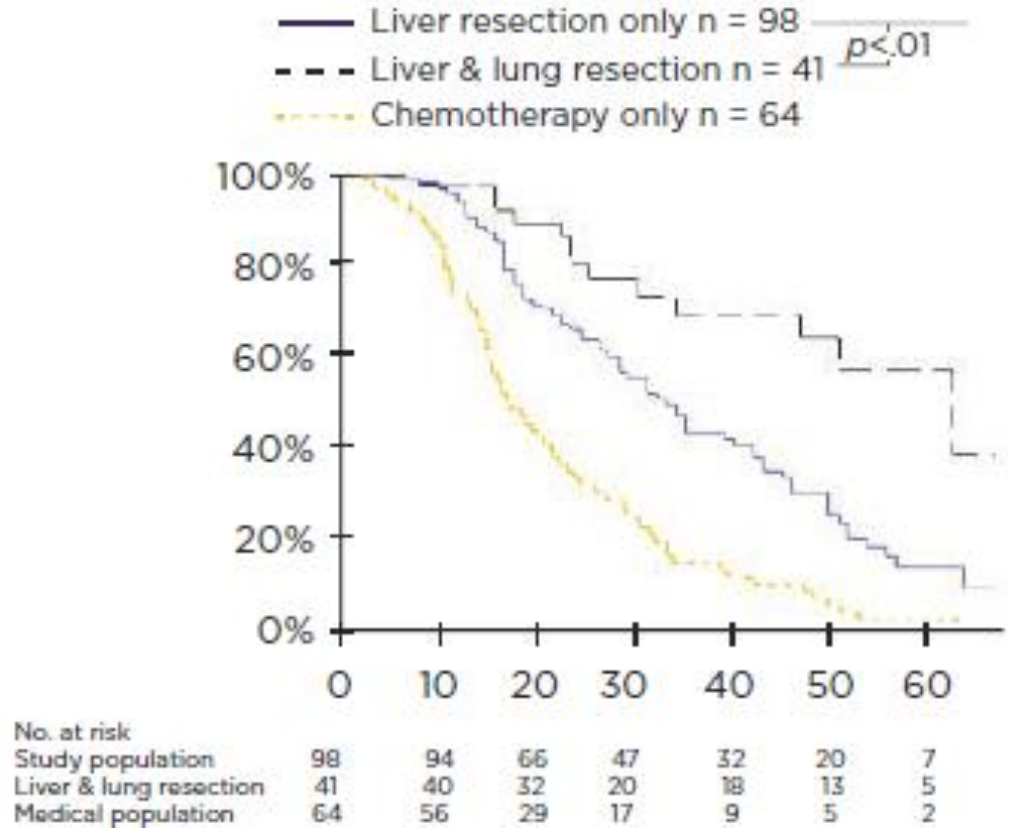
(Nordlinger B et al, Lancet 2008)



Benefit of perioperative chemotherapy is not proven

Nordlinger B et al, The Lancet Oncology 2013; 14: 1208 – 1215

Synchronous CRLM + CRLM resectable



Arvide EM et al, J Adv Pract Oncol 2016; 7: 788-792

Synchronous CRLM resectable - **summary**

- there is no significant difference in the outcomes between these 3 approaches

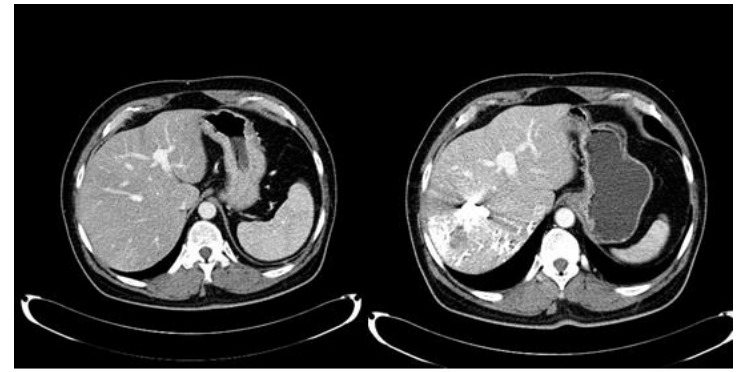
- type and timing depends on: patients characteristics
  protocol of center
- neoadj CTx: 4 - 6 wk after chemotherapy
  7- 8 wk after target therapy
- Benefit of perioperative chemotherapy is not proven

Vallance AE et al, Colorectal Dis 2018; 20: 486-495
Berardi G et al, Eur J Surg Oncol 2018; 44: 1069-1077

Synchronous CRLM unresectable

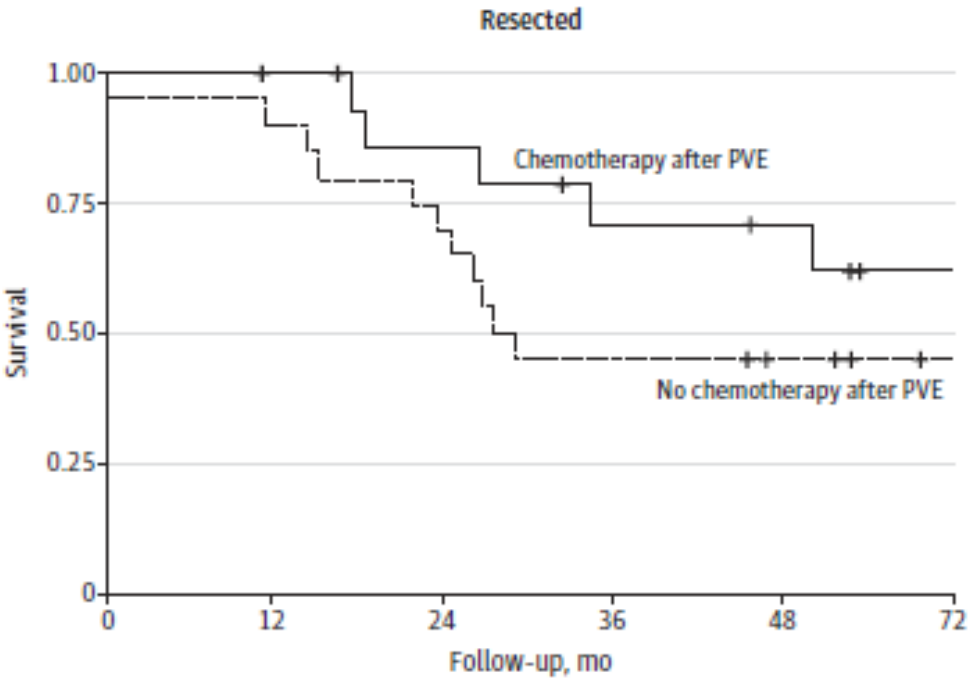
Definition of unresectability:
- multiple bilobar LM requiring > 70 % resection (untumorous tissue)
- tumour invading all 3 hepatic veins
- both branches of hepatic artery or PV
- extrahepatic mets (excl. pulmonary resectable)

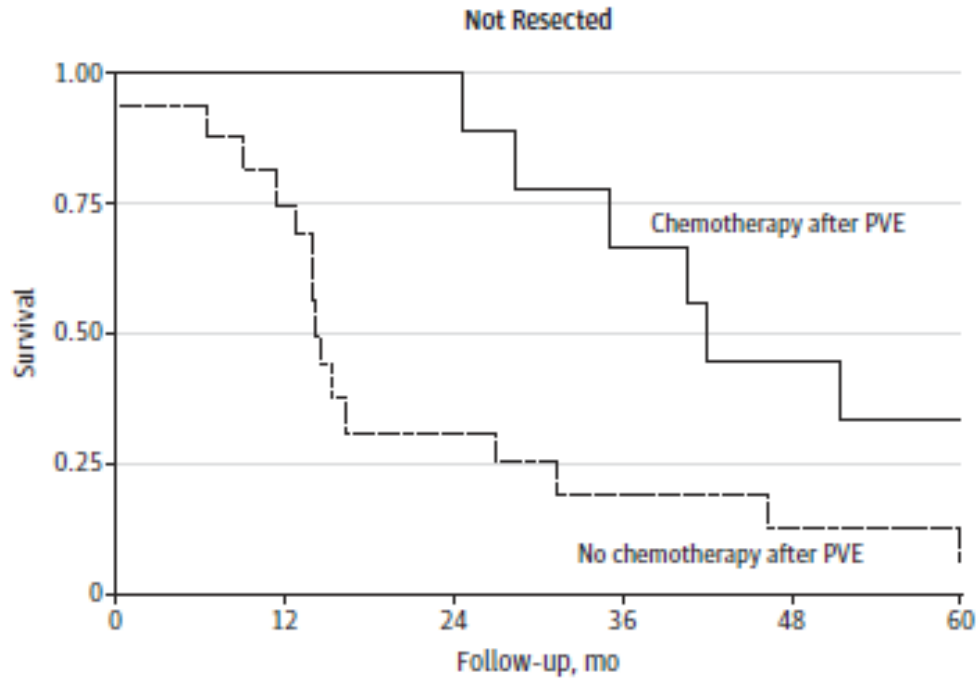
Solutions – conversion therapy
- PVE or PVL (4 – 6 w)
- ALPPS (8 – 11 d)
- conversion chemotherapy
- LTx



PVE ⇒ hypertrofie zdravého parenchymu

Synchronous CRLM unresectable - PVE

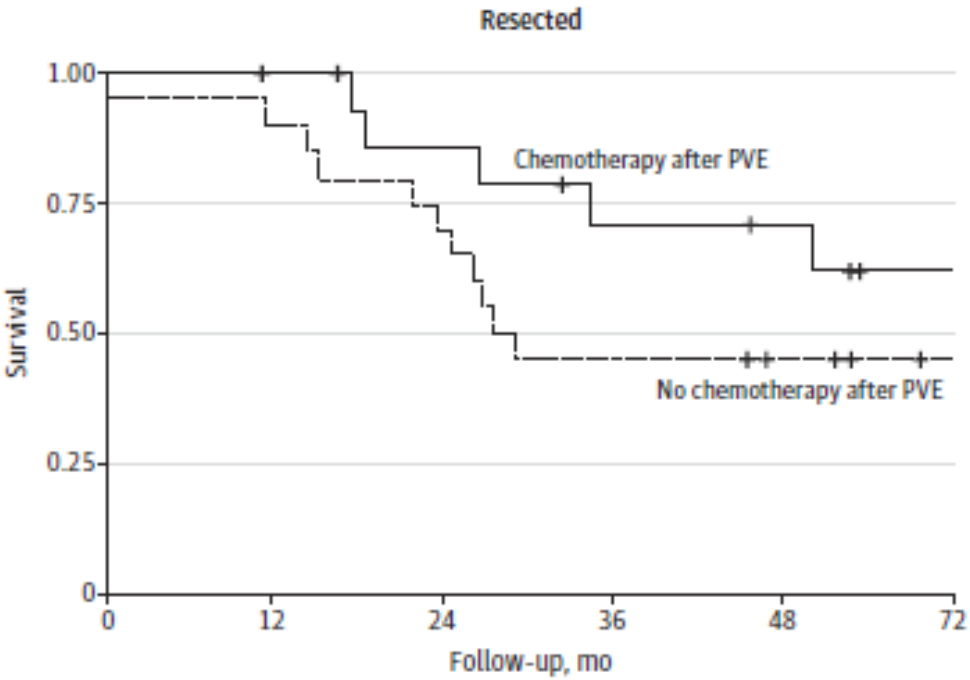


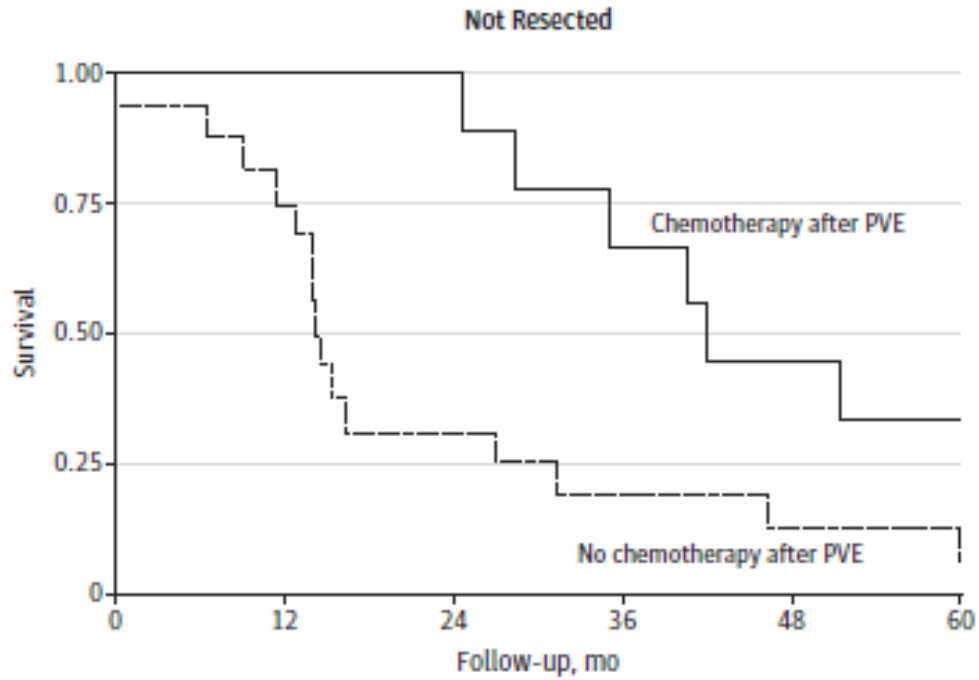


34 % progression after PVE

Fischer C et al, JAMA Surg 2013; 148: 1103-1108
Spelt L et al, HPB (Oxford) 2015; 17: 529-535

Synchronous CRLM unresectable - PVE





30 % after PVE fail to receive second surgery

Fischer C et al, JAMA Surg 2013; 148: 1103-1108
Spelt L et al, HPB (Oxford) 2015; 17: 529-535

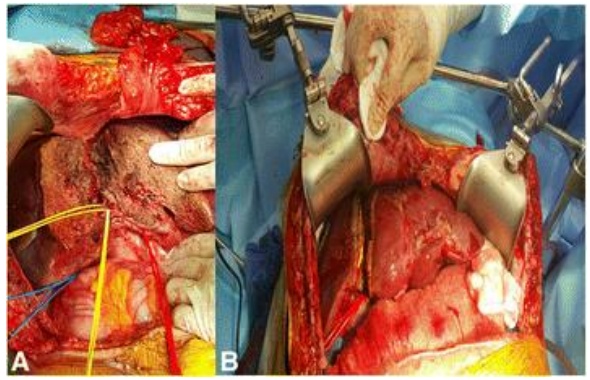
Synchronous CRLM unresectable - ALPPS

2012 – ALPPS - Associating Liver Partition with Portal Vein Ligation for Staged Hepatectomy

2 stages:

1.- ligation of right portal vein, splitting of the liver parenchyma, cleaning of FLR

2.- RHE



Resection rate ….. 92 % vs. 57 %
90d mortality ……. 8.3 %
Dindo > 3a …….. 43 % vs. 43 %

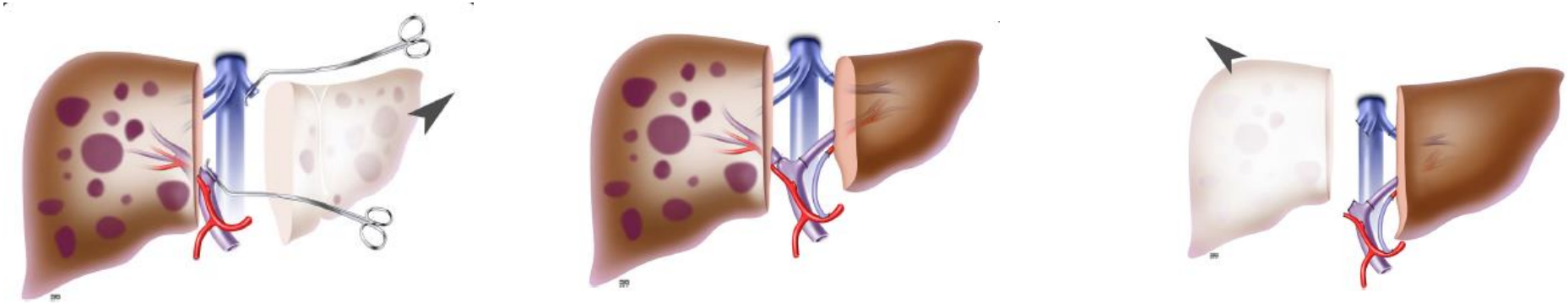
Sandstrom P et al, Ann Surg 2018; 267: 833-840

Synchronous CRLM unresectable – LTx (ultimate)

Pro: LTx – 50 % 5-y survival

Cons: shortage of grafts

selection strategy: LM < 55 mm, time interval > 2y, CEA < 80 ng/l, responsice or stable disease under CTx



Rauchfuß et al. World Journal of Surgical Oncology 2019; 17:11

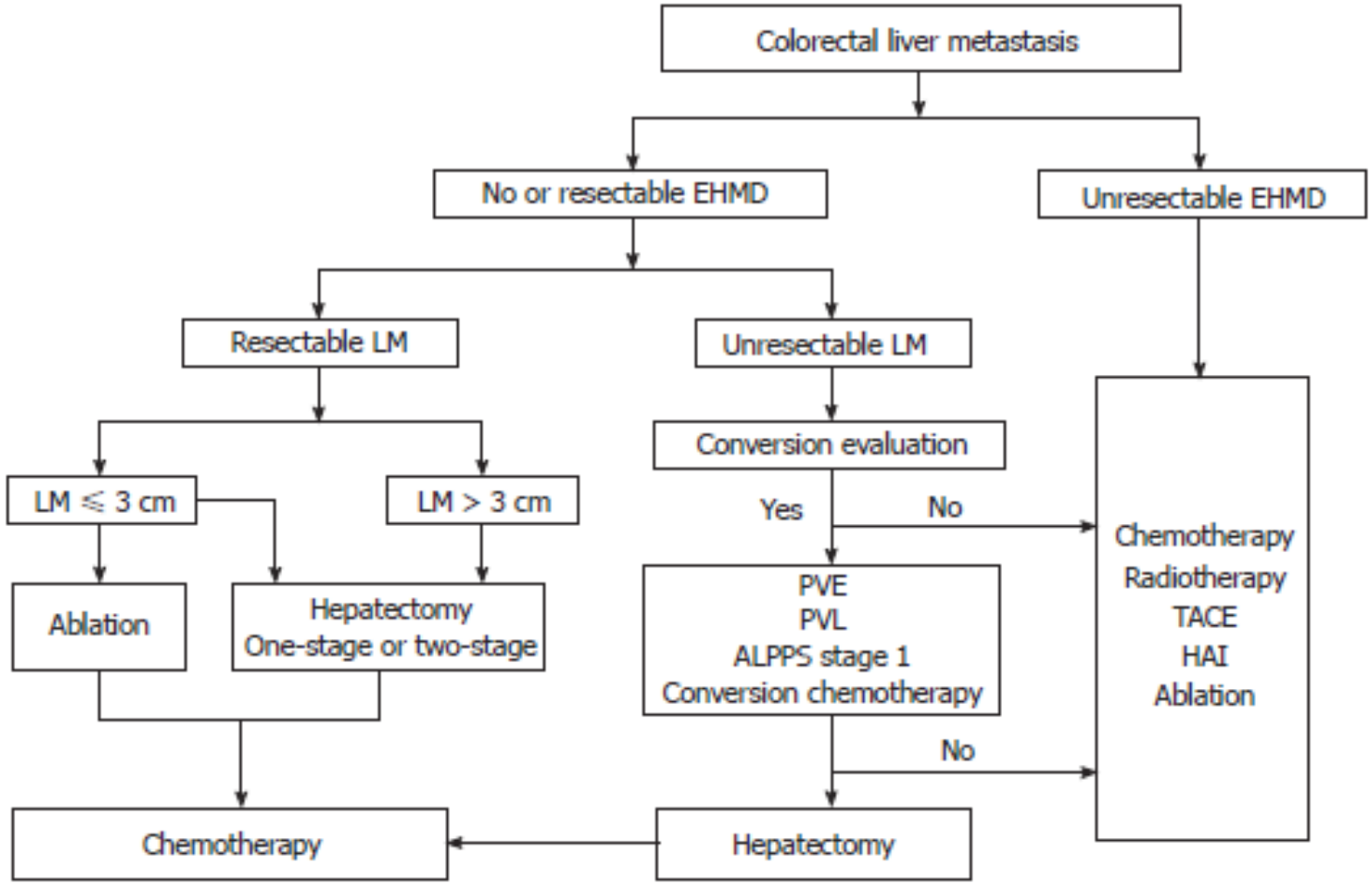
Synchronous CRLM - conclusion

Suggestions, no evidence-based

1 – Simultaneous colorectal and liver metastases whenever possible
2 – neoadjuvant chemotherapy for patients with advanced metastatic tumors to access disease biology and to control lesions
3 – liver first (+ radiotherapy before rectal surgery) vs. bowel first

4 – condition: MDT

Synchronous CRLM - conclusion



Xu F et al, WJCC 2018; 6: 716-734