Colorectal Liver Metastasis

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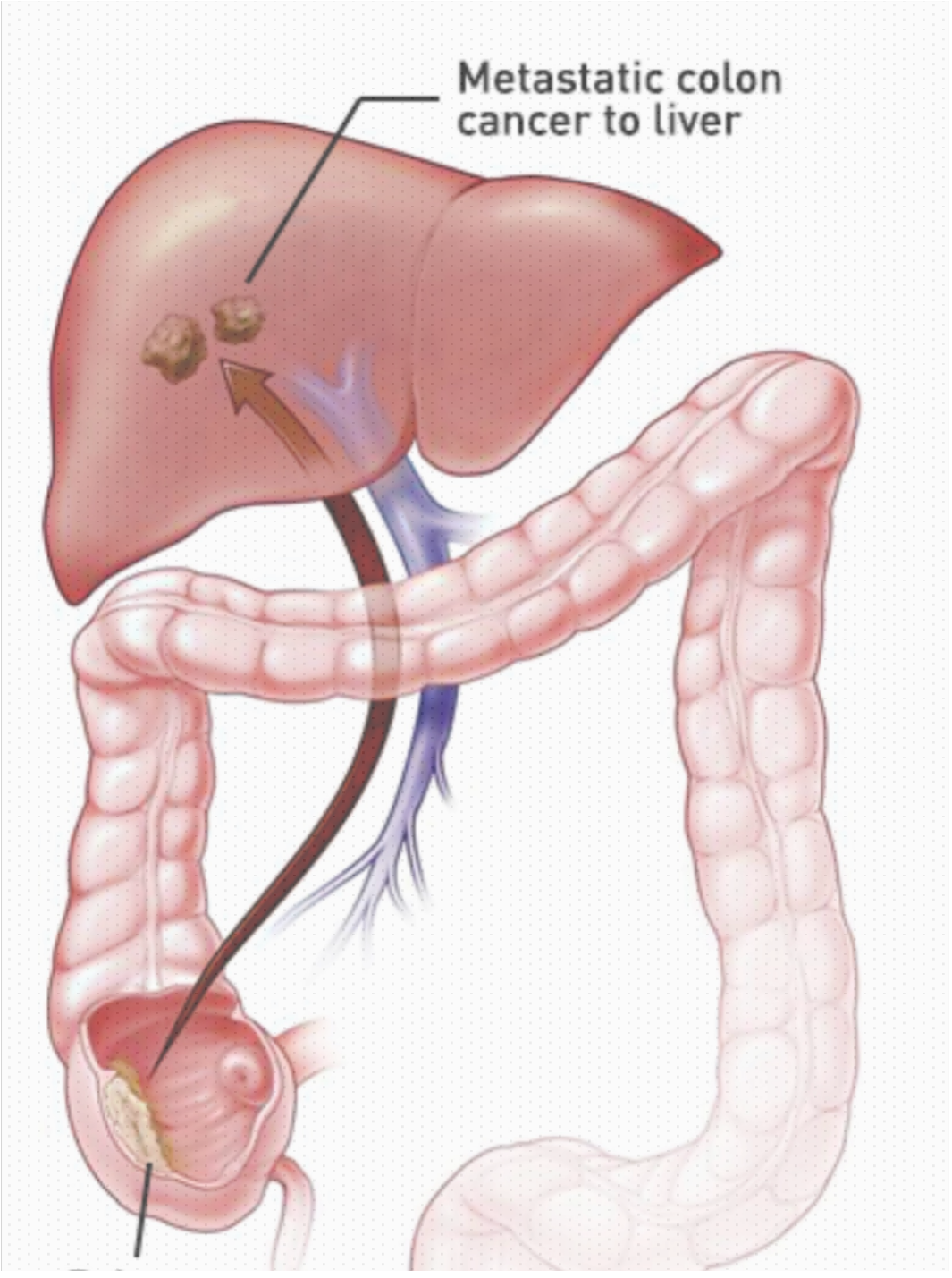
F2 Surgical Oncology

26.3.2024



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- 2nd most common cancer-related death
- In CRLM resection can cure 20% and 5-year OS now can exceed to 50%
- Factors
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  - Technical consideration
  - Disease biology

Chakedis J, Schmidt CR. Surgical Treatment of Metastatic Colorectal Cancer. Surg Oncol Clin N Am. 2018 Apr;27(2):377-399.

Introduction

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- 2nd most common cancer-related death
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  - Medical fitness
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→ **Vascular inflow**
Outflow
Biliary drainage

Chakedis J, Schmidt CR. Surgical Treatment of Metastatic Colorectal Cancer. Surg Oncol Clin N Am. 2018 Apr;27(2):377-399.

Introduction

- CRC cancer 3rd most common cancer diagnosis
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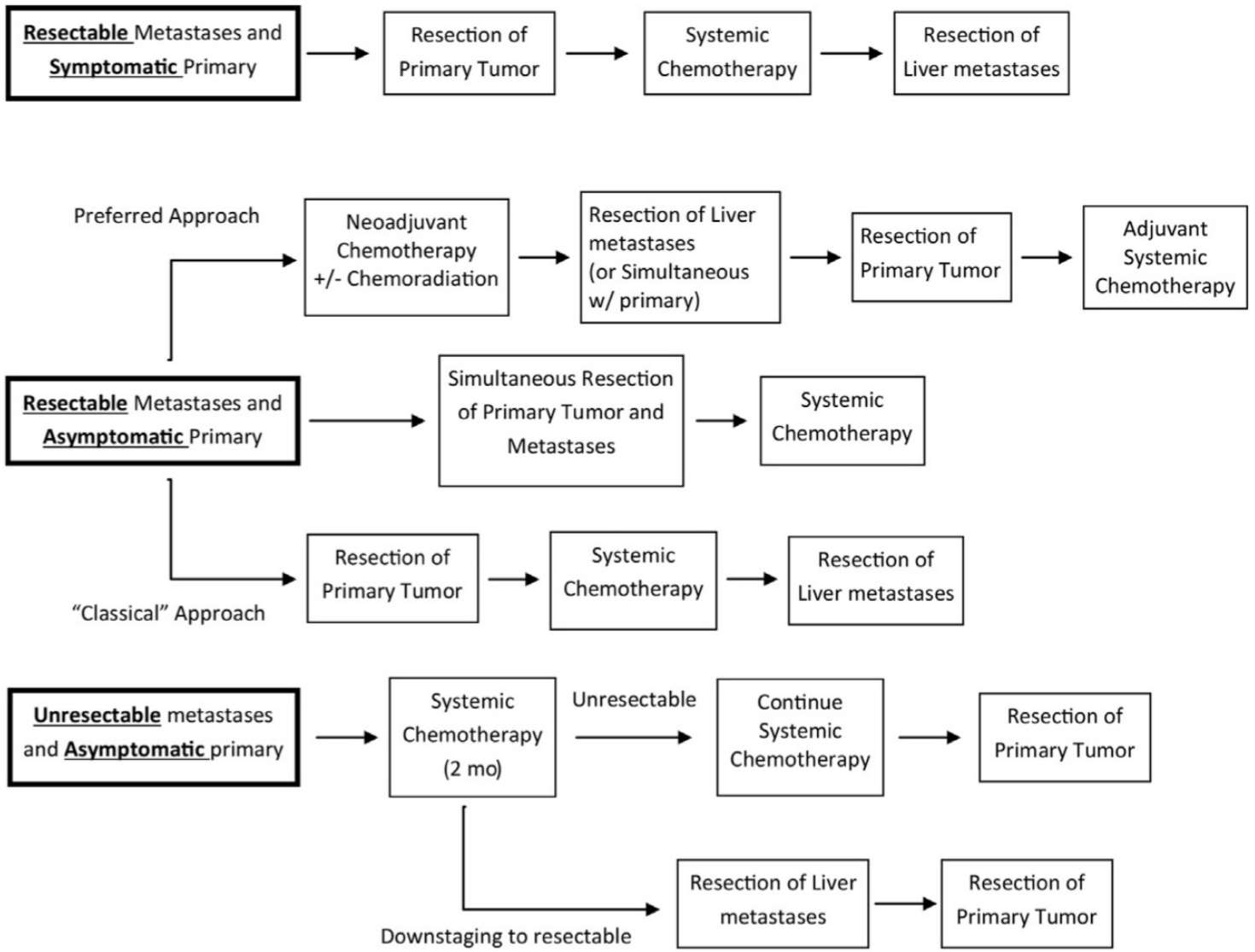
  - Medical fitness
  - Technical consideration
  - Disease biology

Disease burden
size / number / distribution CRLM
Disease biology
rate of disease progression / extrahepatic disease / synchronous or metachronous / 1º tumor sidedness / RAS,BRAF mutation status / MSI status

Chakedis J, Schmidt CR. Surgical Treatment of Metastatic Colorectal Cancer. Surg Oncol Clin N Am. 2018 Apr;27(2):377-399.

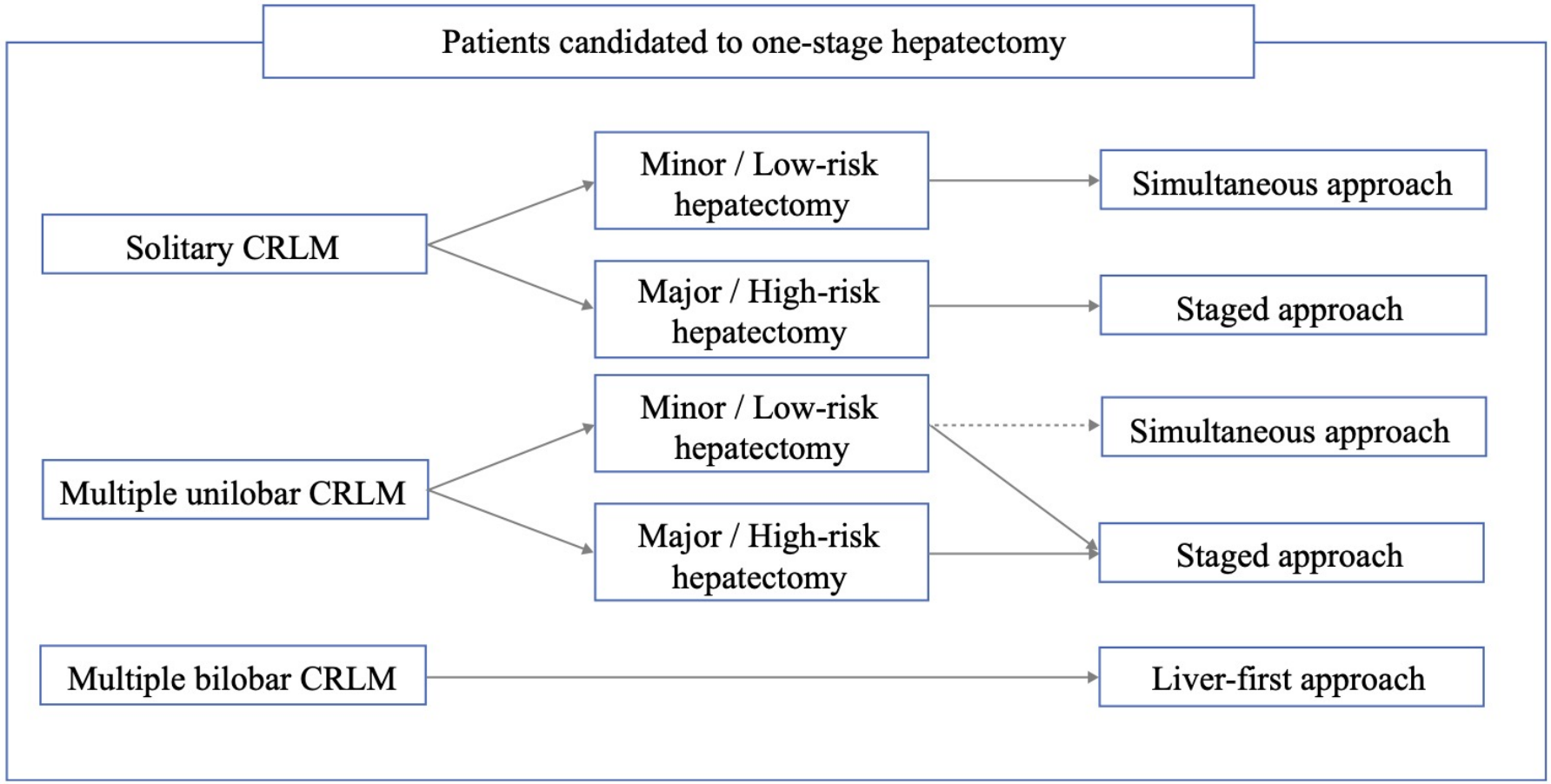
Approach to Synchronous CRLM



EGOSLIM, Chakedis J, Schmidt CR. Surgical Treatment of Metastatic Colorectal Cancer. Surg Oncol Clin N Am. 2018

Surgical Strategy in Synchronous CRLM

FIG. 4 Treatment strategy of synchronous colorectal liver metastases according to hepatic tumor burden and scheduled hepatectomy. *CRLM* colorectal liver metastases



Resection of primary tumor
(simultaneous)

- Minor hepatectomy
  morbidity 15.1% - mortality 1.4%
- Major hepatectomy
  morbidity 36.1% - mortality 8.3%

Chakedis J, Schmidt CR. Surgical Treatment of Metastatic Colorectal Cancer. Surg Oncol Clin N Am. 2018 Apr;27(2):377-399.
Giuliante, F., Viganò, L., De Rose, A.M. *et al.* Liver-First Approach for Synchronous Colorectal Metastases: Analysis of 7360 Patients from the LiverMetSurvey Registry. *Ann Surg Oncol* **28**, 8198–8208 (2021).

Choices of Local Treatemnt

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

Metastatic colorectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

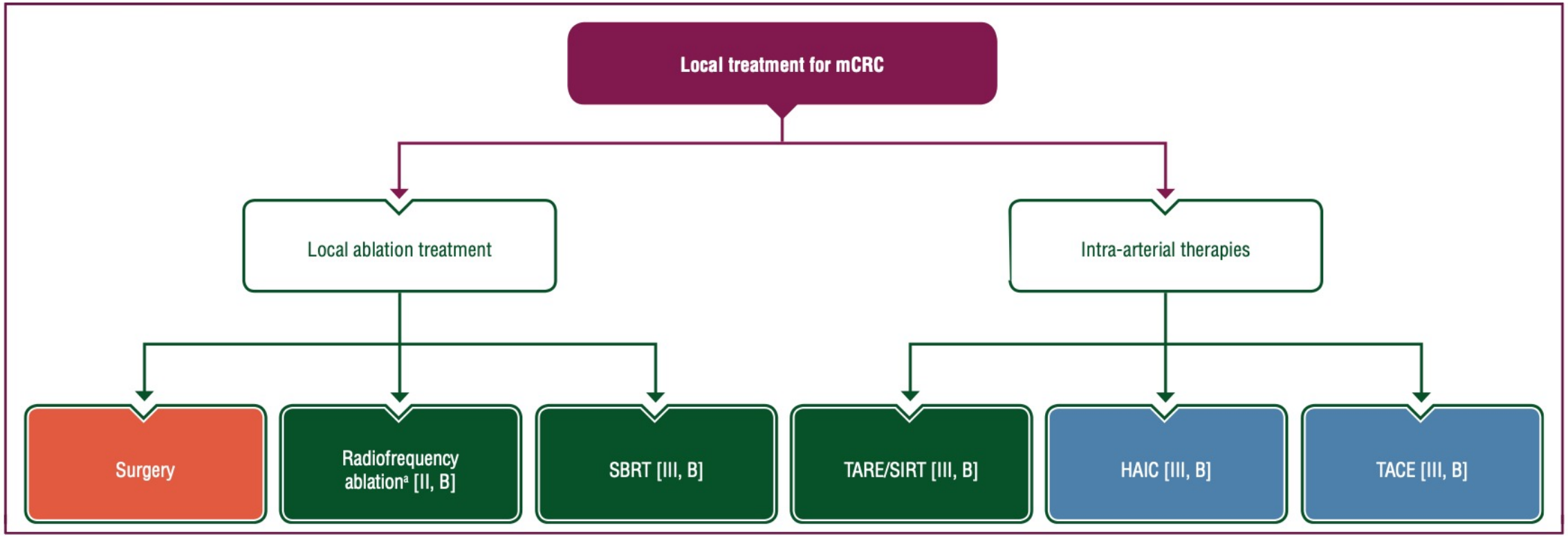


Figure 1. Local treatment of CRC metastases. Purple: general categories or stratification; red: surgery; dark green: radiotherapy; blue: systemic anticancer therapy; white: other aspects of management.

CRC, colorectal cancer; CRLM, colorectal liver metastasis; HAIC, hepatic arterial infusion chemotherapy; mCRC, metastatic colorectal cancer; OMD, oligometastatic disease; SBRT, stereotactic body radiotherapy; SIRT, selective internal radiotherapy; TA, thermal ablation; TACE, transarterial chemoembolisation; TARE, transarterial radioembolisation.

[a]In patients with unresectable CRLMs only, or OMD in the liver, TA can be considered for small metastases [III, B]. In patients with lung-only metastases or OMD including lung lesions, TA may be considered along with resection, according to tumour size, number, location, the extent of lung parenchyma loss, comorbidity or other factors [III, B].

Outcome of Curative Intent Liver Resection of CRLM

Table 2
Outcomes of curative intent liver resection of colorectal metastases

Series Author, Year	Patients (n)	Median DFS (mo)	DFS (%)	Median OS (mo)	OS (%)	Operative Mortality Rate (%)	Major Complication Rate (%)	Minor Resection Rate (%)
Fong et al,[6] 1999	1001	—	—	69	5-y: 37 10-y: 22	2.8	31	37
Pawlik et al,[45] 2005	557	—	—	74	5-y: 58	0.9	—	42.7
Nordlinger et al,[17] 2008; Nordlinger et al,[18] 2013 (RCT)	364	11–18	3-y: 28.1–36.2	54.3–61.3	5-y: 47.8–51.2	1.3	16–25	21
Rees et al,[44] 2008	929	—	—	42.5	5-y: 36 10-y: 23	1.5	25.9	36.2
de Jong et al,[46] 2009	1669	23	5-y: 30	36	5-y: 47.3	—	—	55
House et al,[47] 2010	1600	—	5-y: 33	64	5-y: 43	1	44	39

Abbreviations: DFS, disease-free survival; RCT, randomized controlled trial.

5 yr OS 36-68%

Chakedis J, Schmidt CR. Surgical Treatment of Metastatic Colorectal Cancer. Surg Oncol Clin N Am. 2018 Apr;27(2):377-399.

Box 1
Defining resectability in patients with colorectal liver metastasis

Patient selection criteria for potentially curative resection of hepatic metastases

Ability to obtain R0 resection: no tumor present at margin

Adequate postoperative liver volume and function

- At least 20% of total liver volume with normal function
- At least 30% if any chemotherapy-associated liver injury
- At least 40% if any hepatic fibrosis or cirrhosis from other causes
- At least two functional contiguous segments with intact portal and arterial inflow, venous outflow, and biliary drainage

Limited extrahepatic disease that is resectable

- No portal lymphadenopathy or multiple metastatic sites

Limited progression if received preoperative chemotherapy

- No development of new hepatic lesions

Medically fit to undergo a major operation

Data from Schwarz R, Abdalla E, Aloia T, et al. AHPBA/SSO/SSAT sponsored consensus conference on the multidisciplinary treatment of colorectal cancer metastases. HPB (Oxford) 2013;15(2):89–90; and Adams R, Aloia T, Loyer E, et al. Selection for hepatic resection of colorectal liver metastases: expert consensus statement. HPB (Oxford) 2013;15(2):91–103.

Future liver remnant can be augmented using variety of techniques

- PVE, PVL, LVD
- TSH
- Liver partition – staged hepatectomy

Table 1
Factors used to guide use of perioperative chemotherapy with hepatic resection for metastatic CRC

Treatment Approach	Factors
Liver operation first	Low volume of liver metastases • Largest <5 cm • Unilobar disease • <5 total liver tumors • Favorable location allowing minor hepatectomy Metachronous presentation
Perioperative chemotherapy	Higher volume of liver metastases • Largest >5 cm • Bilobar disease • More than 4 total liver tumors Extrahepatic metastatic disease Synchronous presentation or short disease-free interval <12 mo Tumor response may change surgical strategy • Decrease size of hepatic resection • Achieve R0 resection May not receive postoperative chemotherapy

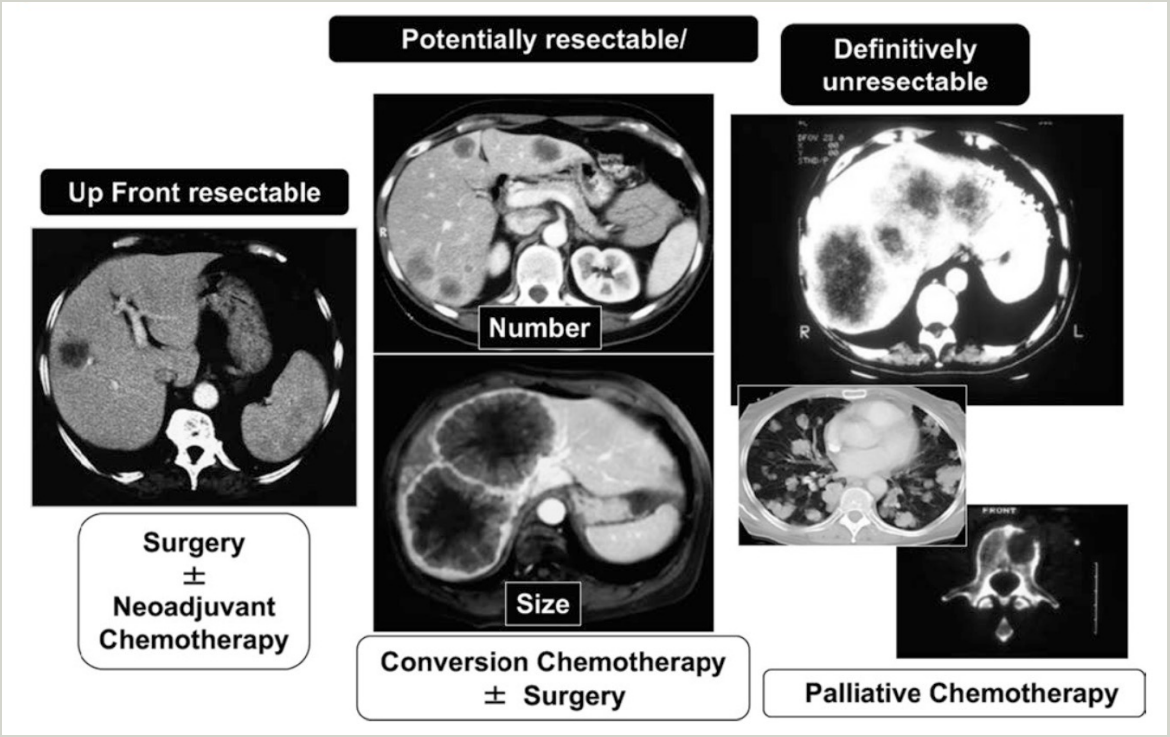
Chakedis J, Schmidt CR. Surgical Treatment of Metastatic Colorectal Cancer. Surg Oncol Clin N Am. 2018 Apr;27(2):377-399.

Management of Liver Lesions in CRLM

Resectable

Potentially Resectable / Borderline

Unresectable



To guide the purpose of treatment

Definition

Table 1. Definitions of common colorectal liver metastases resectability classifications.

Resectability Classification	Definition
Resectable	The CRLM can be completely resected, two adjacent liver segments can be spared, adequate vascular inflow and outflow and biliary drainage can be preserved, and the volume of the future liver remnant will be adequate (i.e., at least 20% of the total estimated liver volume) [30].
Borderline	The CRLM can potentially be completely resected, but there may be technical (i.e., odds of achieving an R0 resection are reduced) and/or biological challenges (i.e., numerous liver metastases, evidence of disease progression, possible extrahepatic disease) [31].
Unresectable	The CRLM cannot be resected due to burden of disease (i.e., greater than 70% of the liver involved or more than six segments, invasion of both portal veins or all hepatic veins) [32].

CRLM, colorectal liver metastases.

Ivey, G.D.; Johnston, F.M.; Azad, N.S.; Christenson, E.S.; Lafaro, K.J.; Shubert, C.R. Current Surgical Management Strategies for Colorectal Cancer Liver Metastases. *Cancers* **2022**, *14*, 1063.

Surgical Strategy for Colorectal Liver Metastasis

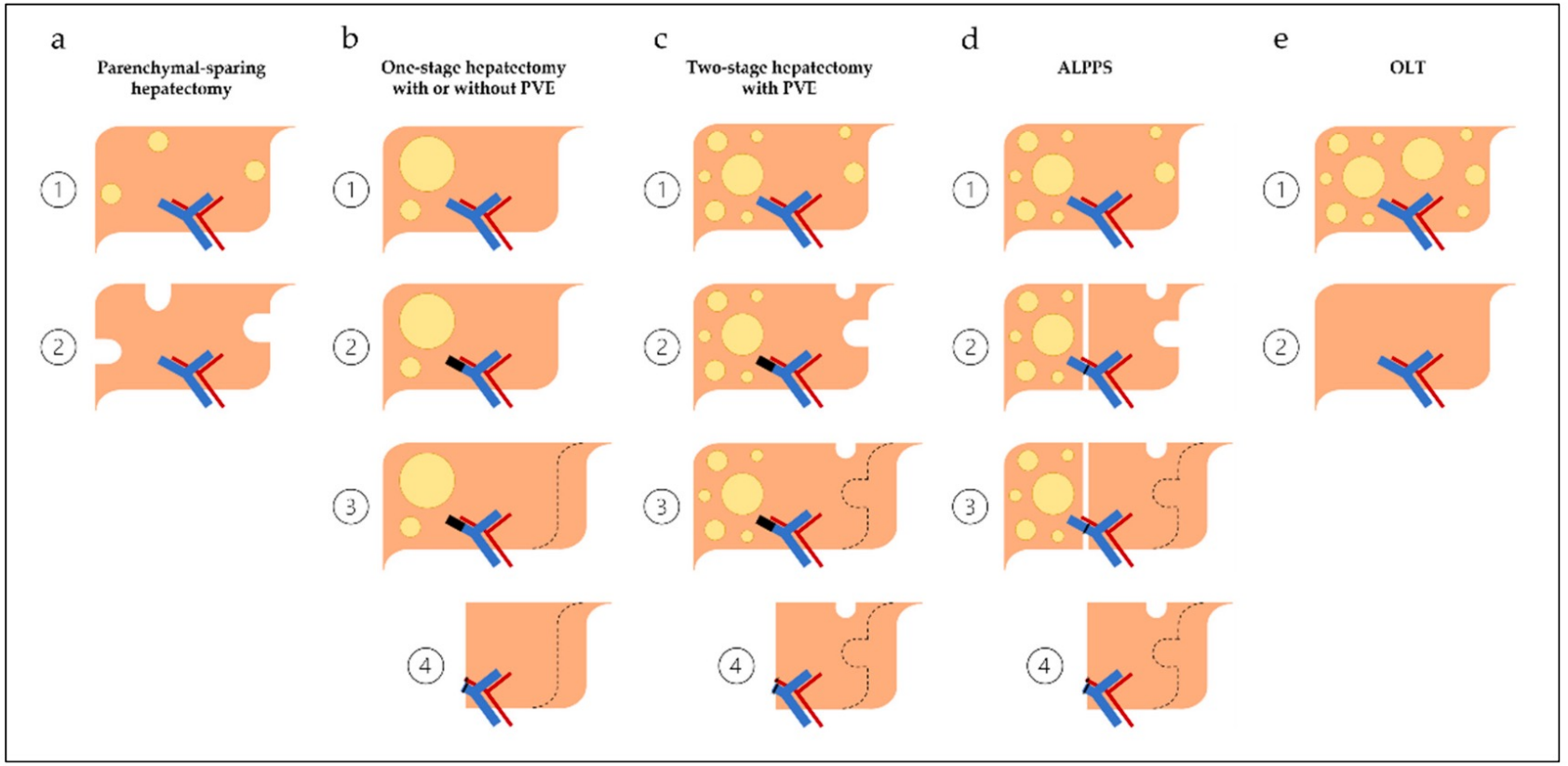


Figure 1. Surgical strategies for colorectal liver metastases. (**a**) Parenchymal-sparing hepatectomy. (**b**) One-stage hepatectomy with or without PVE. (**c**) Two-stage hepatectomy with PVE. (**d**) Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS). (**e**) Orthotopic liver transplantation (OLT). Dashed lines illustrate the future liver remnant prior to augmentation (i.e., PVE; portal vein ligation during ALPPS).

Ivey, G.D.; Johnston, F.M.; Azad, N.S.; Christenson, E.S.; Lafaro, K.J.; Shubert, C.R. Current Surgical Management Strategies for Colorectal Cancer Liver Metastases. *Cancers* **2022**, *14*, 1063.

Primary Resectable CRLM

Primary Technically R0 Resection CRLM

Favorable oncological criteria

- Metachronous lesions
- Fewer metastases
- Unilobar disease
- No extrahepatic disease

Upfront Surgery

Unfavorable oncological criteria

- Synchronous lesion
- More than three metastases
- Bilobar disease
- Limited extrahepatic disease

Favorable surgical criteria

- No vascular infiltration

Perioperative Chemotherapy

Ann Oncol. 2023;34(1):10-32.

Primary Technically R0 Resection CRLM

Favorable oncological criteria

- Metachronous lesions
- Fewer metastases
- Unilobar disease
- No extrahepatic disease

Upfront Surgery

Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial

Bernard Nordlinger, Halfdan Sorbye, Bengt Glimelius, Graeme J Poston, Peter M Schlag, Philippe Rougier, Wolf O Bechstein, John N Primrose, Euan T Walpole, Meg Finch-Jones, Daniel Jaeck, Darius Mirza, Rowan W Parks, Laurence Collette, Michel Praet, Ullrich Bethe, Eric Van Cutsem, Werner Scheithauer, Thomas Gruenberger for the EORTC Gastro-Intestinal Tract Cancer Group, Cancer Research UK,* Arbeitsgruppe Lebermetastasen und-tumoren in der Chirurgischen Arbeitsgemeinschaft Onkologie (ALM-CAO),* Australasian Gastro-Intestinal Trials Group (AGITG),* and Fédération Francophone de Cancérologie Digestive (FFCD)**

Benefit in PFS but not OS

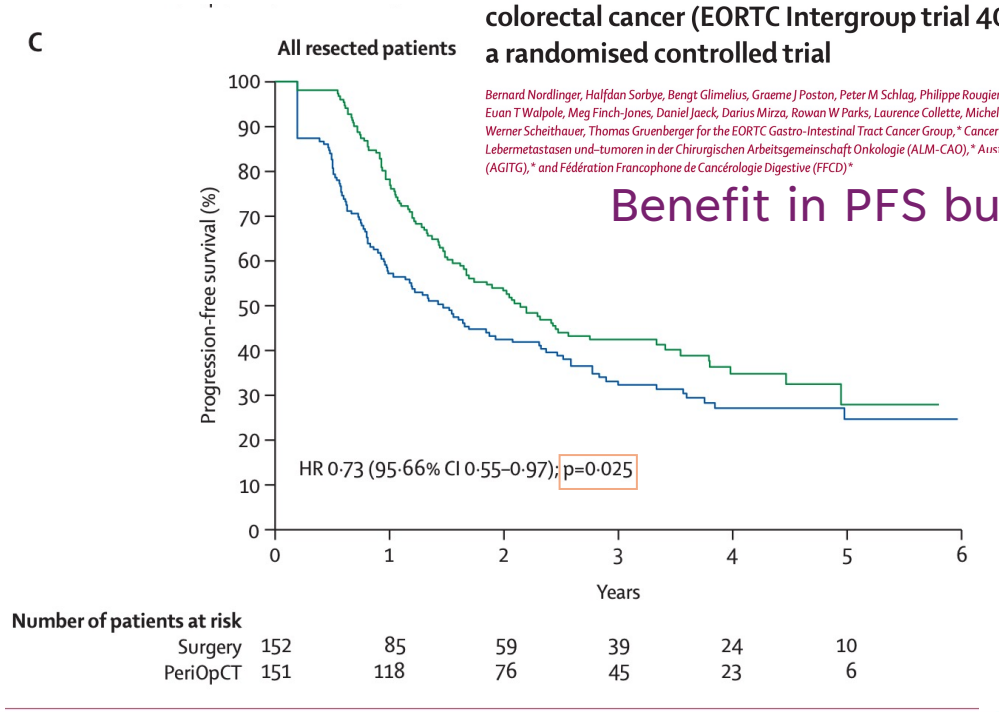


Figure 2: **Progression-free survival by treatment group**
(A) All randomly assigned patients. (B) All eligible patients. (C) All resected patients. For all patients randomly assigned and those who were eligible, no surgery or no resection were regarded as events for the primary endpoint of progression-free survival. PeriOpCT=perioperative chemotherapy with fluorouracil or leucovorin, and oxaliplatin.

Up to four liver metastases
Random; 6 cycles of FOLFOX4 before surgery or 6 cycles after surgery Vs. to surgery alone
(182 in perioperative chemotherapy group vs 182 in surgery group).

(EORTC Intergroup trial 40983): a randomised controlled trial. Lancet. 2008 Mar 22;371(9617):1007-16.

Primary Technically R0 Resection CRLM

Favorable oncological criteria

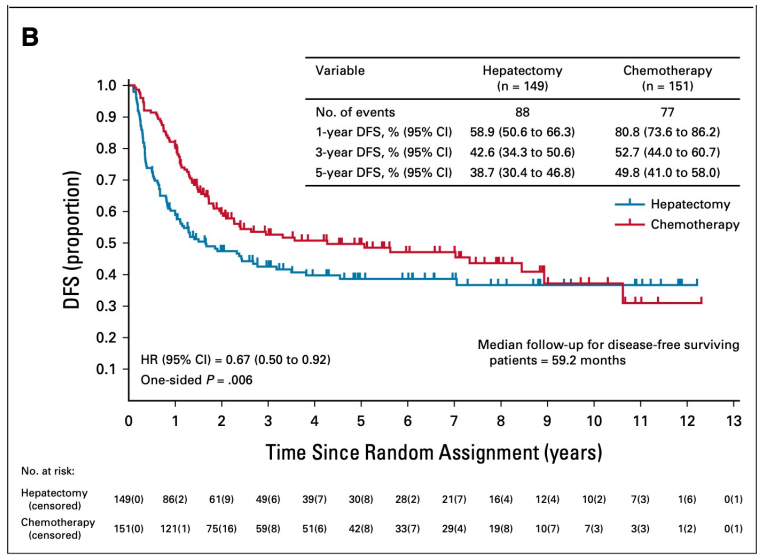
- Metachronous lesions
- Fewer metastases
- Unilobar disease
- No extrahepatic disease

Upfront Surgery

original repor

Hepatectomy Followed by mFOLFOX6 Versus Hepatectomy Alone for Liver-Only Metastatic Colorectal Cancer (JCOG0603): A Phase II or III Randomized Controlled Trial

Yukihide Kanemitsu, MD[1]; Yasuhiro Shimizu, MD, PhD[2]; Junki Mizusawa, ME[1]; Yoshitaka Inaba, MD, PhD[2]; Tetsuya Hamaguchi, MD, PhD[3]; Dai Shida, MD, PhD[1]; Masayuki Ohue, MD, PhD[4]; Koji Komori, MD, PhD[2]; Akio Shiomi, MD[5]; Manabu Shiozawa, MD, PhD[6]; Jun Watanabe, MD, PhD[7]; Takeshi Suto, MD[8]; Yusuke Kinugasa, MD, PhD[9]; Yasumasa Takii, MD[10]; Hiroyuki Bando, MD, PhD[11]; Takaya Kobatake, MD[12]; Masafumi Inomata, MD, PhD[13]; Yasuhiro Shimada, MD[14]; Hiroshi Katayama, MD[1]; and Haruhiko Fukuda, MD[1] on behalf of the JCOG Colorectal Cancer Study Group



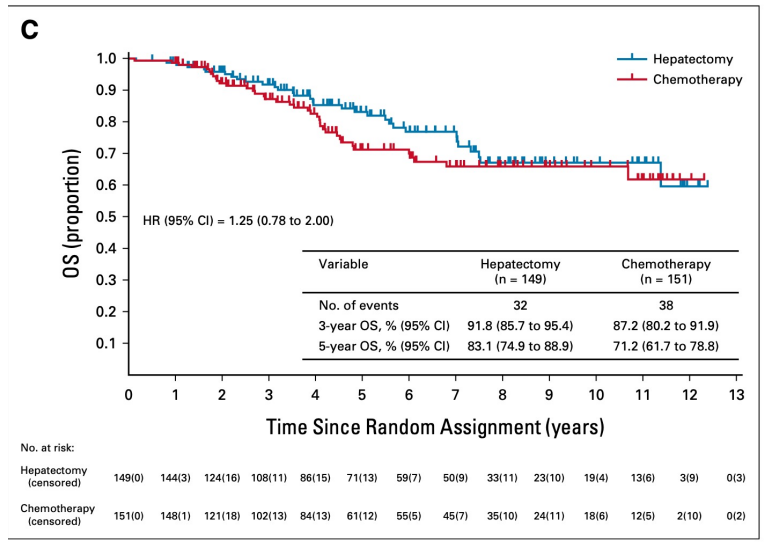


FIG 2. (Continued).

RCT : Hepatectomy vs. Hepatectomy + mFOLFOX6
Any number of CRLM (90% had CRLM 1-3 lesion)
5-yr DFS 38.7% vs. 49.8% p=0.006
5-yr OS no difference p=0.42
It remains unclear whether chemotherapy improves OS

Yukihide Kanemitsu et al., Hepatectomy Followed by mFOLFOX6 Versus Hepatectomy Alone for Liver-Only Metastatic Colorectal Cancer (JCOG0603): A Phase II or III Randomized Controlled Trial. *JCO* **39**, 3789-3799(2021).

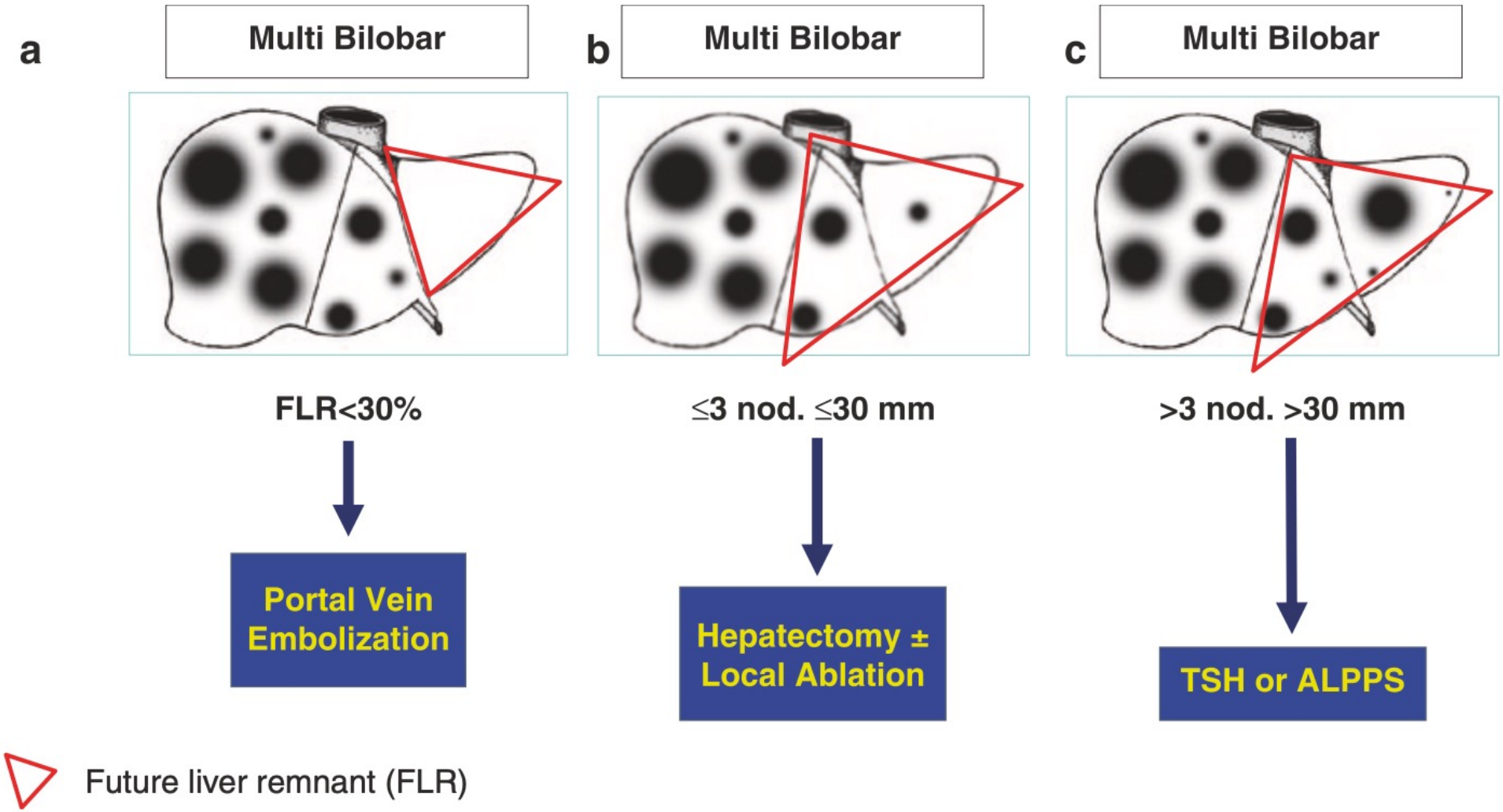
Borderline/Potential Resectable CRLM

Borderline/Potential Resectable CRLM

- Two stage Hepatectomy
- One stage Hepatectomy
- ALPPS
- Modified techniques

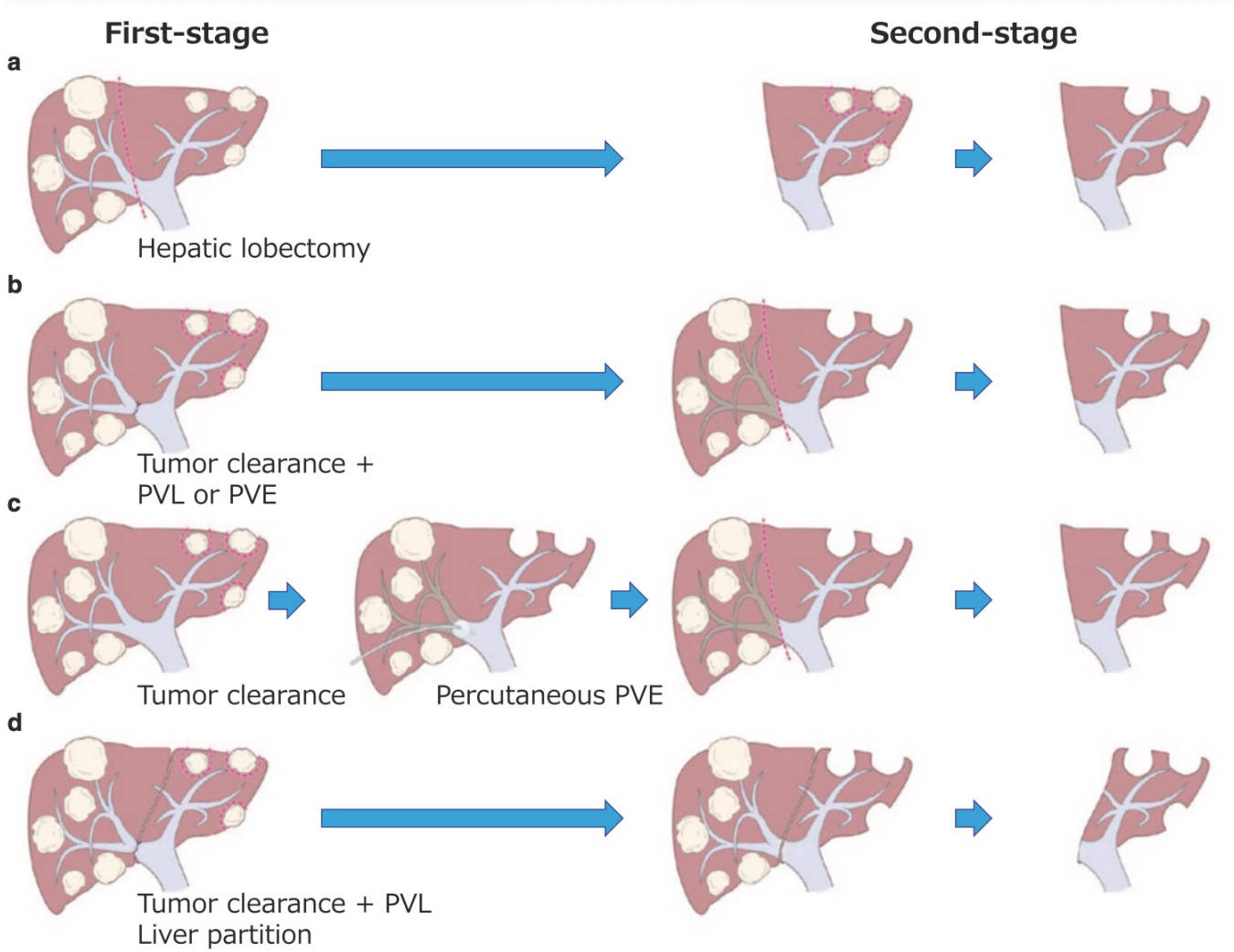
Chakedis J, Schmidt CR. Surgical Treatment of Metastatic Colorectal Cancer. Surg Oncol Clin N Am. 2018 Apr;27(2):377-399.

Future Liver Remnant



Imai, K., Adam, R. (2022). Two-Stage Hepatectomy for Bilobar Colorectal Liver Metastases: Experience of Hôpital Paul-Brousse. In: Vauthey, JN., Kawaguchi, Y., Adam, R. (eds) Colorectal Liver Metastasis. Springer, Cham.

Two Stage Hepatectomy



Right-first approach

Left-first approach → PVE/PVL → 2nd stage operation

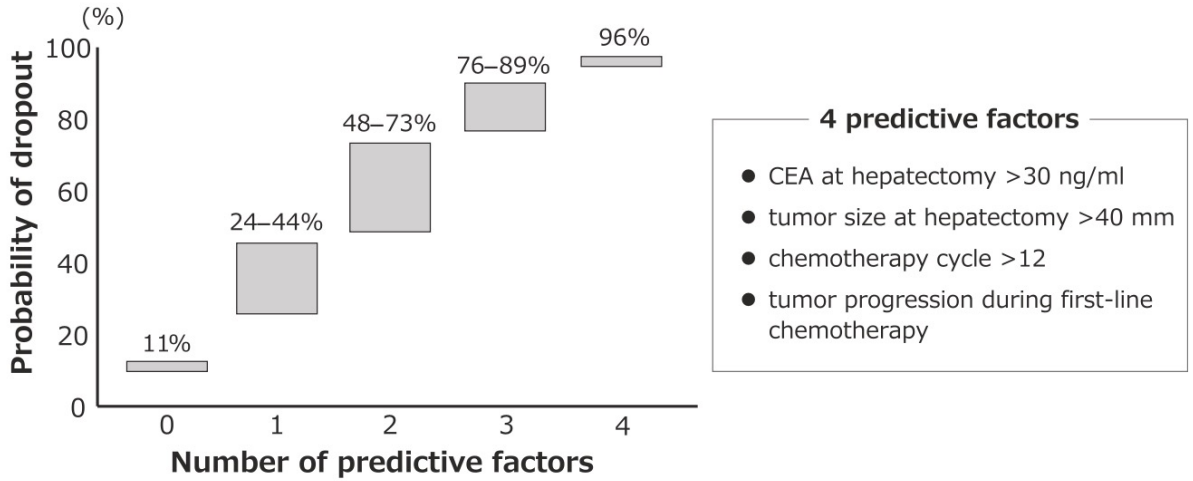
Left-first approach → percutaneous PVE → 2nd operation

ALPPS → intra-op PVL/PVE, in situ splitting hemiliver → 2nd operation

Imai K, Adam R, Baba H. How to increase the resectability of initially unresectable colorectal liver metastases: a surgical perspective. Ann Gastroenterol Surg. 2019;3(5):476–86.

Dropout from Two Stage Hepatectomy

- 35.2% did not proceed to 2nd stage
- Reasons for dropout
  1. Disease progression 88.6%
  2. Insufficient FLR 6.8%
  3. Poor general condition 2.3%
  4. Mortality after 1st stage 2.3%



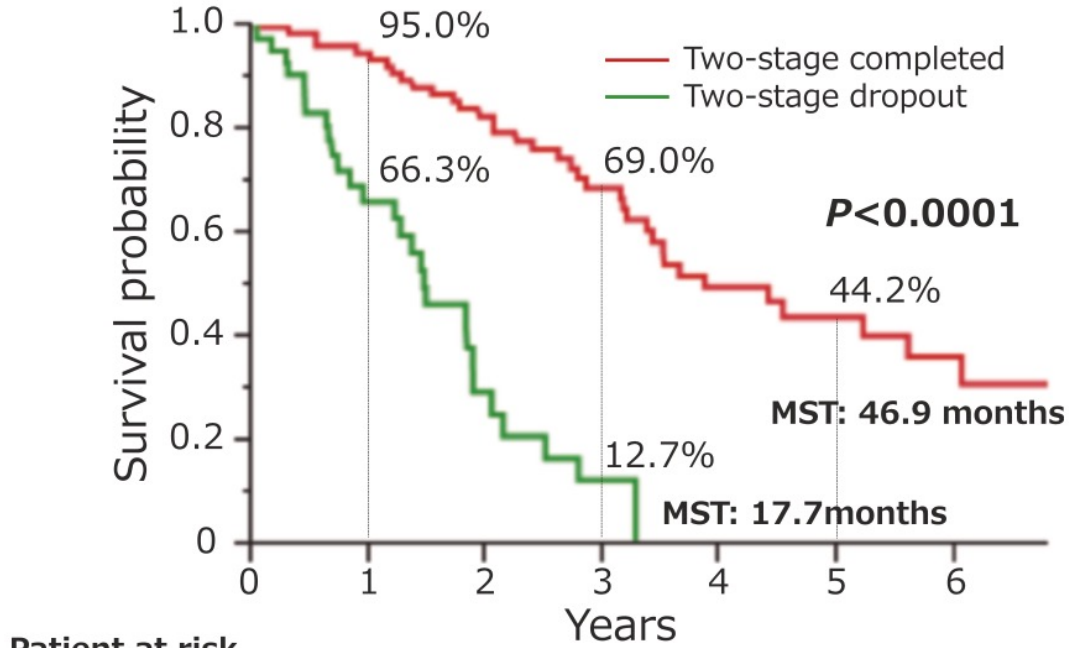


Fig. 8.4 Overall survival for patients who completed two-stage hepatectomy (n = 91) or dropped out (n = 44), between 2000 and 2012. MST, median survival time. ([6], with permission)

Imai K, Benitez CC, Allard MA, Vibert E, Cunha AS, Cherqui D et al. Failure to achieve a 2-stage hepatectomy for colorectal liver metastases: how to prevent it? Ann Surg. 2015;262(5):772–8.

Outcome of Two-Stage Hepatectomy

- Morbidity range 20-59%
- Low motality rates
- Rate of completion both 1st and 2nd stage 63-100%

  Not complete due to

  - Disease progression
  - Insufficient FLR
  - Physical status
  - PV thrombosis
  - Death
- OS 3 yr = 35-85%
- OS 5 yr = 32-64%

Table 7.2 Outcomes after two-stage hepatectomy for bilateral colorectal liver metastases

	Region	Patient no.	Preoperative chemotherapy (%)	PVE (%)	PVL (%)	Completion rate (%)	Postoperative morbidity (%)	Postoperative mortality (%)	3-Year OS (%)	5-Year OS (%)
Adam et al. [3][a]	Europe	16	75	44	0	81	38	15	35	NA
Jaeck et al. [30][b]	Europe	33	91	100	0	76	56	0	54	NA
Tanaka et al. [20]	Asia	24	64	73	0	100	23	0	33	NA
Wicherts et al. [6][a]	Europe	59	97	78	0	69	59	7	60	42
Homayounfar et al. [21]	Europe	24	75	0	100	63	58	5	NA	NA
Tsai et al. [22]	USA/ Europe	45	71	7	71	78	26	6	58	NA
Brouquet et al. [5][c]	USA	65	100	70	0	72	49	6	84	64
Tsim et al. [23]	Europe	38	91	95	0	87	33	0	50	NA
Narita et al. [24][b]	Europe	80	84	86	4	76	54	0	59	32
Muratore et al. [25]	Europe	47	79	58	23	77	44	0	65	NA
Turini et al. [26]	Europe	48	100	100	0	71	20	6	59	35
Passot et al. [4][c,d]	USA	109	100	73	0	82	27	6	68[d]	49[d]
Mizuno et al. [31][c]	USA	126	100	62	0	73	35	4	54	35

NA not available, *OS* overall survival, *PVE* portal vein embolization, *PVL* portal vein ligation
Source: Adapted from Kawaguchi et al. [19]
[a]Reports from Paul Brousse Hospital
[b]Reports from Strasbourg University Hospital
[c]Reports from MD Anderson Cancer Center
[d]In 89 patients who underwent second-stage resection

Outcome of Two-Stage Hepatectomy

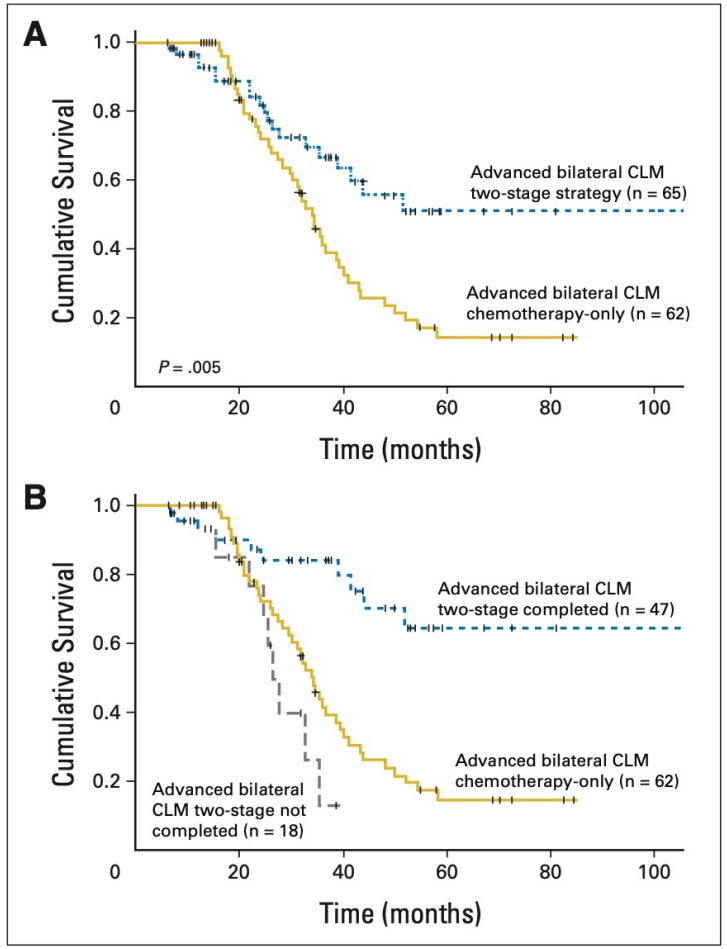


Fig 3. Overall survival in patients with advanced bilateral colorectal liver metastases (CLM) responding to chemotherapy enrolled in two-stage strategy (intent-to-treat analysis including patients undergoing only the first stage of two-stage hepatectomy) or receiving chemotherapy only (A) and stratified on the basis of whether two-stage resection was completed (B).

- TSR 6.7-3.4 CLM / mean size of 4.5 - 3.1 cm.
  vs. Nonsurgical patients 5.9-2.9 CLM / mean size of 5.4 - 3.4 cm (not significant).
- 47 TSR patients (72%) completed the second stage.
- After 50 months median follow-up
  - 5-year survival rate = 51% in the TSR group
  - 5-year survival rate = 15% in the medical group (*P* .005).
  - noncompletion of TSR and major postoperative complications were independently associated with worse survival.
  - 3-year survival rate 13% for first stage only

Brouquet A, et al. High survival rate after two-stage resection of advanced colorectal liver metastases: response-based selection and complete resection define outcome. J Clin Oncol. 2011 Mar 10;29(8):1083-90.

Hybrid Two-Stage Hepatectomy (MD Anderson)

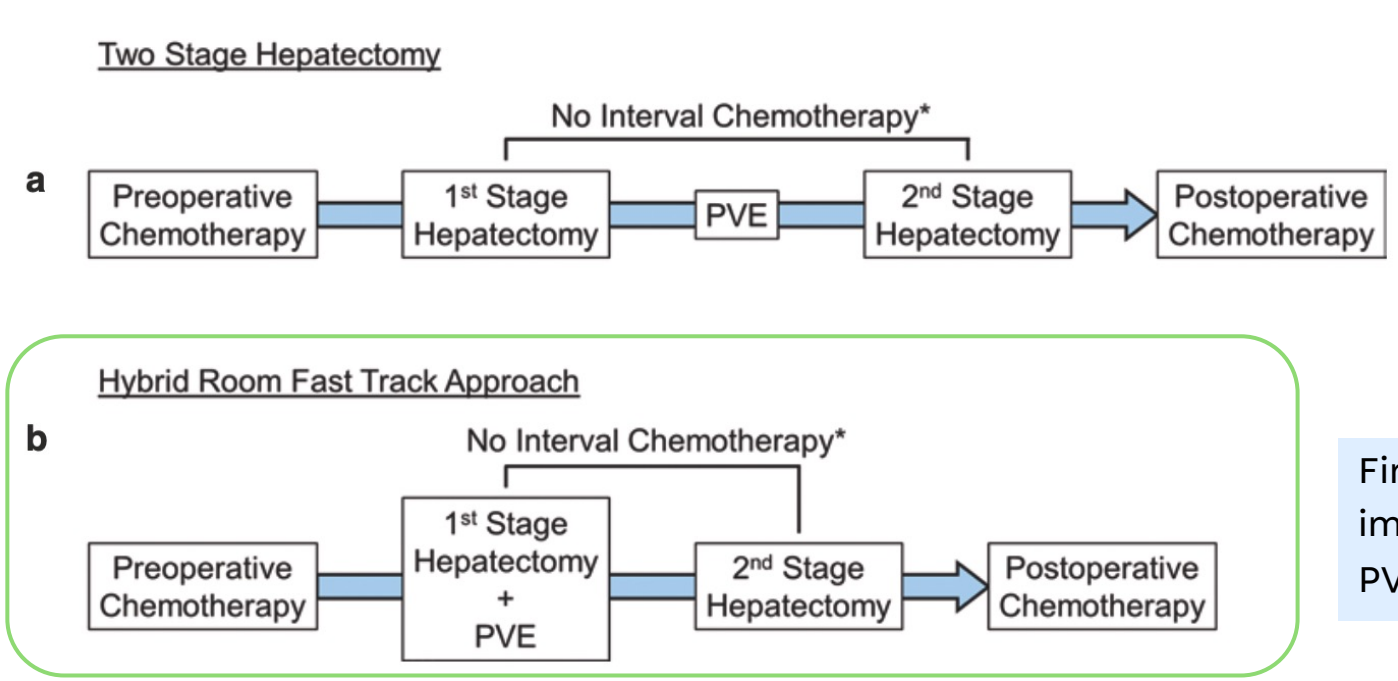


Fig. 7.1 Typical treatment sequence of (**a**) two-stage hepatectomy and (**b**) hybrid room fast-track two-stage hepatectomy approach. PVE: portal vein embolization. *In most patients, chemotherapy is not used between the first and second stage. It is used selectively after first stage hepatectomy based on radiologic response, pathologic response, and somatic gene mutation profile

First stage liver resection + immediate Percutaneous PVE by IR

- Minimize the time between 1st and 2nd stage
  - Previous report interval 2-4 months
  - This study 2nd stage within 4 weeks
- Safe and effective, alternative to ALPPS
- Failure to 2nd stage : lack of FLR hypertrophy, progression of disease from lack of response to chemotherapy and unfavorable biology

Odisio, Bruno C. MD[a].et al. Fast-Track Two-Stage Hepatectomy Using a Hybrid Interventional Radiology/Operating Suite as Alternative Option to Associated Liver Partition and Portal Vein Ligation for Staged Hepatectomy Procedure. Journal of the American College of Surgeons 227(2):p e5-e10, August 2018.

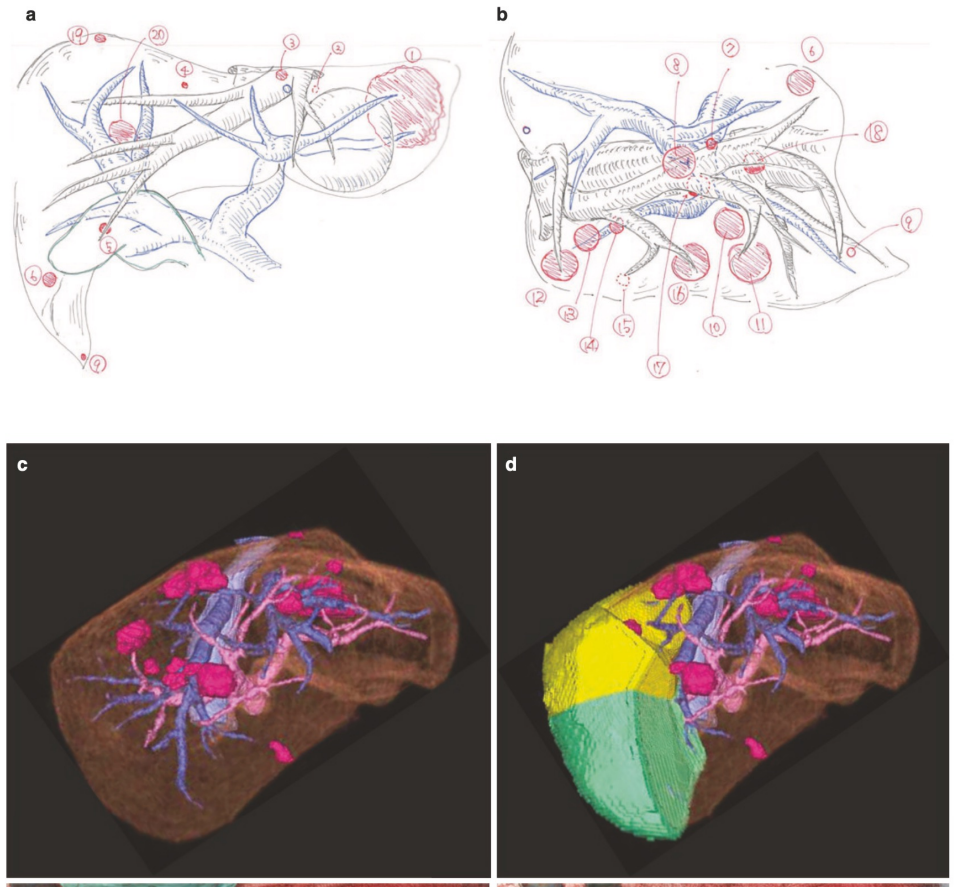
One-Stage Hepatectomy

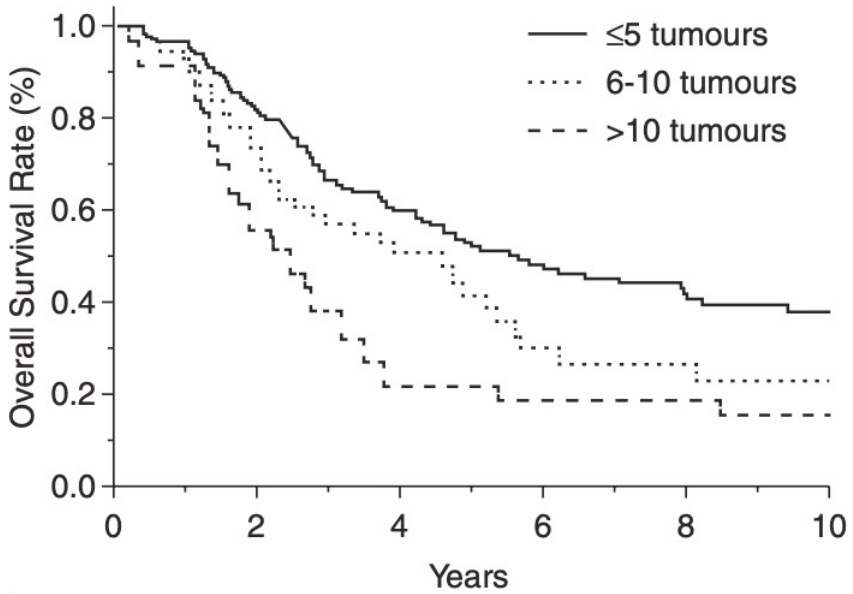
- Complete resection in one operation
- Concept : multiple partial liver resection with or without PVE
- Rarely perform hemi-hepatectomy for bilateral CLM to preserve as many Glissonean pedicles as possible except incases of tumor invasion

- R0 resection 70-80% in one stage hepatectomy
- Severe postop morbidity 10-15%, post-op mortality 1-2%
- 5 yr OS = 40-50%

Nishioka, Y., Kawaguchi, Y., Hasegawa, K. (2022). One-Stage Hepatectomy for Bilateral Colorectal Liver Metastases: Experience of the University of Tokyo. In: Vauthey, JN., Kawaguchi, Y., Adam, R. (eds) Colorectal Liver Metastasis. Springer.

Outcome One-Stage Hepatectomy (TOKYO)





No. at Risk						
≤5 tumours	180	128	79	49	37	23
6-10 tumours	70	47	23	11	9	5
>10 tumours	58	26	10	7	7	6

Fig. 9.4 Overall survival by number of CLMs for patients who underwent one-stage hepatectomy at The University of Tokyo

Nishioka, Y., Kawaguchi, Y., Hasegawa, K. (2022). One-Stage Hepatectomy for Bilateral Colorectal Liver Metastases: Experience of the University of Tokyo. In: Vauthey, JN., Kawaguchi, Y., Adam, R. (eds) Colorectal Liver Metastasis. Springer.

Table 9.1 Outcomes after one-stage hepatectomy and two-stage hepatectomy for bilateral colorectal liver metastases

	Year	Patient no.	Preoperative chemotherapy, %	PVE, %	Major hepatectomy, %	Additional ablation therapy, %	TSH completion, %	R0 resection, %	Postoperative morbidity (all), %	Postoperative morbidity (C-D ≥ 3), %	Postoperative mortality, %	5-Year OS, %
One-stage hepatectomy												
Bolton et al. [35]	2000	44	68	0	52	0	–	NA	NA	NA	6	36
Sakamoto et al. [36]	2010	77	0	14	16	0	–	24	13	NA	1	37
Memeo et al. [37]	2016	691	34	NA	52	25	–	70	30	17	0.2	67 (PSH), 59 (non-PSH)
Philips et al. [38]	2016	101	80	0	46	100	–	86	32	14	1	40
Mizuno et al. [39]	2018	101	93	9	NA	71	–	NA	44	26	8	24
Spelt et al. [40]	2018	119	73	10	50	17	–	84	71	13	0	30 (PSH), 40 (non-PSH)
Torzilli et al. [41]	2019	52	77	0	0	0	–	21	46	8	2	(3-year OS) 43
D'Hondt et al. [42][a]	2021	36	56	0	0	0	–	89	6	3	0	76
Current report	–	308	38	8	25	0	–	76	44	16	0	45
Two-stage hepatectomy												
Passot et al. [6]	2016	109	100	73	100	0	80	61	NA	26	6	49 (TSH completed) 0 (TSH not completed)
Baumgart et al. [27]	2019	50	91	68	100	0	72	70	NA	34	4	22
Chavez et al. [28]	2021	196	92	65	78	28	100	78	47	23	5	44

C-D Clavien-Dindo classification, *NA* not available, *OS* overall survival, *PSH* parenchymal-sparing hepatectomy, *PVE* portal vein embolization, *TSH* two-stage hepatectomy

[a]All the patients underwent laparoscopic surgery

Nishioka, Y., Kawaguchi, Y., Hasegawa, K. (2022). One-Stage Hepatectomy for Bilateral Colorectal Liver Metastases: Experience of the University of Tokyo. In: Vauthey, JN., Kawaguchi, Y., Adam, R. (eds) Colorectal Liver Metastasis. Springer.

ALPPS

Chakedis J, Schmidt CR. Surgical Treatment of Metastatic Colorectal Cancer. Surg Oncol Clin N Am. 2018 Apr;27(2):377-399.

Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS)

Two staged hepatectomy + rapid hypertrophy of the future liver remnant in a short period of time.

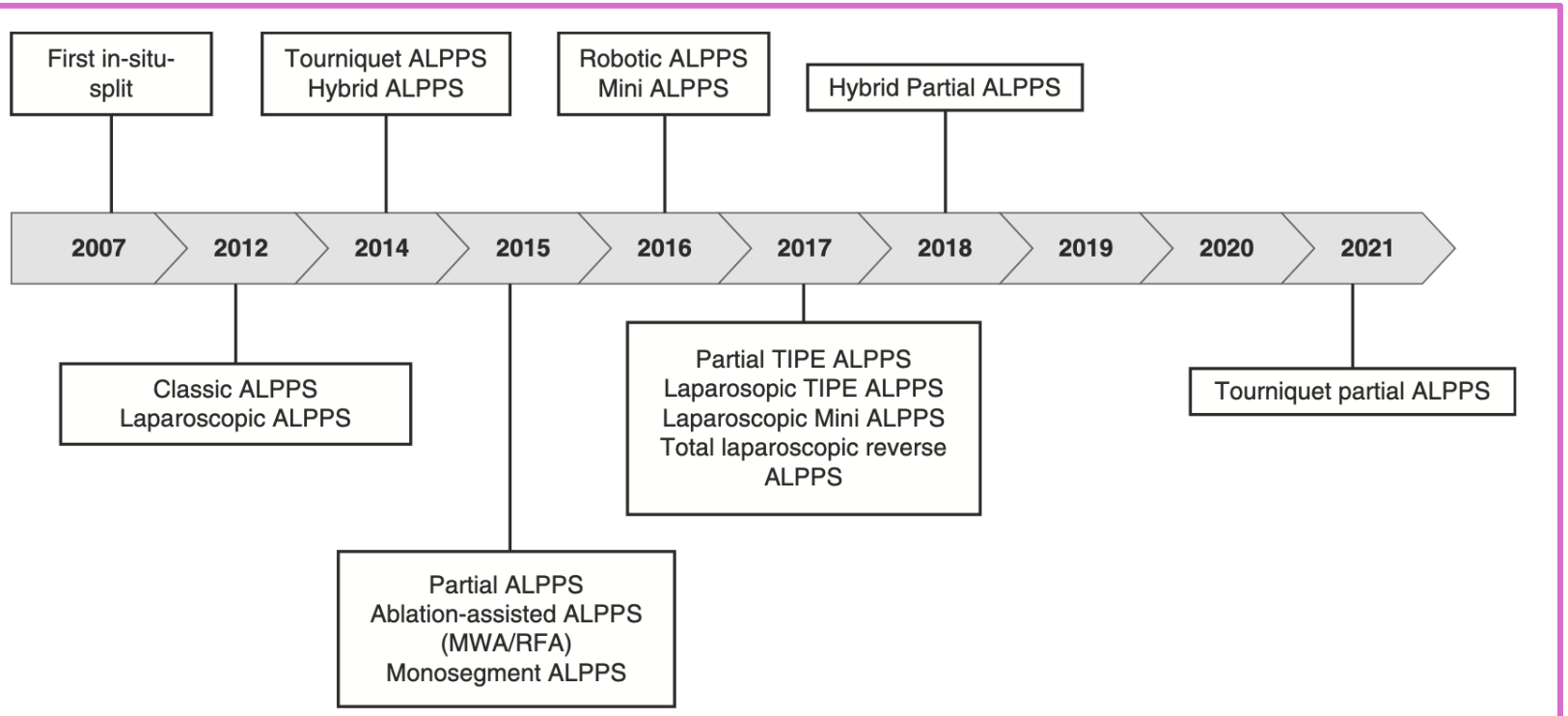


Fig. 10.1 Timeline of technical evolution and modification of the original ALPPS procedure

Early tumor recurrence

Controversy weather massive growth stimulates undetected tumor in FLR

Mittler, J., Baumgart, J., Lang, H. (2022). Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS) for Colorectal Liver Metastasis. In: Vauthey, JN., Kawaguchi, Y., Adam, R. (eds) Colorectal Liver Metastasis. Springer, Cham

Funtional Resectability With ALPPS

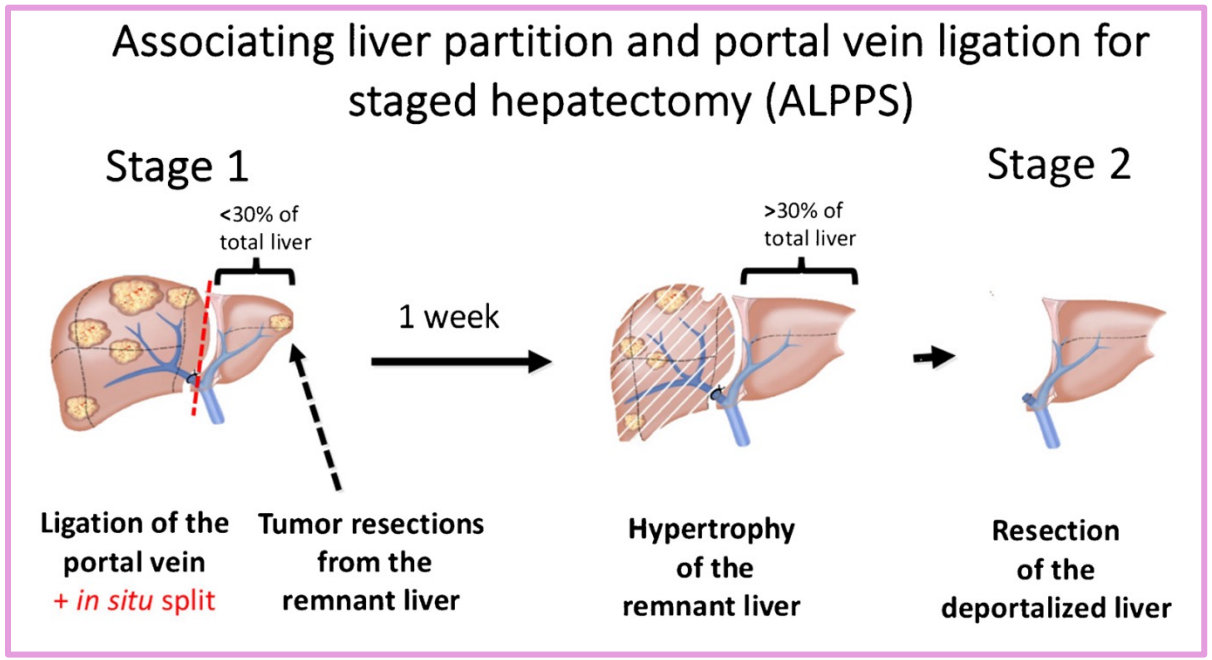
- ALPPS was shown to be effective after failure of PVE and “rescue” or “salvage” procedure.

- Growth rate

TSH	ALPPS
3-5 ml/day	22-35 ml/day

- More deprivation
  - Portal flow
  - Compensatory collaterals

- Median hypertrophy rates 160% (range 90-250%)



Madoff, D.C., Odisio, B.C., Schadde, E. *et al.* Improving the Safety of Major Resection for Hepatobiliary Malignancy: Portal Vein Embolization and Recent Innovations in Liver Regeneration Strategies. *Curr Oncol Rep* **22**, 59 (2020).
Mittler, J., Baumgart, J., Lang, H. (2022). Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS) for Colorectal Liver Metastasis. In: Vauthey, JN., Kawaguchi, Y., Adam, R. (eds) Colorectal Liver Metastasis. Springer, Cham

ALPPS for CRLM in a Curative Intention

ALPPS vs. TSH

- **TSH plus PVE/PVL**
  - Beneficial because longer waiting better assessment of tumor growth and better patient selection
  - Better chance to remove small tumor deposits and metastases during stage one.
- **ALPPS**
  - Interstage = 7-14 days
  - less patients dropping out
  - High rate of complete resections, higher rate resectability
  - May cannot detect tumor progression

Mittler, J., Baumgart, J., Lang, H. (2022). Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS) for Colorectal Liver Metastasis. In: Vauthey, JN., Kawaguchi, Y., Adam, R. (eds) Colorectal Liver Metastasis. Springer, Cham

ALPPS vs. TSH

	ALPPS	TSH
Adam et al. (2016)	Median survival 20 mo.	Median survival 37 mo.
Baumgart et al. (2019)	Recurrence rate 87.5% Median OS 36.2 mo.	Recurrence rate 60% Median OS 26.7 mo.
Bednarsch et al. (2020)	DFS 19 mo.	DFS 10 mo.
Morris et al. (2018) Ratti et al. (2015) Kambakamba et al. (2016)	Similar DFS	

Mittler, J., Baumgart, J., Lang, H. (2022). Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS) for Colorectal Liver Metastasis. In: Vauthey, JN., Kawaguchi, Y., Adam, R. (eds) Colorectal Liver Metastasis. Springer, Cham

Morbidity and Mortality ALPPS

ALPPS Improves Resectability Compared With Conventional Two-stage Hepatectomy in Patients With Advanced Colorectal Liver Metastasis

Results From a Scandinavian Multicenter Randomized Controlled Trial (LIGRO Trial)

Intervention 1	ALPPS (n = 48)	TSH (n = 49)	P
Primary end point:			Odds ratio, P
Resection rates[‡] (%)	(44/48)92	(28/49)57	8.25 (2.6–26.6) P<0.0001
Secondary end points:			
Complications grade ≥3a[§] (%)	(19/44)43	(12/28)43	1.01 (0.4–2.6) P = 0.99
90-d Mortality§(%)	(4/48)8.3	(3/49)6.1	1.39 (0.3–6.6) P = 0.68
90-d Mortality[§] (%)	(4/44)9.1	(3/28)10.7	0.83 (0.2–4.0) P = 0.82
Negative margin in the liver (%)[§,††]	(34/44)77	(16/28)57	2.55 (0.9–7.1) P = 0.11

*Plus–minus values are means ± SD.

No significant difference in the 90-day mortality

No difference in DFS

OS in ALPPS in significantly longer 46 mo. vs TSH 26 mo. (due to higer resection rate in ALPPS)

Sandström P et al. ALPPS Improves Resectability Compared With Conventional Two-stage Hepatectomy in Patients With Advanced Colorectal Liver Metastasis: Results From a Scandinavian Multicenter Randomized Controlled Trial (LIGRO Trial). Ann Surg. 2018

Many Types of ALPPS

- **Partial ALPPS**
  - Limiting the depth and extent of parenchyma transection
  - Lower morbidity, nearly zero mortality
- **RF-ALPPS, MW-ALPPS**
- **Tourniquet ALPPS**
  - Tourniquet around a parenchymal groove of 1 cm in the future transection line
- **Mini-ALPPS**
  - Partial ALPPS + Intra-op PVE, avoid dissection of porta hepatis
- **Hybrid-partial-ALPPS**

Cioffi, L.; Belli, G.; Izzo, F.; Fantini, C.; D'Agostino, A.; Russo, G.; Patrone, R.; Granata, V.; Belli, A. Minimally Invasive ALPPS Procedure: A Review of Feasibility and Short-Term Outcomes. *Cancers* **2023**, *15*, 1700.

Hepatic Artery Infusion Therapy

- Aim
  - High lever of active product in hepatic metastasis
  - Reduce systemic concentration → lower toxicity

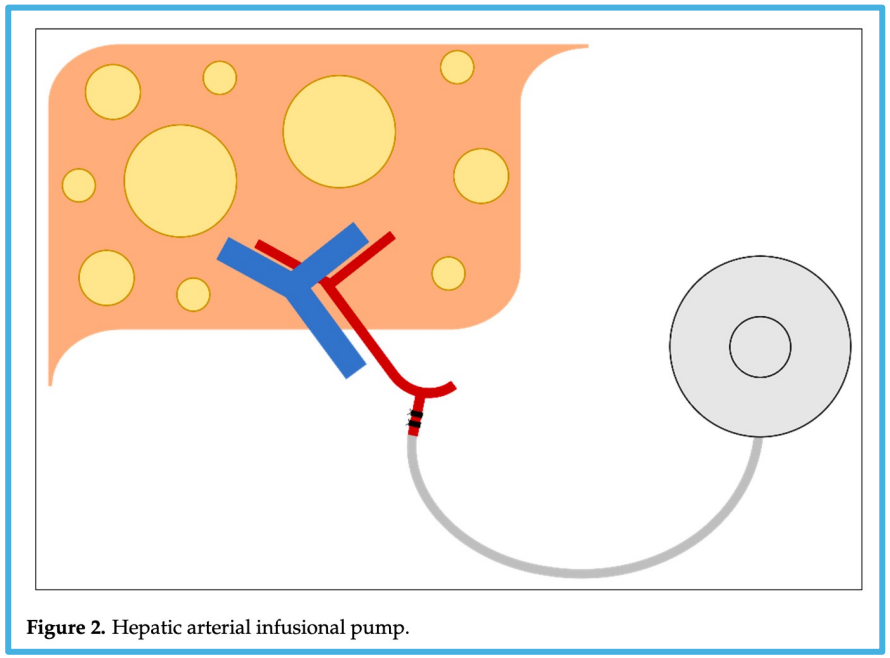


Figure 2. Hepatic arterial infusional pump.

- A metallic device connect with catheter
- Insert into GDA
- Allow direct access for the administration of agents with high first-pass hepatic extraction

- Traditionally has often been used as a strategy to convert patient with initially unresectable CRLM to resectable.

Ivey, G.D.; Johnston, F.M.; Azad, N.S.; Christenson, E.S.; Lafaro, K.J.; Shubert, C.R. Current Surgical Management Strategies for Colorectal Cancer Liver Metastases. *Cancers* **2022**,*14*,1063.

Hepatic Artery Infusion Therapy

- Systemic chemotherapy convert to resectable 10-30%.

Conversion to Complete Resection and/or Ablation Using Hepatic Artery Infusional Chemotherapy in Patients with Unresectable Liver Metastases from Colorectal Cancer: A Decade of Experience at a Single Institution

John B. Ammori, MD[1,4], Nancy E. Kemeny, MD[2], Yuman Fong, MD[1], Andrea Cercek, MD[2], Ronald P. Dematteo, MD[1], Peter J. Allen, MD[1], T. Peter Kingham, MD[1], Mithat Gonen, PhD[3], Philip B. Paty, MD[1], William R. Jarnagin, MD[1], and Michael I. D'Angelica, MD[1]

- Floxuridine (FUDR) as chemotherapeutic of choice.
- Complete resection/ablation 16% (2000-2003)
- Complete resection/ablation 30% (2004-2009)
- 5 year survival from the time of HAI pump placement **59 mo. and 47% patient** who **converted** to complete R/A.
- 5 year survival from the time of HAI pump placement **16 mo. and 6%** patient **who did not converted** to complete R/A. (p=0.001)

TABLE 1 Patient and tumor characteristics

	$N = 373$
Male, *N* (%)	232 (62 %)
Caucasian, *N* (%)	313 (84 %)
Median age, year (range)	56 (21–87)
Clinical risk score ≥3, *N* (%)[a]	291 (87 %)
Bilobar, *N* (%)	359 (96 %)
Largest tumor ≥ 5 cm, *N* (%)	182 (49 %)
≥4 liver tumors, *N* (%)	337 (90 %)
Pre-operative CEA ≥ 200 ng/ml, *N* (%)	113 (32 %)
Lymphovascular invasion of primary tumor, *N* (%)	195 (68 %)
Node-positive primary, *N* (%)	265 (77 %)
Synchronous, *N* (%)	326 (88 %)
On prospective study protocol, *N* (%)	115 (31 %)
Chemotherapy-naïve, *N* (%)	77 (21 %)
Extrahepatic disease, *N* (%)	60 (16 %)
Median follow-up for survivors, years (range)	2.5 (1–11)

[a] One point is assigned to each of the following: nodal-positive primary, synchronous disease defined by disease-free interval <12 months, >1 hepatic metastasis, size of the largest metastasis >5 cm, and pre-operative CEA > 200 ng/ml

Ammori, J.B, *et al.* Conversion to Complete Resection and/or Ablation Using Hepatic Artery Infusional Chemotherapy in Patients with Unresectable Liver Metastases from Colorectal Cancer: A Decade of Experience at a Single Institution. *Ann Surg Oncol* **20**, 2901–2907 (2013).

Hepatic Artery Infusion Therapy

Table 36.1 Results of phase II studies evaluating the use of the main molecules tested in HAI treatment in Europe

HAI drug(s) (doses and schedule)	Other drugs (route, dose and schedule)	Study design dates	N of pts. N of prior chemo lines (median, range) % prior PD	Prior drugs % of pts	Five main Grade 3–4 toxicities, % pts. Catheter dysf, % pts	% ORR [95% CI] % R0-R1 [95% CI]	Median PFS & OS, mo [95% CI] Median OS in R0-R1 pts. [95% CI]	Refs.
Oxaliplatin (100 mg/m^2)	Iv LV-5FU2	Observational Monocentric *2000–2004*	44 pts. Prior lines, 2 (1–5) *70% prior PD* −34% extrahepatic disease	5-FU-LV, 98% oxaliplatin, 77% irinotecan, 84%	Neutropenia, 44% Sensory neuro., 16% Abdominal pain, 14% Thrombocytopenia, 9% Diarrhea, 0% Catheter dysf., 41%	55% [40–69] 18% [*NR*]	7 [*NR*] 16 [*NR*] R0-R1, [*NR*]	Boige Ann Surg Oncol 2008 [18]
Oxaliplatin (80 mg/m^2) Irinotecan (160 mg/m^2) 5-Fluorouracil (2.4 g/m^2) *Chronomodulated* (5d)*	None q-3 weeks	Salvage Monocentric *2000–2006*	29 pts. Prior lines, 3 (1–8) *100% prior PD*	5-FU-LV, 100% oxaliplatin, 100% irinotecan, 89%	Abdominal pain, 14% Diarrhea, 10% Fatigue, 10% Neutropenia, 3% Sensory neuro., 3% Catheter dysf., 31%	34.5% [*NR*] 14% [*NR*]	All pts. 4.5 [2.4–6.5] 18 [5.8–30.2] R0-R1 27+, 35, 77+	Bouchahda Cancer 2009 [19]
Oxaliplatin (85 mg/m^2) Irinotecan (180 mg/m^2) 5-Fluorouracil (2.8 g/m^2) *Chronomodulated* (4d)* *or Conventional (2d)*	Iv Cetuximab (500 mg/m^2) q-2 weeks	Phase II Multicenter International *2008–2012*	64 pts. (RAS wt) Prior lines, 2 (1–3) *48% prior PD* -median, 10 LM −41%, extra-hepatic disease	FU-LV, 95% oxaliplatin, 63% irinotecan, 78%	Neutropenia, 42% Abdominal pain, 26% Fatigue, 18% Diarrhea, 16% Sensory neuro., 3.3% Catheter dysf., 42%	40.6% [28.6–52.3] 29.7% [18.5–40.9]	ITT population 9.3 [7.8–12.3] 25.5 [18.8–32.1] R0-R1 35.2 [32.6–37.8]	Levi Ann Onc 2016 [20]
Oxaliplatin (100 mg/m^2, 2–6 h day 1)	Iv mLV-5FU2/ FOLFIRI and Iv Cetuximab/ Panitumumab/ Bevazucimab q-2 weeks	Retrospective Monocentric *2005–2016*	89 pts. Prior lines, 1 (0–5) *43% prior PD* −34% extrahepatic disease	FU-LV, 93% oxaliplatin, 78% irinotecan, 73% antiEGFR,33% bevazucimab, 67%	Abdominal pain, 43% Neutropenia, 40% Sensory neuro., 12% Thrombocytopenia, 8% Diarrhea, 1% Catheter dysf., 54%,	42% [*NR*] 26.9% [*NR*]	9 [8–11] 20 [15–24] R0-R1 36 [26–59]	Boileve Eur J Cancer 2020 [21]
Raltitrexed (3 mg/m^2, 1 h) Oxaliplatin (130 mg/m^2, 2 h)	Control arm, Standard treatment	Randomized Phase II Multicenter *2010–2016*	HAI, 38 pts. Std tt., 19 pts) Prior lines, 2 (2–4) −31% extrahepatic disease	FU-LV, 100% oxaliplatin, 100% irinotecan, 100% antiEGFR,37% bevazucimab, 94%	Abdominal pain, 37% Neutropenia, 6% Sensory neuro., 12% Thrombocytopenia, 12% Diarrhea, 6% Catheter dysf.,12%,	43.8% R0-R1 *NR*	PFS HAI, 6.7 [3.9–7.2] Std, 2.2 [1.2–4.3] *(P = 0.01)* OS HAI, 11.2 [4.8–17.6] Std., 11.9 [2.8–14.3]	Ghiringhelli J Cancer Res Clin Oncol 2019 [22]
5-FU (0.6–1.2 g/m^2, 4 h) q2-weeks, or Mit-C (7 mg/m^2) q4-weeks	Iv mLV-5FU2/ FOLFIRI and Iv Cetuximab/ Panitumumab/ Bevazucimab q-2 weeks	Retrospective Monocentric *2010–2016*	24 pts. 5-FU, 17 pts. Mit-C, 7 pts. *63% prior PD* - > 8 LM, 75% −42% extrahepatic disease	Prior HAI oxaliplatin, 100% FU-LV, 100% irinotecan, 92% antiEGFR,25% bevazucimab, 67%	Abdominal pain, 0% Neutropenia, 0% Sensory neuro., 0% Thrombocytopenia, 4% Diarrhea, 0% Catheter dysf.,12%,	42% 13%	5.6 25.8	Pernot Clin Res Hepatol Gastroenterol 2018 [23]

Pharmacogenetic determinants of outcomes on triplet hepatic artery infusion and intravenous cetuximab for liver metastases from colorectal cancer (European trial OPTILIV, NCT00852228)

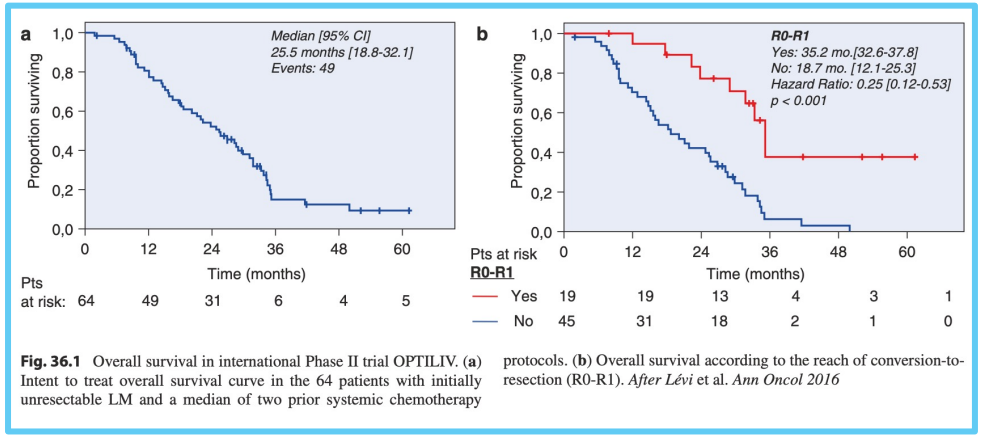


Fig. 36.1 Overall survival in international Phase II trial OPTILIV. (**a**) Intent to treat overall survival curve in the 64 patients with initially unresectable LM and a median of two prior systemic chemotherapy protocols. (**b**) Overall survival according to the reach of conversion-to-resection (R0-R1). *After Lévi* et al. *Ann Oncol 2016*

- PFS ranged from 4.5 to 6.7 mo
- Median OS of early responders 35.1 mo. vs. non-early responders 20.2 mo.
- R0-1 surgical resection rates following HAI-chemotherapy 13-26.8%, OPTILIV study = 29.7%

Lévi F et al. Pharmacogenetic determinants of outcomes on triplet hepatic artery infusion and intravenous cetuximab for liver metastases from colorectal cancer (European trial OPTILIV, NCT00852228). Br J Cancer. 2017 Sep 26;117(7):965-973.

Repeat Hepatectomy for CRLM

- Challenging management
  - Limited due to
    - previous surgery (anatomical landmarks/hypertrophy of FLR)
    - numerous chemotherapy cycles

- Concomitant extrahepatic disease in liver recurrence = 10%
  - Extrahepatic disease predicts lower survival after repeat hepatectomy
  - But worthy for repeat hepatectomy in patient with controlled EHD by systemic therapy e.g. pulmonary metastasis.

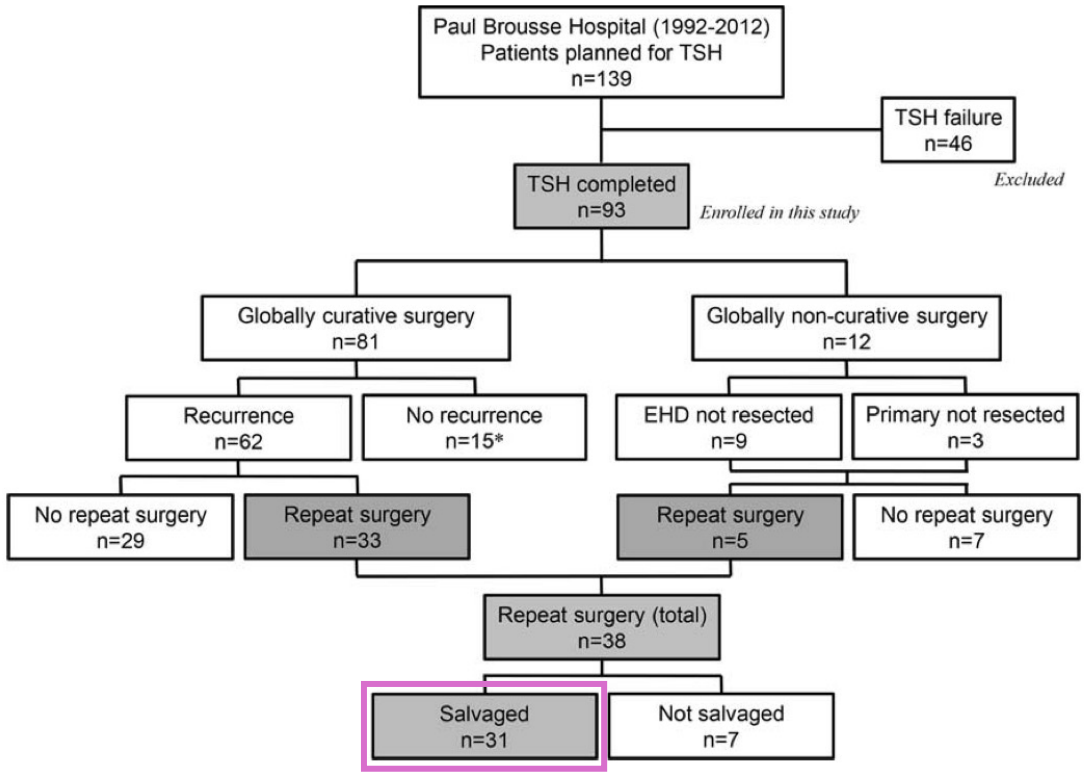
- Repeat hepatectomy should be considered when
  - all complete resection of all macroscopic disease
  - acceptable surgical risk
  - Stable of responsive disease under chemotherapy

Allard, M.A., Adam, R. (2022). Repeat Hepatectomy for Colorectal Liver Metastases. In: Vauthey, JN., Kawaguchi, Y., Adam, R. (eds) Colorectal Liver Metastasis. Springer, Cham.

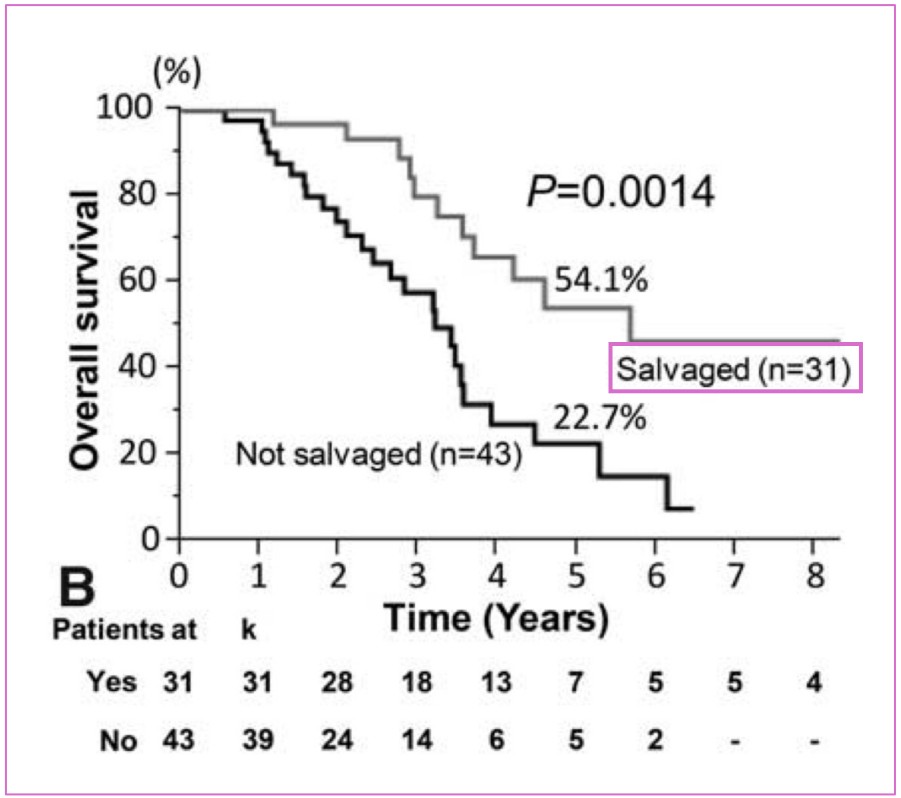
Outcome of Repeat Hepatectomy for CRLM

Impact of Surgical Treatment for Recurrence After 2-Stage Hepatectomy for Colorectal Liver Metastases, on Patient Outcome

Katsunori Imai, MD, PhD,†¶ Carlos Castro Benitez, MD,*†§ Marc-Antoine Allard, MD,*†§ Eric Vibert, MD, PhD,*‡§ Antonio Sa Cunha, MD,*†§ Daniel Cherqui, MD,*‡§ Denis Castaing, MD,*‡§ Henri Bismuth, MD, PhD,* Hideo Baba, MD, PhD,¶ and René Adam, MD, PhD*†§*



Repeat surgery for recurrence after TSH may be crucial for the long-term survival in patients with extensive bilobar CRLM.



Imai, Katsunori MD, PhD et al. Impact of Surgical Treatment for Recurrence After 2-Stage Hepatectomy for Colorectal Liver Metastases, on Patient Outcome. Annals of Surgery 269(2):p 322-330, February 2019.

Outcome of Repeat Hepatectomy for CRLM

Surgical Resection for Recurrence After Two-Stage Hepatectomy for Colorectal Liver Metastases Is Feasible, Is Safe, and Improves Survival

Heather A. Lillemoe[1] · Yoshikuni Kawaguchi[1] · Guillaume Passot[1] · Georgios Karagkounis[1] · Eve Simoneau[1] · Yi-Qian Nancy You[1] · Reza J. Mehran[2] · Yun Shin Chun[1] · Ching-Wei D. Tzeng[1] · Thomas A. Aloia[1] · Jean-Nicolas Vauthey[1]

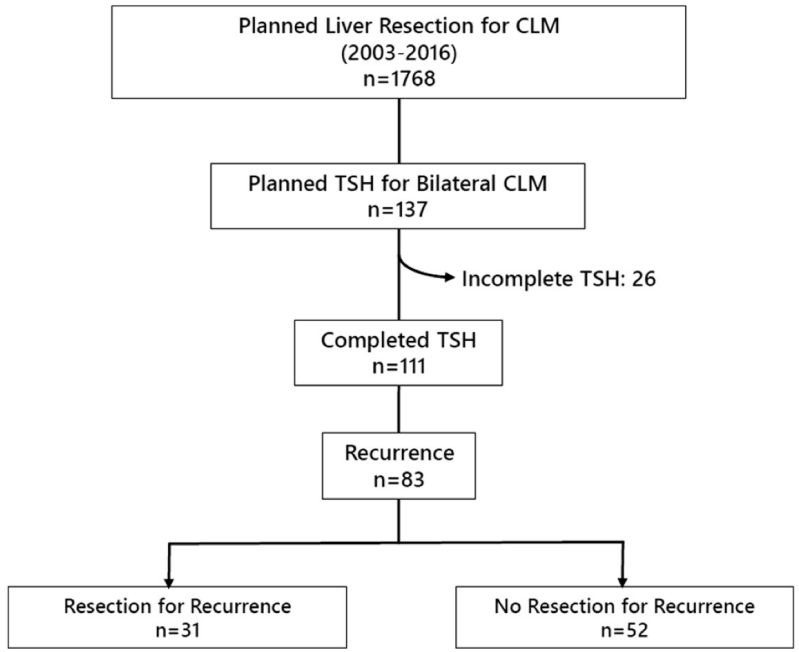
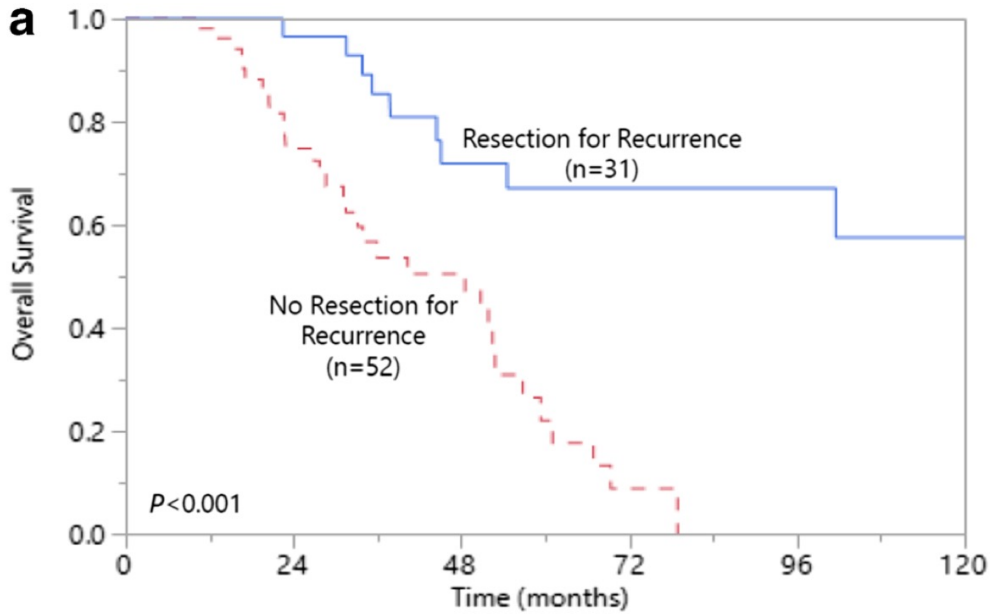


Fig. 1 Patient selection. CLM, colorectal liver metastases; TSH, two-stage hepatectomy



No. at risk						
No Resection for Recurrence	52	34	16	3	0	0
Resection for Recurrence	31	29	17	14	8	5

OS was 143 months for patients who underwent resection for recurrence and 49 months for those who did not undergo resection for recurrence (P < 0.001)

Journal of Gastrointestinal Surgery (2019) 23:84–92

Repeat Hepatectomy - Surgery or Local Ablation

Local ablation

- Effective in small lesions and to preserves liver parenchyma
- Diameter does not exceed 2 cm
- Deep lesion
- May have shorter DFS
- Lower morbidity

- Retroespective studies shows that local ablation has **similar OS** to repeat hepatectomy for intrahepatic CLM recurrence.

Curative-intent treatment of recurrent colorectal liver metastases: A comparison between ablation and resection

Aurélien Dupré [a,b,*], Robert P. Jones [a,c], Rafael Diaz-Nieto [a], Stephen W. Fenwick [a], Graeme J. Poston [a], Hassan Z. Malik [a]

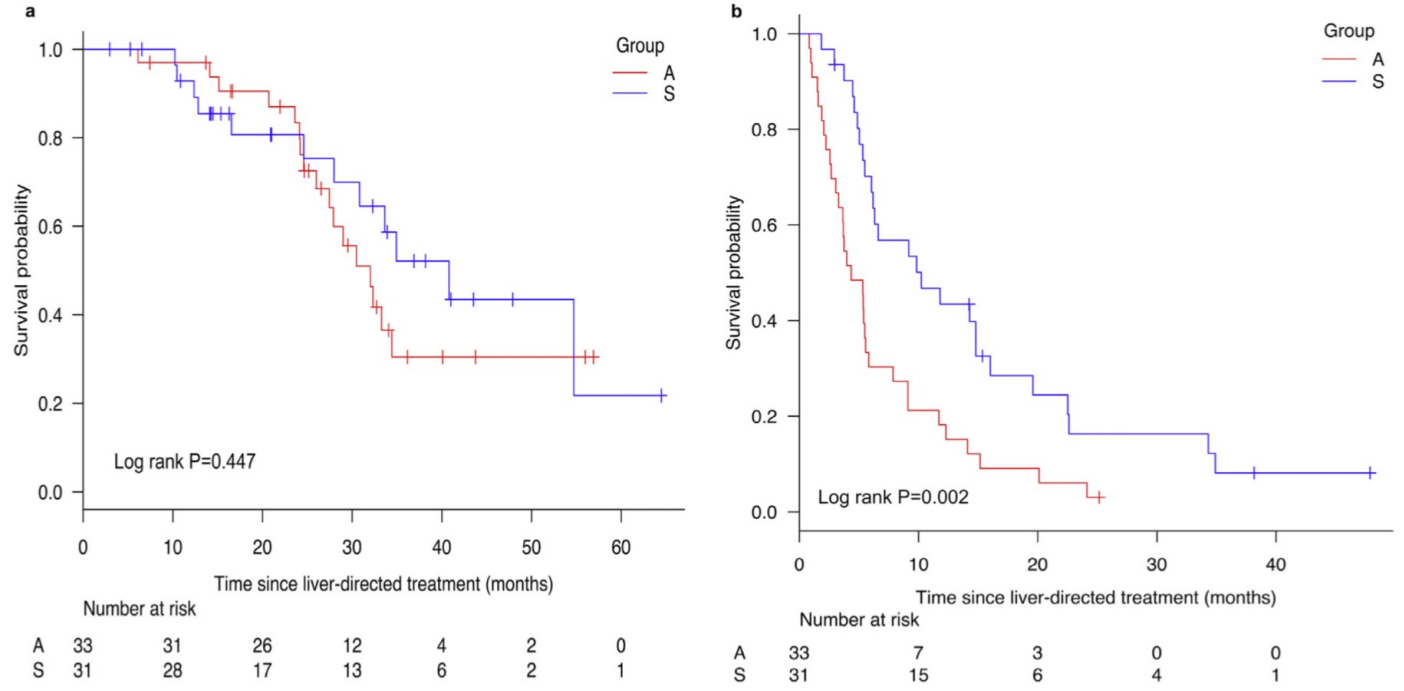


Figure 1. Overall survival (a) and progression-free survival (b) after ablation (group A) or liver resection (group S).

Allard, M.A., Adam, R. (2022). Repeat Hepatectomy for Colorectal Liver Metastases. In: Vauthey, JN., Kawaguchi, Y., Adam, R. (eds) Colorectal Liver Metastasis. Springer, Cham.
Dupré A, Jones RP, Diaz-Nieto R, Fenwick SW, Poston GJ, Malik HZ. Curative-intent treatment of recurrent colorectal liver metastases: A comparison between ablation and resection. Eur J Surg Oncol. 2017 Oct;43(10):1901-1907.

Resection Margin

- Parenchymal sparing hepatectomy (PSH) is considered gold standard
- Frequency of local recurrence with PSH is low.

- Aim at least 1 mm of normal liver tissue from the resection margin to the border of tumor = R0 resection
- To achieve R0 resection : gross margin = 1 cm.

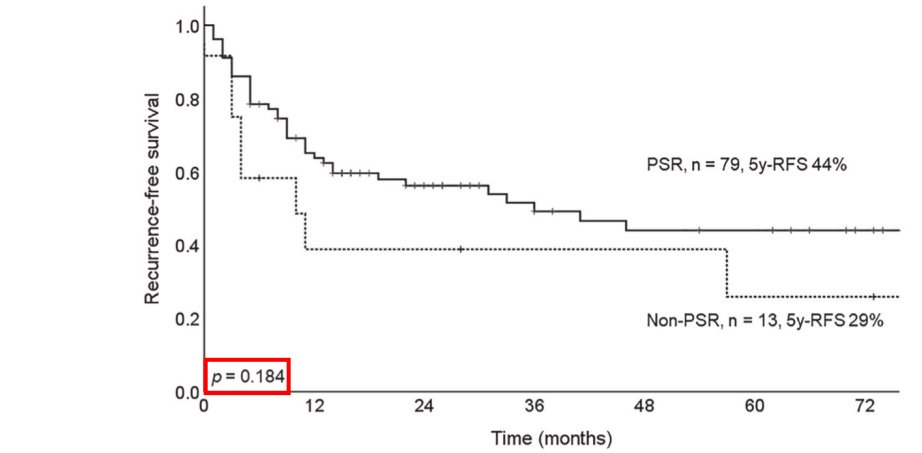
- R1 resection = < 1 mm. from resection margin / R1 vascular
  - Accepted in good respond to preop chemotherapy

Andreou, A., Nishioka, Y., Brudvik, K.W. (2022). Resection Margins. In: Vauthey, JN., Kawaguchi, Y., Adam, R. (eds) Colorectal Liver Metastasis. Springer, Cham.

Resection Margin in Parenchymal Sparing Hepatectomy

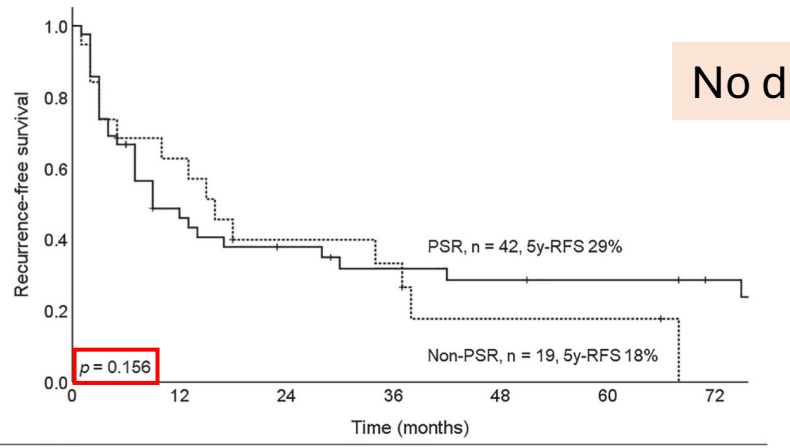
- Parenchymal sparing hepatectomy (PSH)
  - Help lowering risk for small FLR volume and subsequent liver failure
  - Benefit in patients with previous pre-operative chemotherapy
  - Older studies said there's a **risk of higher R1 resection**

  But recent studies **PSH was non inferior to non PSH**



Number of patients at risk							
PSR	79	47	30	21	17	16	11
Non-PSR	13	4	4	3	3	2	2

Fig. 2. Recurrence-free survival of patients with TBS <4.5 who underwent PSR vs. non-PSR for CRLM.



Number of patients at risk							
PSR	42	17	13	10	9	8	6
Non-PSR	19	11	6	5	2	2	0

Fig. 4. Recurrence-free survival of patients with TBS ≥4.5 who underwent PSR vs. non-PSR for CRLM.

No difference in RFS

Andreou A et al. Parenchymal-sparing hepatectomy for colorectal liver metastases reduces postoperative morbidity while maintaining equivalent oncologic outcomes compared to non-parenchymal-sparing resection. Surg Oncol. 2021 Sep;38:101631.

Resection Margin in Parenchymal Sparing Hepatectomy

Parenchymal-sparing hepatectomy for colorectal liver metastases reduces postoperative morbidity while maintaining equivalent oncologic outcomes compared to non-parenchymal-sparing resection

Andreas Andreou [1], Severin Gloor [1], Julia Inglin, Claudine Di Pietro Martinelli, Vanessa Banz, Anja Lachenmayer, Corina Kim-Fuchs, Daniel Candinas, Guido Beldi [*]

From the Department of Visceral Surgery und Medicine, Inselspital, Bern University Hospital, University of Bern, Switzerland

Table 3
Comparison of outcomes between patients who underwent PSR vs. non-PSR for CRLM.

Variable	TBS <4.5		TBS ≥4.5		p^1	p^2
	non-PSR (n = 13)	PSR (n = 79)	non-PSR (n = 19)	PSR (n = 42)		
Length of ICU stay, days, median (range)	2 (0–3)	2 (0–9)	2 (0–9)	2 (0–4)	0.672	0.197
Length of hospital stay, days, median (range)	9 (2–13)	5 (2–37)	9 (4–34)	6 (2–50)	0.006	0.005
90-day complications, n (%)	6 (46)	12 (15)	12 (63)	14 (33)	0.009	0.031
90-day major complications, n (%)	3 (23)	7 (9)	8 (42)	10 (24)	0.129	0.150
90-day mortality, n (%)	0 (0)	0 (0)	1 (5)	1 (2)	1.000	0.562
Postoperative liver failure, n (%)	0	0	1 (5)	0	1.000	0.127
Postoperative bleeding, n (%)	1 (8)	2 (3)	1 (5)	2 (5)	0.548	0.898
Need for transfusion, n (%)	4 (31)	8 (10)	6 (32)	8 (19)	0.042	0.285
Wound infection, n (%)	1 (8)	3 (4)	2 (11)	5 (12)	0.526	0.877
Organ/space infection, n (%)	1 (8)	0	2 (10.5)	1 (2.4)	0.014	0.177
Urinary tract infection, n (%)	0	1 (1)	0	0	0.685	1.000
Pneumonia, n (%)	0	0	1 (5)	0	1.000	0.137
Intrahepatic recurrence, n (%)	7 (54)	32 (41)	9 (47)	20 (48)	0.263	0.568
Repeat hepatectomy for patients with intrahepatic recurrence, n (%)	4 (57)	18 (56)	4 (44)	10 (50)	0.722	1.000
Microwave ablation for patients with intrahepatic recurrence, n (%)	3 (43)	9 (28)	2 (22)	3 (15)	0.548	0.534

TBS, Tumor Burden Score; CRLM, colorectal liver metastases; ICU, intensive care unit.
p1 TBS <4.5: non-PSR vs. PSR.
p^2 TBS ≥4.5: non-PSR vs. PSR.

Andreou A et al. Parenchymal-sparing hepatectomy for colorectal liver metastases reduces postoperative morbidity while maintaining equivalent oncologic outcomes compared to non-parenchymal-sparing resection. Surg Oncol. 2021 Sep;38:101631.

Resection Margin

Effect of Surgical Margin Status on Survival and Site of Recurrence After Hepatic Resection for Colorectal Metastases

Timothy M. Pawlik, MD, MPH, Charles R. Scoggins, MD,* Daria Zorzi, MD,* Eddie K. Abdalla, MD,* Axel Andres, MD,‖ Cathy Eng, MD,† Steven A. Curley, MD,* Evelyne M. Loyer, MD,‡ Andrea Muratore, MD,§ Gilles Mentha, MD,‖ Lorenzo Capussotti, MD,§ and Jean-Nicolas Vauthey, MD**

TABLE 2. Patterns of Recurrence Stratified by Surgical Margin Status (n = 225)

	No. (%) of Patients With Recurrence			
Type of recurrence	**Positive (n = 45)**	**1–4 mm (n = 129)**	**5–9 mm (n = 85)**	**≥1 cm (n = 298)**
Surgical margin	5 (11)	7 (5)	2 (2)	7 (2)
Other intrahepatic	5 (11)	13 (10)	9 (11)	29 (10)
Extrahepatic	8 (18)	15 (12)	14 (16)	45 (15)
Intra- + extrahepatic	5 (11)	15 (12)	10 (12)	36 (12)
Any recurrence	23 (51)	50 (39)	35 (41)	117 (39)

similar overall recurrence rates (P > 0.05)

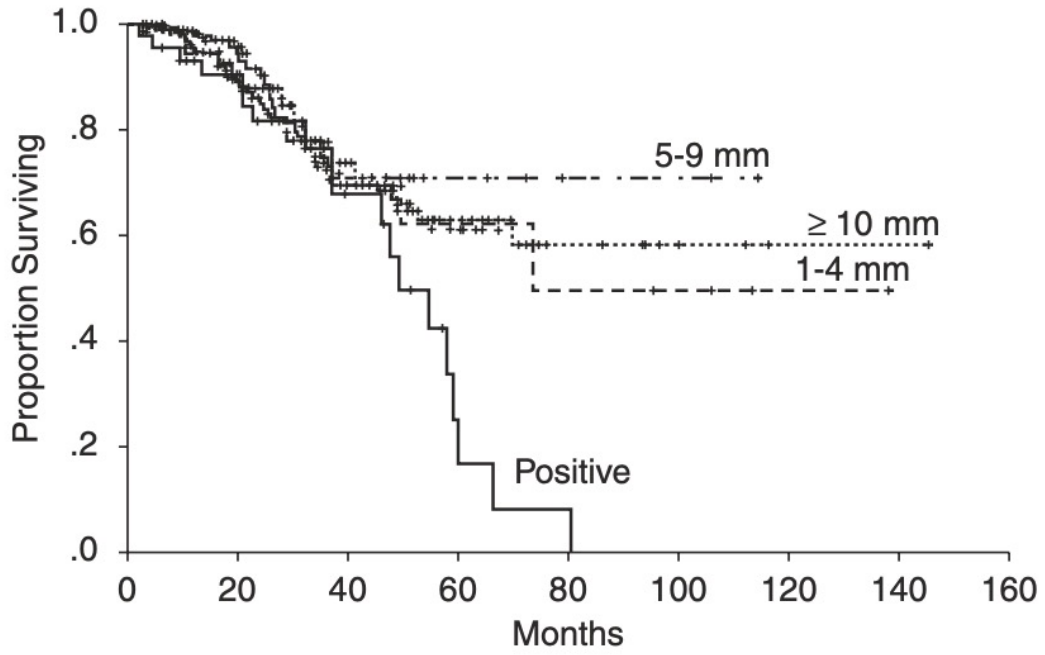
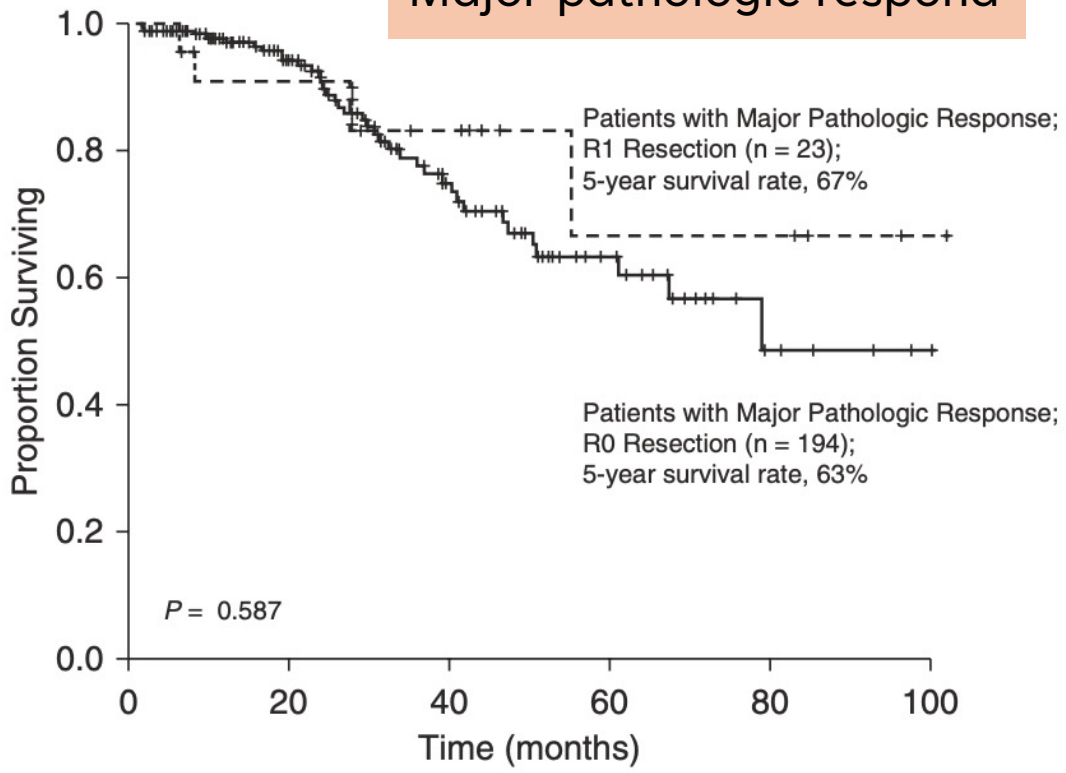


Fig. 17.1 Overall survival stratified by surgical margin width. Survival in patients with positive margins was significantly lower than that in patients with negative margins (p = 0.005), while no significant difference in survival was seen in patients with a negative surgical margin, regardless of the width of the margin. (Adapted from Pawlik, et al. Ann Surg 2005 [3] with permission)

Pawlik TM et al. Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases. Ann Surg. 2005 May;241(5):715-22

Resection Margin in Good Respond Patients

Major pathologic respond



Minor pathologic respond

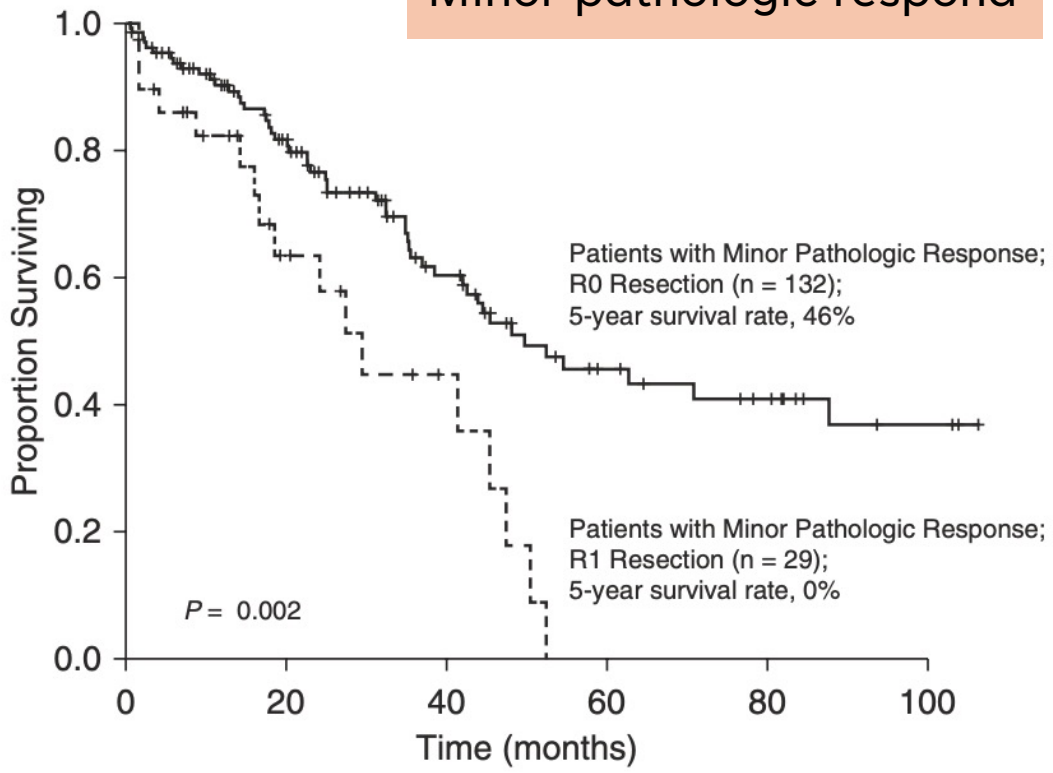


Fig. 17.2 Overall survival by surgical margin status in patients who underwent hepatectomy for colorectal liver metastases with (**a**) a major pathologic response to preoperative chemotherapy and (**b**) a minor pathologic response to preoperative chemotherapy. (Adapted from Andreou, et al. Ann Surg 2013 [6] with permission)

Andreou A et al. Margin status remains an important determinant of survival after surgical resection of colorectal liver metastases in the era of modern chemotherapy. Ann Surg. 2013 Jun;257(6):1079-88.

Resection Margin and Minimal Invasive Hepatectomy

- Minimal invasive ; benefit in vulnerable patients – elderly
- Comparable R1 resection rates in open and mis.

Laparoscopic Versus Open Resection for Colorectal Liver Metastases

The OSLO-COMET Randomized Controlled Trial

Åsmund Avdem Fretland, MD,†‡ Vegar Johansen Dagenborg, MD,§‡¶ Gudrun Maria Waaler Bjørnelv, MPhil,*†††*
*Airazat M. Kazaryan, MD, PhD,** Ronny Kristiansen,*†† Morten Wang Fagerland, MSc, PhD,‡‡*
John Hausken, MD,§§ Tor Inge Tønnessen, MD, PhD,‡§§ Andreas Abildgaard, MD, PhD,¶¶
Leonid Barkhatov, MD,‖‖‡ Sheraz Yaqub, MD, PhD,† Bård I. Røsok, MD, PhD,†*
*Bjørn Atle Bjørnbeth, MD, PhD,† Marit Helen Andersen, RN, PhD,***††† Kjersti Flatmark, MD, PhD,¶§‡*
Eline Aas, MPhil, PhD,††† and Bjørn Edwin, MD, PhD†‡ on behalf of the Oslo-CoMet study group*

TABLE 2. Operative Results (Modified Intention-to-treat, n = 273)

Result	Open (n = 144)	Laparoscopic (n = 129)	*P*
Postoperative complications, Accordion grade 2 or higher	44 (31%)	24 (19%)	0.021
Comprehensive Complication Index,[25] mean (95% CI)	9.3 (6.6–12.0)	5.2 (3.1–7.3)	0.021
Operation time (minutes), median (95% CI)	120 (106–134)	123 (108–138)	0.76
Blood loss (mL), median (95% CI)	200 (126–273)	300 (224–375)	0.062
Unfavorable peroperative incidents	9 (6%)	14 (11%)	0.16
Conversion to laparotomy/hand assisted	–	2 (2%)/7 (5%)	
Postoperative analgesia, PCA/EDA/none (n)	67/76/1	129/0/0	
Postoperative hospital stay (h), median (95% CI)	96 (89–103)	53 (45–61)	<0.001
Transfusion during hospital stay	12 (8%)	10 (8%)	0.91
Postoperative morphine equivalents, median (95% CI)	170 (149–191)	52 (29–74)	<0.001
Stay in recovery ward (h), median (95% CI)	4.27 (3.91–4.63)	3.67 (3.29–4.05)	0.024
Discharge to referring hospital	30 (21%)	15 (11%)	0.042
Intensive care treatment	1 (1%)	3 (2%)	0.24
Readmissions within 30 days	12 (8%)	13 (10%)	0.60
Reoperations within 30 days	6 (4%)	5 (4%)	0.88
Resection margin >1 mm	102 (71%)	92 (71%)	0.83
Resection margin <1 mm but not involved	32 (22%)	29 (22%)	0.94
Involved resection margin	10 (7%)	8 (6%)	0.88
Missed lesion	2 (1%)	4 (3%)	0.32
Changes from initial strategy			
No (parenchyma-sparing resection performed as planned)	137	124	
Converted to ablation only	1	0	
Converted to hemihepatectomy	1	2	
Exploration only	3	2	
Converted to resection + ablation	1	1	
Need for vascular reconstruction	1	0	

Unless otherwise stated, numbers are n (%).
CI indicates confidence interval; EDA, epidural analgesia; PCA, patient-controlled analgesia.

Fretland ÅA et al. Laparoscopic Versus Open Resection for Colorectal Liver Metastases: The OSLO-COMET Randomized Controlled Trial. Ann Surg. 2018 Feb;267(2):199-207.

R1 Resection as a Predictor of Recurrence at the Hepatic Resection Margin

- Buismann et al. (2008) indicated positive surgical margin were not associate with increased marginal recurrence despite more frequent intrahepatic metastasis.
- R1 resection – surrogate marker for tumor biology
- Recurrence at the resection margin did not have worse OS than intrahepatic or extrahepatic recurrences.

Nishioka et al.
N= 552 , attempt R0 resection CLM
+ genetic analysis by using NGS

- RAS/TP53 co-mutation
  Increase incidence of intrahepatic recurrence
- Local recurrence did not differ in RAS/TP53, BRAF, SMAD4, FBXW7 mutations

Findings suggest that prognosis likely is driven by tumor biology

Table 17.2 Patterns of recurrence by surgical margin width

	Margin				
	<1.0 mm[a] (*n* = 137)	1.0–4.9 mm (*n* = 153)	5.0–9.9 mm (*n* = 121)	≥10 mm (*n* = 141)	*P* value
Any recurrence, no. (%)	112 (82)	119 (78)	95 (79)	109 (77)	
Local recurrence, no. (%)	11 (8)	12 (8)	7 (6)	8 (6)	0.840
Other intrahepatic recurrence, no. (%)	73 (53)	73 (48)	57 (47)	62 (44)	
Extrahepatic recurrence alone, no. (%)	28 (20)	34 (22)	31 (26)	39 (28)	
No recurrence, no. (%)	25 (18)	34 (22)	26 (21)	32 (23)	

[a]R0 resection
Adapted from Nishioka, et al. J Gastrointest Surg 2021 [72] with permission

Nishioka Y, Arango NP, Oppliger BF, et al. Neither surgical margin status nor somatic mutation predicts local recurrence after R0-intent resection for colorectal liver metastases. J GastrointestSurg. 2022;26(4):791–801

R1 Vascular

Is Tumor Detachment from Vascular Structures Equivalent to R0 Resection in Surgery for Colorectal Liver Metastases? An Observational Cohort

Luca Viganò, MD, PhD, Fabio Procopio, MD, Matteo Maria Cimino, MD, Matteo Donadon, MD, PhD, Andrea Gatti, MD, Guido Costa, MD, Daniele Del Fabbro, MD, and Guido Torzilli, MD, PhD, FACS

Department of Hepatobiliary & General Surgery, Humanitas Clinical and Research Center - IRCCS, Humanitas University, Rozzano, Milan, Italy

- 627 resection areas (226 patients)

TABLE 2 Local recurrence incidence and details

	R0	R1Par	*p* (R0 vs. R1Par)	R1Vasc	*p* (R0 vs. R1Vasc)
Local recurrence (per-patient)	5/95 (5.3 %)	21/107 (19.6 %)	**0.002**	2/46 (4.3 %)	n.s.
Local recurrence (per-resection area)	6/399 (1.5 %)	24/177 (13.6 %)	**<0.0001**	2/51 (3.9 %)	n.s.
Isolate local recurrence	2	6	n.s.	1	n.s.
Local recurrence + additional liver metastases	2	11	n.s.	1	n.s.
Local recurrence + additional liver and extrahepatic disease	1	4	n.s.	0	n.s.
Delay surgery-local recurrence	10 (4-12)	5.5 (2-18)	n.s.	36.5 (34-39)	**0.003**
Local recurrence if…					
Synchronous metastases	3/46 (6.5 %)	13/51 (25.5 %)	**0.025**	0 %	n.s.
>1 metastasis	3/63 (4.8 %)	15/85 (17.6 %)	**0.034**	2/42 (4.8 %)	n.s.
>3 metastases	2/29 (6.9 %)	12/59 (20.3 %)	n.s.	0 %	n.s.
>50 mm metastasis	3/20 (15.0 %)	10/26 (38.5 %)	n.s.	0 %	n.s.
Bilobar metastases	1/27 (3.7 %)	12/59 (20.3 %)	n.s.	0 %	n.s.
Preoperative chemotherapy	2/44 (4.5 %)	10/57 (17.5 %)	**0.045**	1/29 (3.4 %)	n.s.
Response to chemotherapy (partial/complete)	2/30 (6.7 %)	4/29 (13.8 %)	n.s.	1/14 (7.1 %)	n.s.
Disease progression while on chemotherapy	0 %	6/18 (33.3 %)	n.s.	0 %	n.s.
Adjuvant chemotherapy	2/43 (4.7 %)	3/43 (7.0 %)	n.s.	1/18 (5.6 %)	n.s.

Bold values are statistically significant

- LR risk was **similar** between the **R0 and R1Vasc** groups

(per-patient analysis 5.3 vs. 4.3 %; per-resection area analysis 1.5 vs. 3.9 %, p = n.s.)

- LR increased in the R1Par group (19.6 and 13.6 %, p = 0.05 for both)

- The R1Par group had a higher rate of hepatic-only recurrences (49.5 vs. 36.1%, p = 0.042).

R1Par resection is not adequate. R1Vasc surgery achieves outcomes equivalent to R0 resection

Viganò L, Procopio F, Cimino MM, Donadon M, Gatti A, Costa G, Del Fabbro D, Torzilli G. Is Tumor Detachment from Vascular Structures Equivalent to R0 Resection in Surgery for Colorectal Liver Metastases? An Observational Cohort. Ann Surg Oncol. 2016 Apr;23(4):1352-60.

Unresectable CRLM

Chakedis J, Schmidt CR. Surgical Treatment of Metastatic Colorectal Cancer. Surg Oncol Clin N Am. 2018 Apr;27(2):377-399.

Treatment Options

Unresectable CRLM

Table 3
Treatment options for unresectable liver metastasis as conversion or palliative therapies

Treatment Option	Therapeutic Use
Systemic chemotherapy	FOLFOX, FOLFIRI, CAPEOX, FOLFOXIRI ± bevacizumab or panitumumab/cetuximab (KRAS WT) • Phase III CELIM and BOXER trials[83,84]: 71%–78% response rate and 28%–40% converted to resectable
RFA	Locoregional therapy: percutaneous using ultrasound/CT guidance or laparoscopic • Phase II trial[72]: improved 5-y survival 43.1% compared with 30.3% with systemic treatment alone
Stereotactic body radiotherapy	Locoregional therapy using 34–75 Gy delivered in 3–6 fractions • Phase II trial[85]: 2-y local control 91%, 2-y OS and PFS 65% and 35%
Y-90 selective internal radiotherapy	Locoregional therapy using glass or resin beads with Y-90 delivered through the hepatic artery, doses of 100–3000 Gy that penetrates 2.5–11 mm • Phase III trials currently ongoing: EPOCH, FOXFIRE, SIRFLOX
Isolated hepatic perfusion	Open operation infuses melphlan or oxaliplatin through the hepatic artery • Phase I trial[86]: oxaliplatin used, 66% response rate
Drug-eluting beads preloaded with irinotecan (TACE - DEBIRI)	Locoregional therapy of drug-eluting beads delivered through the hepatic artery to the entire right or left lobe of the liver • Phase III RCT[87]: improved OS (22 vs 15 mo) and PFS (7 vs 4 mo) with TACE-DEBIRI over systemic FOLFIRI
Hepatic artery infusion pump	FUDR infused through the hepatic artery used in combination with systemic chemotherapy for palliative therapy or conversion to resectability • Phase II trial[88]: overall response rate of 76% with 47% converted to resectable in a median of 6 mo

Abbreviations: PFS, progression-free survival; RCT, randomized controlled trial; Y-90, yttrium-90.

Chakedis J, Schmidt CR. Surgical Treatment of Metastatic Colorectal Cancer. Surg Oncol Clin N Am. 2018 Apr;27(2):377-399.

Unresectable

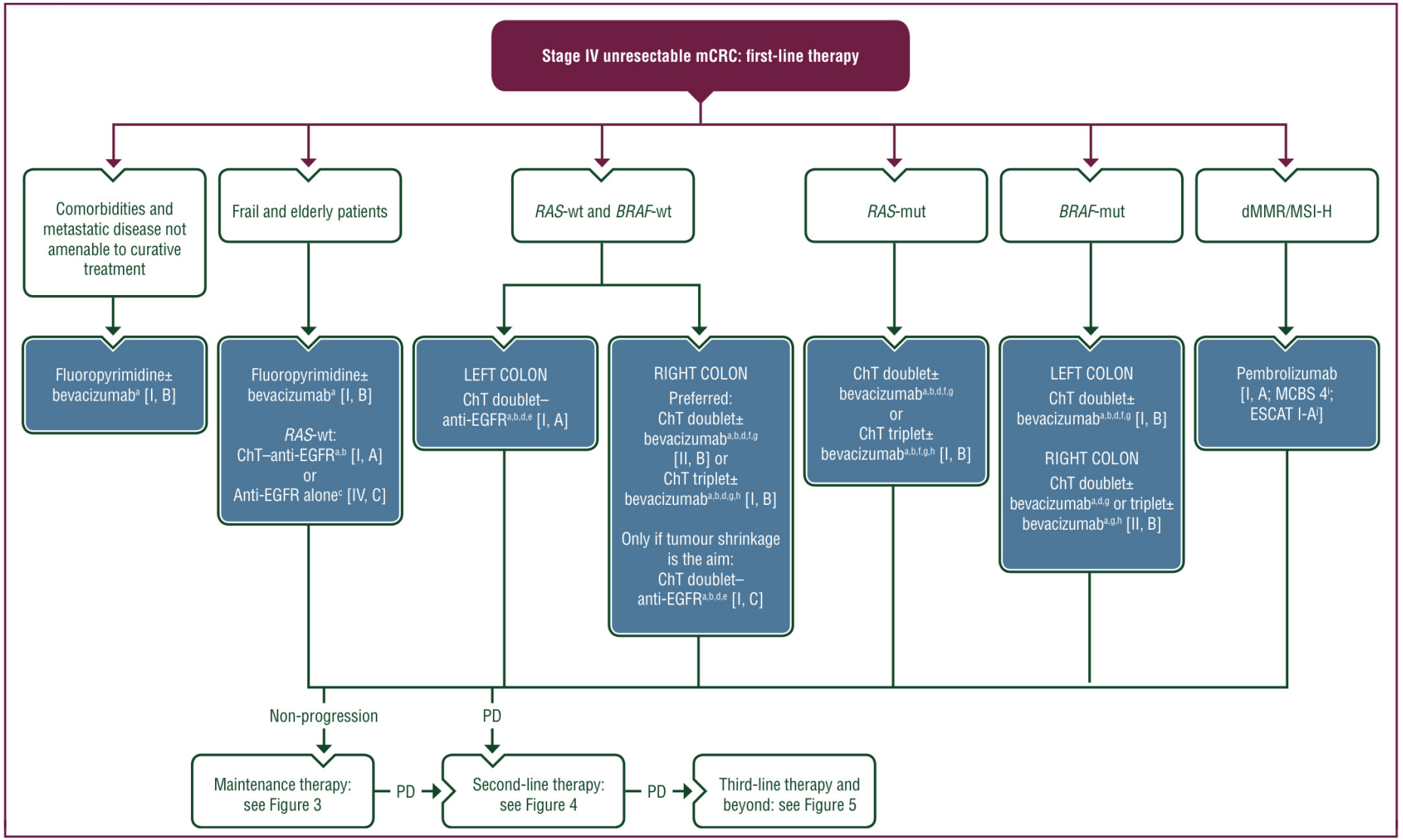


Figure 2. Management of stage IV unresectable mCRC in first-line therapy. Purple: general categories or stratification; blue: systemic anticancer therapy; white: other aspects of management.

Ann Oncol. 2023;34(1):10-32.

Optimal Timing for Periop Chemotherapy

Perioperative Chemotherapy

- Small lesion (<2 cm) → Disappearing
  - **Neoadjuvant chemotherapy should not exceed 2 months**
- Patients with pre-op chemotherapy for CRLM
  - **Resection should be considered after 2-4 months of chemotherapy**
- Post operative chemotherapy
  - **6 months 5-FU + Oxaliplatin base**
- Target agents not recommend during perioperative therapy in patients with upfront resectable metastases

Ann Oncol. 2023;34(1):10-32.

Optimal Timing for Pre-op Chemotherapy

Journal of Surgical Oncology 2008;97:601–604

Assessing the Optimal Duration of Chemotherapy in Patients With Colorectal Liver Metastases

REBEKAH R. WHITE, MD,[1] LAWRENCE H. SCHWARTZ, MD,[2] JOSE A. MUNOZ, BA,[3] GREER RAGGIO, MD,[3] WILLIAM R. JARNAGIN, MD,[1] YUMAN FONG, MD,[1] MICHAEL I. D'ANGELICA, MD,[1] AND NANCY E. KEMENY, MD[3]*

[1]Department of Surgical Oncology, Memorial Sloan-Kettering Cancer Center, New York, New York
[2]Department of Radiology, Memorial Sloan-Kettering Cancer Center, New York, New York
[3]Department of Medical Oncology, Memorial Sloan-Kettering Cancer Center, New York, New York

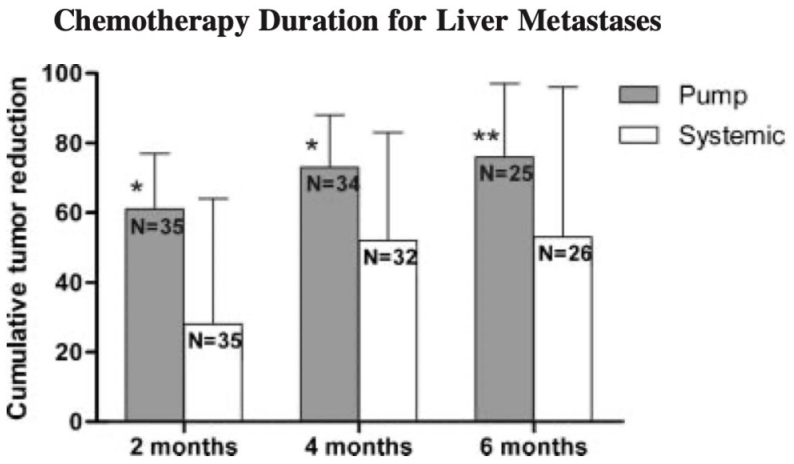


Fig. 4. Mean cumulative tumor reduction in all patients treated. (*$P < 0.01$; **$P = 0.03$; PUMP + SYSTEMIC vs. SYSTEMIC).

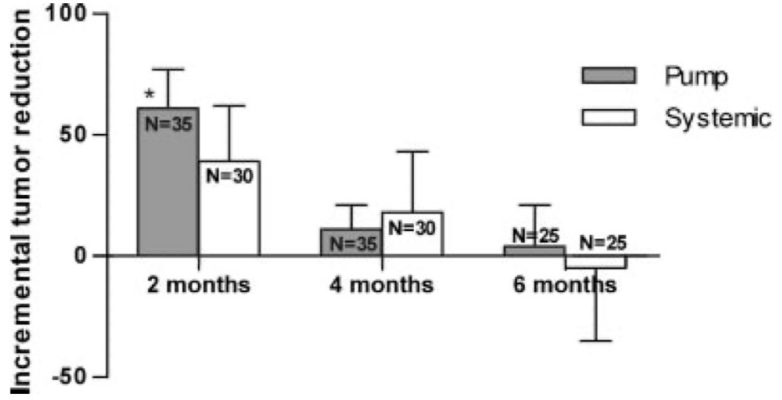


Fig. 5. Mean incremental tumor reduction in patients with any initial tumor reduction. (*$P < 0.01$; PUMP + SYSTEMIC vs. SYSTEMIC).

In responders to preoperative therapy, surgical resection should be considered after 2–4 months, when most patients have achieved maximal response.

Resection should be considered after 2-4 months of chemotherapy, as long as there's no disease progression.

White RR, Schwartz LH, Munoz JA, Raggio G, Jarnagin WR, Fong Y, D'Angelica MI, Kemeny NE. Assessing the optimal duration of chemotherapy in patients with colorectal liver metastases. J Surg Oncol. 2008 Jun 1;97(7):601-4.

Liver Injury Associate Chemotherapy

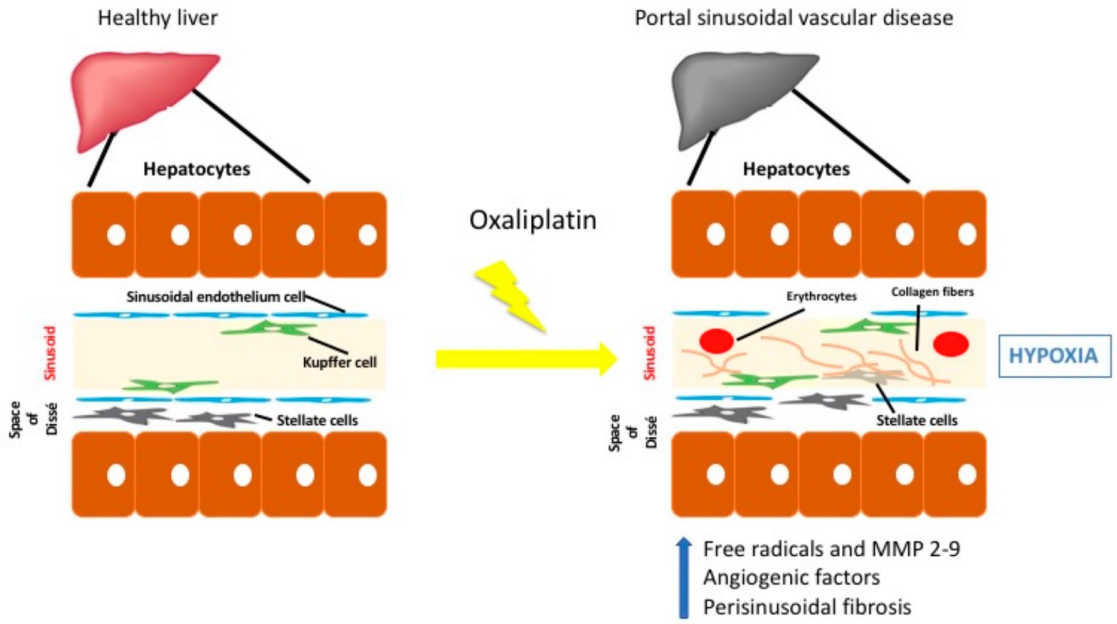


Figure 1. Proposed oxaliplatin liver injury mechanisms of sinusoidal damage: first, oxaliplatin increases porosity of the sinusoidal endothelium cellular fenestrations, stimulating the release of free radicals and depletion of glutathione transferase, followed by an increase of metalloproteinases (MMP-2 and MMP-9). This damage favors the migration of erythrocytes into the space of Dissé and formation of perisinusoidal fibrosis. In this hypoxic situation, an increase of angiogenic factors (and activation of metalloproteinases in turn increasing vascular damage is induced. Second, nodular regenerative hyperplasia is favored by the chronic hypoxia of the centrilobular areas. Third, oxaliplatin can generate an obliteration of the blood capillaries and areas of parenchymal extinction that interrupt portal circulation and eventually elevate portal pressures.

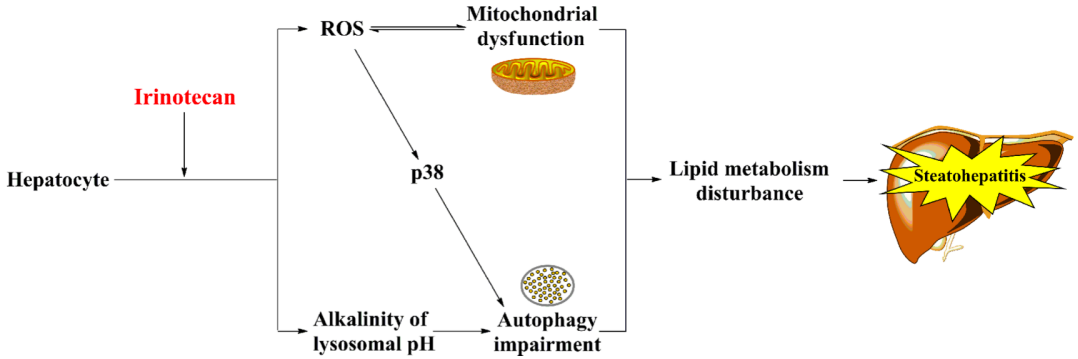


FIGURE 2 | The potential mechanisms of IIS. Irinotecan-caused mitochondrial dysfunction and autophagy impairment result in lipid metabolism disturbance ultimately, which may involve in the pathogenesis of IIS.

Table 4. Summary of liver pathologies caused by preoperative chemotherapy

Pathology	Associated chemotherapy	Notable postoperative morbidities
Steatosis	5-fluorouracil	Liver failure
	Irinotecan	Infectious complications
	Oxaliplatin	Biliary leakage
Steatohepatitis	Irinotecan	Liver failure
Sinusoidal dilation	Oxaliplatin	Biliary complications
		Liver failure
		More perioperative blood transfusions

Han J, Zhang J, Zhang C. Irinotecan-Induced Steatohepatitis: Current Insights. Front Oncol. 2021 Oct 11;11:754891.

Puente, A.; Fortea, J.I.; Del Pozo, C.; Huelin, P.; Cagigal, M.L.; Serrano, M.; Cabezas, J.; Arias Loste, M.T.; Iruzubieta, P.; Cuadrado, A.; et al. Porto-Sinusoidal Vascular Disease Associated to Oxaliplatin: An Entity to Think about It. *Cells* **2019**, *8*, 1506.

pMMR – Resectable – Synchronous Liver Metastasis

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
pMMR/MSS Colon Cancer

NCCN Guidelines Index
Table of Contents
Discussion

TREATMENT
Resectable[h] synchronous liver and/or lung metastases only
pMMR/MSS

ADJUVANT TREATMENT[b] (UP TO 6 MO PERIOPERATIVE TREATMENT) (resected metastatic disease)

Synchronous or staged colectomy[aa] with liver or lung resection (preferred) and/or local therapy[bb]
or
Neoadjuvant therapy (for 2–3 mo) FOLFOX (preferred) or CAPEOX (preferred) or FOLFIRI (category 2B) or FOLFIRINOX (category 2B) followed by synchronous or staged colectomy[aa] and resection (preferred) and/or local therapy[bb] of metastatic disease
or
Colectomy,[aa] followed by chemotherapy (for 2–3 mo) FOLFOX (preferred) or CAPEOX (preferred) or FOLFIRI (category 2B) or FOLFIRINOX (category 2B) and staged resection (preferred) and/or local therapy[bb] of metastatic disease

→ **FOLFOX (preferred)**
or
CAPEOX (preferred)
or
Capecitabine or 5-FU/leucovorin

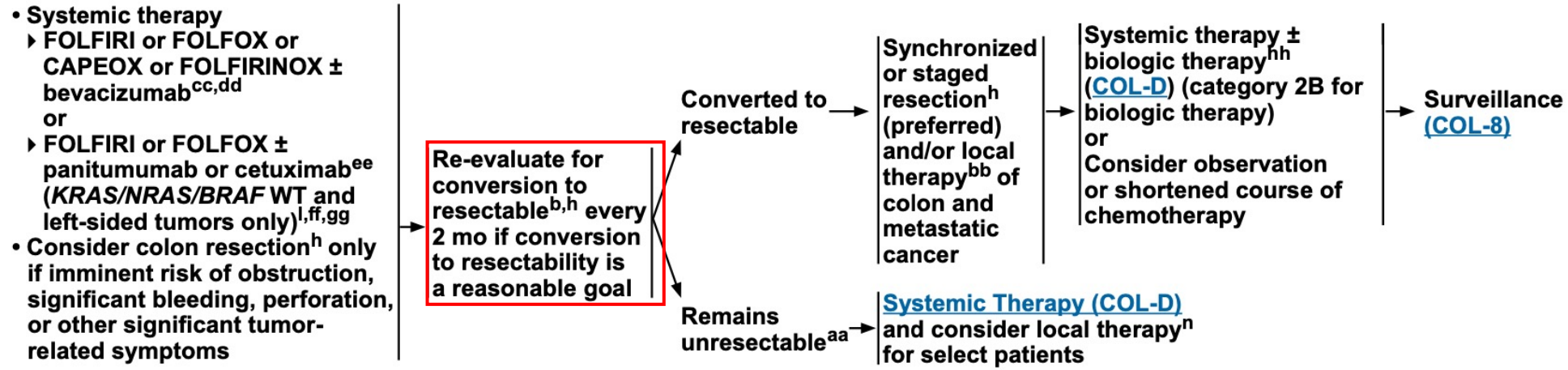
→ **Surveillance (COL-8)**

NCCN Guidelines Version 1.2024
pMMR/MSS Colon Cancer

pMMR – Unresectable – Synchrochronous Liver Metastasis

TREATMENT
Unresectable[h] synchronous liver and/or lung metastases only
pMMR/MSS

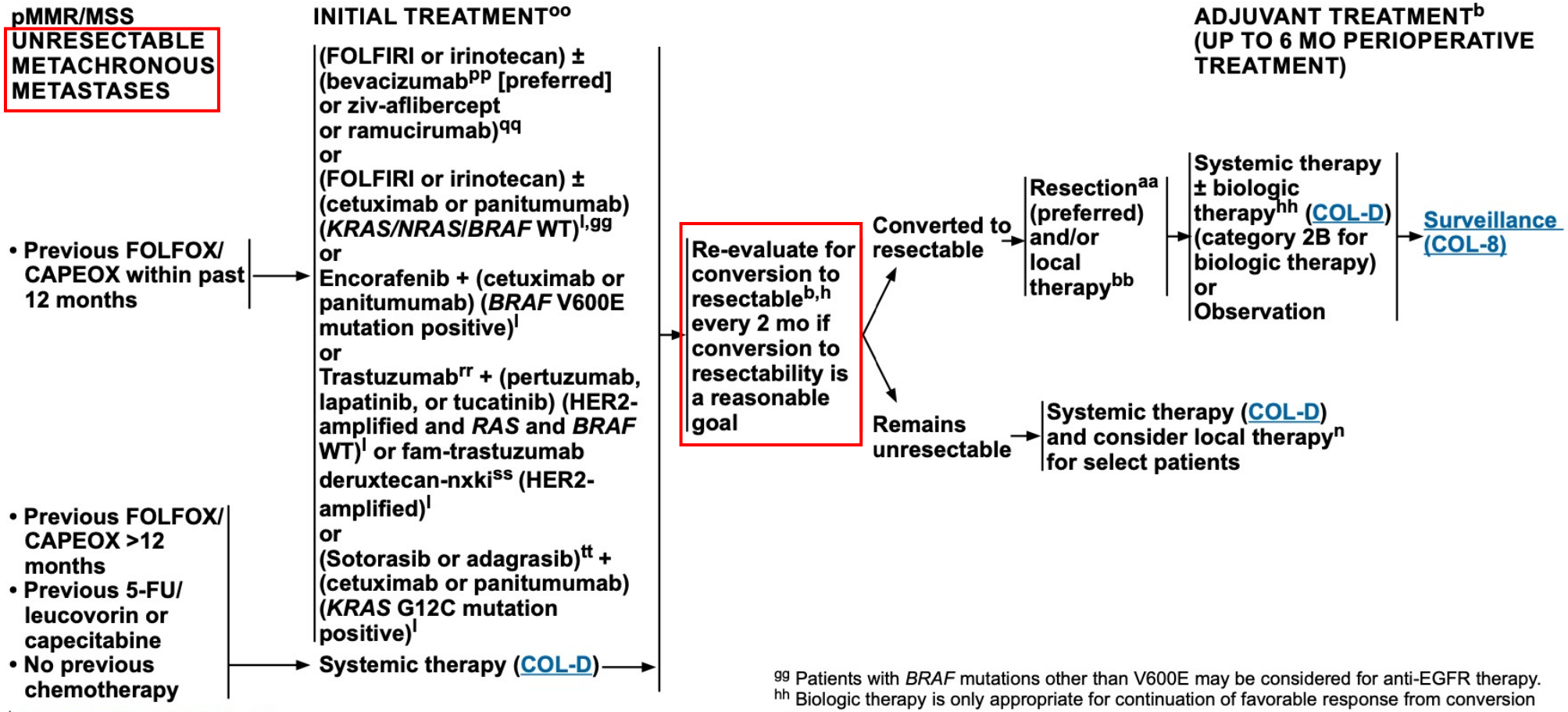
ADJUVANT TREATMENT[b] (UP TO 6 MO PERIOPERATIVE TREATMENT)



[b] Principles of Imaging (COL-A).
[h] Principles of Surgery (COL-C 2 of 3).
[l] Principles of Pathologic Review (COL-B 4 of 10) - *KRAS*, *NRAS*, and *BRAF* Mutation Testing.
[n] Principles of Radiation and Chemoradiation Therapy (COL-E).
[aa] Hepatic artery infusion ± systemic 5-FU/leucovorin (category 2B) is also an option at institutions with experience in both the surgical and medical oncologic aspects of this procedure.
[bb] Resection is preferred over locally ablative procedures (eg, image-guided thermal ablation or SBRT). However, these local techniques can be considered for liver or lung oligometastases (COL-C and COL-E).
[cc] There should be at least a 6-week interval between the last dose of bevacizumab and elective surgery and re-initiation of bevacizumab at least 6 to 8 weeks postoperatively. There is an increased risk of stroke and other arterial events, especially in those aged ≥65 years. The use of bevacizumab may interfere with wound healing.
[dd] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[ee] There are conflicting data regarding the use of FOLFOX + cetuximab in patients who have potentially resectable liver metastases.
[ff] Cetuximab or panitumumab should only be used for left-sided tumors. The panel defines the left side of the colon as splenic flexure to rectum. Evidence suggests that patients with tumors originating on the right side of the colon (hepatic flexure through cecum) are unlikely to respond to cetuximab and panitumumab. Data on the response to cetuximab and panitumumab in patients with primary tumors originating in the transverse colon (hepatic flexure to splenic flexure) are lacking.
[gg] Patients with *BRAF* mutations other than V600E may be considered for anti-EGFR therapy.
[hh] Biologic therapy is only appropriate for continuation of favorable response from conversion therapy.

NCCN Guidelines Version 1.2024
pMMR/MSS Colon Cancer

pMMR – Unresectable – Metachronous Liver Metastasis



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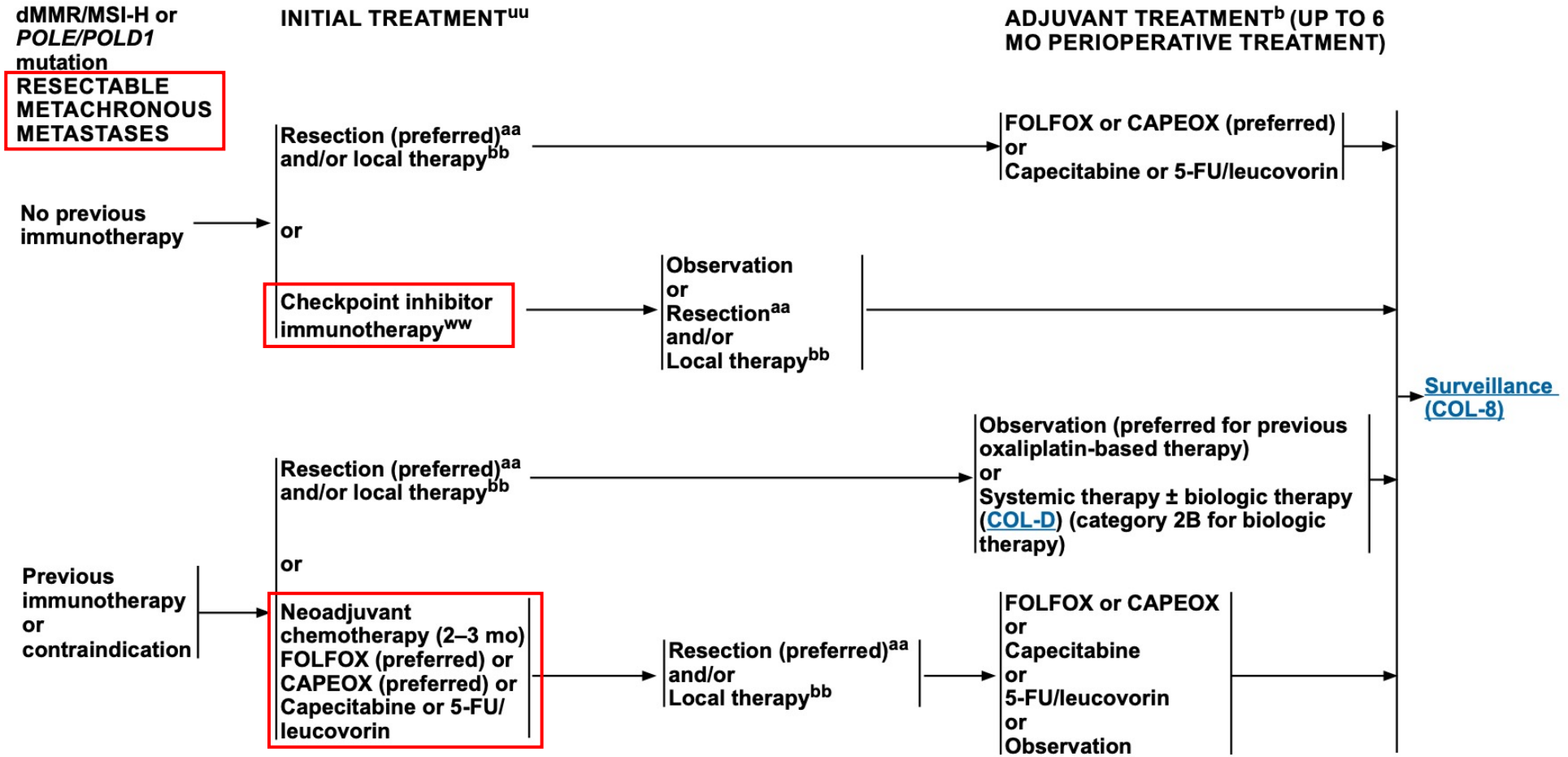
[gg] Patients with *BRAF* mutations other than V600E may be considered for anti-EGFR therapy.
[hh] Biologic therapy is only appropriate for continuation of favorable response from conversion therapy.
[oo] For infection risk, monitoring, and prophylaxis recommendations for targeted therapies, see INF-A in the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.
[pp] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[qq] Bevacizumab is the preferred anti-angiogenic agent based on toxicity and/or cost.
[rr] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.
[ss] Some activity was seen after a previous HER2-targeted regimen. May not be indicated in patients with underlying lung issues due to lung toxicity (2.6% report of deaths from interstitial lung disease).
[tt] If patient is unable to tolerate EGFR inhibitor due to toxicity, single-agent adagrasib or sotorasib can be considered.

dMMR – Resectable – Metachronous Liver Metastasis

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
dMMR/MSI-H Colon Cancer



[b] Principles of Imaging (COL-A).

[aa] Hepatic artery infusion ± systemic 5-FU/leucovorin (category 2B) is also an option at institutions with experience in both the surgical and medical oncologic aspects of this procedure.

[bb] Resection is preferred over locally ablative procedures (eg, image-guided thermal ablation or SBRT). However, these local techniques can be considered for liver or lung oligometastases (COL-C and COL-E).

[uu] Patients with dMMR/MSI-H or *POLE/POLD1* mutation disease who are not candidates for immunotherapy should be treated as recommended for pMMR/MSS disease. See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

[ww] Checkpoint Inhibitor therapy options include: nivolumab ± ipilimumab, pembrolizumab, or dostarlimab-gxly.

Disappearing CRLM

Chakedis J, Schmidt CR. Surgical Treatment of Metastatic Colorectal Cancer. Surg Oncol Clin N Am. 2018 Apr;27(2):377-399.

Disappearing CRLM Lesion

- Disappearing liver metastasis up to 37% (range 7-48%) in patients undergoing systemic treatment.
- The median time to CRLM disappearance = 5 mo. from chemotherapy initiation
- 90% of DLM occur by 9 mo.
- Dilemma : to resect or not

Healthcare (Basel). 2022 Sep 28;10(10):1898.

Disappearing CRLM Lesion

- MRI evaluation in all CRLM, especially with steatosis
  Fat suppressing techniques improve accuracy to detect DLM.

Table 2. Imaging in Disappearing Colorectal Liver Metastases and Their Accuracy

	Number of Patients	dCRLM With Complete Response			Median Follow-up (months)
		CT	MRI	+IOUS	
Radiology. 2017;284(2): 423-431	87	35%	78%	94%	12
J Surg Oncol. 2018;117(2): 191-197	20	59%	85%	86%	27
HPB. 2018;20(8): 708-714	59	51%	65%	92%	27

Source: World J Surg Oncol. 2020;18(1):264.

dCRLM, disappearing colorectal liver metastases; **IOUS,** intraoperative ultrasound

Predictive Factors for Disappearing CRLM Lesion

Table 1. Predictive factors of DLM and complete response. LM: liver metastasis, DLM: disappearing liver metastasis, RR: risk ratio; CEA: carcinoembryonic antigen; HAI: Hepatic arterial infusion; OR: Odd ratio.

Author (Year)	Predictors
Benoist (2006) [44]	• Mean maximum size of LM at diagnosis (cm) (DLM: 2.2 ± 1.5 vs. no DLM: > 4.5)
Adam (2008) [39]	• Age ≤ 60 years (RR = 4.1; $p = 0.03$) • Size of LM at diagnosis ≤ 3 cm (RR = 3.1; $p = 0.05$) • CEA level at diagnosis ≤ 30 ng/mL (RR = 5.6; $p = 0.03$)
Tanaka (2009) [41]	• Smaller size at diagnosis (mm) (DLM: 15.9 ± 14.3 vs. no DLM: 24.4 ± 22.3; $p < 0.001$) • Fewer microscopic cancer deposits surrounding macroscopic tumors (%) (DLM: 21.7 vs. no DLM: 52.5%; $p < 0.05$)
Auer (2010) [38]	• HAI chemotherapy (OR 6.2; $p = 0.02$) • Inability to observe LM on MRI (OR 4.7; $p = 0.005$) • Normalization of CEA levels (OR 4.6; $p = 0.006$)
van Vledder (2010) [42]	• Smaller size of LM (cm) (DLM: 1.0 (0.3–3.5) vs. no DLM: 2.1 (0.4–16); $p < 0.001$) • No. of cycles of preoperative chemotherapy (OR 1.18; $p = 0.03$) • No. of LM at diagnosis >3 (OR 13.1; $p < 0.001$)
Ferrero (2012) [45]	• No. of cycles of preoperative chemotherapy (OR 0.231; $p = 0.022$)
Owen (2015) [46]	• Synchronous LM (OR 11.25; $p = 0.015$) • No. of LM at diagnosis (DLM: 14.5 (4–39) vs. no DLM: 3.5 (1–30); $p < 0.001$)
Kim (2016) [40]	• Mean size of LM at diagnosis (mm) (DLM: 6.8 ± 3.4 vs. no DLM: 9.33 ± 4.1; $p < 0.001$)
Park (2017) [47]	• No. of LM at diagnosis (DLM: 6.0 ± 2.5 vs. no DLM: 4.1 ± 2.6; OR 1.390; $p = 0.001$)
Tani (2018) [48]	• No. of LM [DLM: 14.5 (4–39) vs. no DLM: 3.5 (1–30); $p < 0.0001$] • Smaller size of LM (cm) (DLM: 0.6 (0.4–2.0) vs. no DLM: 1.4 (0.3–13.0); $p < 0.0001$) • Oxaliplatin-based chemotherapy (%) (DLM: 100% vs. no DLM: 75.8%; $p = 0.017$)
Oba (2018) [49]	• Median size of LM at diagnosis: 8 mm (range: 3–34 mm)
Xu (2020) [43]	• Size of LM < 3 vs. >3 cm (OR: 20.542; $p = 0.003$) • Preoperative CEA levels ≤ 20 vs. >20 ng/mL (OR: 7.656; $p = 0.049$) • Primary T stage T1–2 vs. T3–4 (OR: 3.131; $p = 0.018$) • Primary tumor location (right vs. left-sided) (OR: 2.808; $p = 0.017$)

Age ≤ 60 years

Size ≤ 3 cm

CEA at Dx ≤ 30 ng/ml / normal

Number of LM

Synchronous CRLM

Cycles of systemic therapy

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Outcome of Watch and Wait vs. Resection

Patients Operated On for Initially Unresectable Colorectal Liver Metastases With Missing Metastases Experience a Favorable Long-Term Outcome

Diane Goèré, MD, Sébastien Gaujoux , MD, Frédéric Deschamp, MD, Frédéric Dumont, MD, Amine Souadka, MD, Clarisse Dromain, MD, Michel Ducreux, MD, PhD, and Dominique Elias, MD, PhD

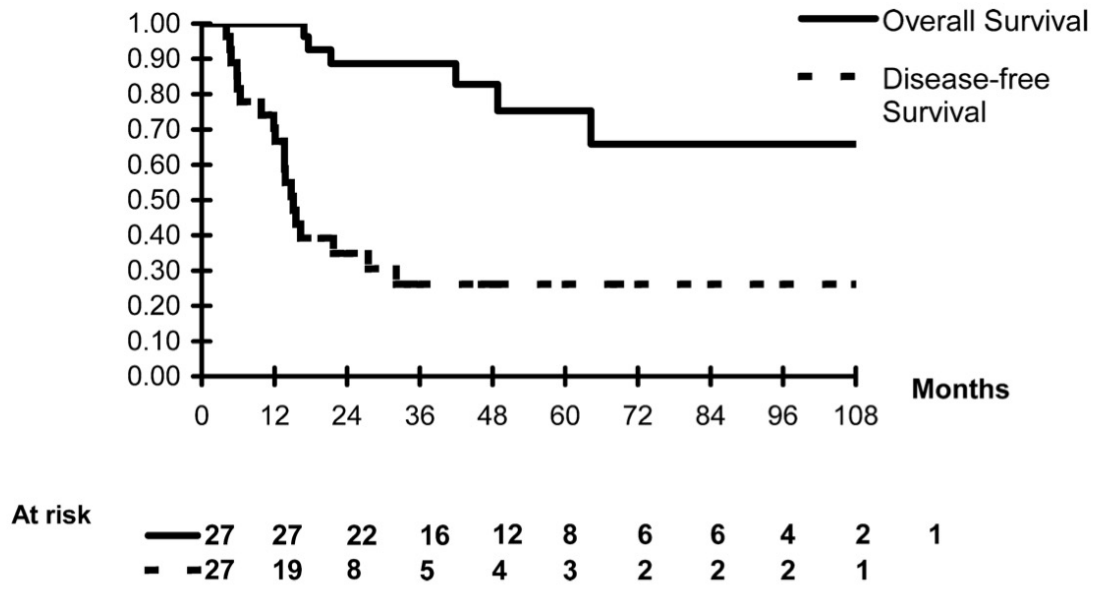

FIGURE 1. Overall and disease-free survival of the 27 patients with missing CRLM left in the remnant liver after liver surgery.

5 years OS = 80% and DFS = 23% in DLM
Median recurrence time 13.8 - 21 mo.

Table 23.3 Patient survival: resection of disappearing liver metastases vs. no resection

Study	Lesions resected	Lesions left in-situ	Resection vs. no resection
Elias 2007	–	3-year OS: 94%	–
	–	3-year DFS: 64%	–
Van Vledder 2010	1-, 3-, and 5-year OS: 93%, 59%, and 38%	1-, 3-, and 5-year OS: 94%, 64%, and 64%	Not significant
	1- and 3-year DFS: 69% and 35%	1- and 3-year DFS: 40% and 16%	$p = 0.04$
Tanaka 2009	Median OS: 53 months	Median OS: 63 months	Not significant
	Median DFS: 22 months	Median DFS: 16 months	Not significant
Goéré 2011	–	3- and 5-year OS: 87% and 80%	–
	–	3- and 5-year DFS: 23% and 23%	–
Owen 2016	Median DFS: 483 days	Median DFS: 360 days	Not significant

OS overall survival, *DFS* disease free survival

DLM resection may benefit in terms of RFS

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Time to Recurrence

Table 23.1 Outcomes of patients with disappearing liver metastases

Study	Patients with DLM (%)	Initial CRLM	DLM	DLM/ patient	CPR/ resected DLM	CCR/DLM left in situ	Time to recurrence (months)	Median follow-up (months)	DLM with CR	DLM with CR + IOUS
Benoist 2006	38 (7)	183	66	1.7	3/15	8/31	–	12	17%	24%
Elias 2007	16 (7)	134	69	4.3	n/a	10/16	–	50	–	–
Auer 2010	39 (9)	166	118	3	44/68	31/50	Mean 21	41	64%	65%
Tanaka 2009	23 (37)	472	86	3.7	6/17	16/27	Median 14	44	69%	80%
Goéré 2011	27 (n/a)	523	96	3.6	n/a	18/27	Median 14	55	–	–
Van Vledder 2010	40 (24)	–	127	3.2	26/67	24/45	–	20	45%	54%
Ferrero 2012	33 (19)	624	67	2	22/57	4/10	Median < 12	–	39%	64%
Park 2017	87 (n/a)	393	CT 203	0.6	CT 47/168	CT 24/35	Median < 12	12	CT 35%	CT 69%
			MRI 55	(MRI)	MRI 28/39	MRI 15/16			MRI 78%	MRI 94%
Kim 2017	43 (31)	289	168	3.9	8/8	128/150	–	22	85%	–
Arita 2014	11 (15)	234	32	0.4	10/37	4/7	–	–	41%	IOUS 46%
										CE-IOUS 75%
Owen 2016	11 (48)	200	77	7	10/36	20/41	–	46	40%	–
Tani 2018	20 (24)	619	111	5.6	CT 54/78	CT 11/33	Median 8	27	CT 59%	86%
					MRI 24/29	MRI 16/18			MRI 85%	
Sturesson 2015	29 (16)	141	66	2.3	24/56	3/4	–	–	45%	96%
Oba 2018	59 (32)	764	275	4.7	103/233	36/42	–	27	CT 51%	92%
									MRI 65%	

DLM disappearing liver metastases, *CRLM* colorectal liver metastases, *CPR* complete pathologic response, *CCR* complete clinical response, *CR* complete response, *IOUS* intraoperative ultrasound, *CE-CT* contrast-enhanced computed tomography, *MRI* magnetic resonance imaging, *CE-IOUS* contrast-enhanced intraoperative ultrasound

Median time to recurrence = 12-21 mo. or less

Chakedis J, Schmidt CR. Surgical Treatment of Metastatic Colorectal Cancer. Surg Oncol Clin N Am. 2018 Apr;27(2):377-399.

Technique : Fiduary Markers and Complete Ablation

- Surgical planning to remove all lesion

- For deeply located small lesions → sequiential strategy :
  Planned incomplete resection and post-op ablation

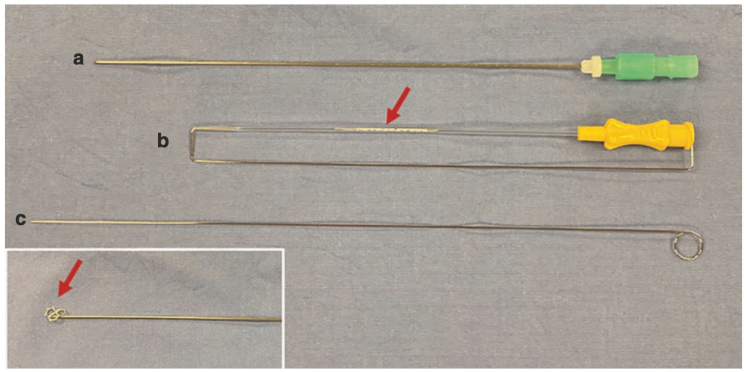


Fig. 6.2 Guide needle and coil utilized for percutaneous fiducial placement. (**a**) A 21-gauge 15-cm long Chiba biopsy needle. (**b**) A 6 × 6 mm pushable coil (arrow). (**c**) Coil plunger. Inset: Coil (arrow) partially deployed within the tip of the 21-gauge needle

- 0.018 in. fibered platinum coils of 4-6 mm.
- Limited streaking artifact on CT
- Easily identified by U/S
- MSKCC 2005-2015
  41 CLM mark with coil
  Treat with ablation 10
  Resection 31
  No LR during median F/U 14 mo

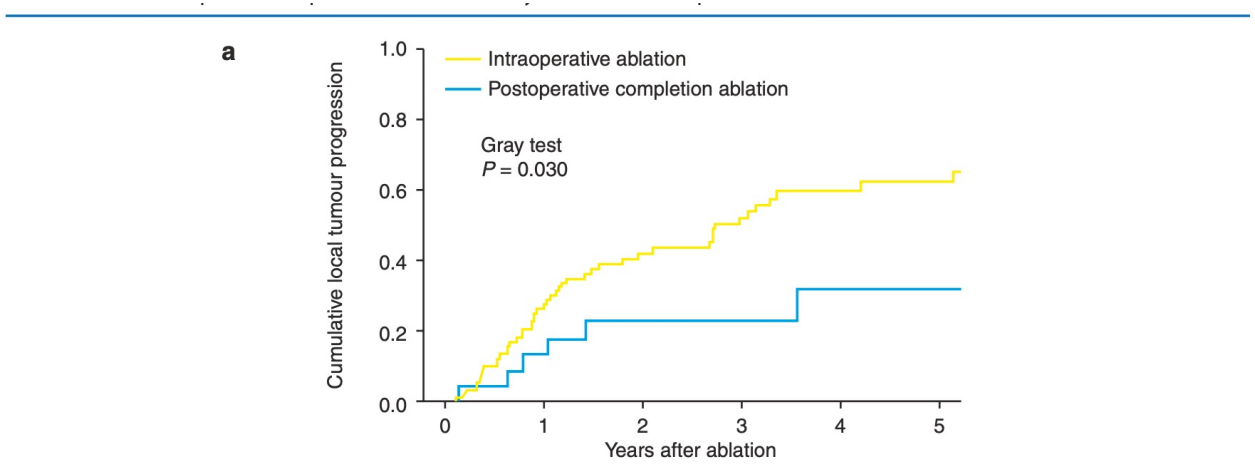
Passot, G., Odisio, B.C., Zorzi, D. *et al.* Eradication of Missing Liver Metastases After Fiducial Placement. *J Gastrointest Surg* **20**, 1173–1178 (2016).

Okuno, M., Kawaguchi, Y., Odisio, B.C. (2022). Advanced Techniques in Multiple Metastases: Fiduciary Markers and Completion Ablation. In: Vauthey, JN., Kawaguchi, Y., Adam, R. (eds) Colorectal Liver Metastasis. Springer, Cham.

Technique : Fiduary Markers and Complete Ablation

- Eligible for ablation ≤ 5 CRLM , largest < 3 cm.

- Result
  - Resection + post-op ablation complication 21% vs. intra-op ablation 48% (*p=0.033*)
  - Local tumor progression at the ablation site 31.7%
  - OS → no difference



Patients at risk							5-year cumulative local recurrence rate
Intraoperative ablation	92	60	36	26	16	13	62.4%
Postoperative completion ablation	23	19	12	10	5	1	31.7%

Okuno, M., Kawaguchi, Y., Odisio, B.C. (2022). Advanced Techniques in Multiple Metastases: Fiduciary Markers and Completion Ablation. In: Vauthey, JN., Kawaguchi, Y., Adam, R. (eds) Colorectal Liver Metastasis. Springer, Cham.

Diagnosis and Management Guide for DLM

Table 23.2 Factors predisposing to the development of disappearing liver metastases

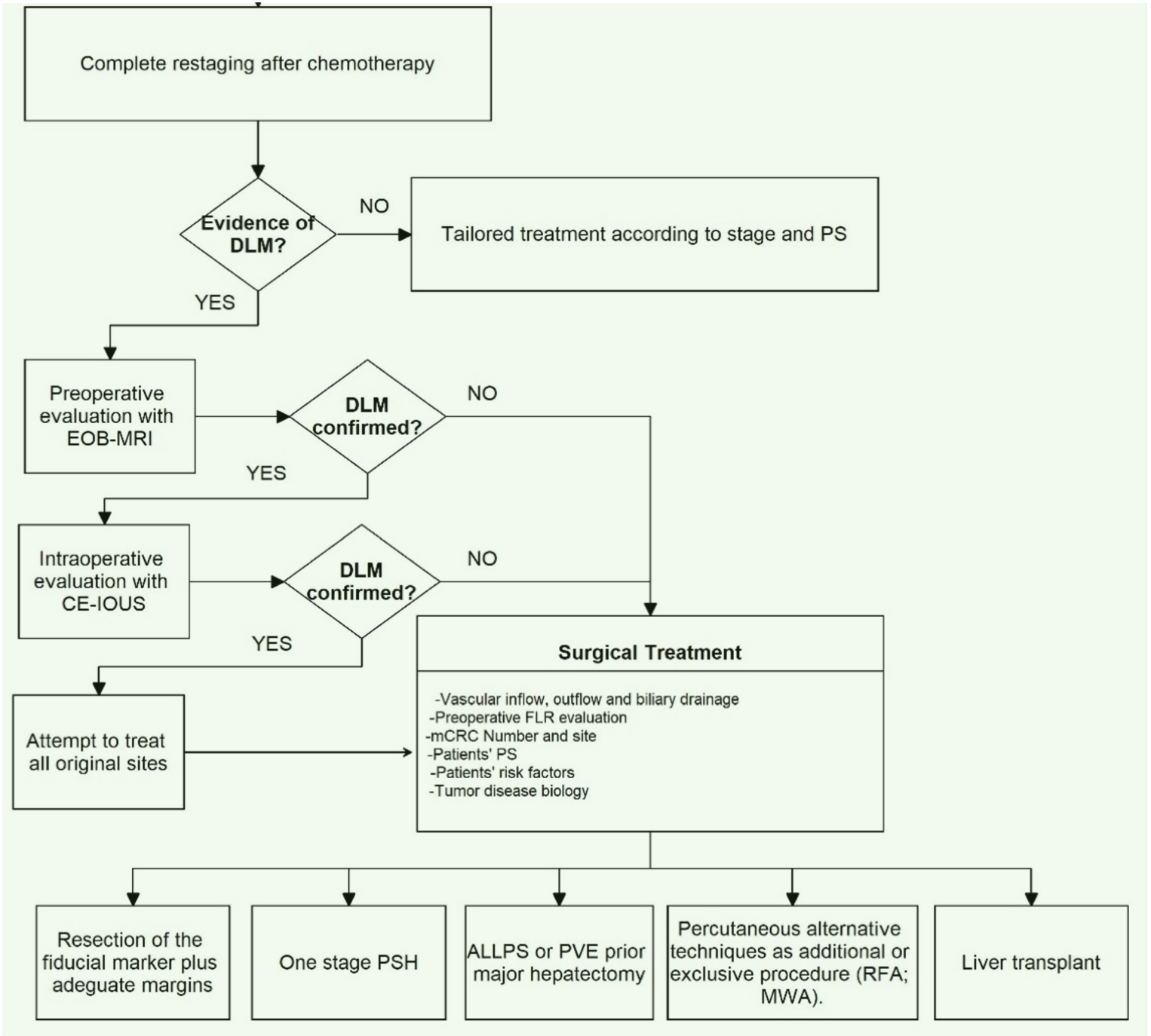
Smaller size (<2 cm) of liver metastases
Greater number of liver metastases (≥3)
Synchronous disease
Greater number of chemotherapy cycles tolerated
Platin-based chemotherapy

Table 23.4 Basic principles of disappearing liver metastases diagnosis and management

• DLM definition: Complete response (disappearance) of CRLM after chemotherapy on cross-sectional imaging studies
• Predisposing factors: Small size (<2 cm), increased number of chemotherapy cycles, oxaliplatin-based therapy, increased number of CRLM (≥3), synchronous CRLM
• Imaging: Baseline and preoperative MRI with IV contract (preferred)
• Pretreatment fiducial placement may guide identification of DLM during surgery
• HAI chemotherapy administration, young patients (<60 years) with an initially low CEA, and patients without detectable lesions on preoperative imaging have the highest chance of a pathologic complete response
• Intraoperative exploration with palpation and IOUS after full liver mobilization, especially in the absence of preoperative MRI
• Resection of all DLM sites is preferred as resection has been associated with lower intrahepatic recurrence
• Leaving DLM in-situ has been associated with a higher incidence of intrahepatic recurrence but not necessarily worse overall survival
• Treatment of patients with DLM should be guided by a multidisciplinary approach as treatment is highly individualized and may include surgical resection, additional systemic or local therapy, or close surveillance

DLM disappearing liver metastases, *CRLM* colorectal liver metastases, *CEA* carcinoembryonic antigen, *MRI* magnetic resonance imaging

Proposed Algorithm for Disappearing Lesion in CRLM



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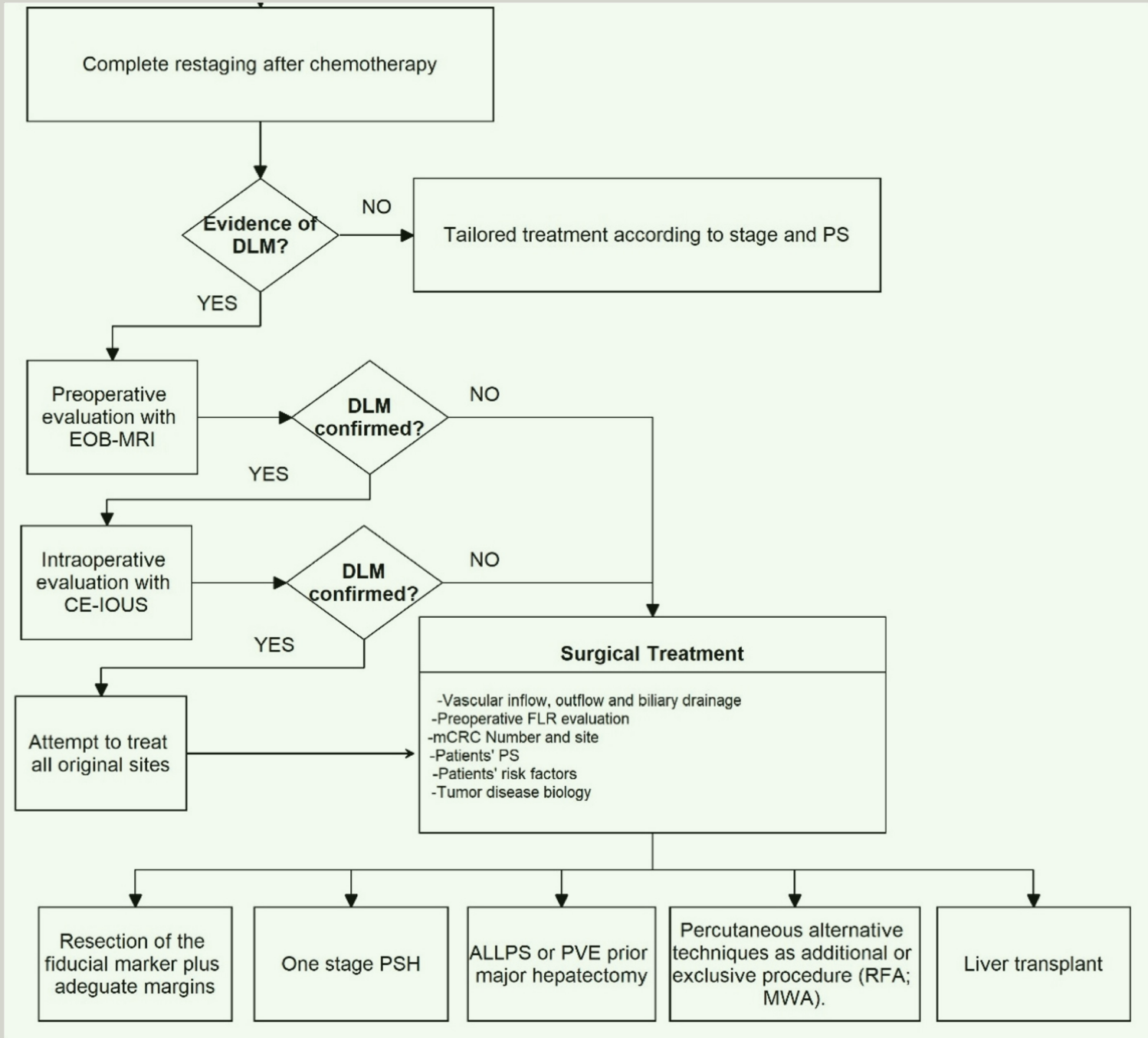
Complete restaging after chemotherapy
Evidence of DLM?
NO
Tailored treatment according to stage and PS
YES
Preoperative evaluation with EOB-MRI
DLM confirmed?
NO
YES
Intraoperative evaluation with CE-IOUS
DLM confirmed?
NO
YES
Attempt to treat all original sites
Surgical Treatment
-Vascular inflow, outflow and biliary drainage
-Preoperative FLR evaluation
-mCRC Number and site
-Patients' PS
-Patients' risk factors
-Tumor disease biology
Resection of the fiducial marker plus adeguate margins
One stage PSH
ALLPS or PVE prior major hepatectomy
Percutaneous alternative techniques as additional or exclusive procedure (RFA; MWA).
Liver transplant

Conclusion

- Surgical management and techniques in CRLM
  - Planning of Liver resection or alternative local treatment
  - Avoiding hepatic insufficiency
  - Minimizing postoperative complication
- Overall survival of liver resection in CRLM patients change throughout the years along with the changes of systemic therapy, radiointervention and radiation therapy.
- Patients actually need a team of doctors to cure them - MDT


THANK YOU