Liver Transplantation For Colorectal Metastases

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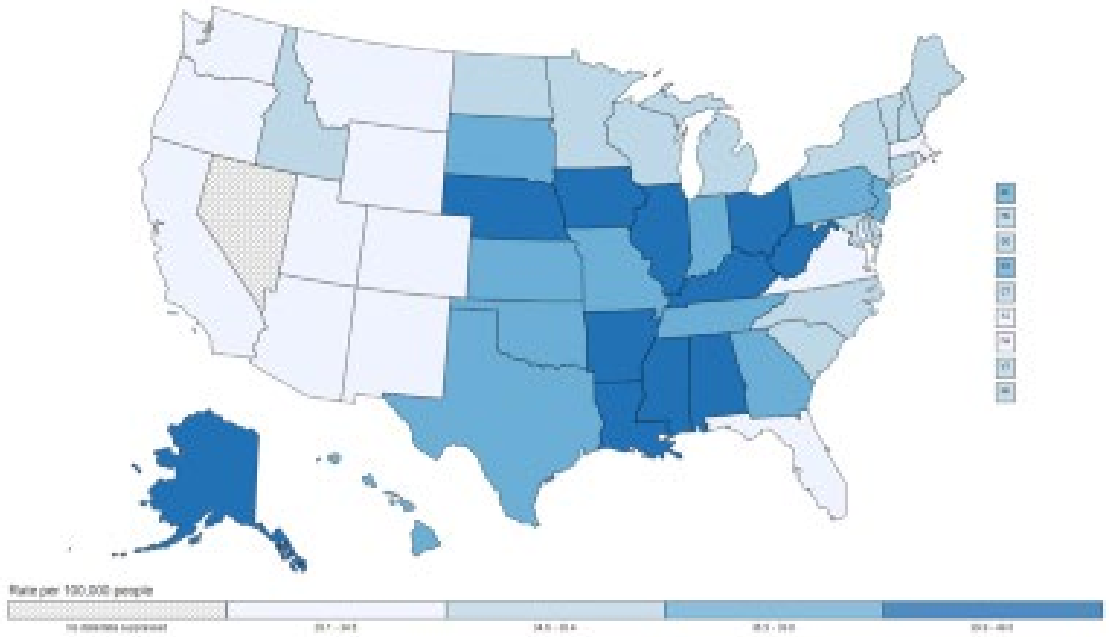
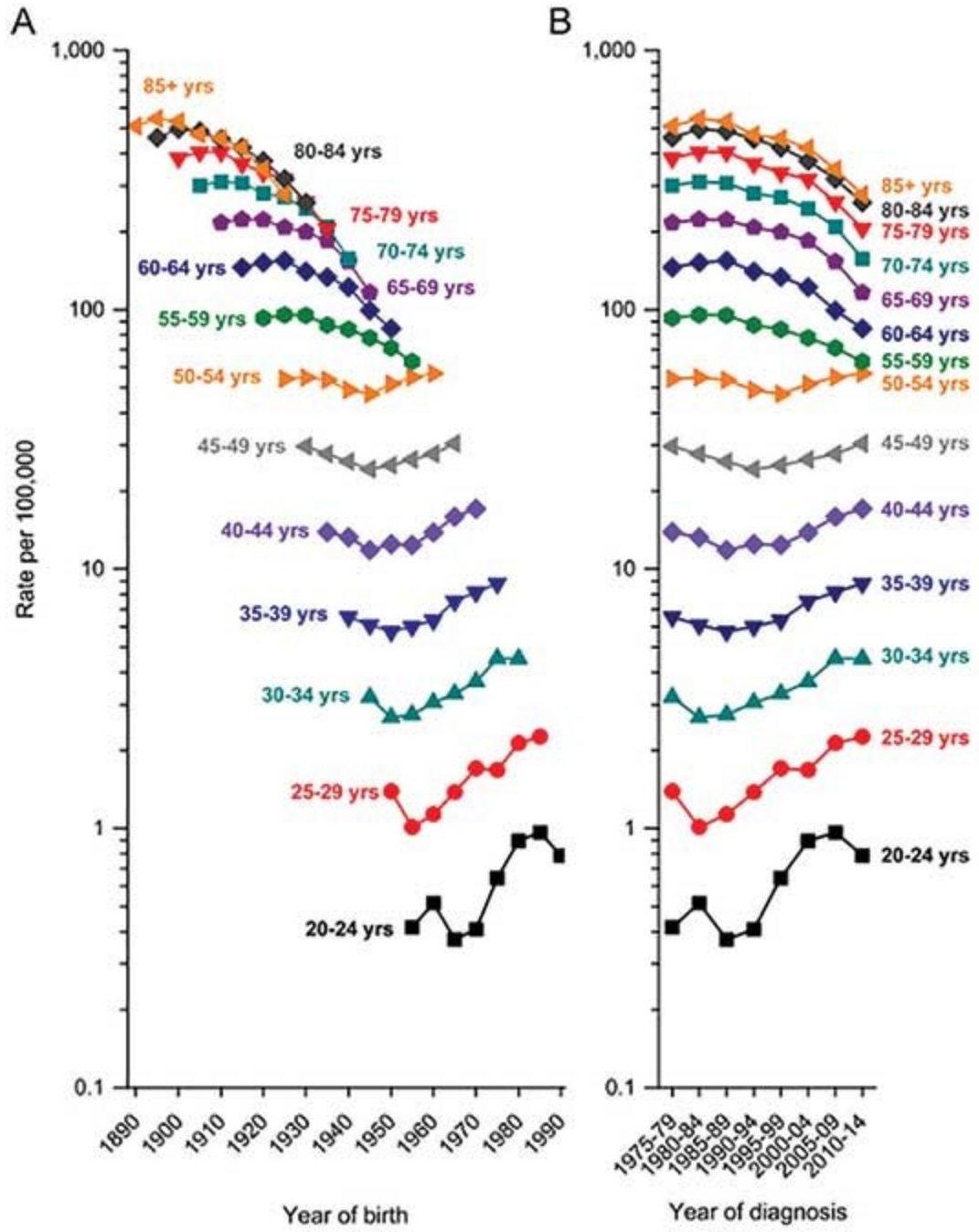
COLORECTAL CANCER

Rate of New Cancers in the United States, 2018
Colon and Rectum, All Ages, All Races and Ethnicities, Male and Female



~149.000 new cases U.S. in 2021



~ 50% Colorectal cancer
will develop liver metastases

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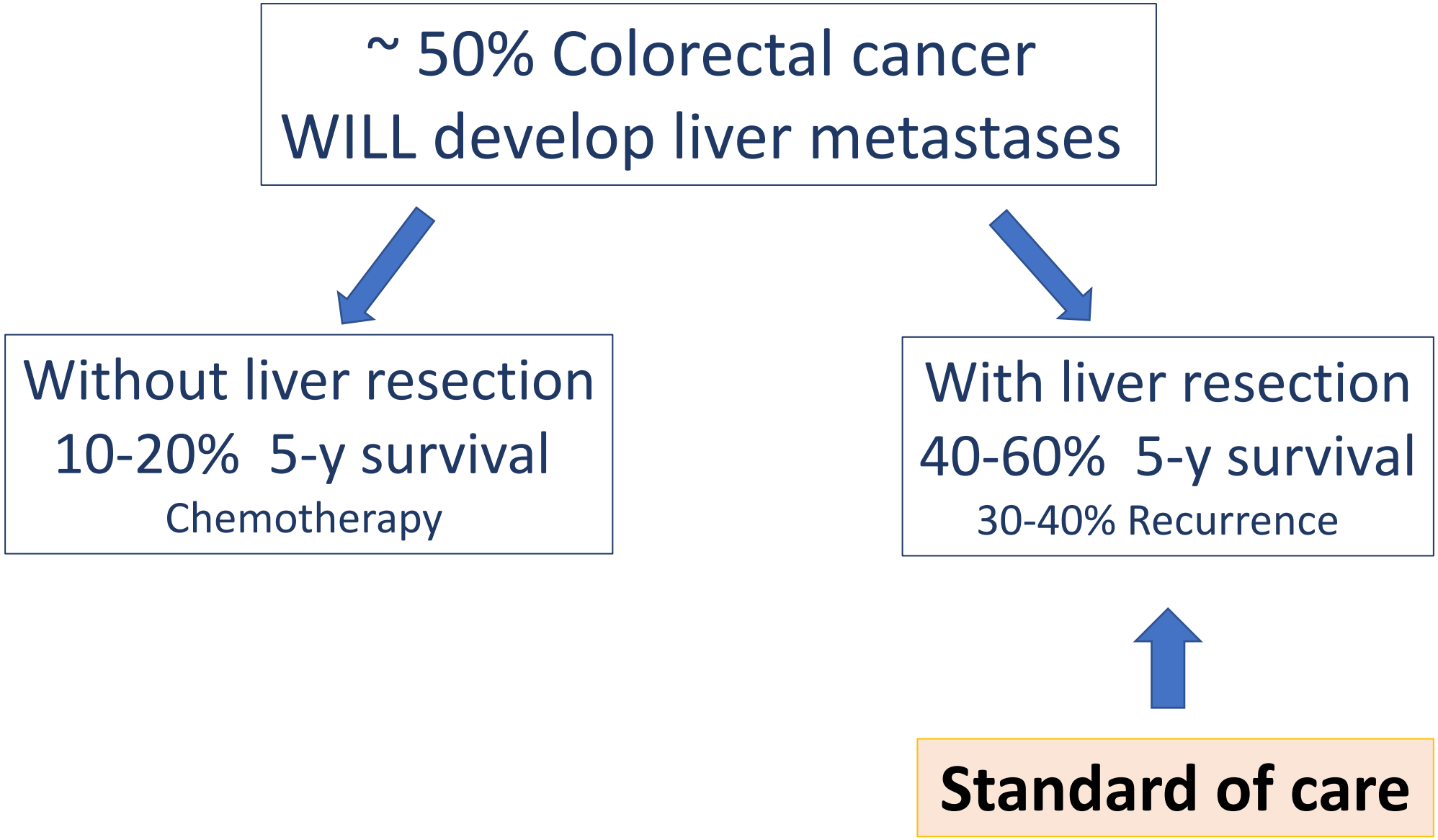
WILL develop liver metastases

Without liver resection
10-20% 5-y survival
Chemotherapy


~ 50% Colorectal cancer
WILL develop liver metastases
Without liver resection
10-20% 5-y survival
Chemotherapy
With liver resection
40-60% 5-y survival
30-40% Recurrence
Standard of care

~ 50% Colorectal cancer
WILL develop liver metastases

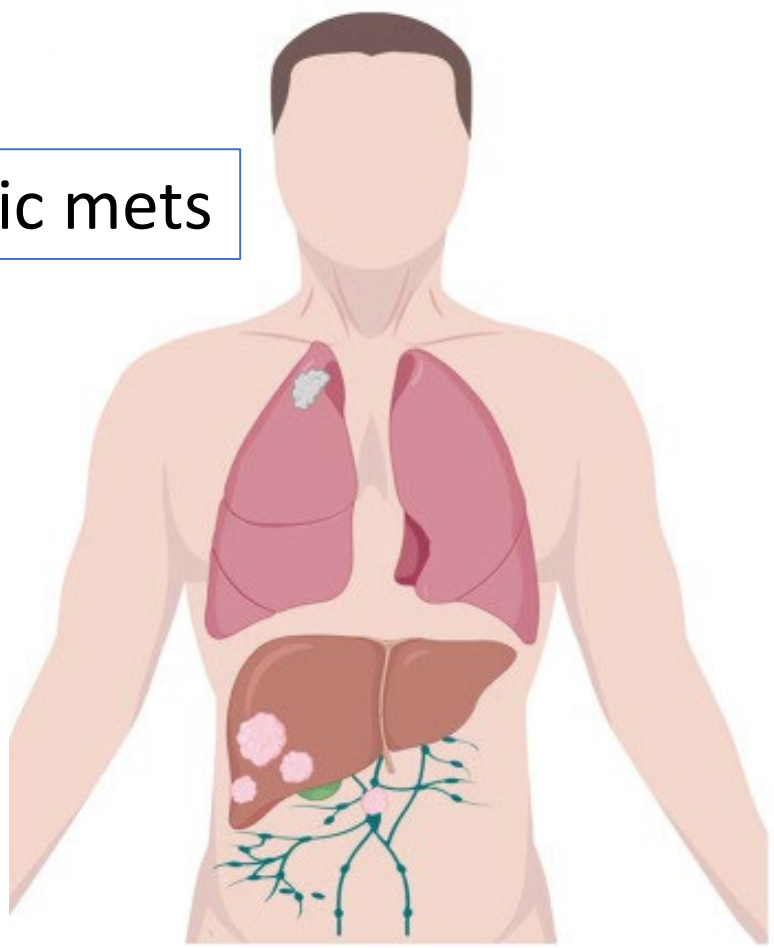
Without liver resection
10-20% 5-y survival
Palliative chemotherapy

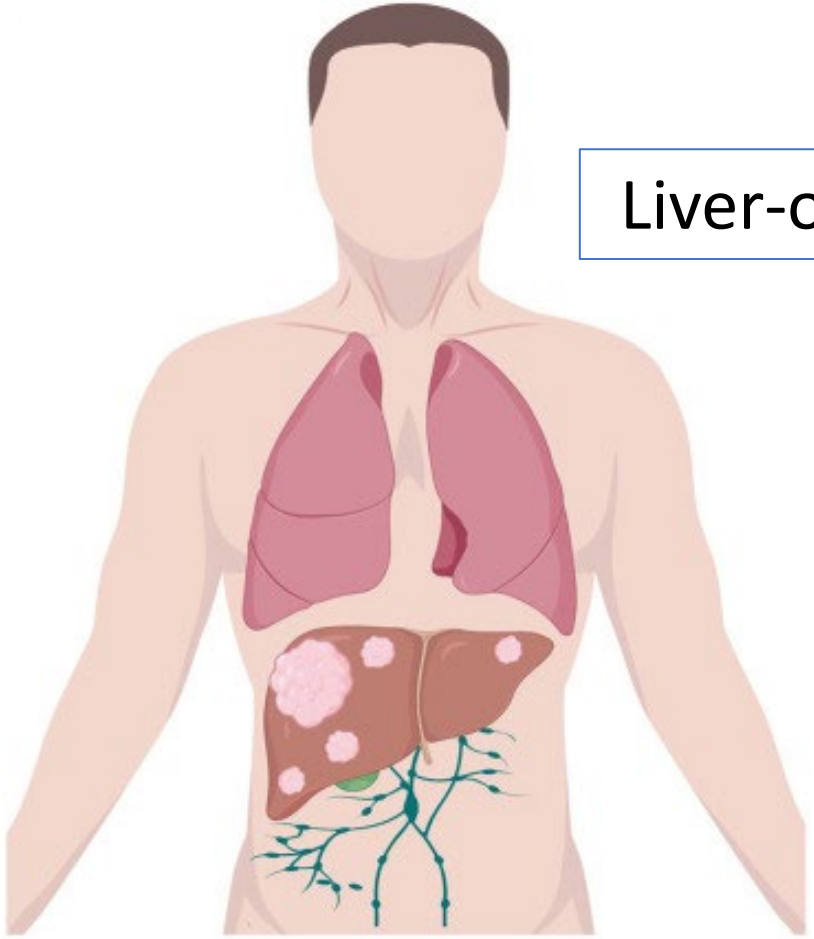
With liver resection
40-60% 5-y survival
30-40% Recurrence

Only **~30%** candidates for liver resection

Unresectability CRLM

Extra-hepatic mets





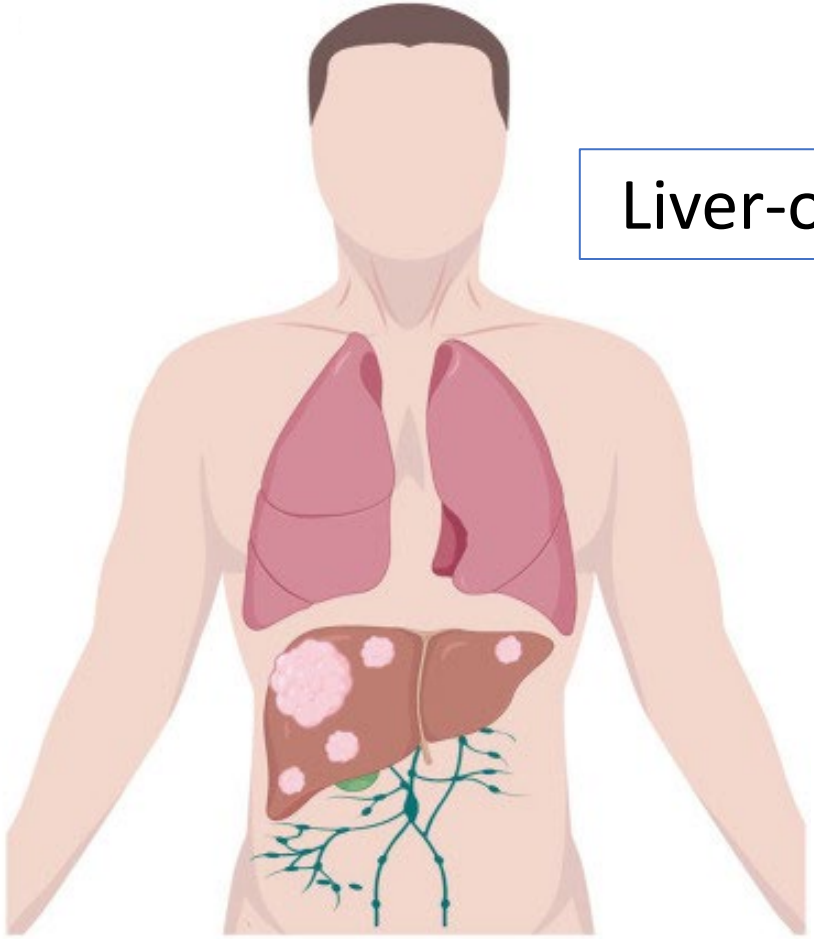
Liver-only mets

Hepatobiliary Surg Nutr 2020 9(6):797-800

Liver Resection CRLM

Major limitation:

Insufficient Functional Remnant Liver



Liver-only mets

Hepatobiliary Surg Nutr 2020 9(6):797-800

Resectability CRLM

Major limitation:

Insufficient Functional Remnant Liver

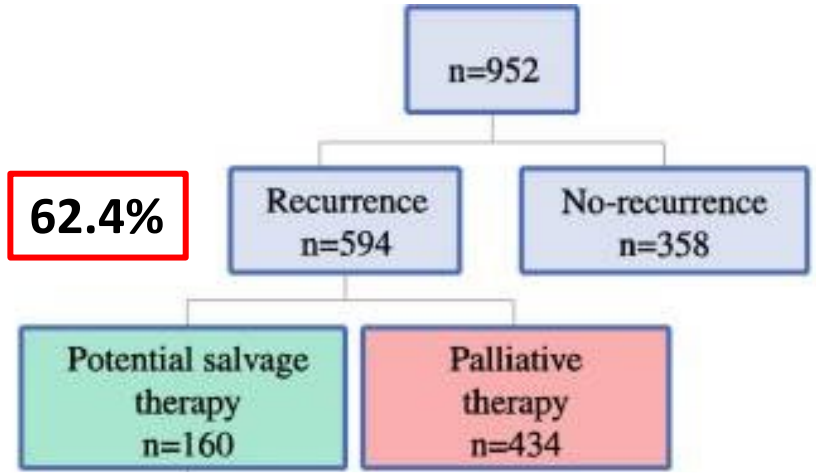
- Volume (>30-25%)
- Hepatic steatosis
- Chemo hepatoxicity
- Tumor location

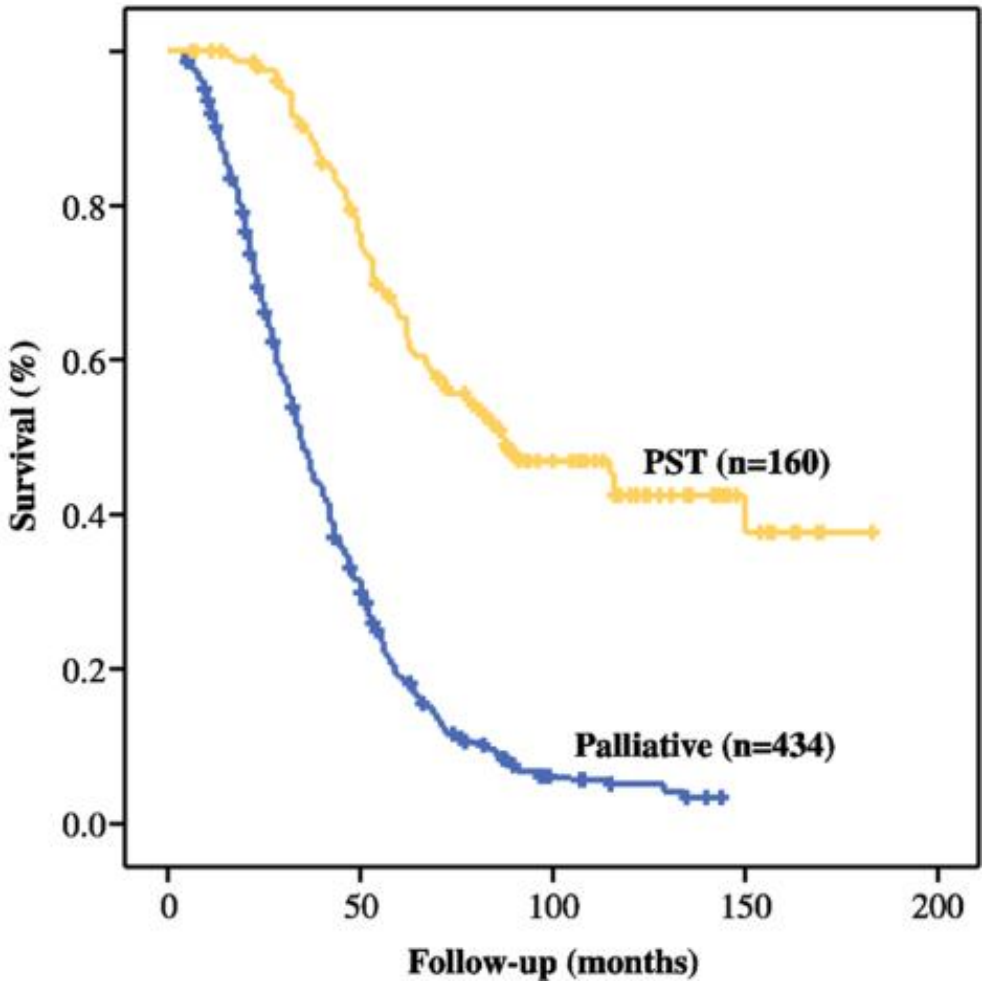
Strategies:

- ❖ Reduce tumor burden
  - ○ Neoadjuvant therapy
- ❖ Increase FRL
  - ○ Hypertrophy
  - ○ Staged surgery

Recurrence After Partial Hepatectomy for Metastatic Colorectal Cancer

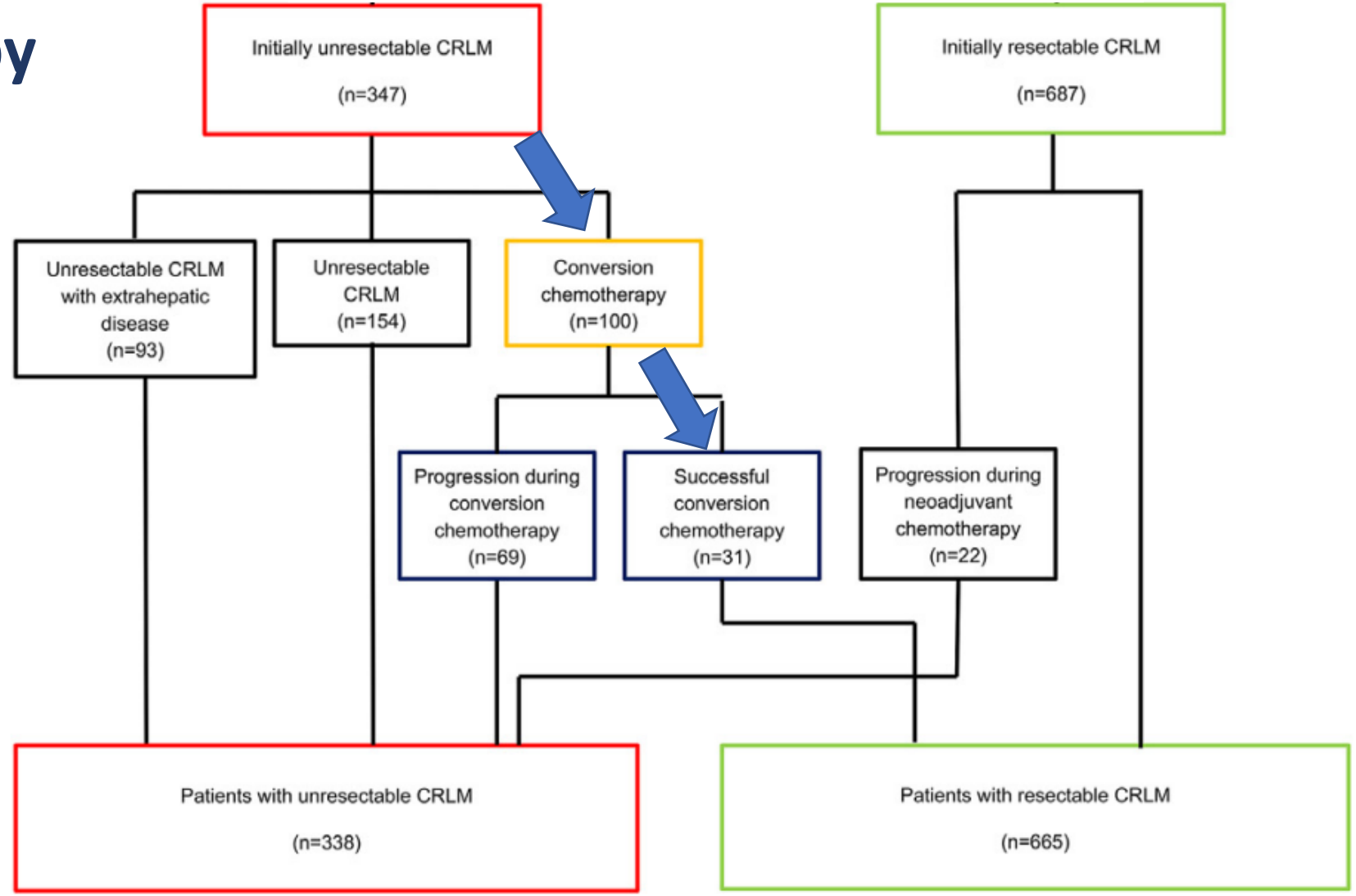
<u>without</u> neoadjuvant therapy





Ann Surg Oncol 2015 22(8):2761

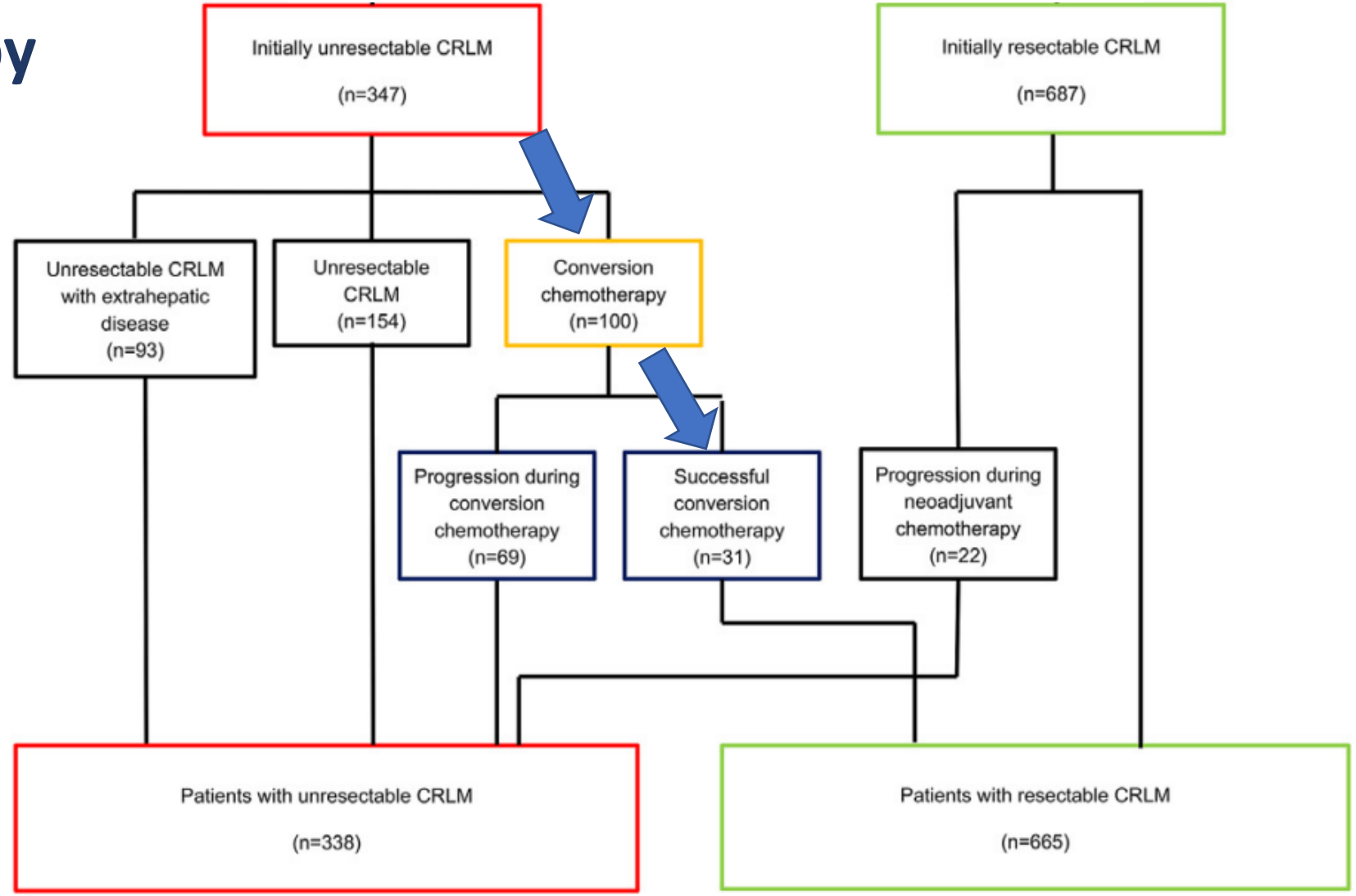
Conversion therapy in patients with CRLM



European Journal of Surgical Oncology 2021 (47)2038

Conversion therapy in patients with CRLM

Despite chemotherapy, the majority of patients never become eligible for resection



European Journal of Surgical Oncology 2021 (47)2038

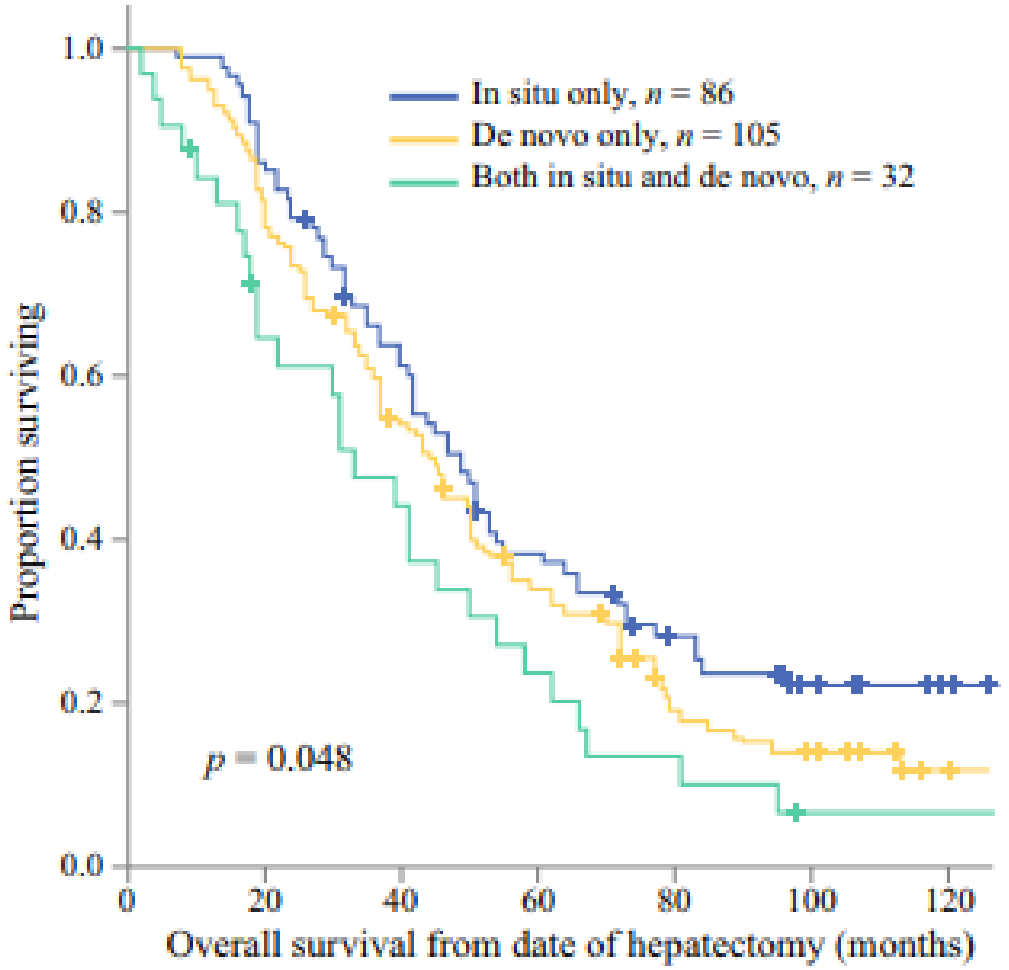
Intrahepatic Recurrence Patterns Predict Survival After Resection of Colorectal Liver Metastases
Ann Surg Oncol 2019 26:275

Neoadjuvant therapy + resection

Local recurrence 227/819 (27.2%)

Local recurrence:

- disappearing or missed metastases
- margin recurrence
- tumor progression after ablation



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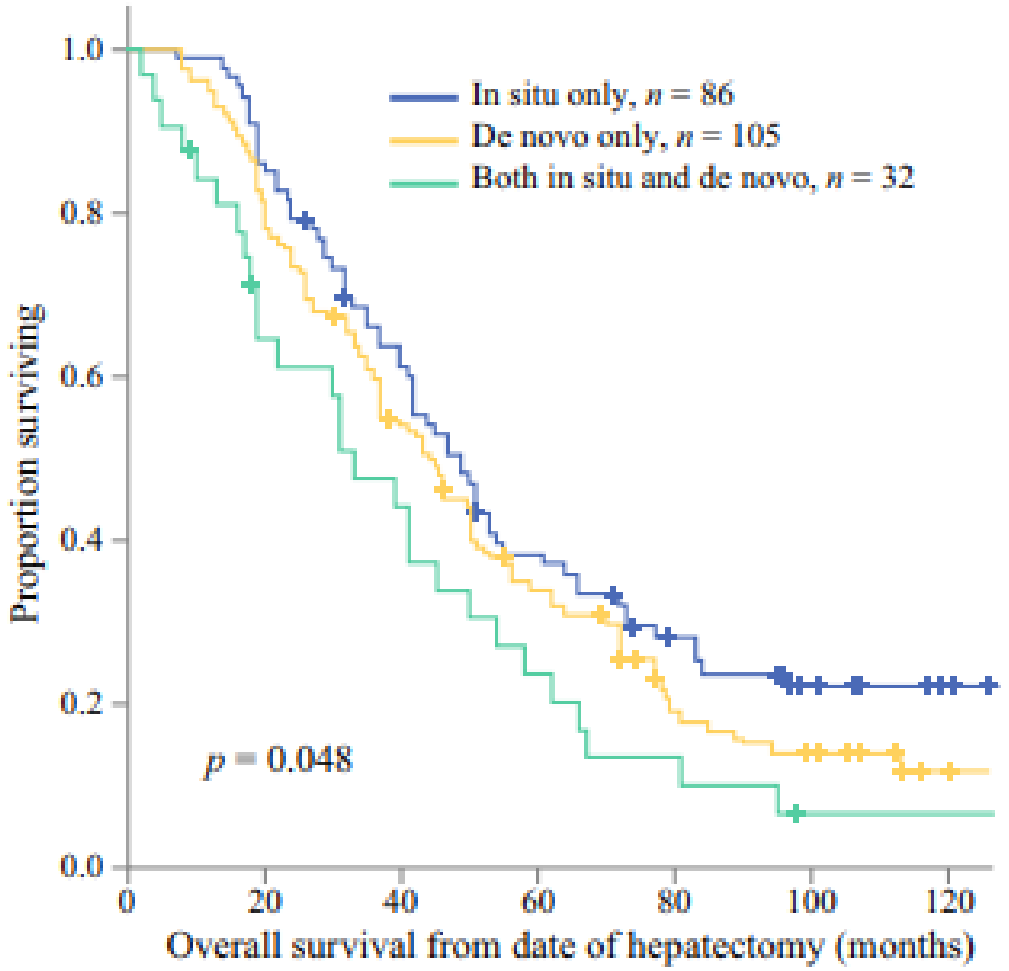
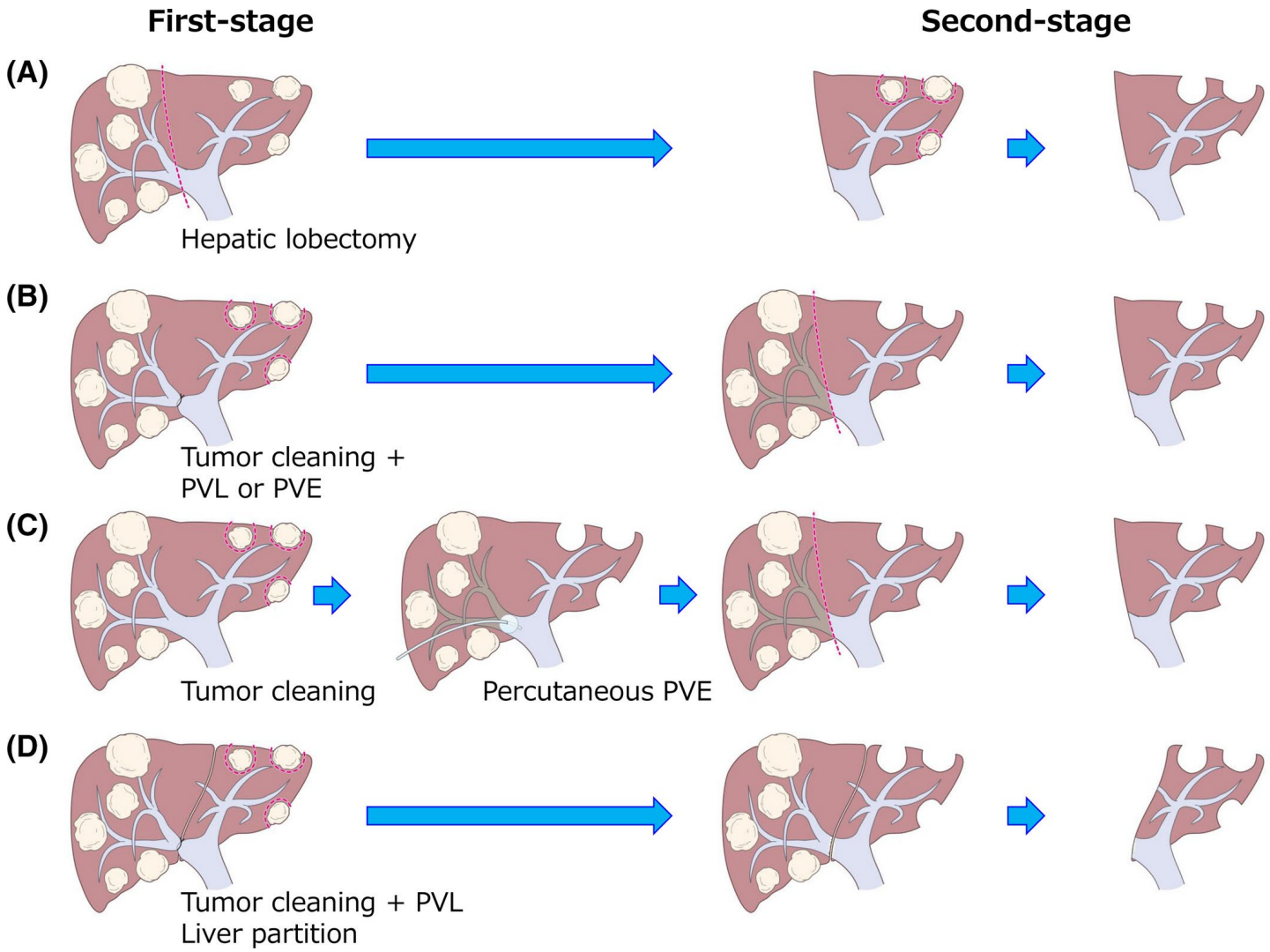
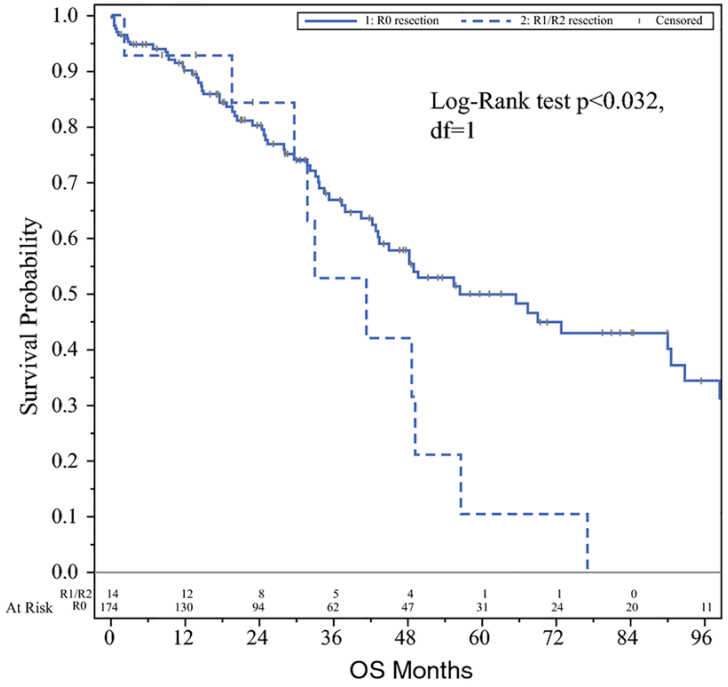


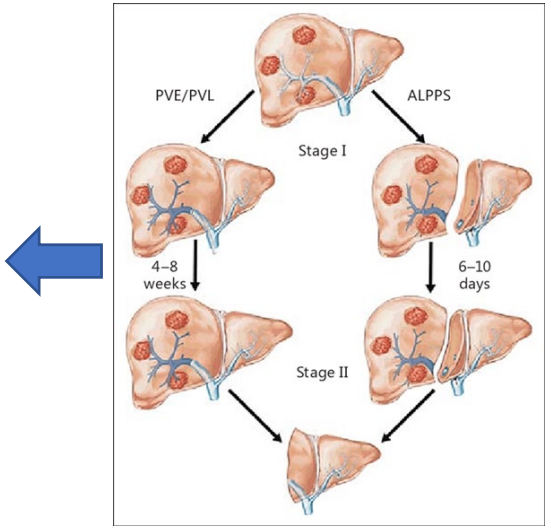
Extreme liver resection



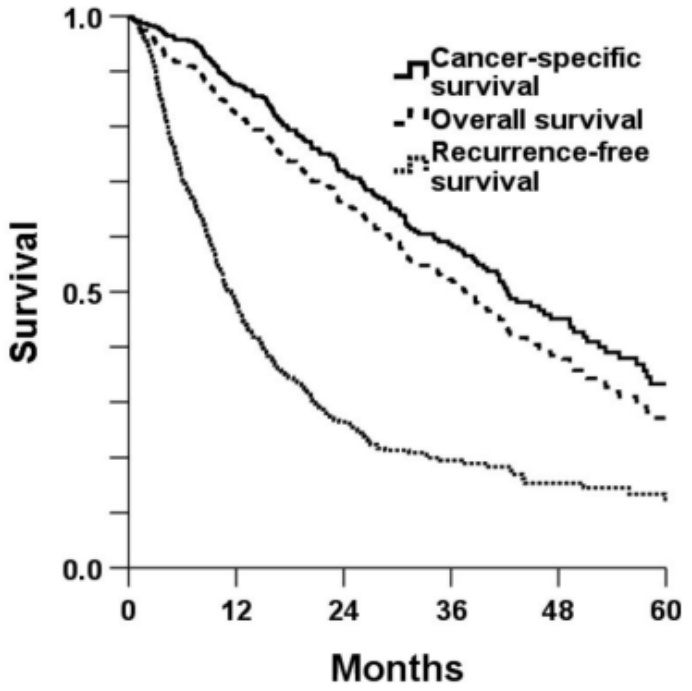
Two-Stage Hepatectomy for Colorectal Liver Metastases



Ann Surg Oncol 2021 28:1457-1465



ALPPS Procedure in Colorectal Liver Metastases



Annals of Surgery 2020 272(5)793

What if...
we remove the whole liver ?

Liver Transplantation for Colorectal Mets

Early experience (1980's - 1990's)

1 and 5-year survival 62% and 18%

Colorectal (CRC) liver metastases was considered as an absolute contraindication to liver transplantation.

Liver Transplantation for Colorectal Mets

Early experience (1980's - 1990's)

1 and 5-year survival 62% and 18%

Colorectal (CRC) liver metastases was considered as an absolute contraindication to liver transplantation.

However,

- 44% graft loss unrelated to CRC
- Improvement in LT outcomes
- Improvement in chemotherapy
- Alternative IS – antineoplastic (sirolimus)

Chemotherapy or Liver Transplantation for *Nonresectable* Liver Metastases from Colorectal Cancer

Norway study

Nordic VII

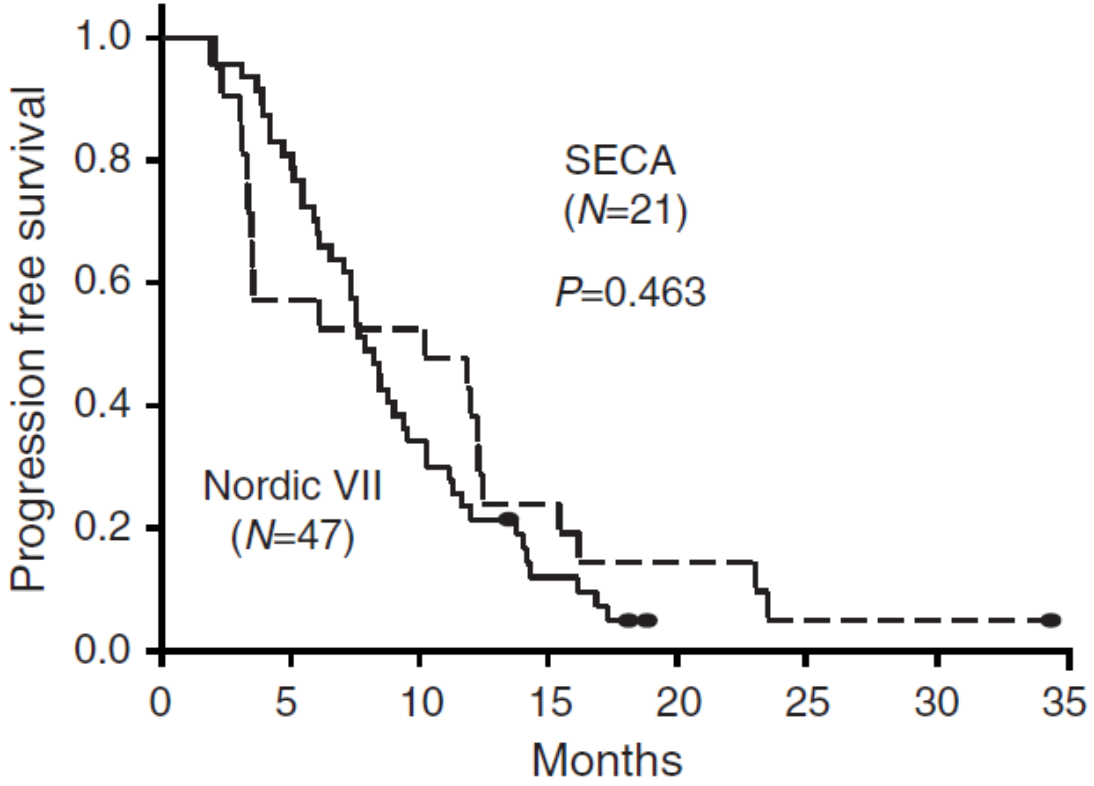
- 47 patients, < 66 yo,
  BRAF neg, non-resectable, liver only mets
- Randomized, MTC
  Flox, Flox-cetuximab intermittently
  and Flox-cetuximab continuous
- All patients first line of treatment

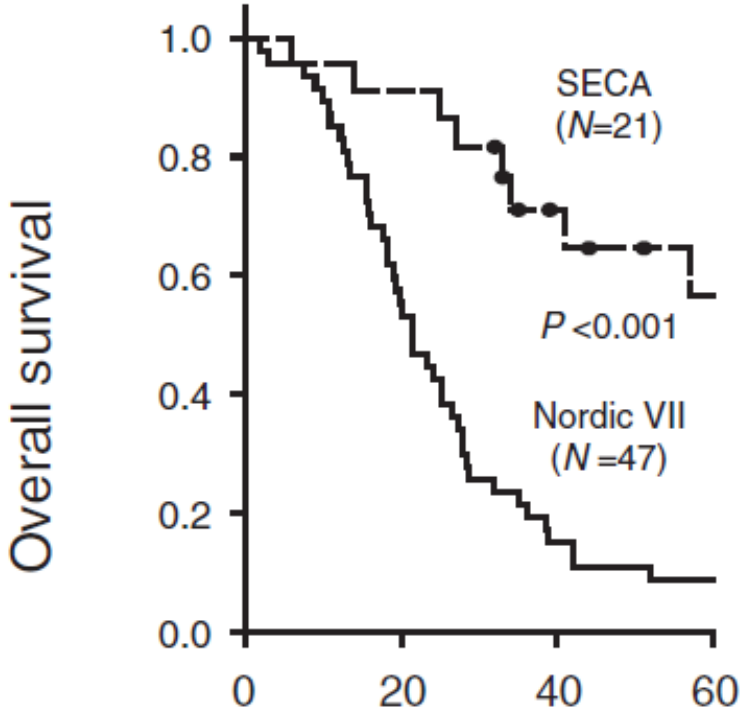
VS.

Secondary Cancer (SECA-1)

- 21 patients < 65 yo.
  BRAF neg, non-resectable, liver only mets.
- 57% 2-3 line of treatment
  (6 patients with progression disease)
- **Liver transplantation**
- *No* chemotherapy post-LT

Chemotherapy or Liver Transplantation for *Nonresectable* Liver Metastases from Colorectal Cancer





56%

9%

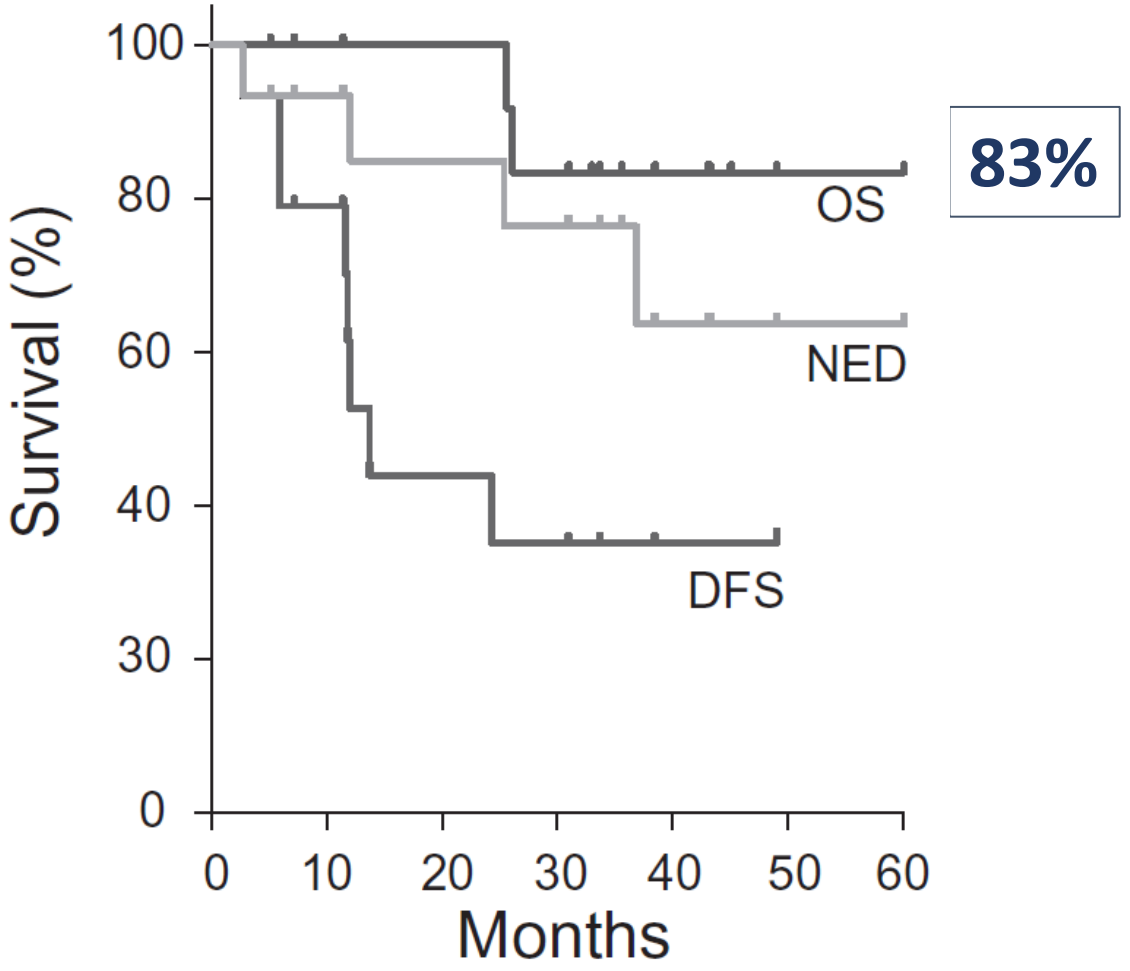
Annals of Surgery • Volume 261, Number 5, May 2015

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

Survival Following Liver Transplantation for Patients with *Nonresectable* Liver-only Colorectal Metastases

Risk factors

- Synchronic vs. Metachronous
- Functional status (ECOG >2)
- CEA > 80 ng/L
- Progressive disease
- Tumor markers: kras, BRAF V6000
- Tumor burden (> 70 grs)
- Oslo score 3-4



83%

Annals of Surgery 2020 271(2) 212

- Am J Transplant 2020;20(2):530-537
- Lancet Gastroenterol Hepatology 2021;6(11):933-946

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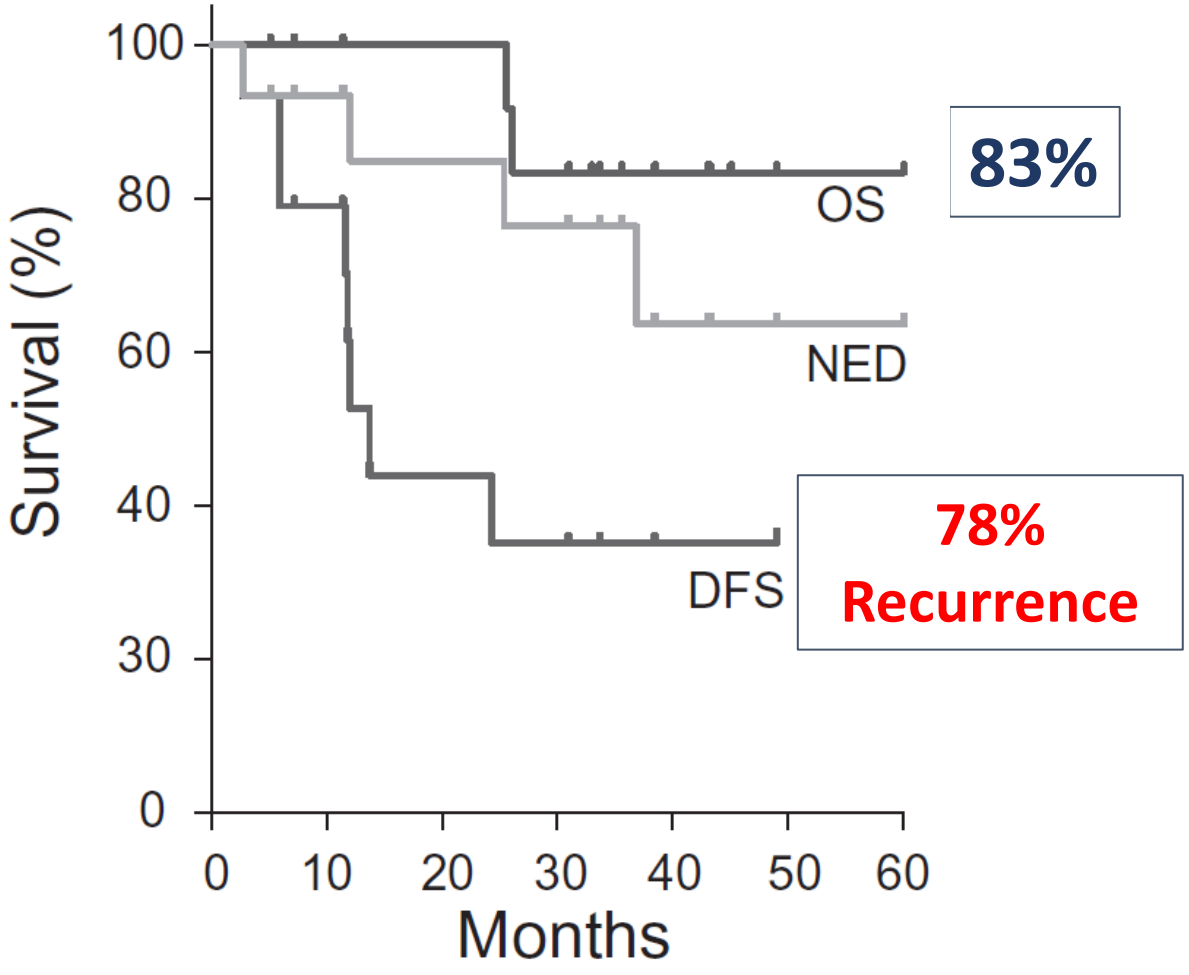

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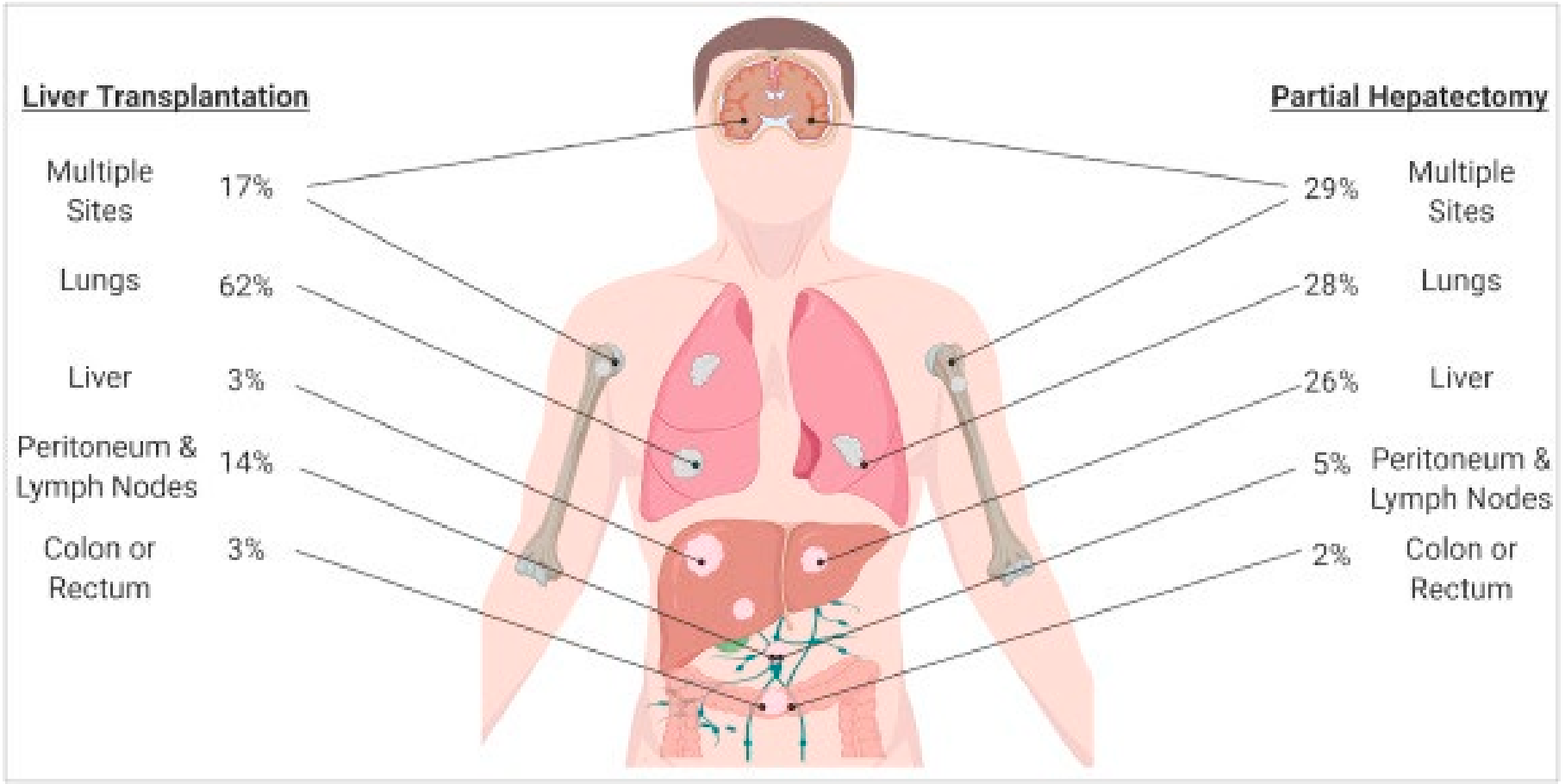
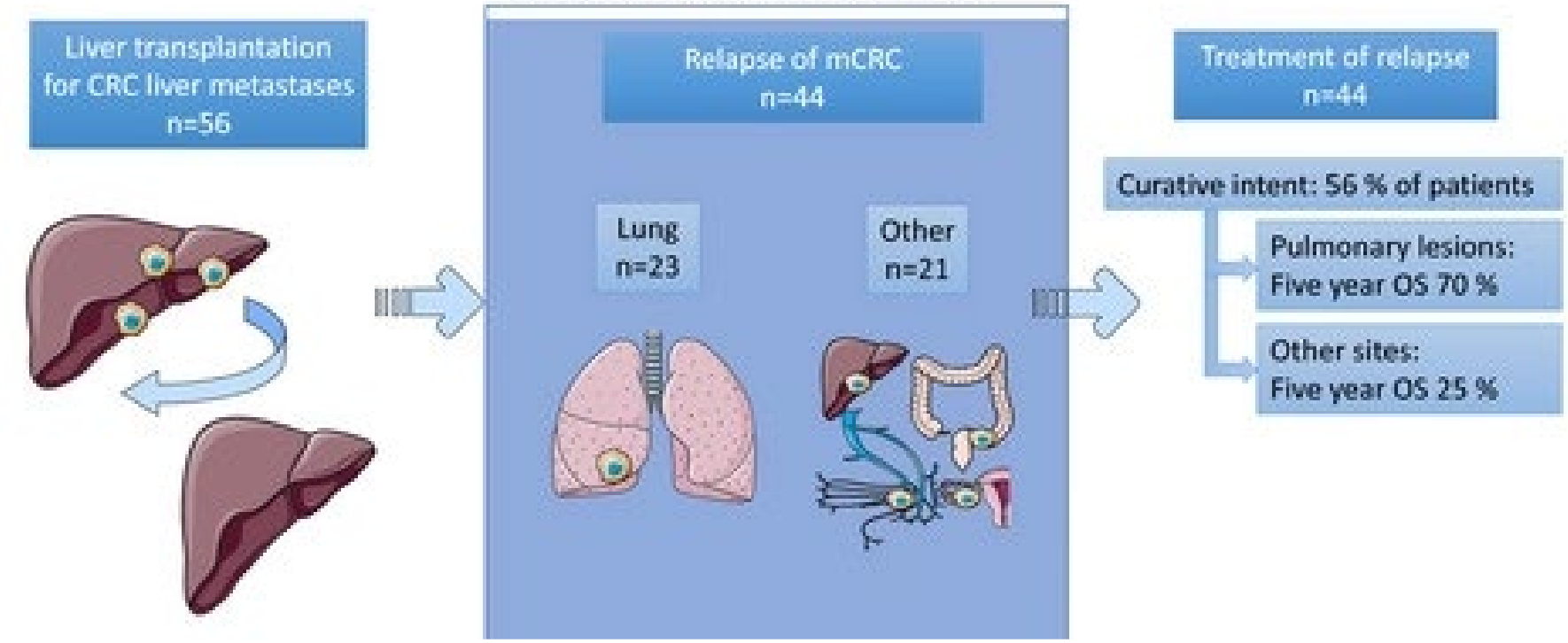
Annals of Surgery 2020 271(2) 212

Patterns of recurrence



Line, International Journal of Surgery 2020, 82:87-92

Treatment of relapse and survival outcomes after liver transplantation in patients with colorectal liver metastases



Trial Protocol	Clinical trial Identifier	Country	Protocol Timeline	Design
SECA II	NCT01479608	Norway	2011–2027	LT vs. surgical Resection
RAPID	NCT02215889	Norway	2014–2028	Liver resection and partial section 2-3 transplantation with two-stage hepatectomy
TRANSMET	NCT02597348	France	2015–2027	Chemo + LT vs. Chemo
SECA III	NCT03494946	Norway	2016–2027	LT vs. chemo or ablation
Toronto Protocol	NCT02864485	Canada	2016–2023	Chemo + LDLT vs. Chemo
LIVERT(W) OHEAL	NCT03488953	Germany	2018–2023	LDLT with two-stage hepatectomy
COLT	NCT03803436	Italy	2019–2024	Chemo + LT vs. Chemo
SOULMATE	NCT04161092	Sweden	2020–2029	Chemo + LT with ECD vs. Chemo

LT for CRLM is Growing in USA

Courtesy Dr Hernandez-Alejandro

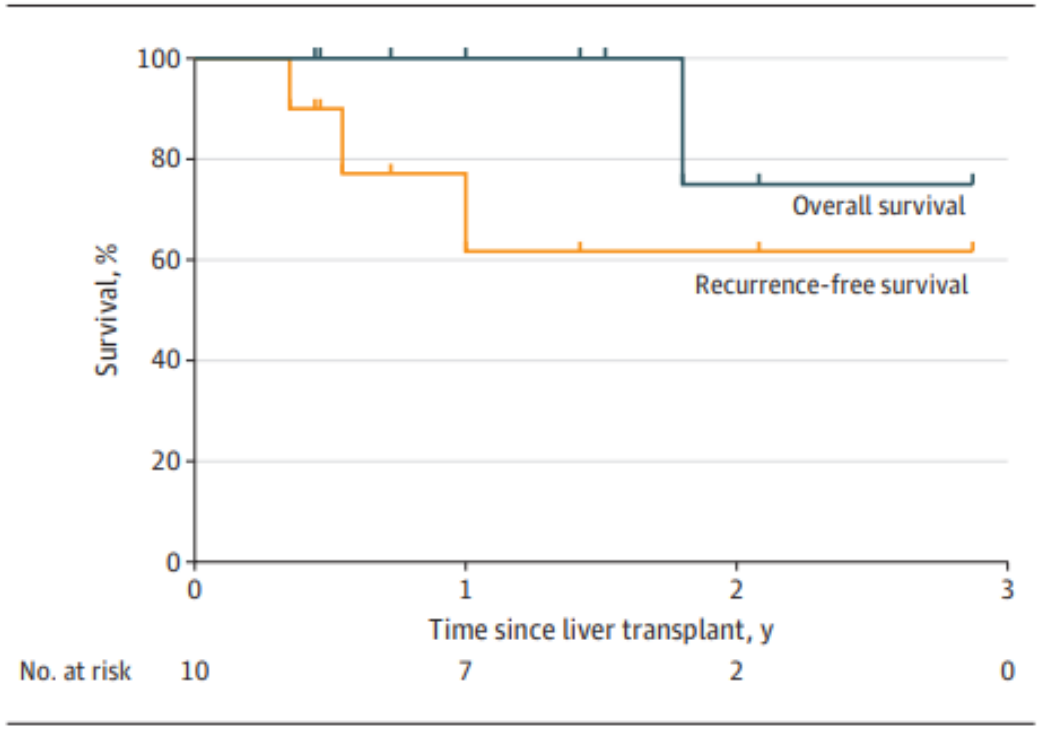
Unpublished Data From UNOS

JAMA Surgery | Original Investigation

Recipient and Donor Outcomes After Living-Donor Liver Transplant for Unresectable Colorectal Liver Metastases

Table 2. Oncologic Treatment Characteristics of Patients Who Underwent Total Hepatectomy and Living-Donor LT

Patient	Timing of CRLM	Systemic treatment	Prior resection	Local therapy	Time from diagnosis of CRLM to LT, y
1	Synchronous metastases	FOLFOX, FOLFIRI, targeted agent	None	None	1.6
2	Synchronous metastases	FOLFOX, FOLFIRI, targeted agent	None	None	5.5
3	Synchronous metastases	FOLFOX, FOLFIRI, targeted agent	Wedge resection, aborted ALPPS	None	1.6
4	Synchronous metastases	FOLFOX, FOLFIRI, targeted agent	None	None	1.4
5	Synchronous metastases	FOLFOX, targeted agent	Right hemihepatectomy	Ablation	1.1
6	Synchronous metastases	FOLFOXIRI, targeted agent	Bisegmentectomy	Hepatic artery infusion	1.4
7	Synchronous metastases	FOLFOX, FOLFIRI, targeted agent	None	Ablation	2.3
8	Metachronous metastases	FOLFIRI, targeted agent	Right posterior sectionectomy, wedge resection	Ablation, hepatic artery infusion	7.8
9	Synchronous metastases	FOLFIRI, targeted agent	None	None	1.7
10	Synchronous metastases	FOLFIRI, targeted agent	None	Hepatic artery infusion	2.0



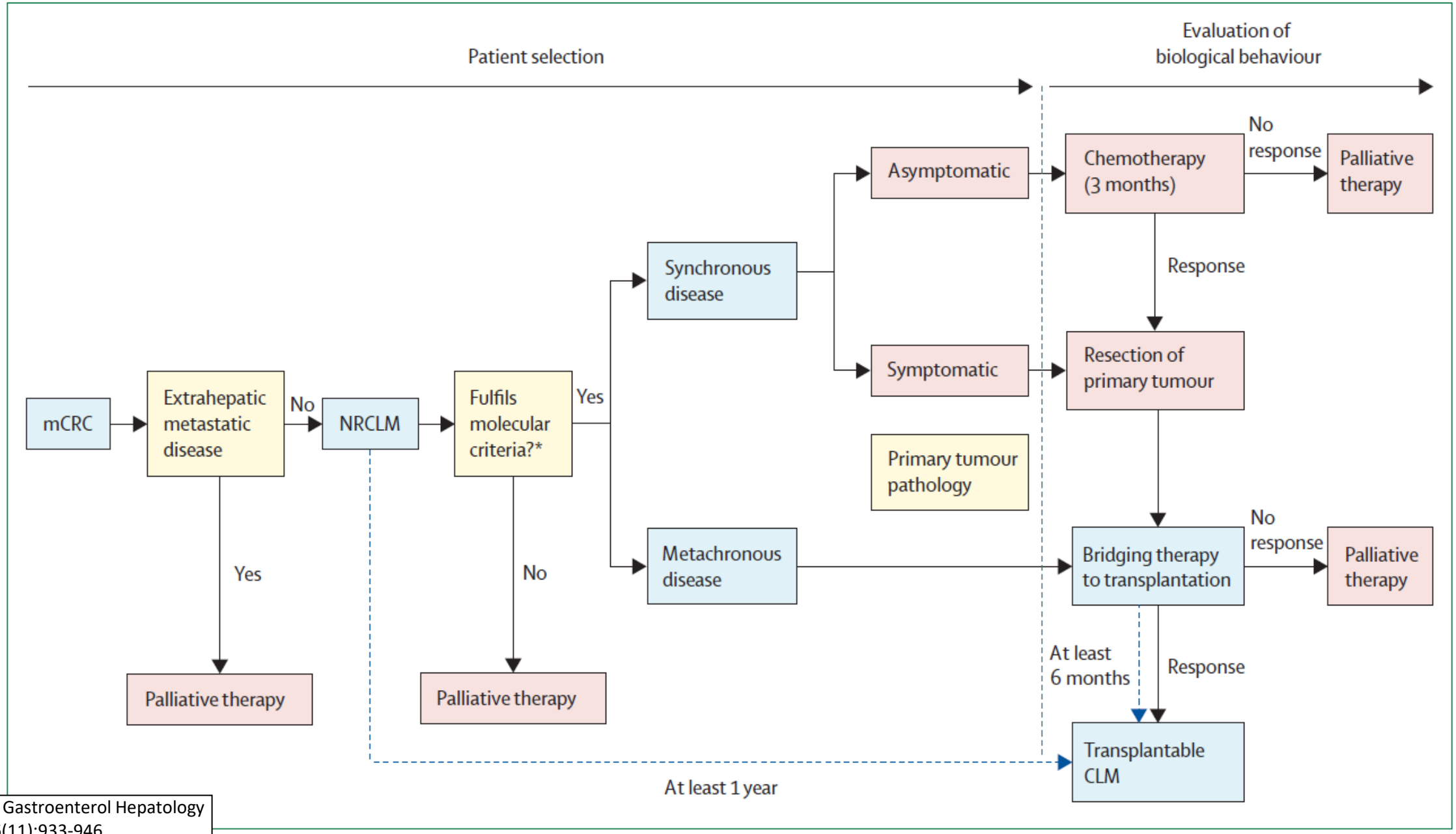
JAMA Surgery 2019 154(8):768

THE LANCET
Gastroenterology & Hepatology

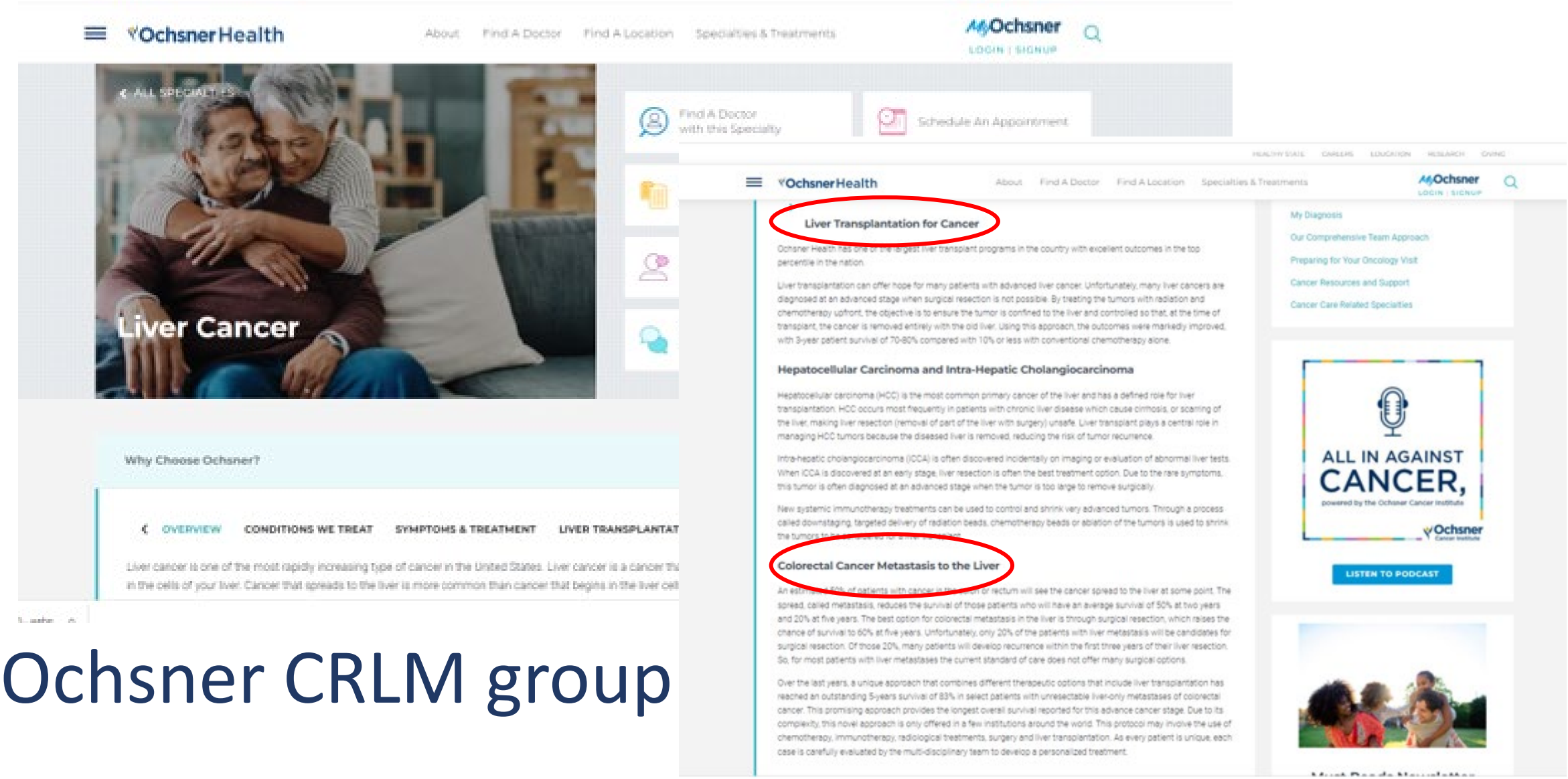
REVIEW | VOLUME 6, ISSUE 11, P933-946, NOVEMBER 01, 2021

Liver transplantation for non-resectable colorectal liver metastases: the International Hepato-Pancreato-Biliary Association consensus guidelines

Glenn K Bonney, FRCS • Claire Alexandra Chew, MBChB • Prof Peter Lodge, MD • Joleen Hubbard, MD • Karim J Halazun, MD • Pavel Trunecka, PhD • Prof Paolo Muiesan, FRCS • Prof Darius F Mirza, FRCS • John Isaac, FRCS • Richard W Laing, PhD • Shridhar Ganpathi Iyer, FRCS • Cheng Ean Chee, FACP • Wei Peng Yong, FRCP • Mark Dhinesh Muthiah, FRCP • Prof Fabrizio Panaro, PhD • Prof Juan Sanabria, FACS • Prof Axel Grothey, MD • Prof Keymanthri Moodley, DPhil • Prof Ian Chau, MD • Albert C Y Chan, FRCS • Chih Chi Wang, MD • Krishna Menon, FRCS • Gonzalo Sapisochin, PhD • Morten Hagness, MD • Svein Dueland, PhD • Prof Pål-Dag Line, PhD • Prof René Adam, PhD • Show less



Lancet Gastroenterol Hepatology 2021;6(11):933-946



Ochsner CRLM group

Potential candidates:

Patients with liver-only metastases from colorectal cancer

- Unresectable lesions
- High-risk resection options: Extensive liver resection(s) required with concern for remnant liver volume and function.
- Recurrence after liver resection for CLRM
- Extensive bilobar CRLM “disappearing” lesions during chemotherapy treatment.
- Extensive bilobar disease associate to chemotherapy toxicity

Ochsner CRLM – LT

Inclusion Criteria:

- Adults ≥ 18 years
- Primary colorectal cancer resected with negative margins
- No signs of local recurrence post resection (negative colonoscopy)
- Absence of extrahepatic metastatic disease in all these studies
- Functional status: ECOG 0-1.
- BRAF wild type mutation, KRAS wild type or KRAS mutant with Tp53 wild type.
- Serum CEA level < 80 ng/dL. CEA > 80 ng/ml might consider if decreasing trend and other favorable tumor factors.
- Received at least one line of systemic treatment.
- No disease progression (radiological or tumor marker) for at least 6 months.
- Interval from diagnosis of CRLM to LT > 1 year

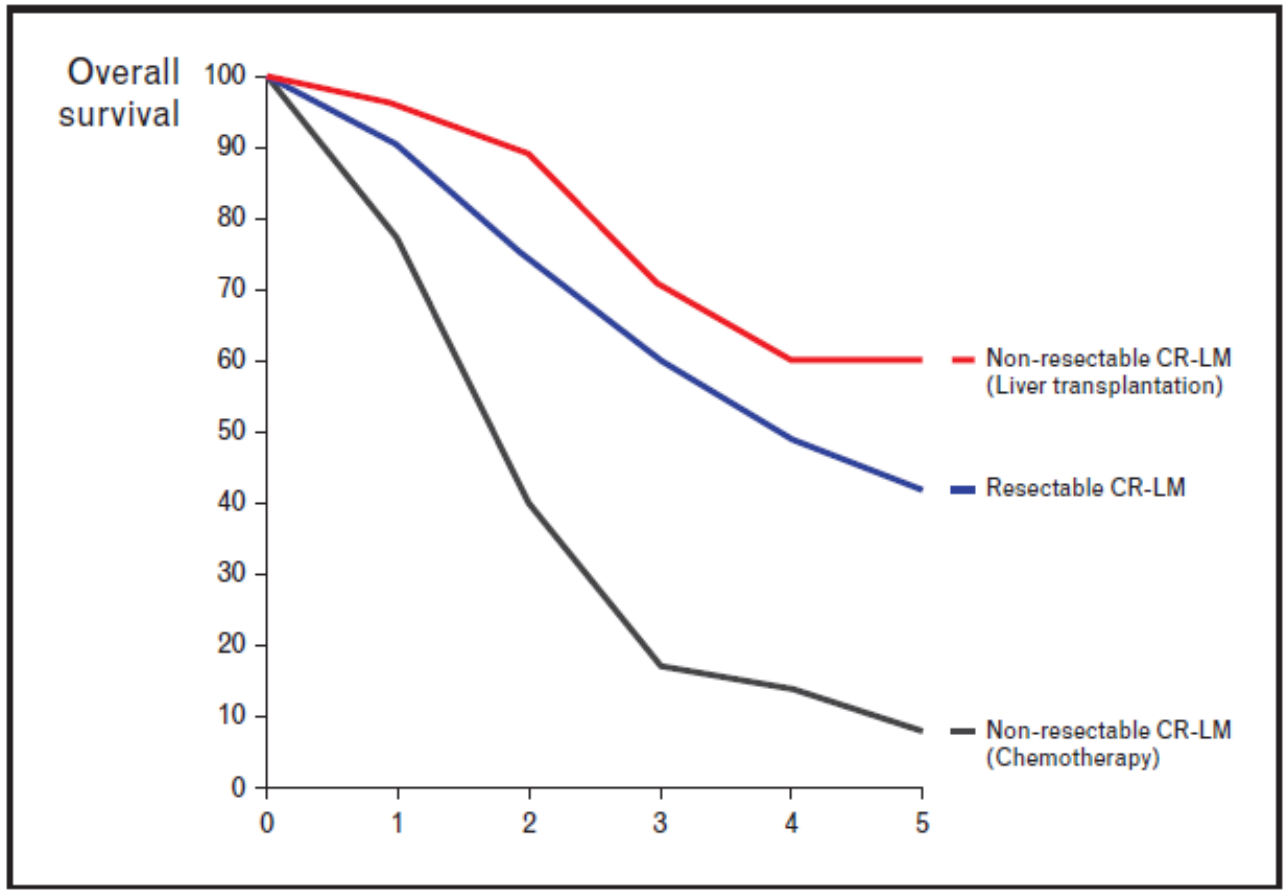
Patients otherwise suitable for liver transplantation

Ochsner CRLM – LT

Exclusions:

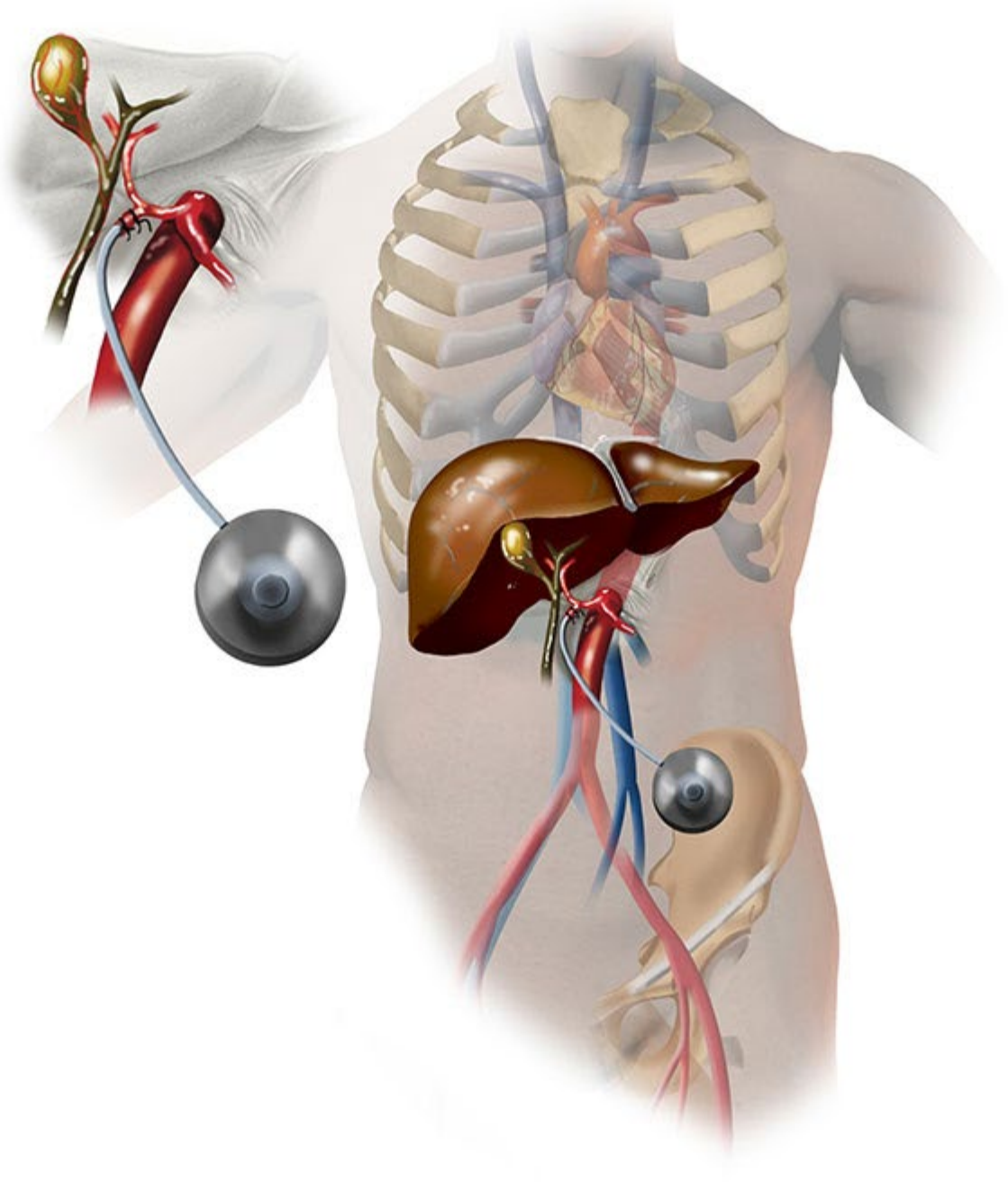
- Primary tumor pathology:
  undifferentiated adenocarcinoma or signet ring carcinoma.
- BRAF V600E
- ECOG 3 or 4
- Fatigue score ≥30
- Oslo score 3-4
- Non curative resection of primary CR cancer
- Unable or unwilling to complete the protocol
- Contraindication for LT

Overall survival of Colo-Rectal Liver Mets



Foss, Current Opinion in Transplantation, 2014 (19):235-44

Controversies, limitations, potential



Hepatic artery infusion pump

Table. Select Trials of Initially Unresectable Colorectal Liver Metastases Treated With Combination Hepatic Artery Infusion and Systemic Chemotherapy

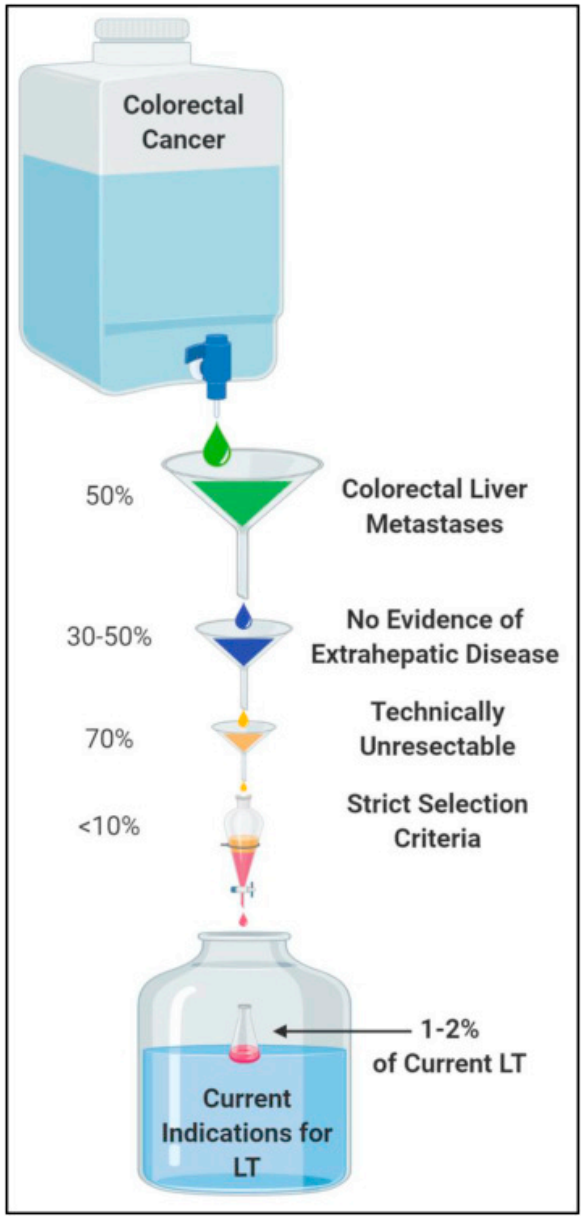
Source	No. of Patients	Treatment	RR, %	Conversion to Resection, %	Overall Survival, Median, mo
Allen-Mersh et al,[49] 2000	84	HAI-FUDR and systemic FU and LV vs systemic FU and LV alone	45 vs 23	NR	NR
Fallik et al,[50] 2003	75	HAI-pirarubucin and systemic FU and LV	34.4	NR	20
Mancini et al,[51] 2003	123	HAI-cisplatin and systemic FU	52	NR	18
Ducreux et al,[52] 2005	26	HAI-OX and systemic FU and LV	64	17.8	27
Shimonov et al,[53] 2005	23	HAI-IRI and systemic FU and LV + CARBO	40	NR	NR
Fiorentini et al,[48] 2006	76	HAI-FU and LV and systemic FU and LV vs HAI alone	47.5 vs 41.7	NR[a]	20 vs 14
Tsutsumi et al,[54] 2008	16	HAI-FU and LV and systemic UFT and LV	87.5	NR	22
Idelevich et al,[55] 2009	21	HAI-IRI + FU and LV and systemic UFT and LV	65	NR	36
Kemeny et al,[56] 2009	49	HAI-FUDR and DEX and systemic IRI + OX	92[b]	47	51 (Chemotherapy naive) 35 (prior chemotherapy)
Goéré et al,[57] 2010	87	HAI-OX and systemic FU and LV	55	26	NR[c]
D'Angelica et al,[58] 2015	49	HAI-FUDR and DEX and best systemic therapy	76	47	38
Pak et al,[59] 2018	64	HAI-FUDR and DEX and best systemic therapy[d]	73	52	81

Hepatic artery infusion pump

- RR 35-92%
- OS 18-80 months
- Resection 18-52%

- Use for months – years
- Requires systemic therapy
- Complication rate 20%
- G-I chemo-toxicity 20%

Jama Surgery 2019;154(8):768-776



CRLM – LT

Highly selective

Line, International Journal of Surgery 2020, 82:87-92

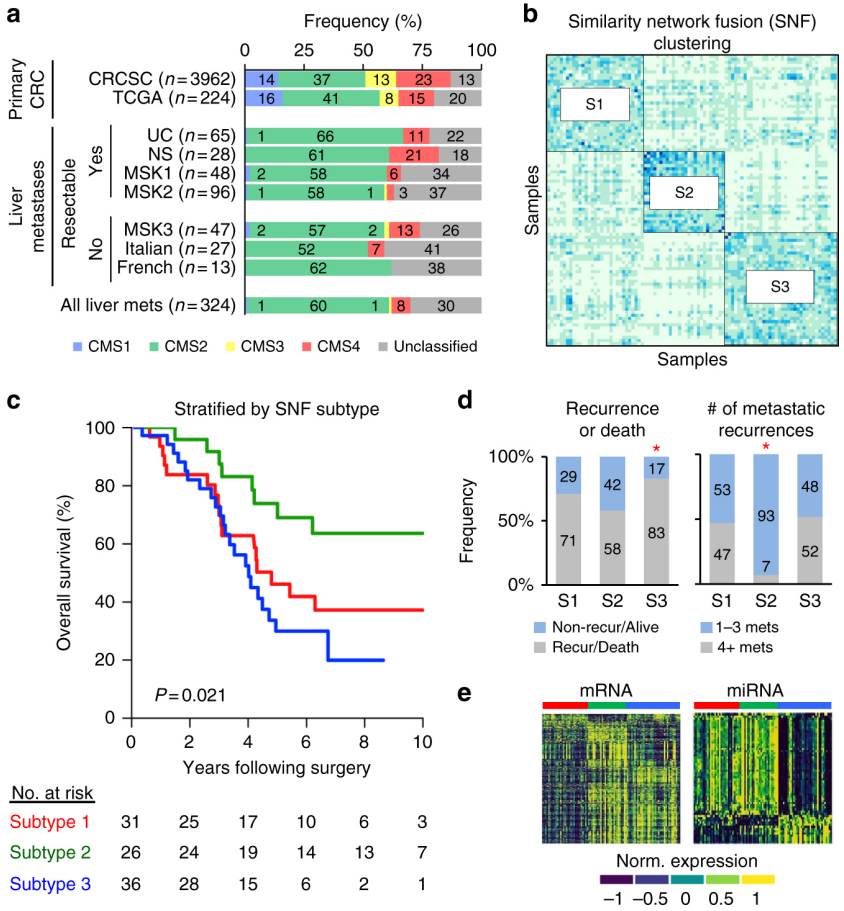
Organ availability limitations

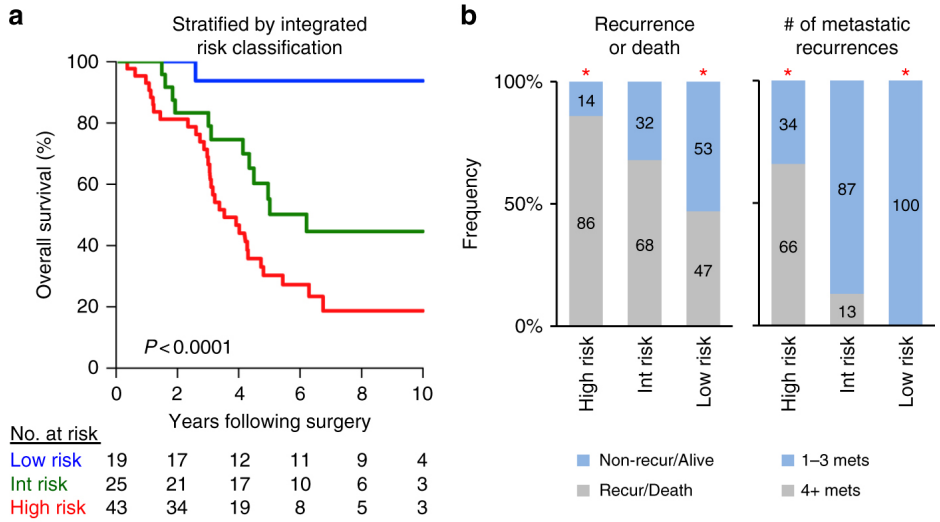
Affecting patients with accepted indications

- Living donor
- Deceased donor (Extended criteria)

Colorectal Ca: Personalized medicine

patient – biology selection





c

	Subtype 1 canonical	Subtype 2 immune	Subtype 3 stromal
Frequency	33%	28%	39%
Molecular signatures	↓Immune and stroma E2F/MYC signaling DNA damage and cell cycle	↑Immune Interferon signaling p53 pathway	↑Stroma KRAS signaling EMT and angiogenesis
Specific mutations	*NOTCH1* and *PIK3C2B*	*NRAS*, *CDK12*, and *EBF1*	*SMAD3*
Metastatic recurrences	Many	Few	Many
Overall survival	Intermediate	Favorable	Unfavorable

Nature communications, 2018, 9:1793

Take home points

- Surgery (resection-transplantation) goal in CRLM.
- Favorable response to chemotherapy allows more aggressive liver resections.
- Patients with unresectable CRLM have option to different treatments modalities and should explore more than one opinion.
- Multidisciplinary team approach is necessary – essential.
- Liver transplantation is part of the surgery box and an option in selective patients.

Alone we can do so little;
together we can do so much.
– Helen Keller