



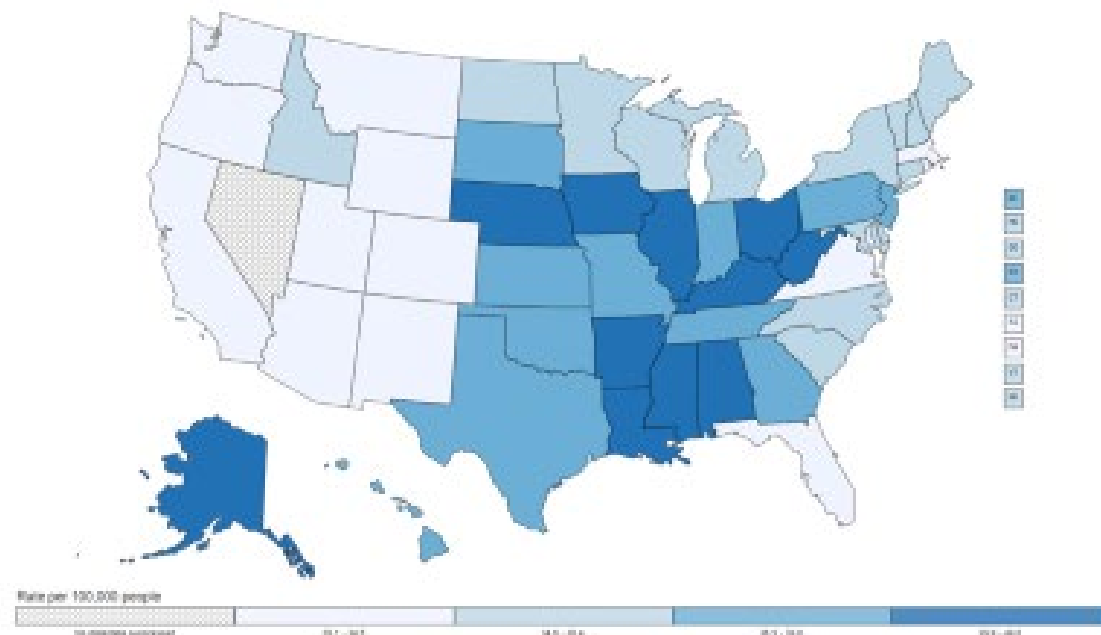
Liver Transplantation For Colorectal Metastases



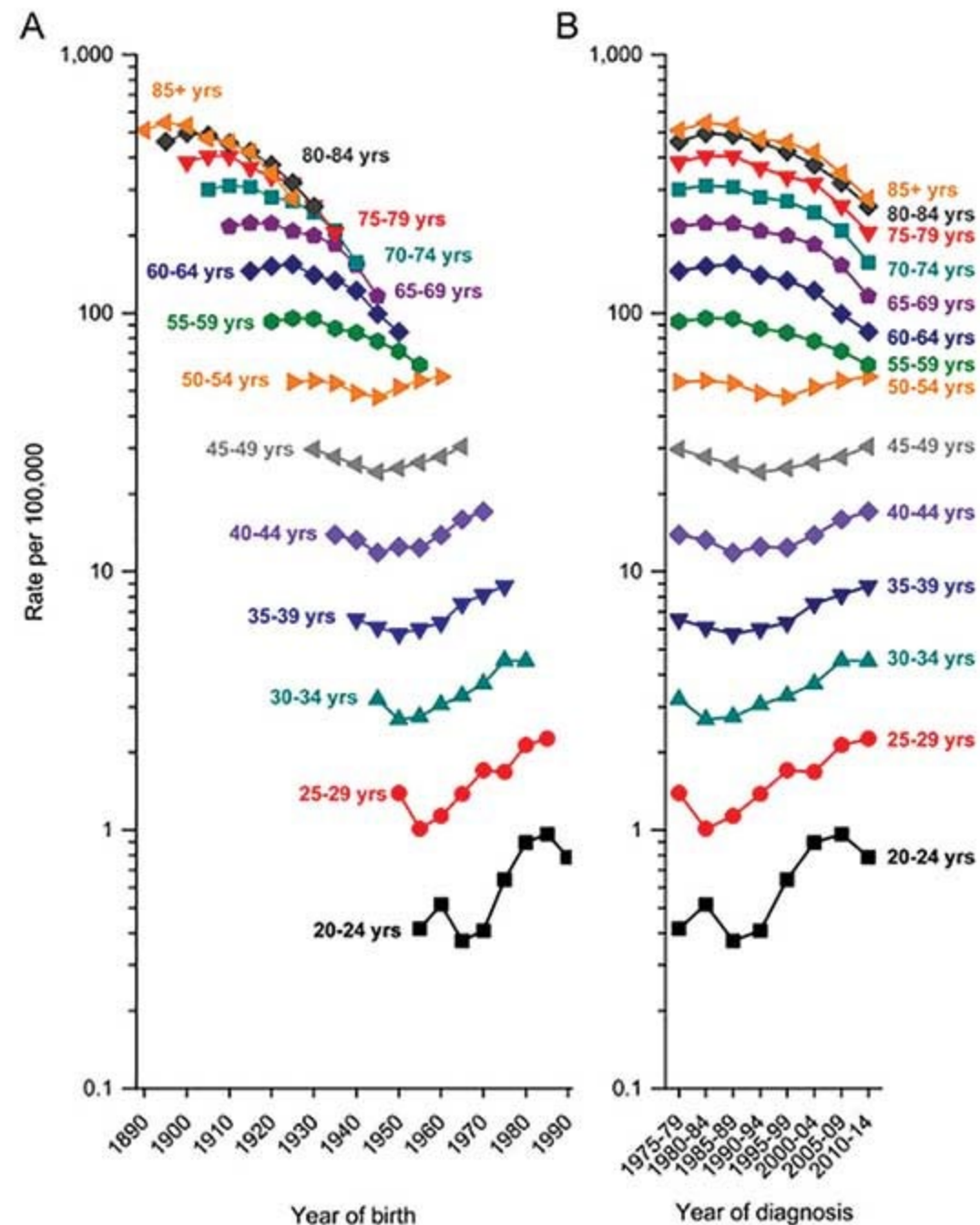
Humberto Bohorquez, MD
Abdominal Transplant Surgery
Surgical Director, Pancreas Transplantation
Ochsner Health
New Orleans, LA

COLORECTAL CANCER

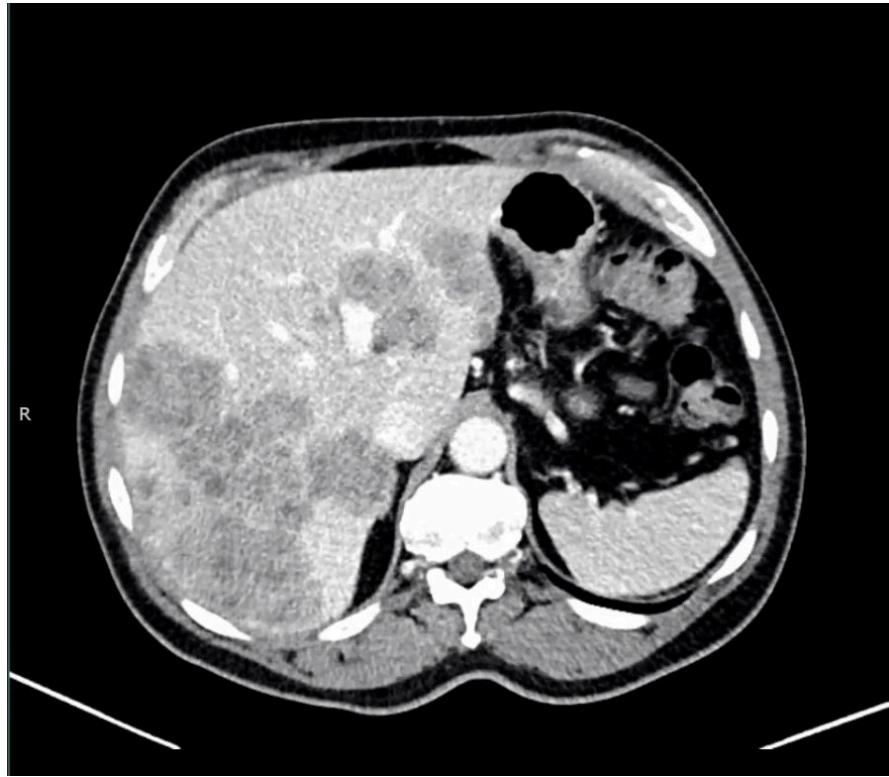
Rate of New Cancers in the United States, 2018
Colon and Rectum, All Ages, All Races and Ethnicities, Male and Female



~149.000 new cases U.S. in 2021



~ 50% Colorectal cancer
will develop liver metastases



~ 50% Colorectal cancer
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

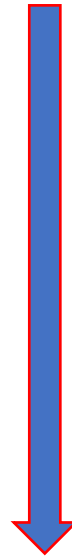
~ 50% Colorectal cancer
WILL develop liver metastases



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



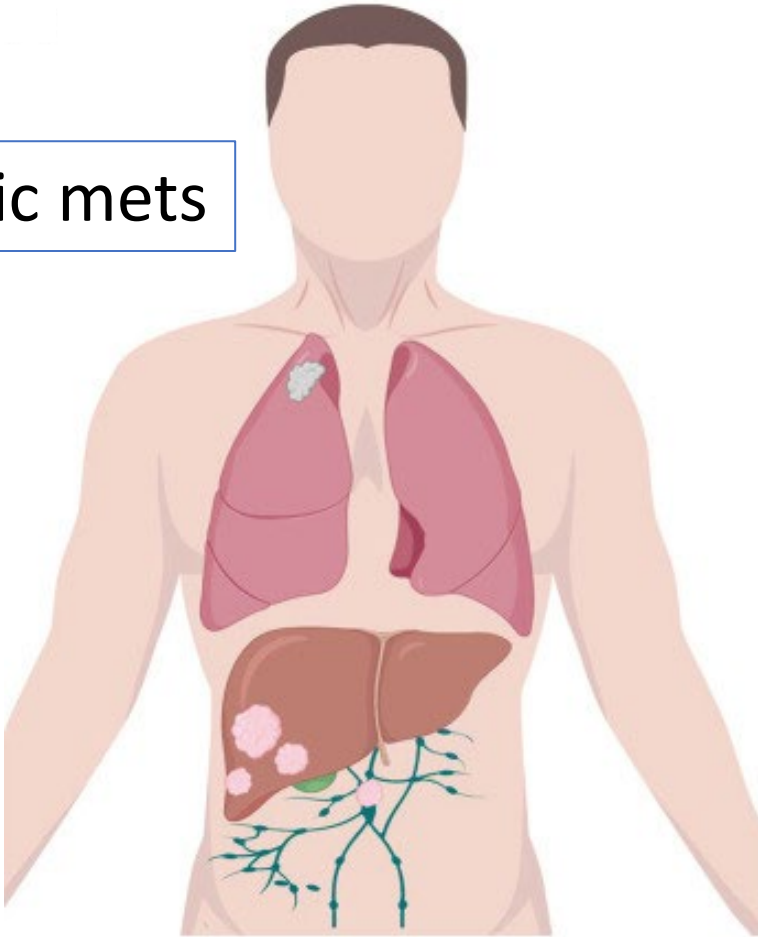
With liver resection
40-60% 5-y survival
30-40% Recurrence



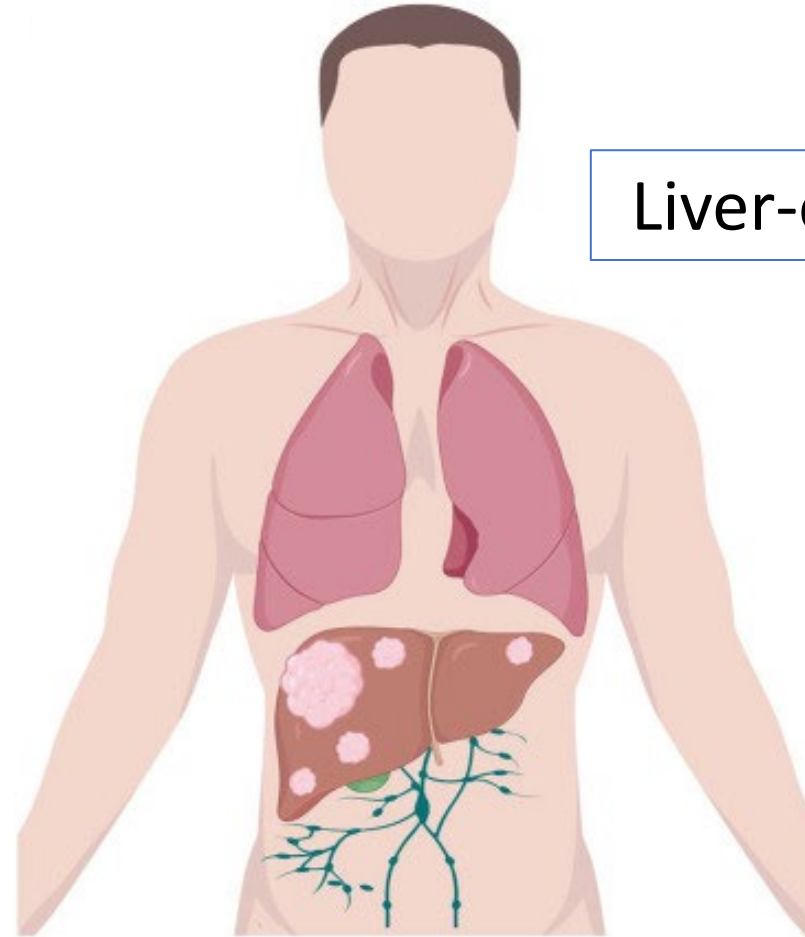
Only ~**30%** candidates for liver resection

Unresectability CRLM

Extra-hepatic mets



Liver-only mets

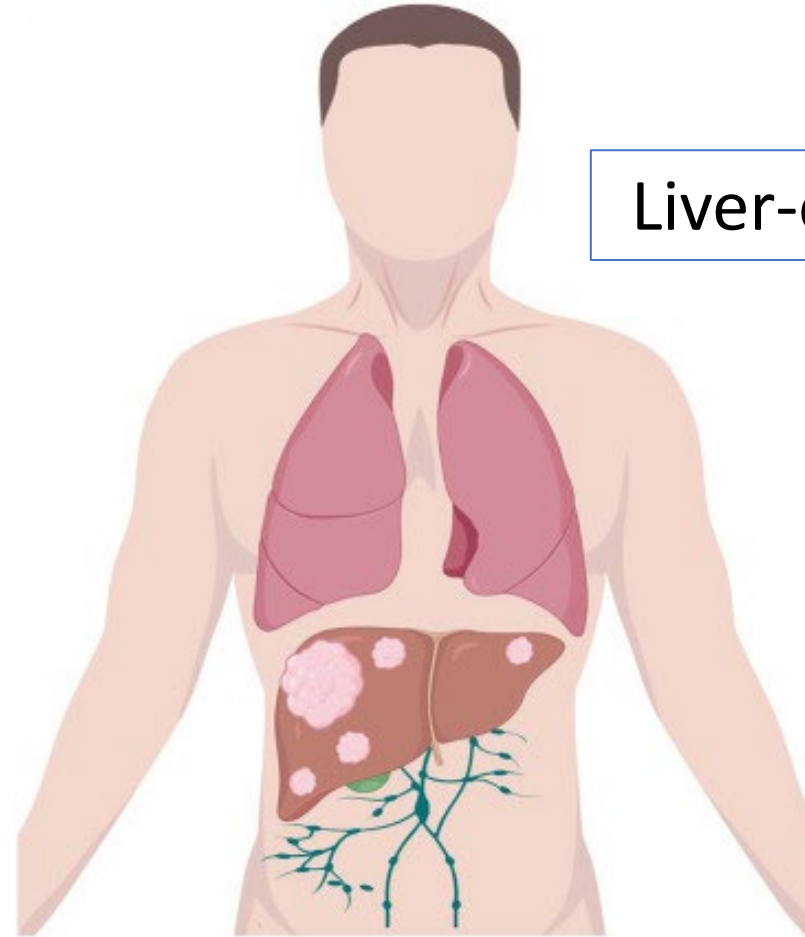


Liver Resection CRLM

Major limitation:

Insufficient Functional
Remnant Liver

Liver-only mets



Resectability CRLM

Major limitation:

Insufficient Functional Remnant Liver

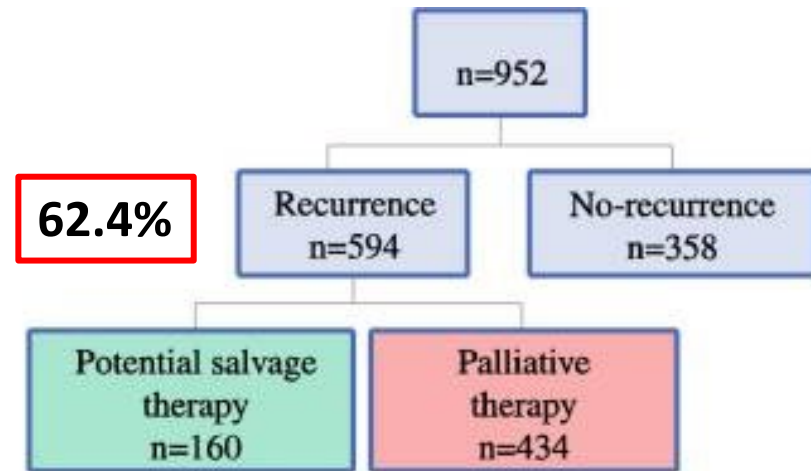
- Volume (>30-25%)
- Hepatic steatosis
- Chemo hepatotoxicity
- Tumor location



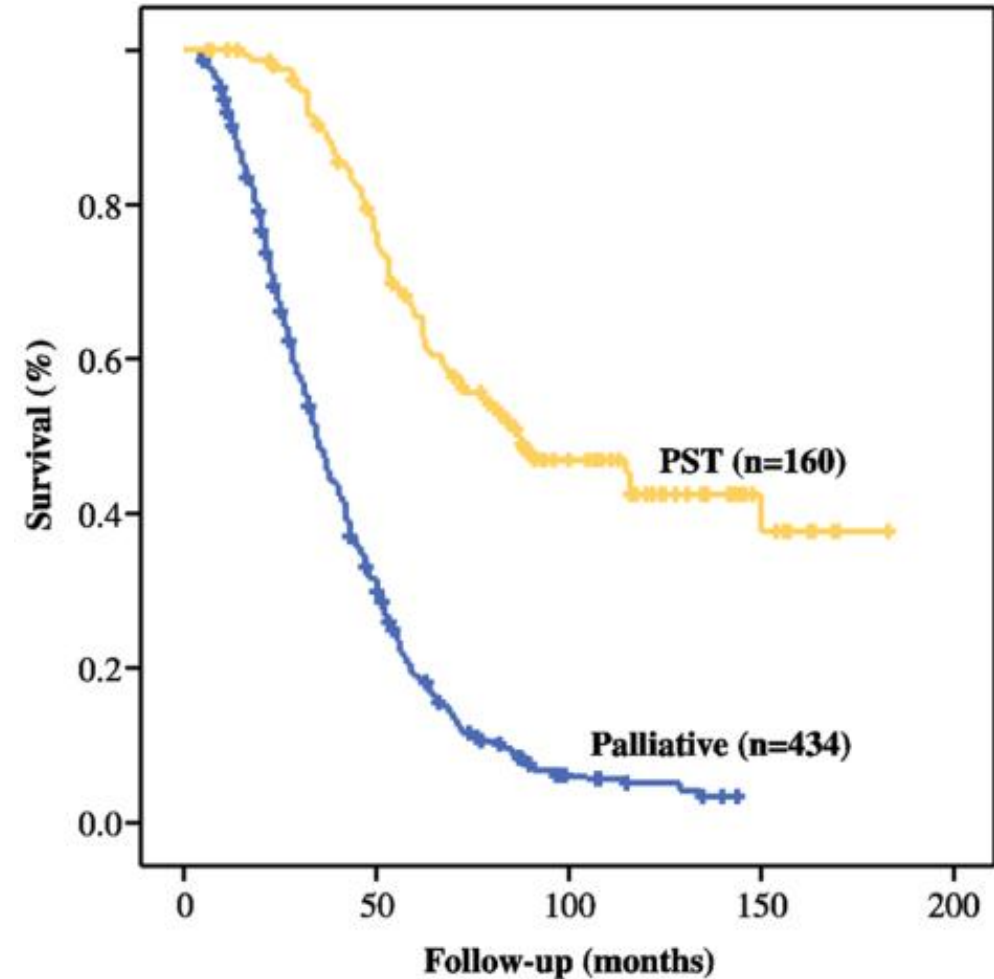
Strategies:

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

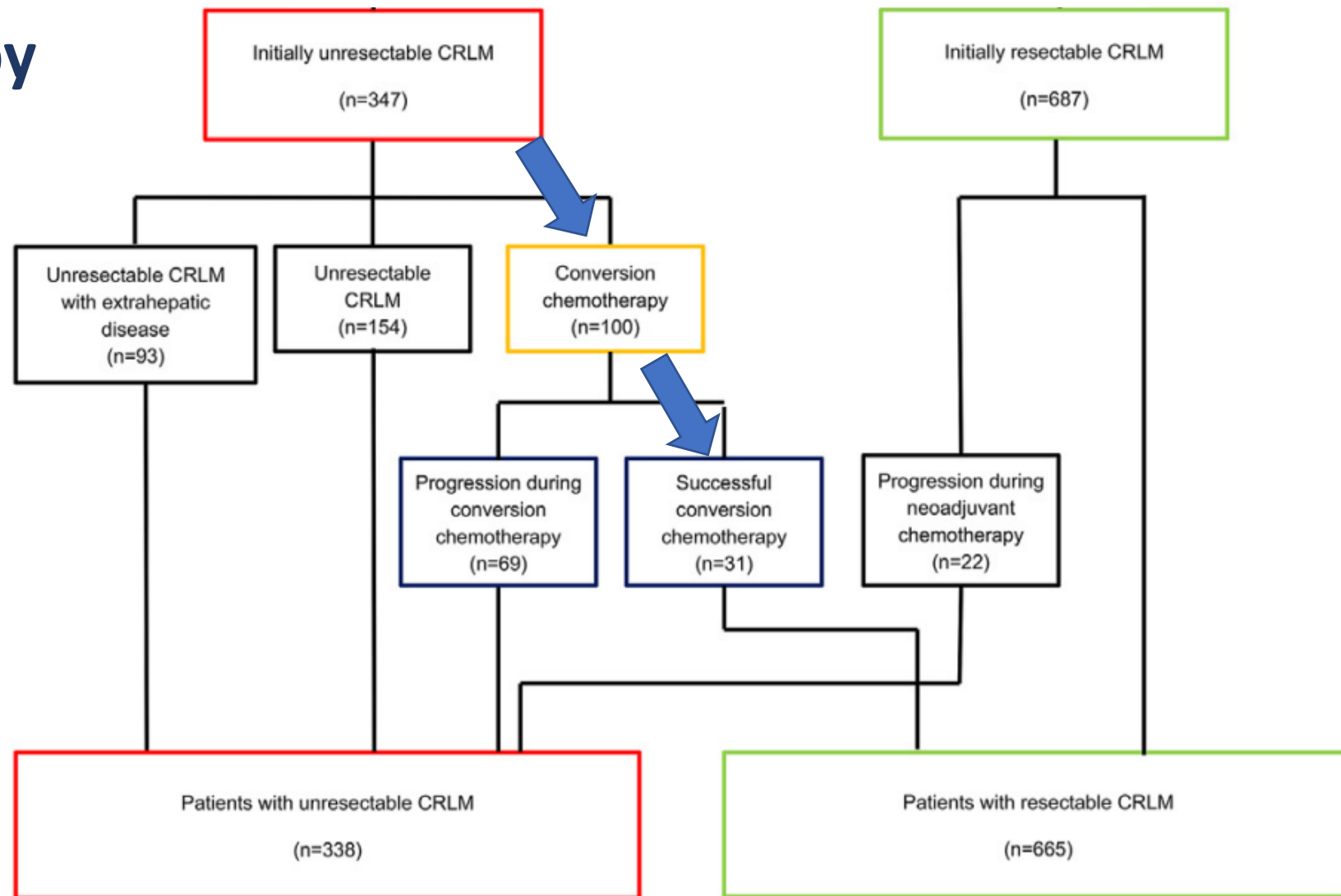
Recurrence After Partial Hepatectomy for Metastatic Colorectal Cancer without neoadjuvant therapy



Ann Surg Oncol 2015 22(8):2761

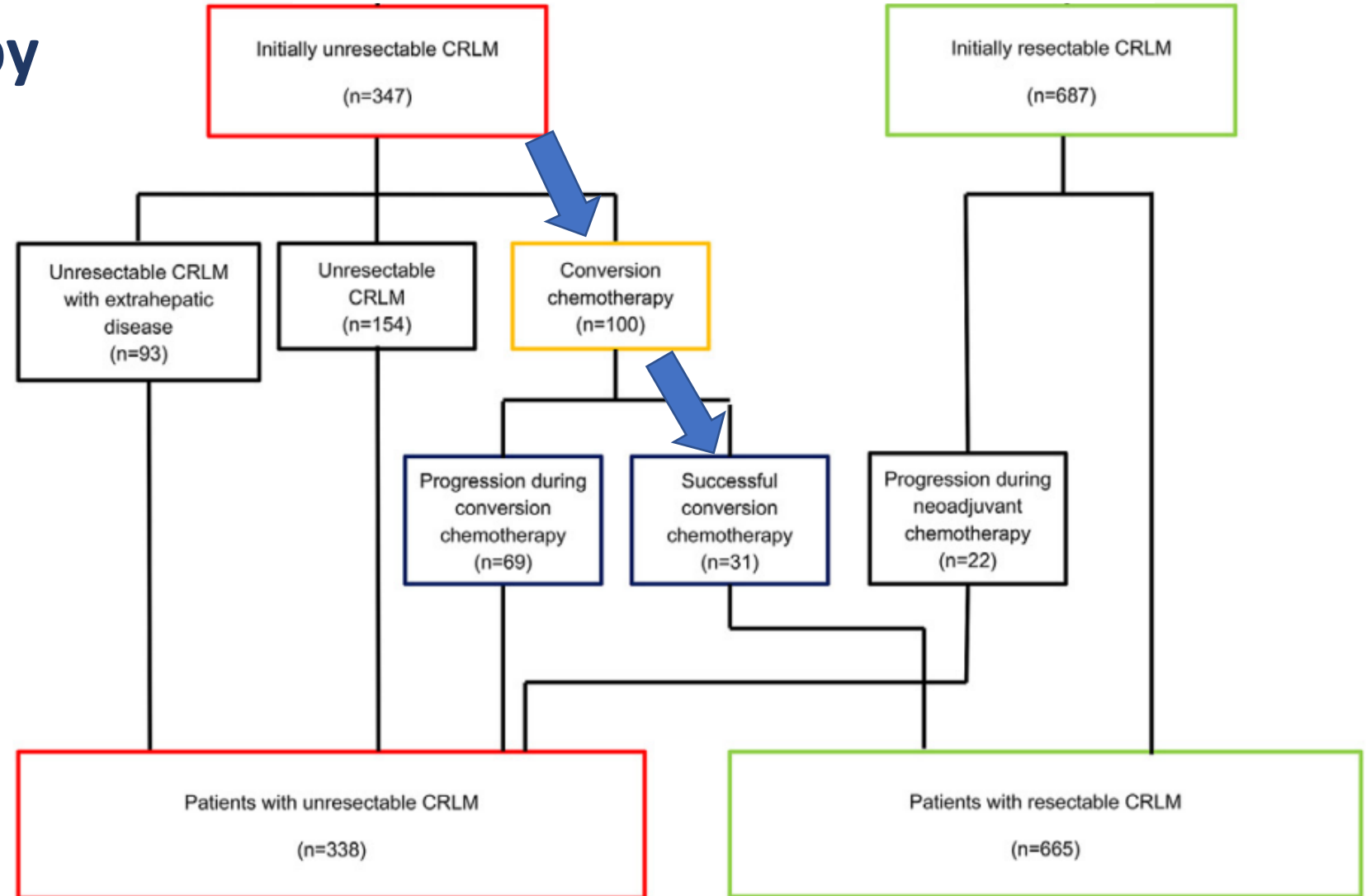


Conversion therapy in patients with CRLM



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

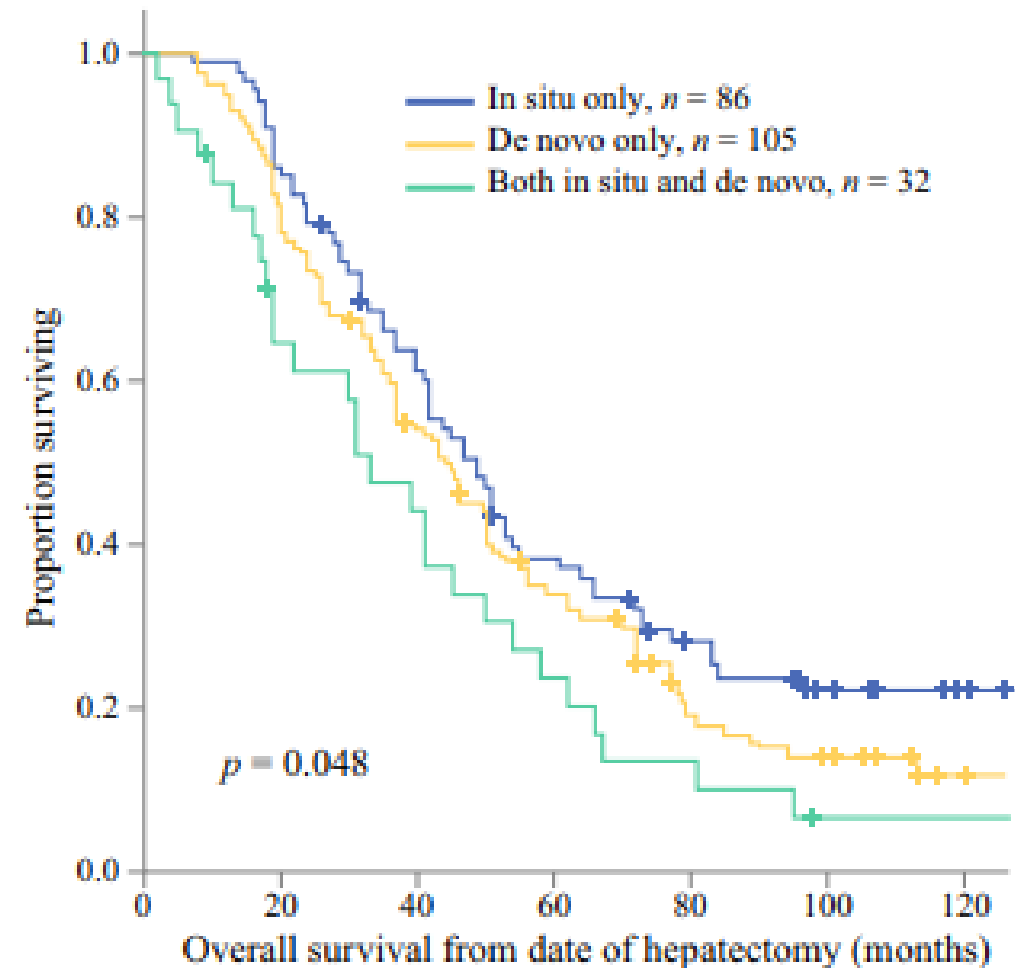
Ann Surg Oncol 2019 26:275

Neoadjuvant therapy + resection

Local recurrence 227/819 (**27.2%**)

Local recurrence:

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



Intrahepatic Recurrence Patterns Predict Survival After Resection of Colorectal Liver Metastases

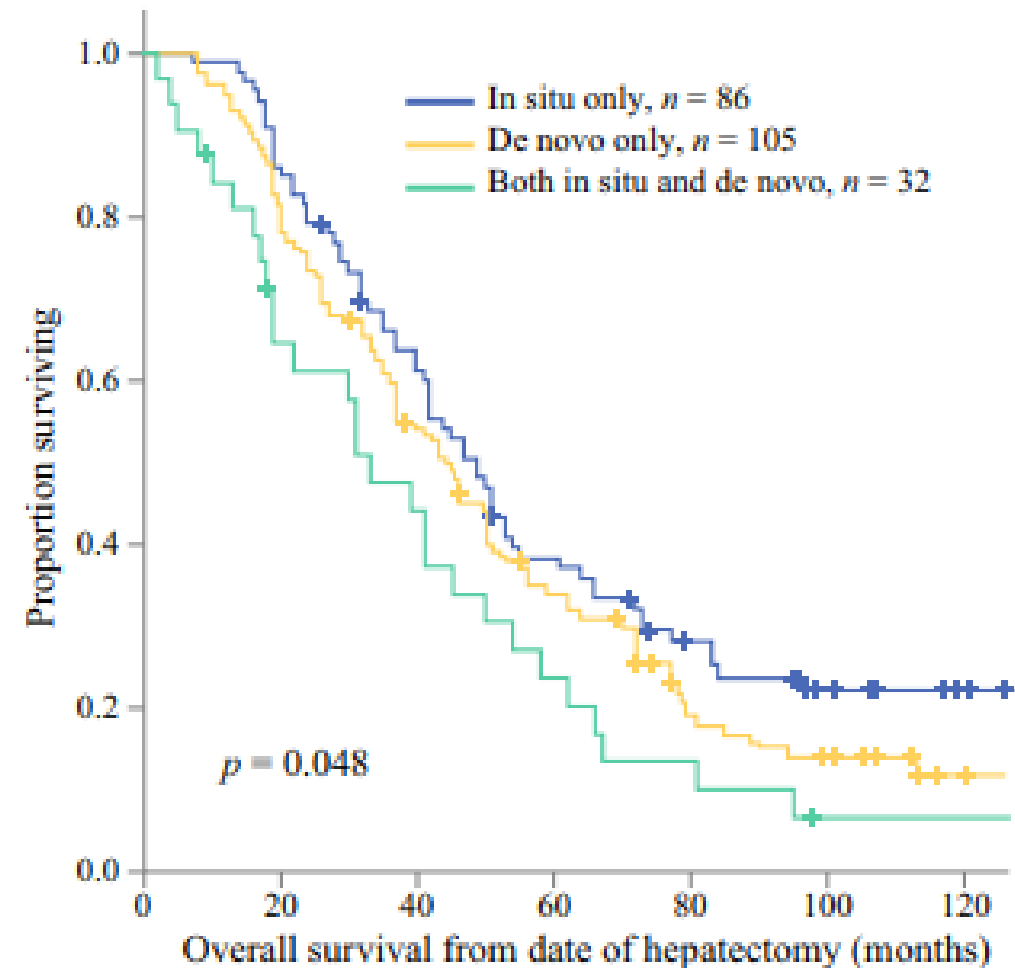
Ann Surg Oncol 2019 26:275

Neoadjuvant therapy + resection

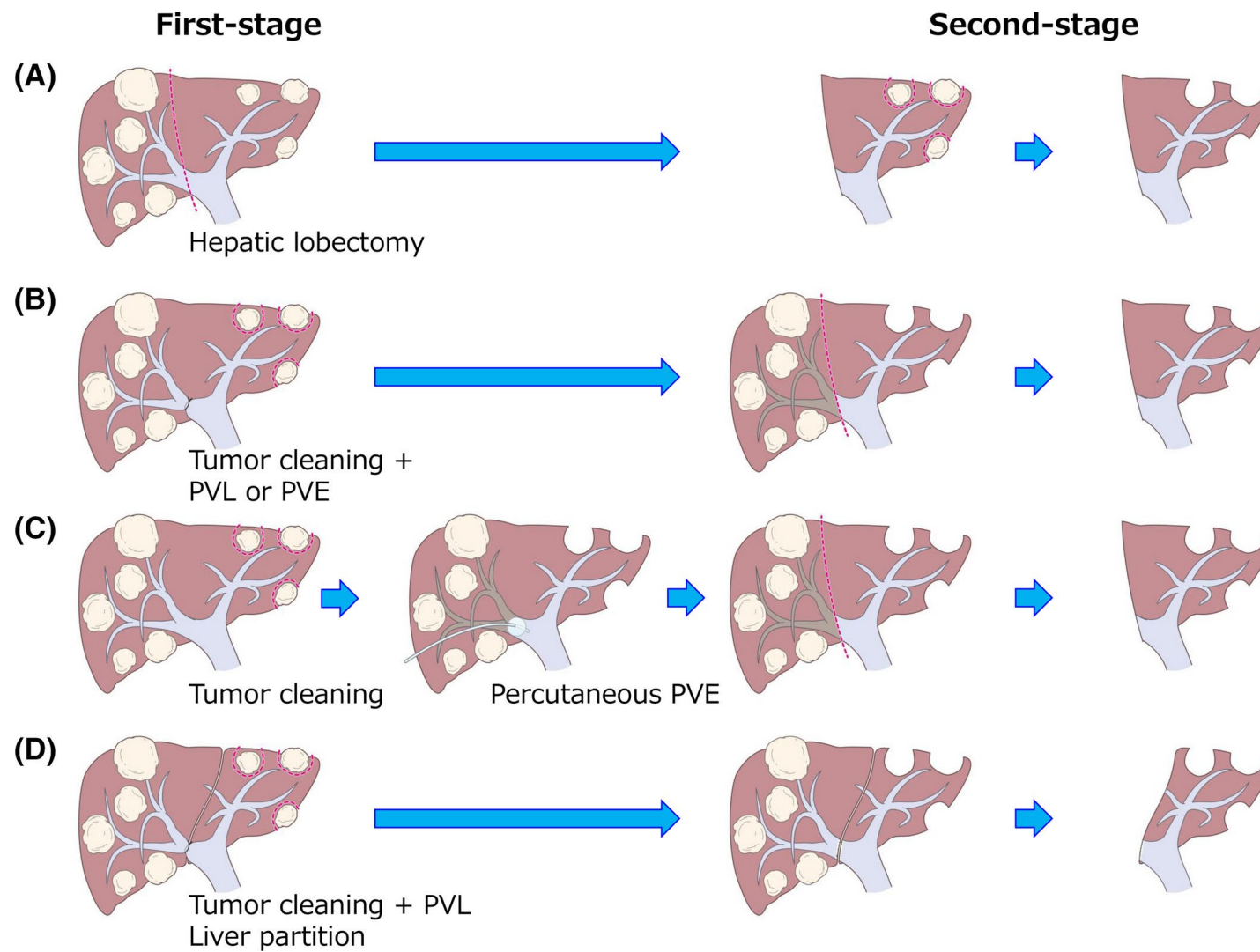
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Local recurrence:

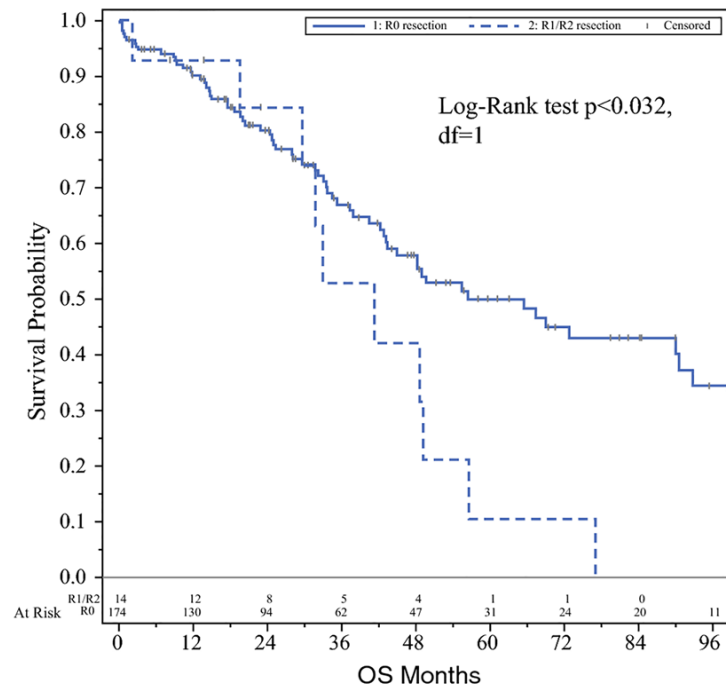
- disappearing or missed metastases
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- tumor progression after ablation



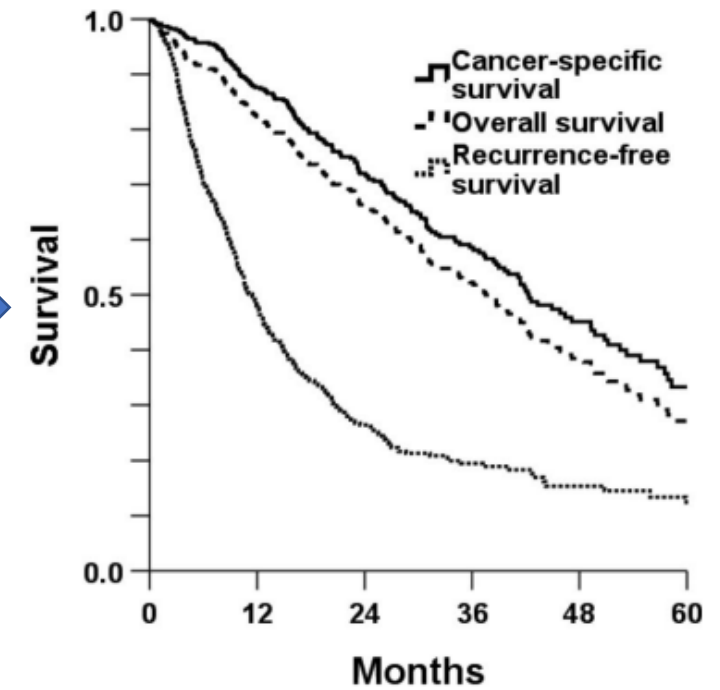
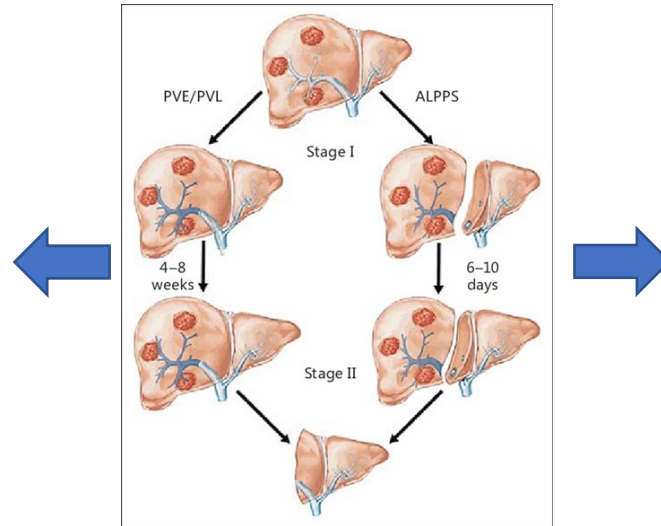
Extreme liver resection



Two-Stage Hepatectomy for Colorectal Liver Metastases



Ann Surg Oncol 2021 28:1457-1465



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

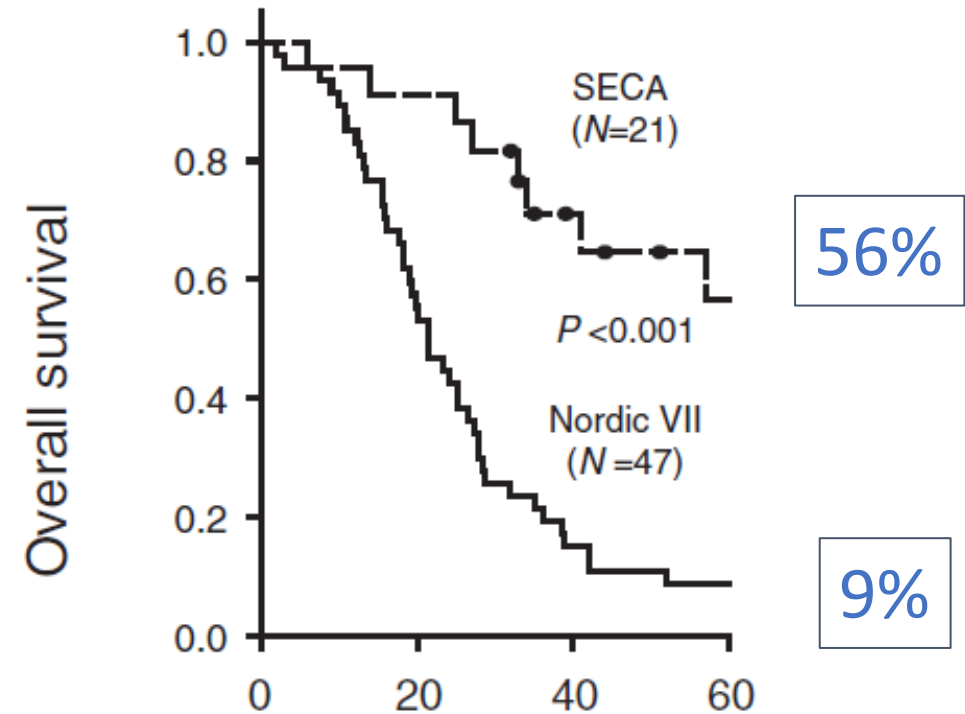
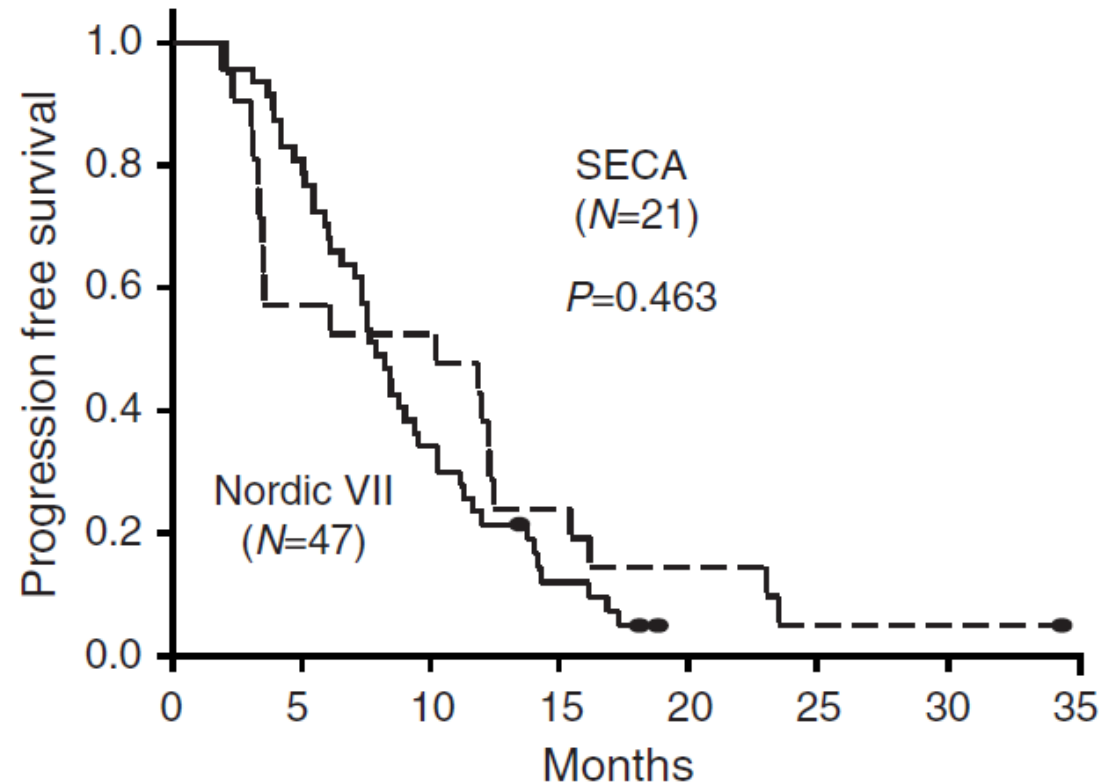
- 47 patients, < 66 yo,
BRAF neg, non-resectable, liver only mets
- Randomized, MTC
Flox, Flox-cetuximab intermittently
and Flox-cetuximab continuous
- All patients first line of treatment

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



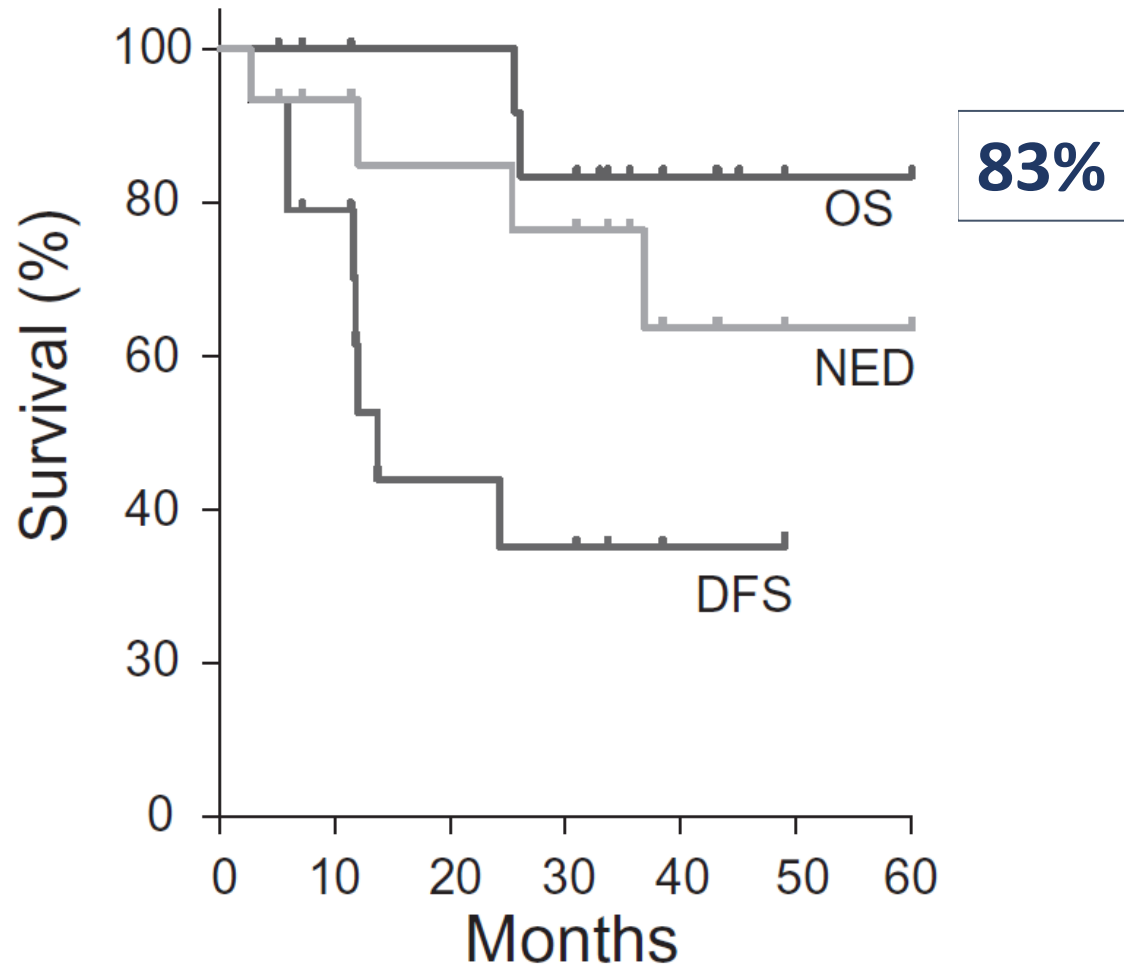
Annals of Surgery • Volume 261, Number 5, May 2015

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

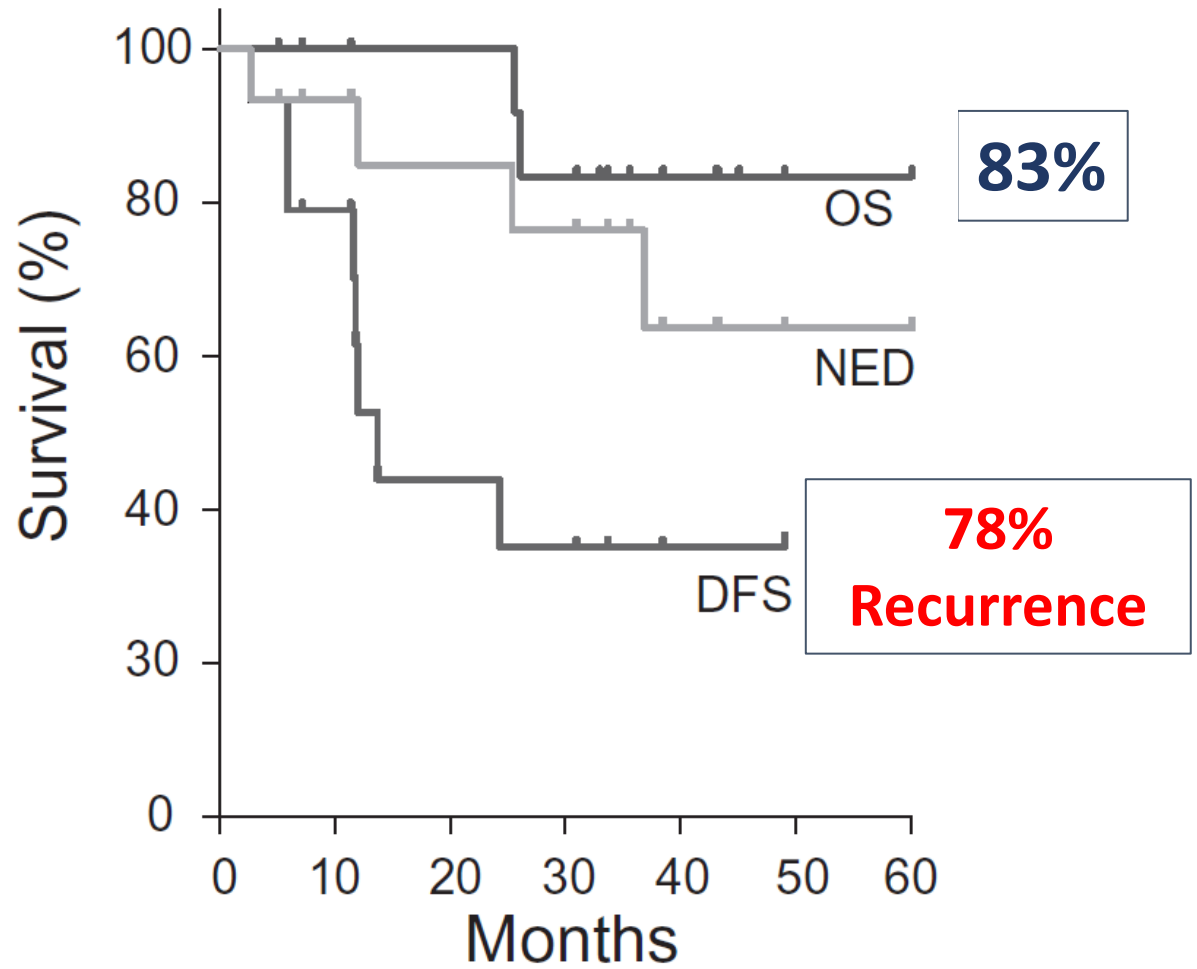


- Am J Transplant 2020;20(2):530-537
- Lancet Gastroenterol Hepatology 2021;6(11):933-946

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

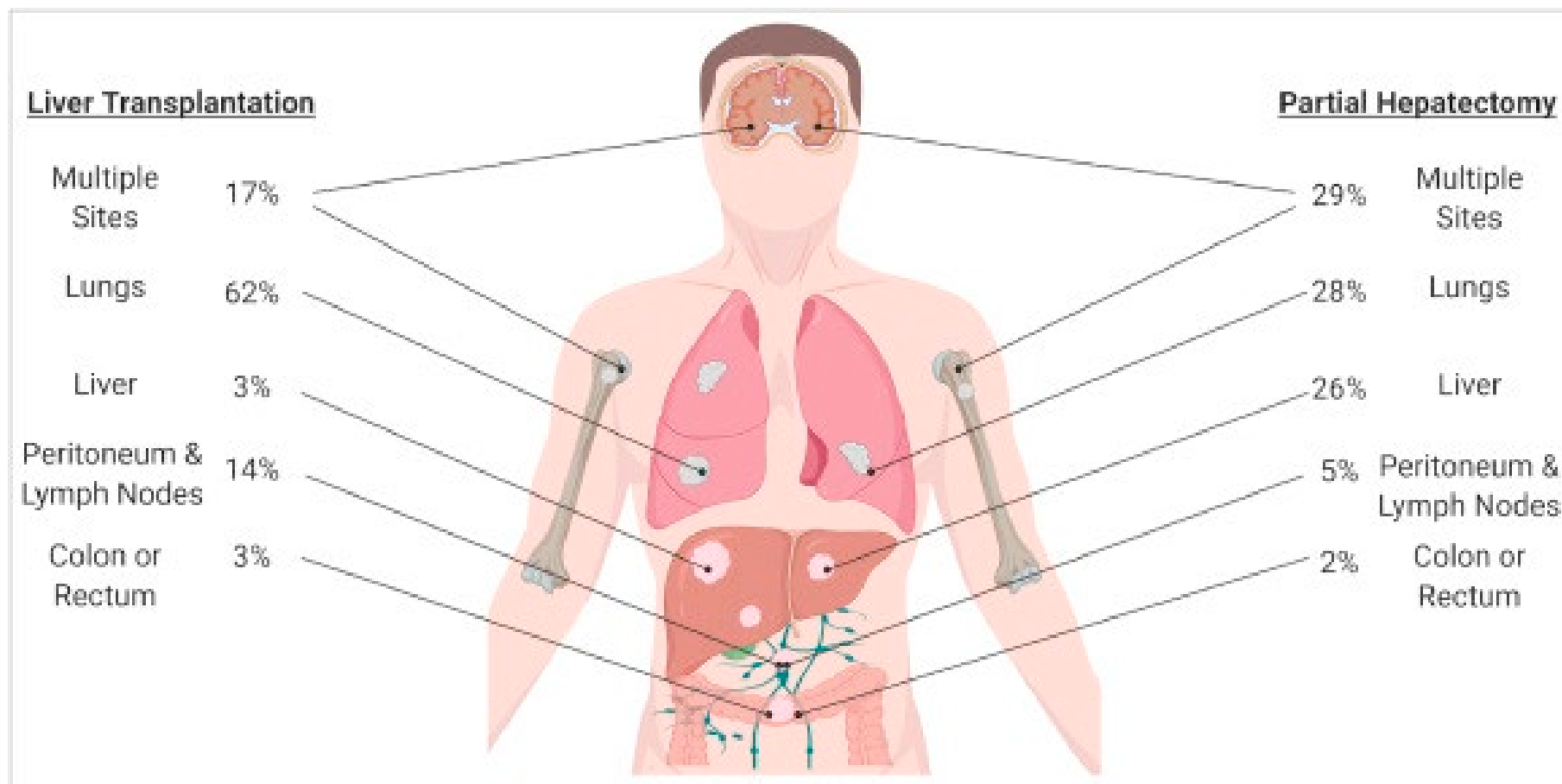
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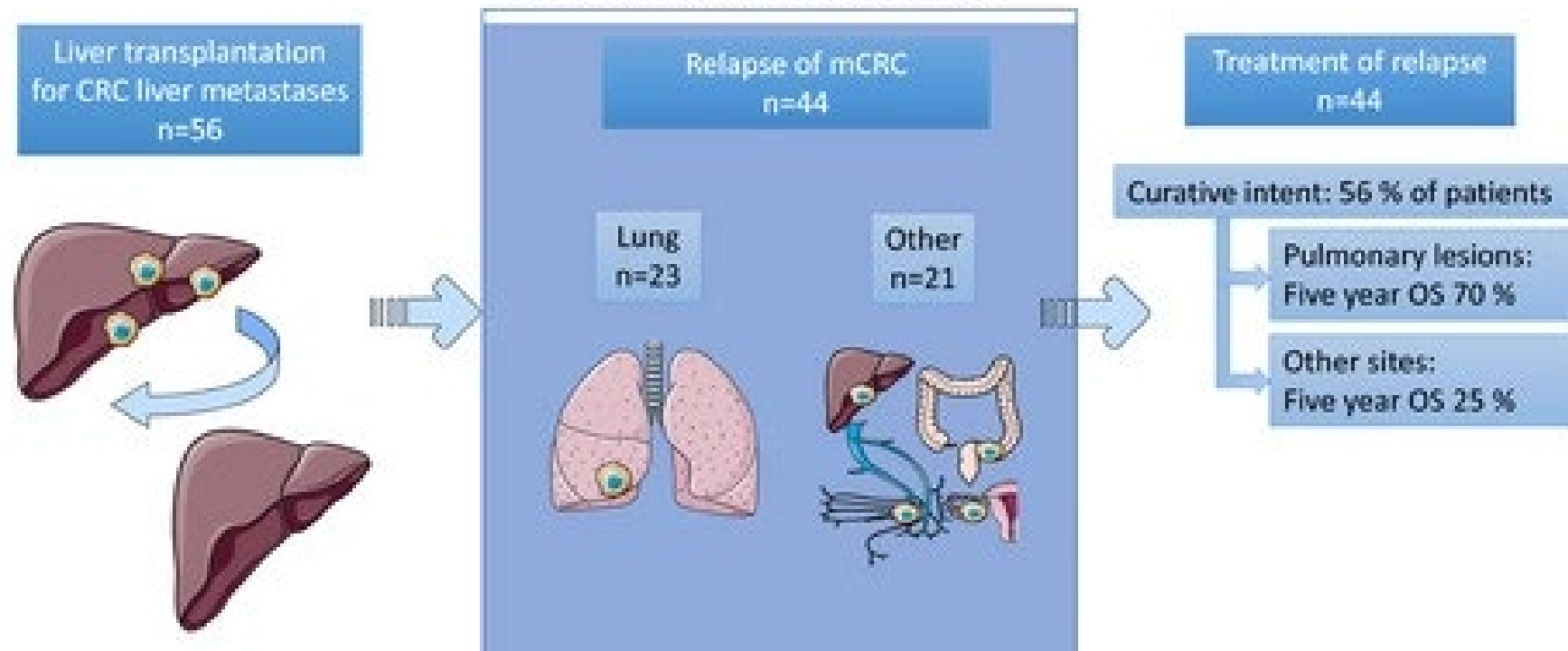
- Am J Transplant 2020;20(2):530-537
- Lancet Gastroenterol Hepatology 2021;6(11):933-946

Patterns of recurrence



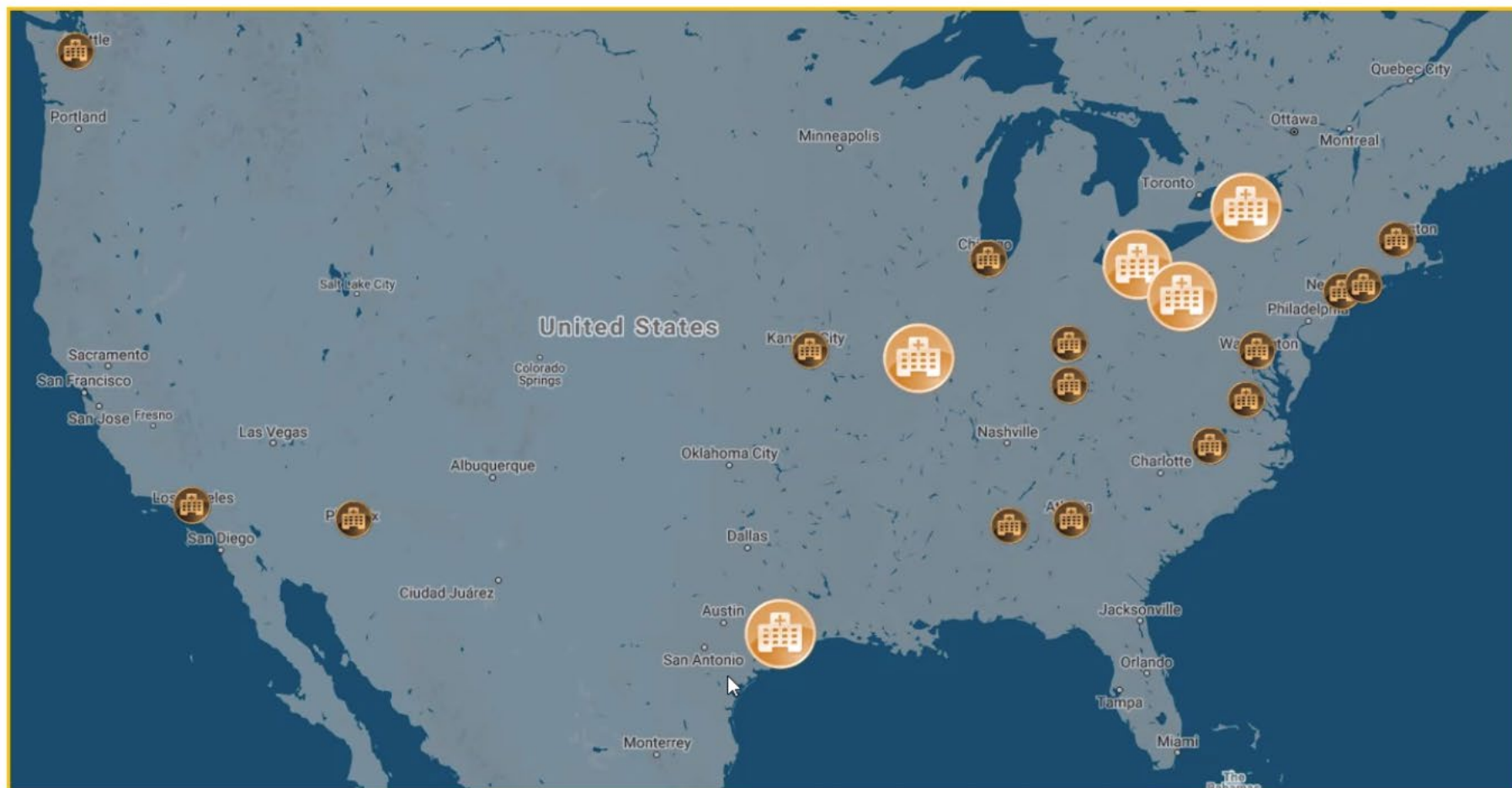
Line, International Journal of Surgery 2020, 82:87-92

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



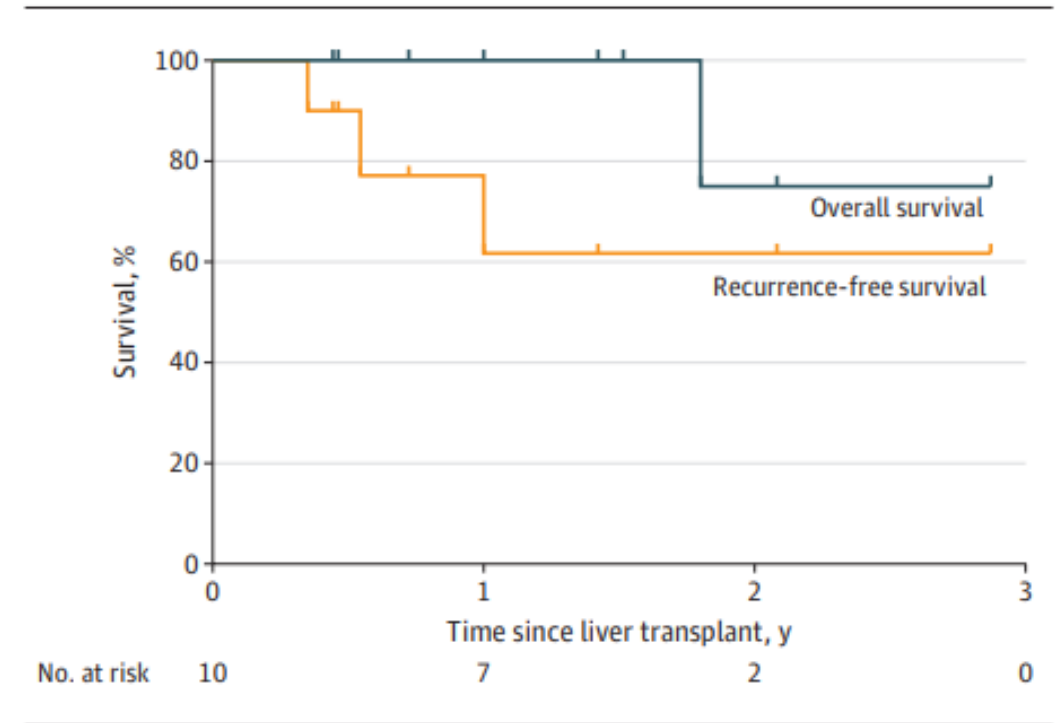
Courtesy Dr Hernandez-Alejandro

Unpublished Data From UNOS

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



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](#) •

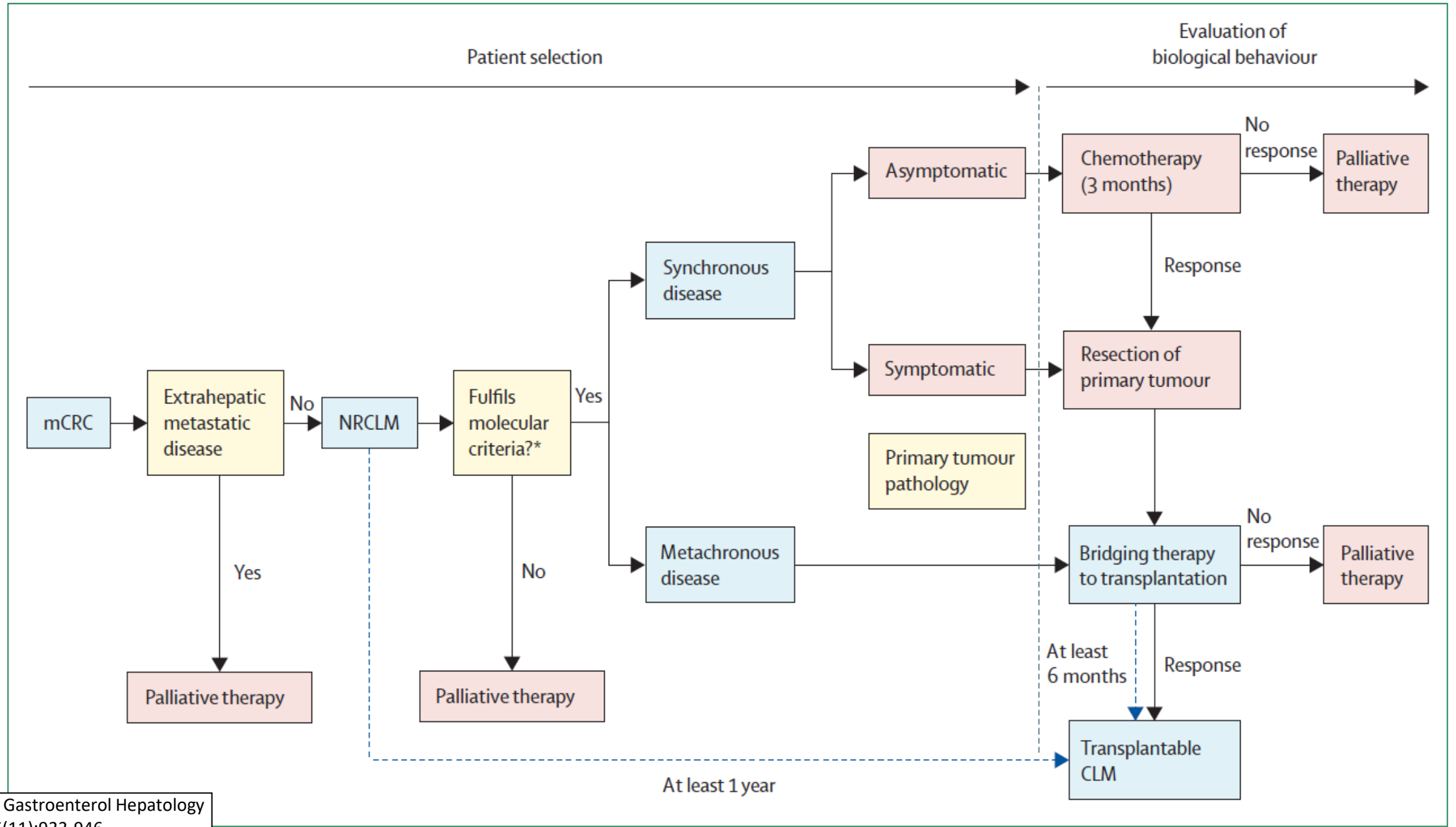
[John Isaac, FRCS](#) • [Richard W Laing, PhD](#) • [Shridhar Ganpathi Iyer, FRCS](#) • [Cheng Ean Chee, FACP](#) •

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Liver Cancer

Why Choose Ochsner?

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Liver cancer is one of the most rapidly increasing type of cancer in the United States. Liver cancer is a cancer that begins in the cells of your liver. Cancer that spreads to the liver is more common than cancer that begins in the liver cell.



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Schedule An Appointment

Liver Transplantation for Cancer

Ochsner Health has one of the largest liver transplant programs in the country with excellent outcomes in the top percentile in the nation.

Liver transplantation can offer hope for many patients with advanced liver cancer. Unfortunately, many liver cancers are diagnosed at an advanced stage when surgical resection is not possible. By treating the tumors with radiation and chemotherapy upfront, the objective is to ensure the tumor is confined to the liver and controlled so that, at the time of transplant, the cancer is removed entirely with the old liver. Using this approach, the outcomes were markedly improved, with 3-year patient survival of 70-80% compared with 10% or less with conventional chemotherapy alone.

Hepatocellular Carcinoma and Intra-Hepatic Cholangiocarcinoma

Hepatocellular carcinoma (HCC) is the most common primary cancer of the liver and has a defined role for liver transplantation. HCC occurs most frequently in patients with chronic liver disease which cause cirrhosis, or scarring of the liver, making liver resection (removal of part of the liver with surgery) unsafe. Liver transplant plays a central role in managing HCC tumors because the diseased liver is removed, reducing the risk of tumor recurrence.

Intra-hepatic cholangiocarcinoma (IHCA) is often discovered incidentally on imaging or evaluation of abnormal liver tests. When IHCA is discovered at an early stage, liver resection is often the best treatment option. Due to the rare symptoms, this tumor is often diagnosed at an advanced stage when the tumor is too large to remove surgically.

New systemic immunotherapy treatments can be used to control and shrink very advanced tumors. Through a process called downstaging, targeted delivery of radiation beads, chemotherapy beads or ablation of the tumors is used to shrink the tumors to be considered for liver transplant.

Colorectal Cancer Metastasis to the Liver

An estimated 50% of patients with cancer in the colon or rectum will see the cancer spread to the liver at some point. The spread, called metastasis, reduces the survival of those patients who will have an average survival of 50% at two years and 20% at five years. The best option for colorectal metastasis in the liver is through surgical resection, which raises the chance of survival to 60% at five years. Unfortunately, only 20% of the patients with liver metastasis will be candidates for surgical resection. Of those 20%, many patients will develop recurrence within the first three years of their liver resection. So, for most patients with liver metastases the current standard of care does not offer many surgical options.

Over the last years, a unique approach that combines different therapeutic options that include liver transplantation has reached an outstanding 5-years survival of 83% in select patients with unresectable liver-only metastases of colorectal cancer. This promising approach provides the longest overall survival reported for this advance cancer stage. Due to its complexity, this novel approach is only offered in a few institutions around the world. This protocol may involve the use of chemotherapy, immunotherapy, radiological treatments, surgery and liver transplantation. As every patient is unique, each case is carefully evaluated by the multi-disciplinary team to develop a personalized treatment.

My Diagnosis

Our Comprehensive Team Approach

Preparing for Your Oncology Visit

Cancer Resources and Support

Cancer Care Related Specialties



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Must Reads Newsletter

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 \geq 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

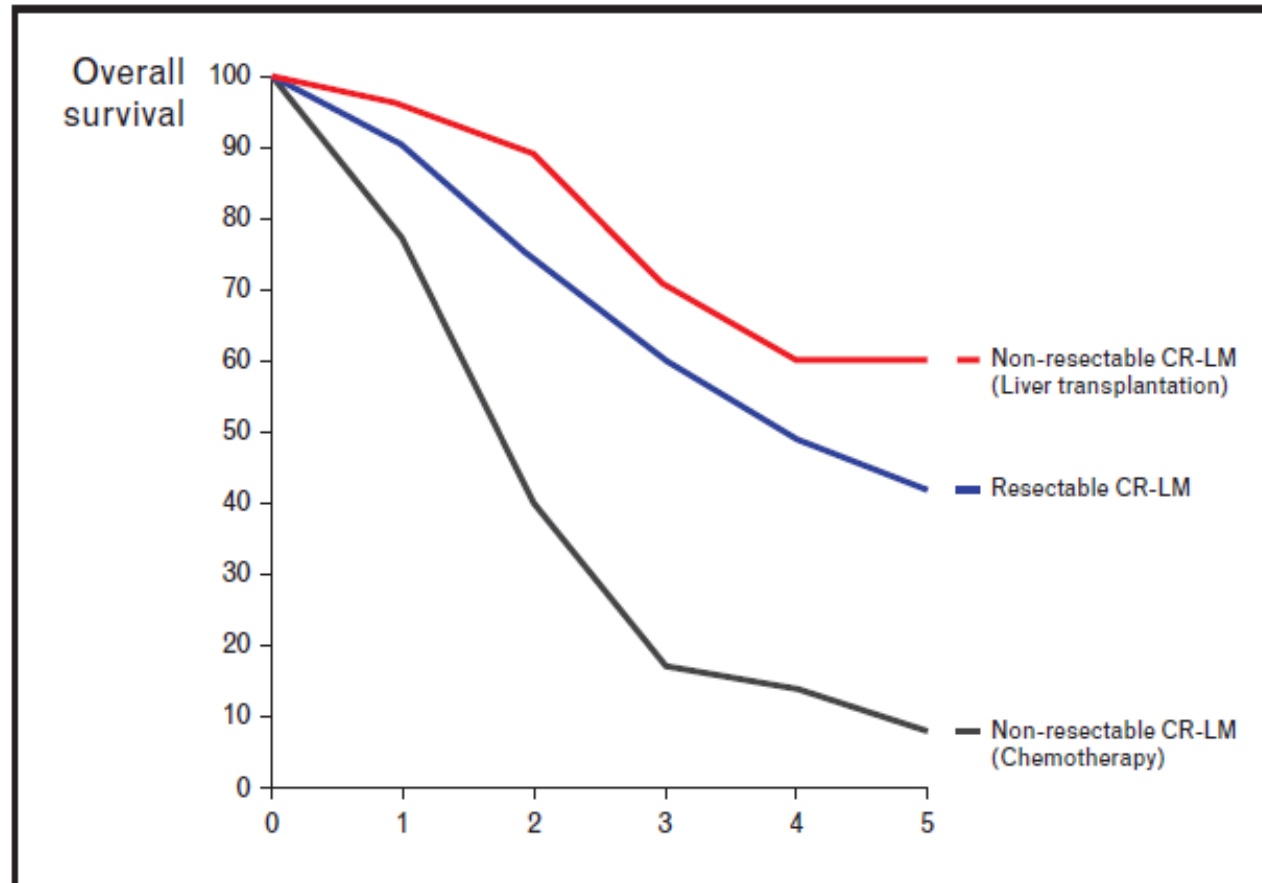
Patients otherwise suitable for liver transplantation

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

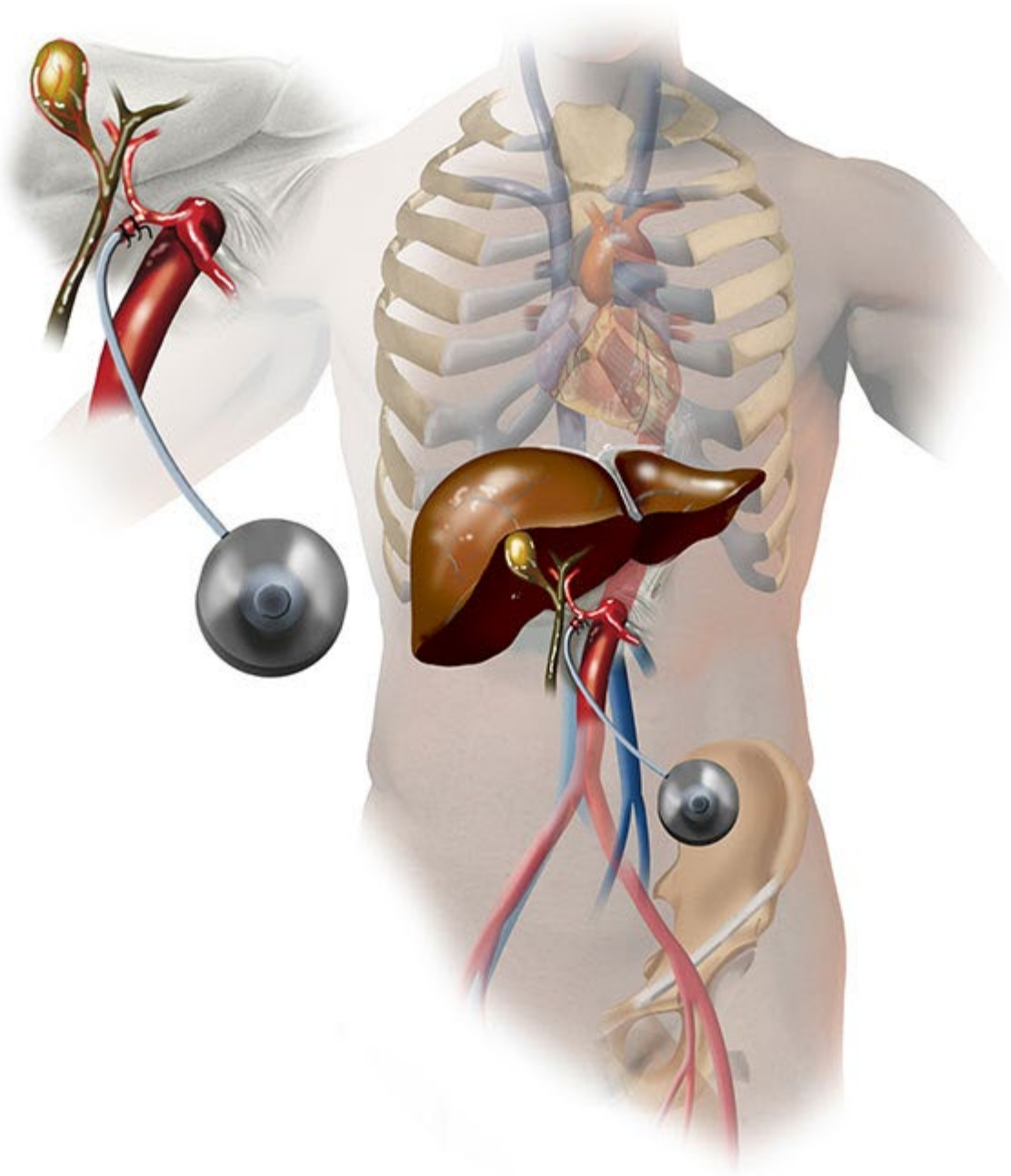
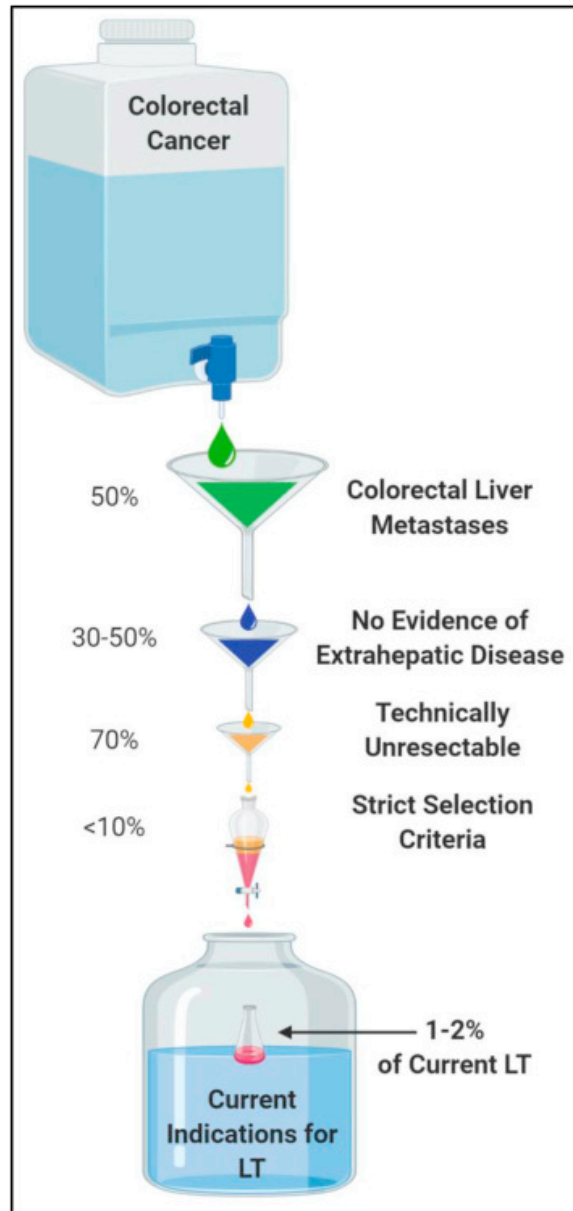


Table. Select Trials of Initially Unresectable Colorectal Liver Metastases Treated With Combination Hepatic Artery Infusion and Systemic Chemotherapy

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-pirarubicin 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%



CRLM – LT

Highly selective

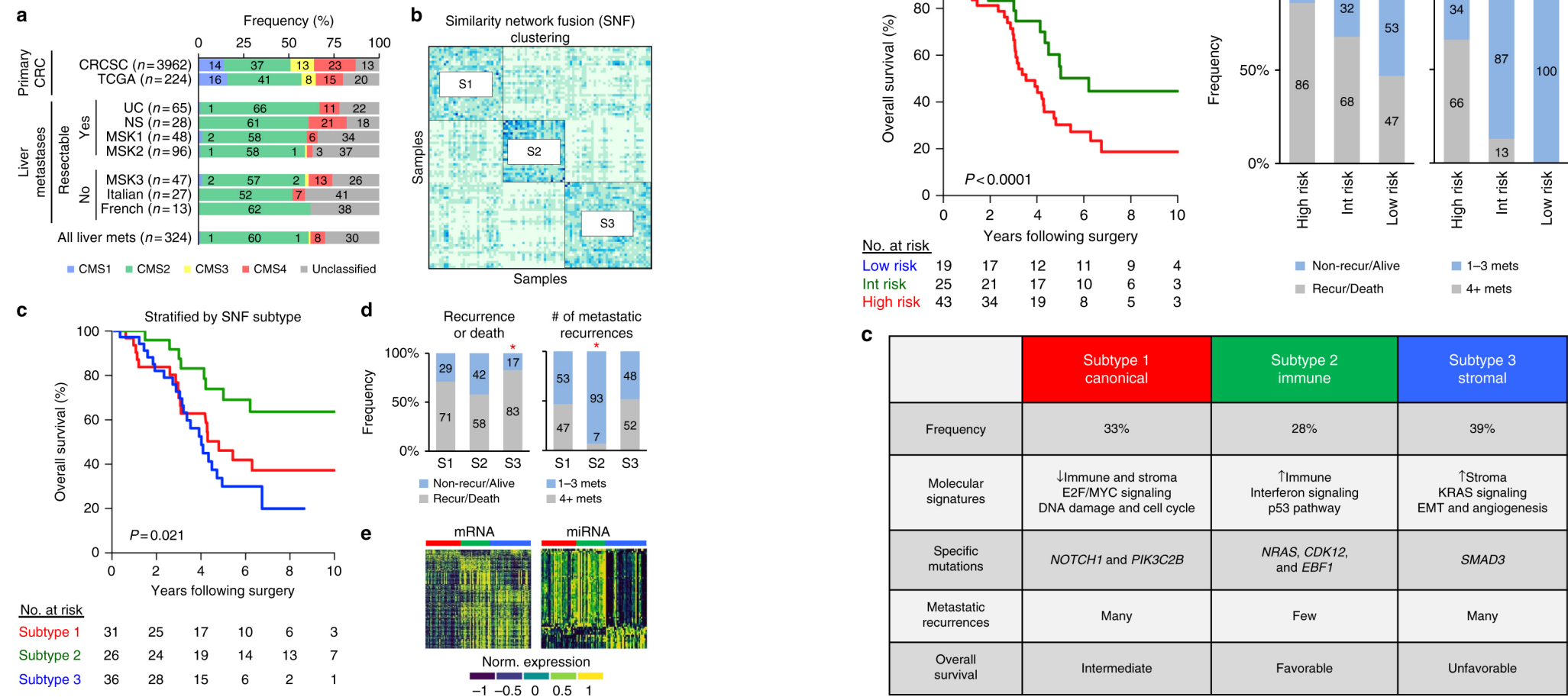
Organ availability limitations

Affecting patients with accepted indications

- Living donor
- Deceased donor (Extended criteria)

Colorectal Ca: Personalized medicine

patient – biology selection



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

