# Identifying the ideal candidate for transplantation Colorectal Liver Metastasis


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NUHS National University Health System

# “Curing” Metastatic Disease

Without treatment, 5-year survival of CLM = 5 %

With chemotherapy, 5 year survival of CLM = 25-40%

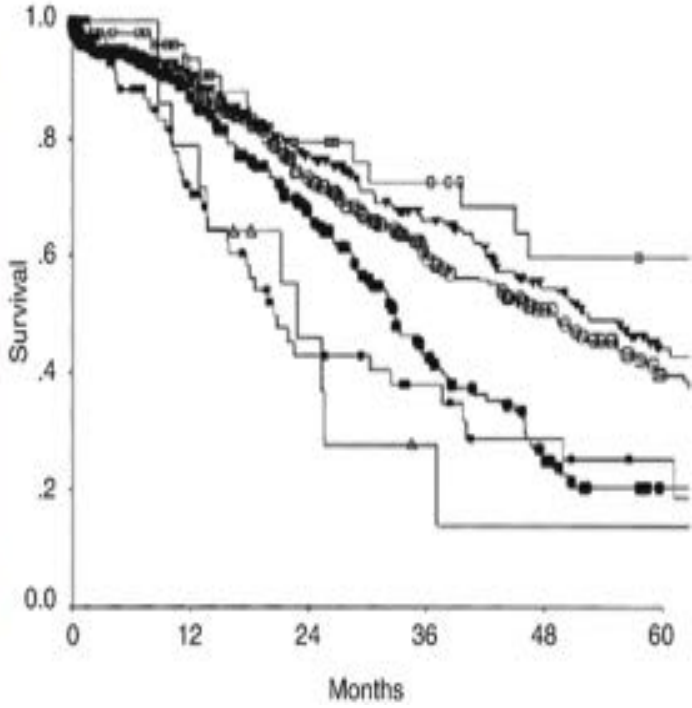
Combination of surgery and chemotherapy= 58%

Multiple predictive factors of disease :
R1
Synch vs Met
Primary Nodal Disease
Number of Metastasis

Multiple clinical scoring systems:
Fong Criteria
Nordlinger Criteria
Nagashima Criteria
Konopke Criteria

**Fong scoring system**

- Colorectal cancer metastatic to lymph nodes;
- Disease-free interval from the primary to discovery of the liver metastases <12 months;
- Number of tumors in the liver >1;
- Pre-operative CEA level >200 ng/ml;
- Size of the largest liver tumor >5 cm.



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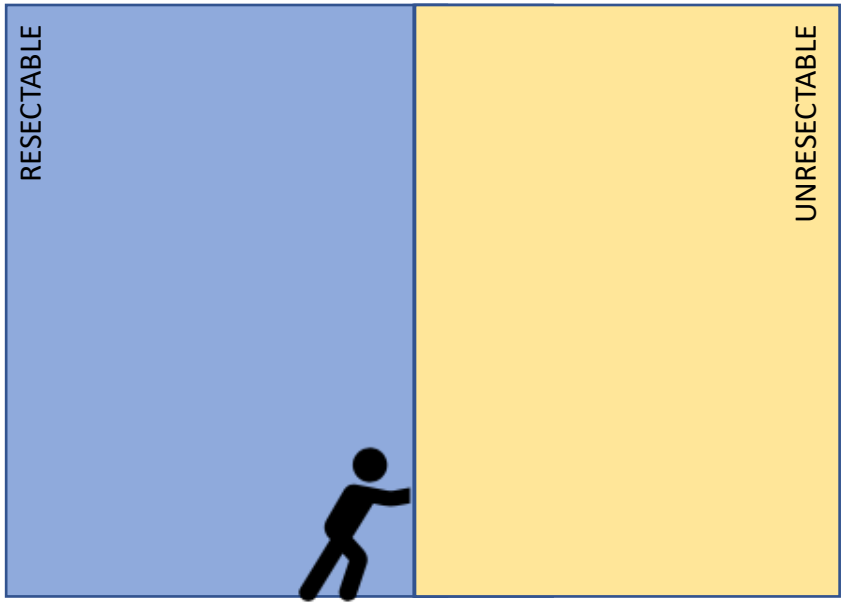
# Increasing resectability vs survivability



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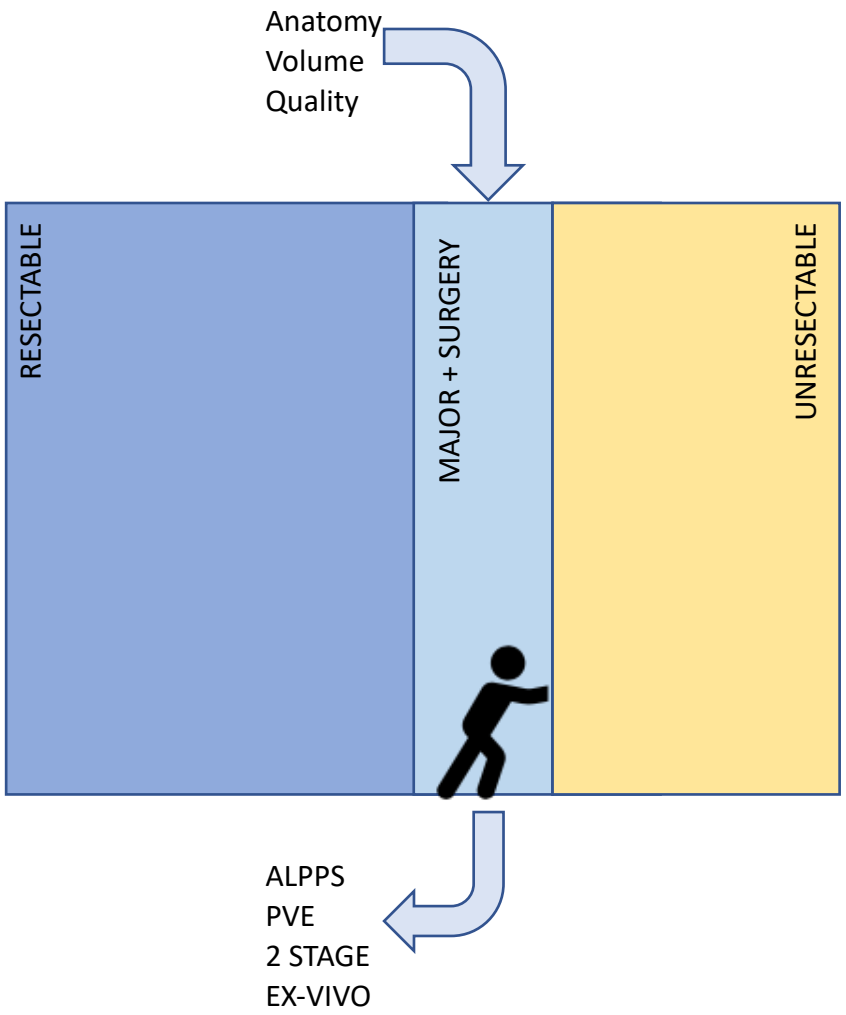

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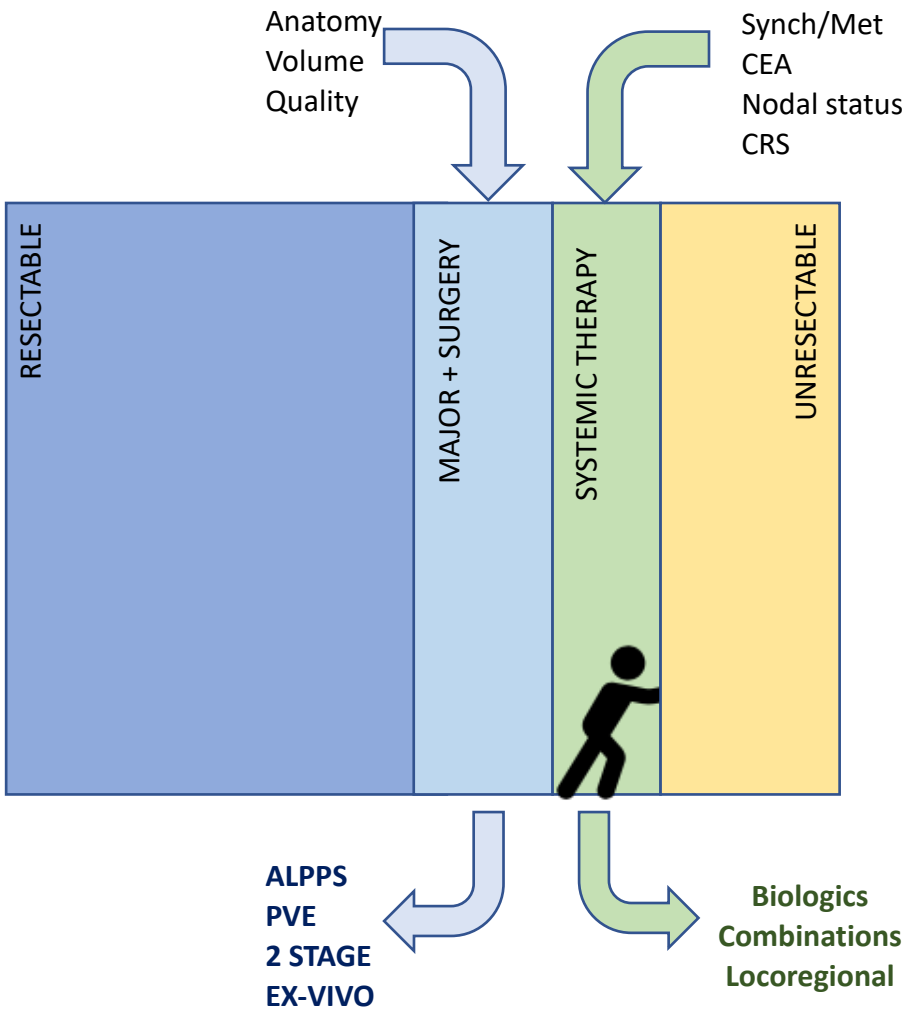

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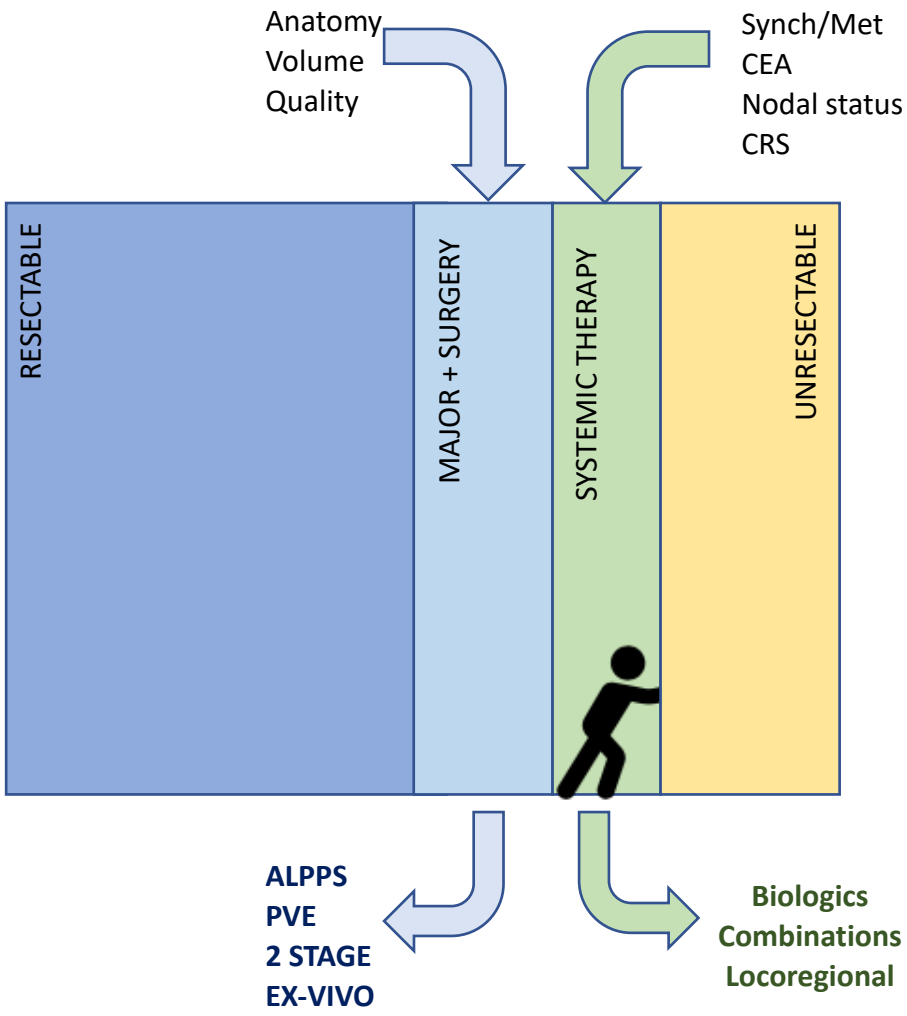
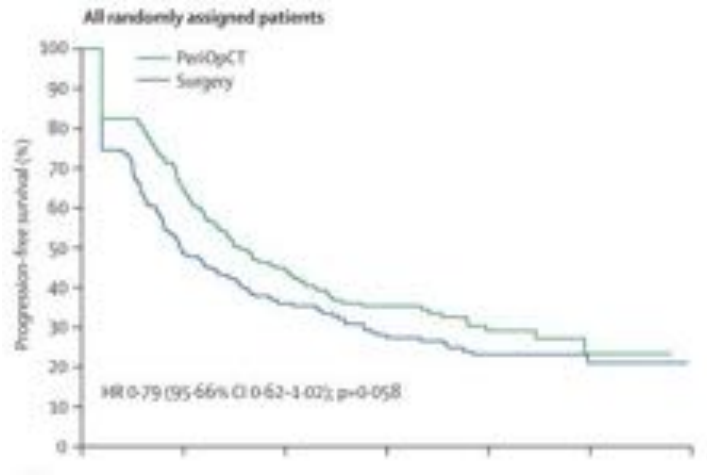
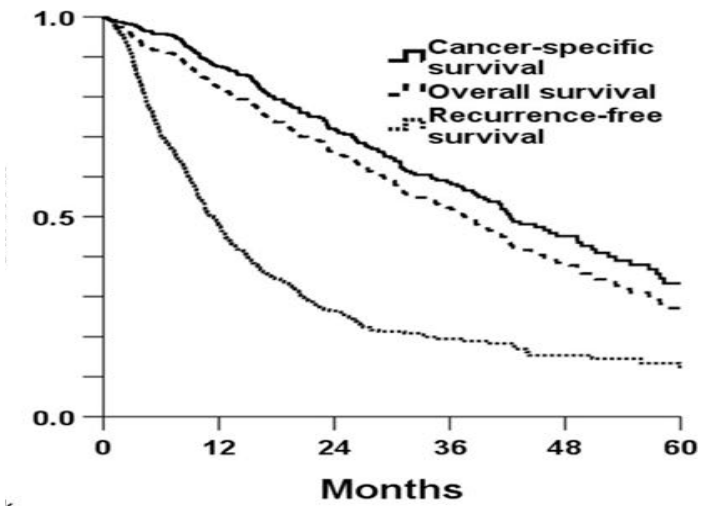



*Improvement in PFS at 3y from 33% to 42%*

Nordlinger et al Lancet 2008




*Median overall survival, CSS, and RFS were 39, 42, and 15 months*

Petrowski et al Ann Surg 2020

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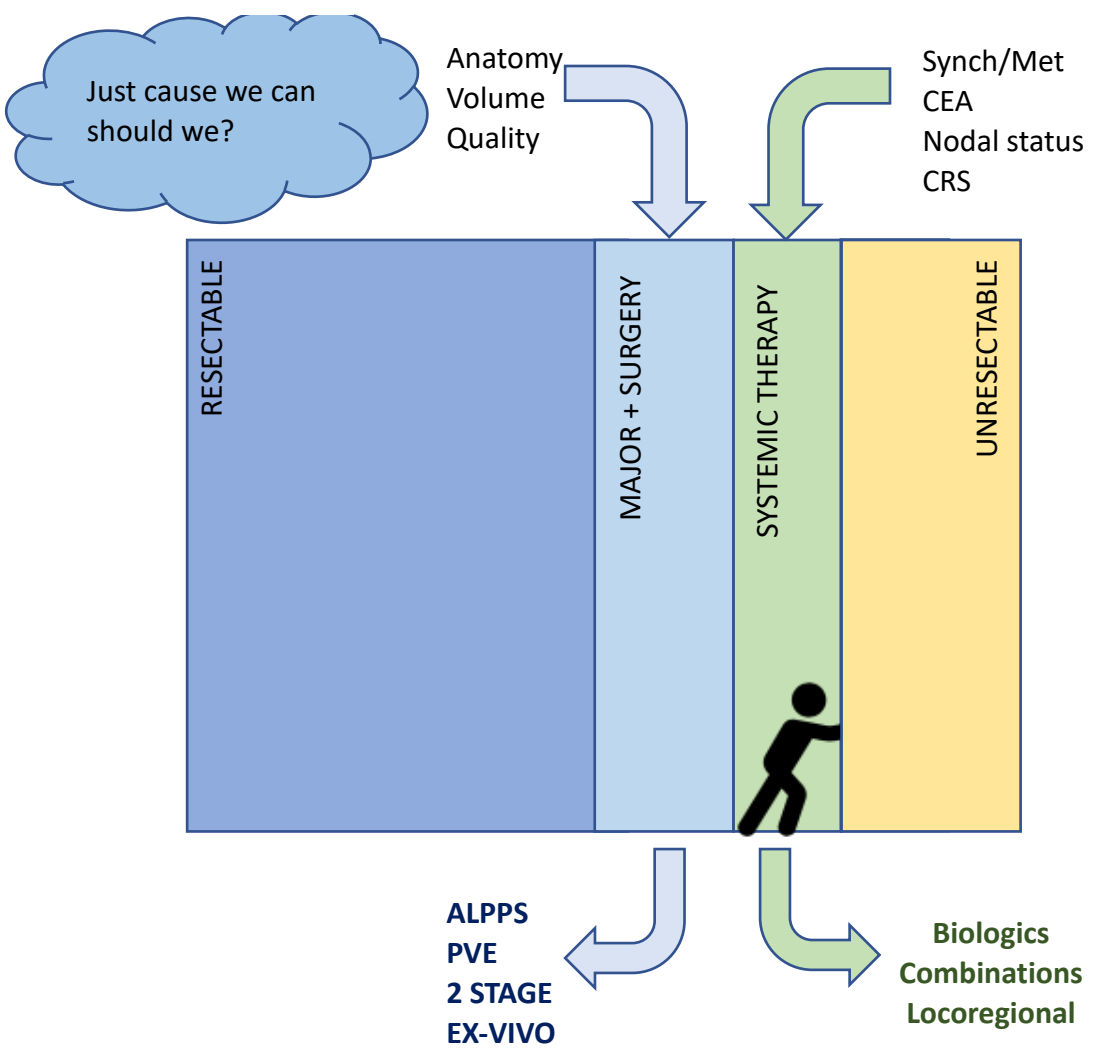
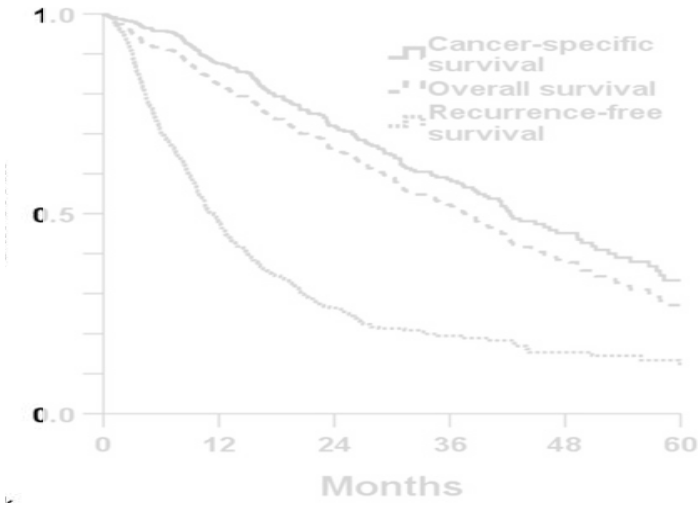
# Increasing resectability vs survivability




*Improvement in PFS at 3y from 33% to 42%*

**Improvement in systemic therapy AND operative strategies have increased RESECTABILITY with a *modest* effect on SURVIVABILITY**

Nordlinger et al Lancet 2008

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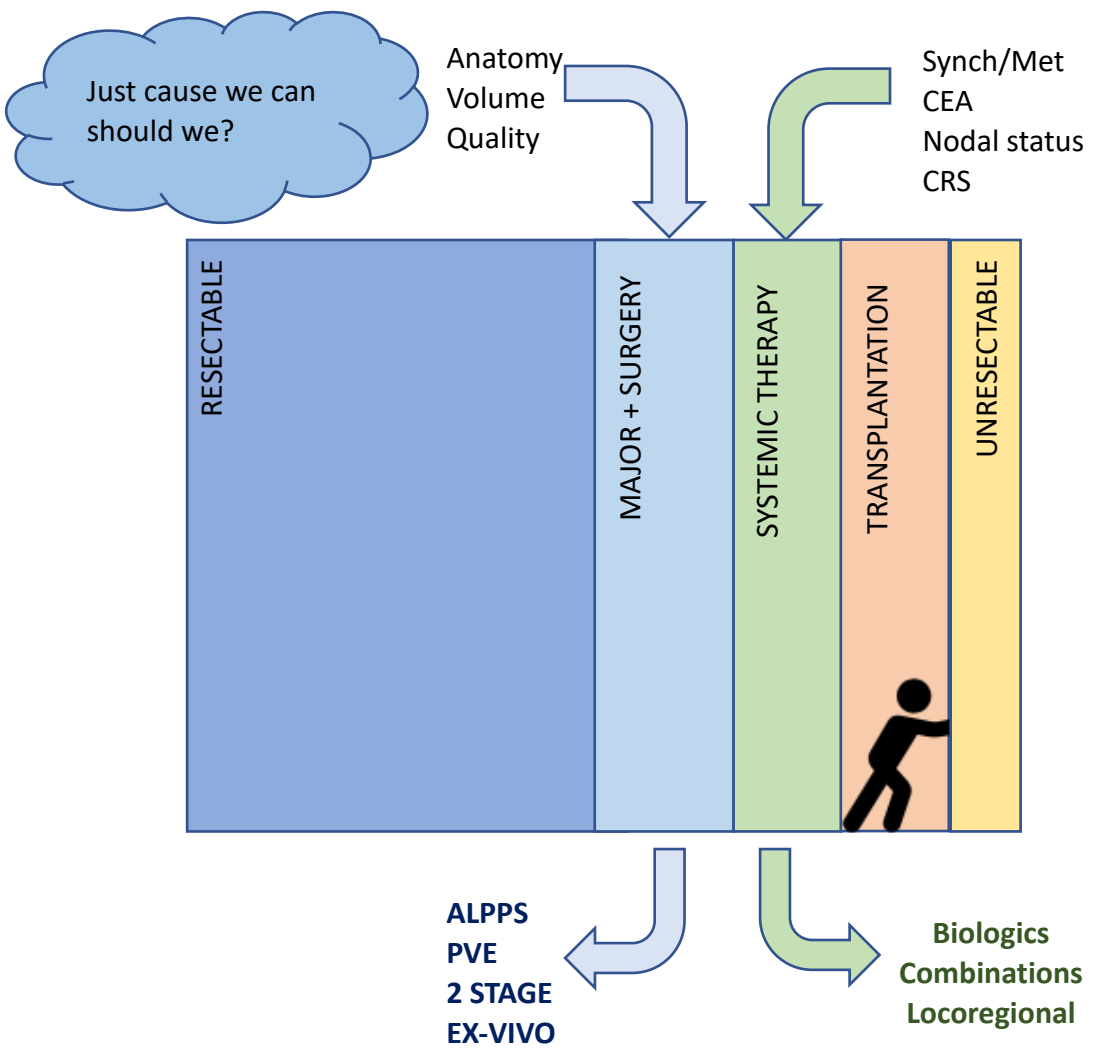


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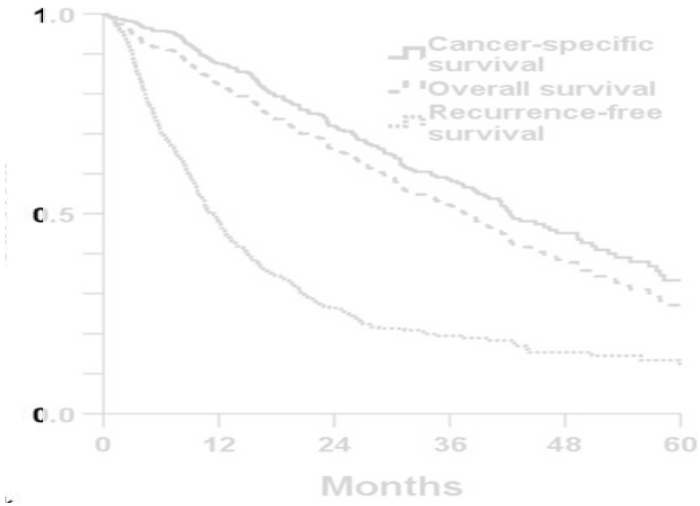


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Petrowski et al Ann Surg 2020

*Biology is King.*

*Selection of cases is Queen.*

*Surgical procedures are princes and princesses of the realm who try to overthrow the King and Queen*

*Blake Cady MD*

*(RIP: 15th July 2023)*

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# Transplantation for CLM

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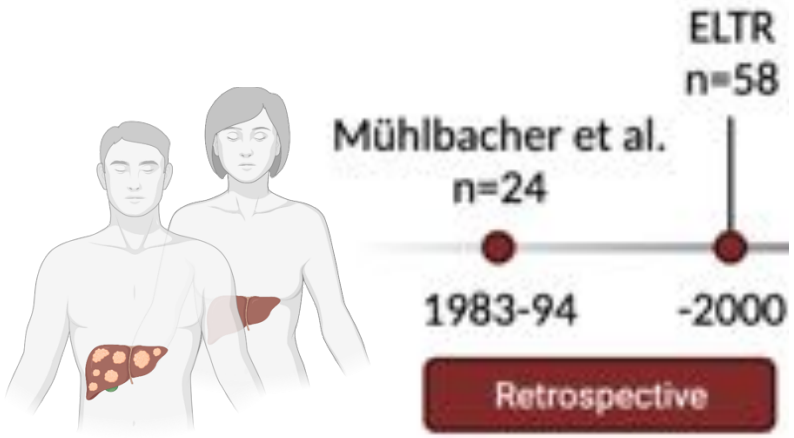


Technically successful

Lack of modern chemotherapy agent and complete understanding of CRC

Failure of adoption

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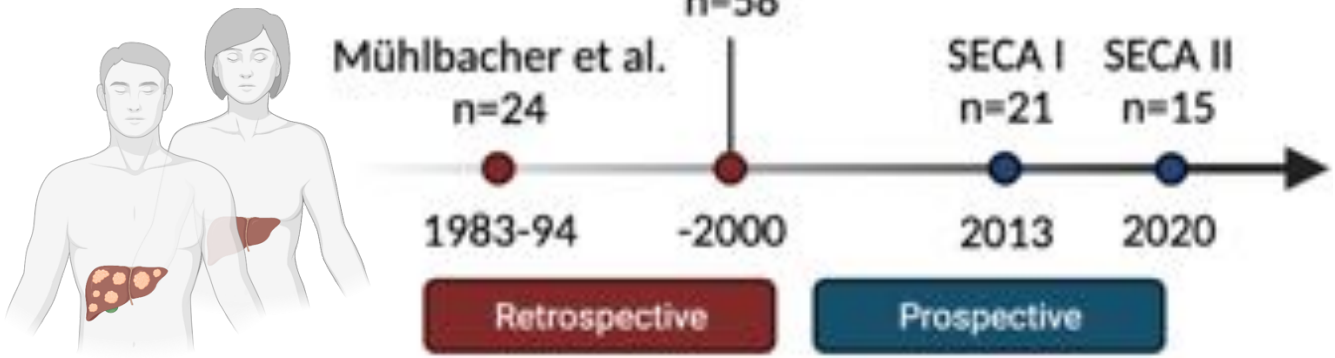
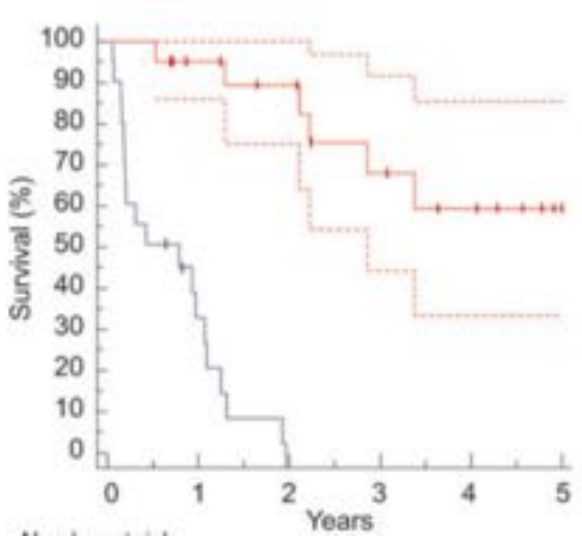
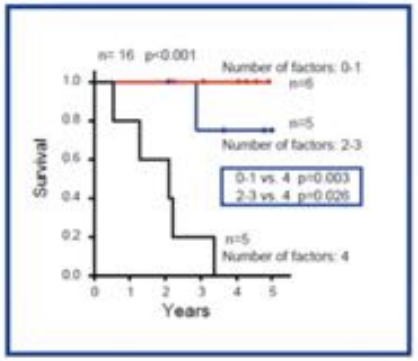
# Transplantation for CLM




| Oslo Score | |
|---|---|
| Maximal Tumor diameter > 5,5 cm | 1 |
| Pre transplant CEA > 80 µg/l | 1 |
| Progression on chemotherapy | 1 |
| Time interval: diagnosis to tx < 2 yrs | 1 |
| Summary score | 0-4 |




SECA 1:
Single Centre (Oslo) n=21
Inclusion: Primary resection, 6 weeks chemo, liver only
1,3,5 y survival of 95,68,60%

Hagness et al Ann Surg 2013

Oslo Score

SECA 2:
Single Centre (Oslo) n=15
1,3,5 year survival of 100, 83, 83%

Dueland et al Ann Surg 2020

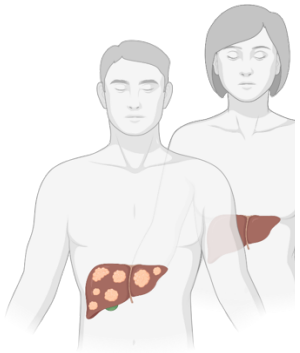
**TABLE 1.** Inclusion-exclusion Criteria SECA-II Study

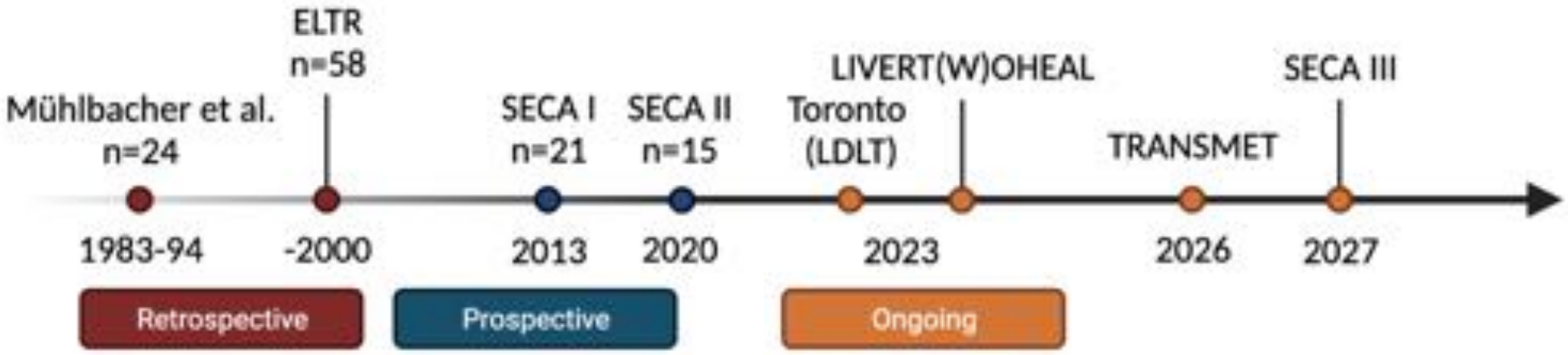
Inclusion Criteria
- Histologically verified adenocarcinoma in colon or rectum
- No signs of extra hepatic metastatic disease or local recurrence according to PET/CT scan
- No signs of extra hepatic metastatic disease or local recurrence according to CT or MR (thorax/abdomen/pelvis) scan within 4 wks before the faculty meeting at the transplant unit
- No signs of local recurrence judged by colonoscopy/CT colography within 12 mo before the faculty meeting at the transplant unit
- Good performance status, ECOG 0 or 1
- Satisfactory blood tests Hb >10 g/dL, neutrophiles >1.0 (after any G-CSF), TRC >75, Bilirubin <2 x upper normal level, ASAT, ALAT <5 x upper normal level, Creatinine <1.25 x upper normal level. Albumin above lower normal level.
- Standard surgical resection procedure of primary tumor with adequate resection margins, including circumferential resection margins (CRM) of at least ≥2 mm for rectal cancer patients
- Signed informed consent and expected cooperation of the patients for the treatment and follow-up must be obtained and documented according to GCP, and national/local regulations.
- Relapse of liver metastases after second liver resection or liver metastases not eligible for curative liver resection
- Received first-line treatment
- Before start of chemotherapy, no lesion should be larger than 10 cm, if more than 30 lesions all should be less than 5 cm and the patients should have at least 30% response by RECIST-criteria.
- At least 10% response (RECIST-criteria) on chemotherapy. Patients must be accepted for transplantation before progressive disease on ongoing chemotherapy.
- Patients with less than 10% response on chemotherapy may be included if they obtain at least 20% response after TACE (DEB-IRI) or by $^{90}$Y-spheres.
- At least 1-year time span from CRC diagnosis and date of being listed on the transplantation list.

Exclusion Criteria

Patients will be excluded from the study if they meet any of the following criteria:
- Weight loss >10% the last 6 mo
- Patient BMI >30
- Other malignancies
- Know hypersensitivity to rapamycin
- Prior extra hepatic metastatic disease or local relapse
- Patients who have not received standard preoperative, per-operative, or postoperative treatment for the primary CRC
- Palliative resection of primary CRC tumor
- Women who are pregnant or breast feeding
- Any reason why, in the opinion of the investigator, the patient should not participate

# Transplantation for CLM






Large number of recruiting trials in CLM Tranpslant

Varied inclusion/exclusion criteria

Varied donor grafts (ECD/ DDLT/ LDLT)

| NCT number | Country | Study name | Patients (*n*) | Completion | Study Design | Phase | Study arms | Primary outcome | Time frame (years) |
|---|---|---|---|---|---|---|---|---|---|
| NCT03494946 | Norway | SECA III [56] | 30 | 2027 | RCCT | III | Chemotherapy* vs. LT | OS | 2 |
| NCT02215889 | Norway | RAPID ^ [60] | 20 | 2028 | CT | I/II | Single Arm^ | OS | 5 |
| NCT03488953 | Germany | LIVERT(W)OHEAL [37] | 40 | 2023 | CT | NA | Single Arm^^ | OS | 3 |
| NCT02597348 | France | TRANSMET [61] | 90 | 2027 | RCCT | III | chemotherapy + LT vs. chemotherapy alone | OS | 5 |
| NCT02864485 | Canada | Toronto^^^ [62] | 20 | 2023 | CT | NA | Single Arm^^^ | OS/DFS | 5 |

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

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

Aim :

1. Standardise nomenclature
2. Principles of selection, investigations, management

Bonney et al. Lancet Gastroenterol Hepatol 2021

# Methods

Modified Delphi Process

- Scientific Committee, Expert Panel, Transplant Centre Representatives
- Scoping Literature review in specific domains
- Nov 2020- Jan 2021
- Final voting with at least 70% for consensus (14th March 2021)

Bonney et al. Lancet Gastroenterol Hepatol 2021

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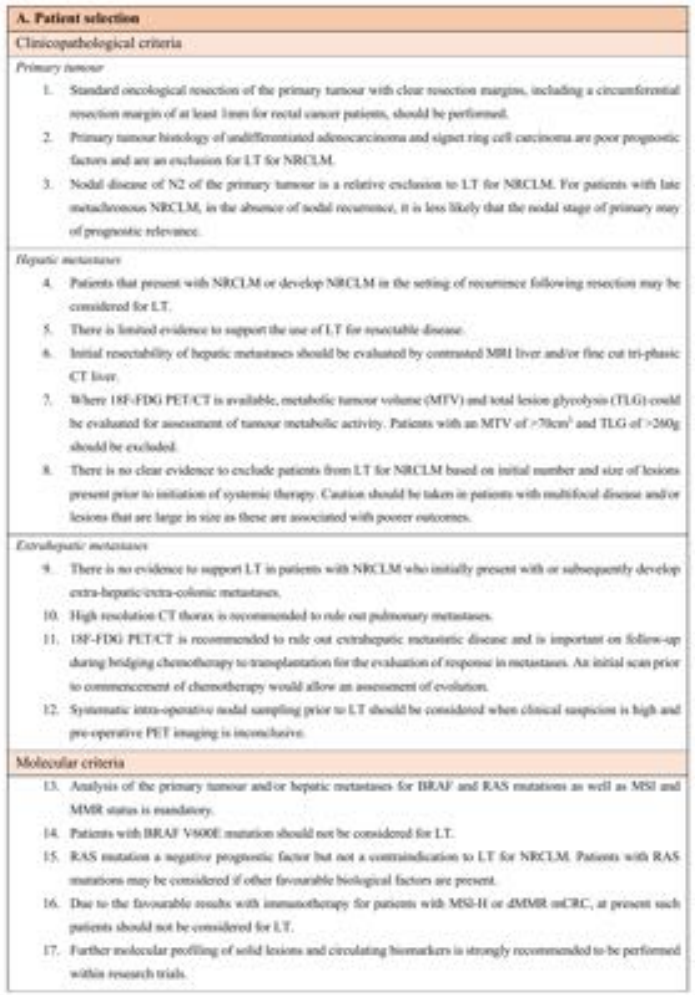
# Results

1. Definitions

2. Treatment algorithm
    - Patient Selection
    - Evaluation of biological behaviour
    - Graft selection and allocation
    - Recipient Considerations
    - Outcome

# Results



**A. Patient selection**

Clinicopathological criteria

*Primary tumour*

1. Standard oncological resection of the primary tumour with clear resection margins, including a circumferential resection margin of at least 1mm for rectal cancer patients, should be performed.
2. Primary tumour histology of undifferentiated adenocarcinoma and signet ring cell carcinoma are poor prognostic factors and are an exclusion for LT for NRCLM.
3. Nodal disease of N2 of the primary tumour is a relative exclusion to LT for NRCLM. For patients with late metachronous NRCLM, in the absence of nodal recurrence, it is less likely that the nodal stage of primary may of prognostic relevance.

*Hepatic metastases*

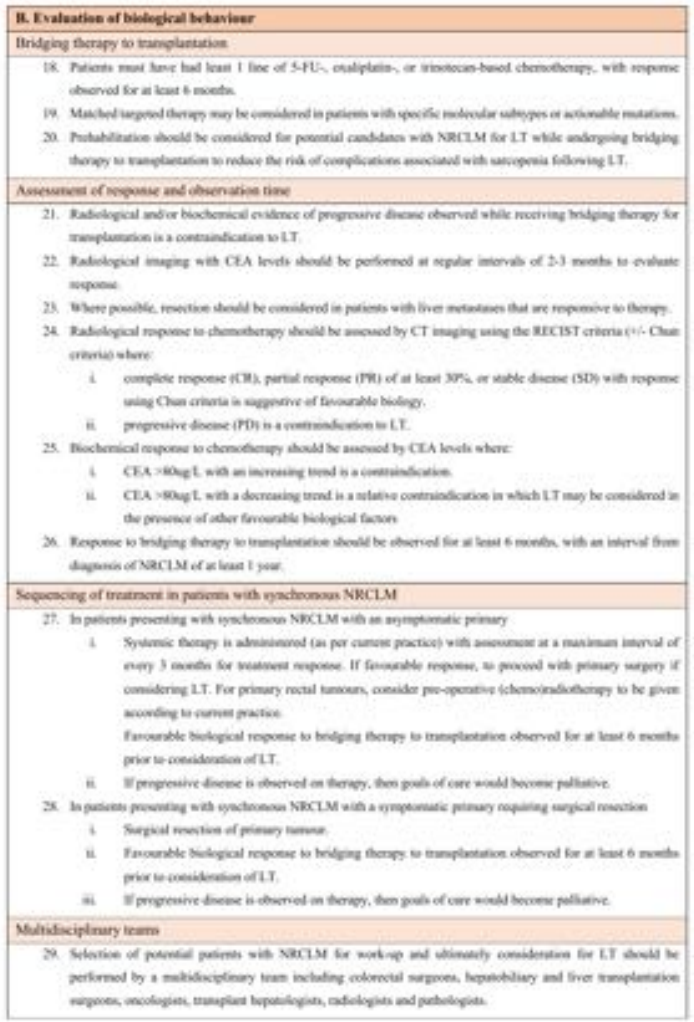
4. Patients that present with NRCLM or develop NRCLM in the setting of recurrence following resection may be considered for LT.
5. There is limited evidence to support the use of LT for resectable disease.
6. Initial resectability of hepatic metastases should be evaluated by contrasted MRI liver and/or fine cut tri-phasic CT liver.
7. Where 18F-FDG PET/CT is available, metabolic tumour volume (MTV) and total lesion glycolysis (TLG) could be evaluated for assessment of tumour metabolic activity. Patients with an MTV of >70cm$^3$ and TLG of >260g should be excluded.
8. There is no clear evidence to exclude patients from LT for NRCLM based on initial number and size of lesions present prior to initiation of systemic therapy. Caution should be taken in patients with multifocal disease and/or lesions that are large in size as these are associated with poorer outcomes.

*Extrahepatic metastases*

9. There is no evidence to support LT in patients with NRCLM who initially present with or subsequently develop extra-hepatic/extra-colonic metastases.
10. High resolution CT thorax is recommended to rule out pulmonary metastases.
11. 18F-FDG PET/CT is recommended to rule out extrahepatic metastatic disease and is important on follow-up during bridging chemotherapy to transplantation for the evaluation of response in metastases. An initial scan prior to commencement of chemotherapy would allow an assessment of evolution.
12. Systematic intra-operative nodal sampling prior to LT should be considered when clinical suspicion is high and pre-operative PET imaging is inconclusive.

Molecular criteria

13. Analysis of the primary tumour and/or hepatic metastases for BRAF and RAS mutations as well as MSI and MMR status is mandatory.
14. Patients with BRAF V600E mutation should not be considered for LT.
15. RAS mutation a negative prognostic factor but not a contraindication to LT for NRCLM. Patients with RAS mutations may be considered if other favourable biological factors are present.
16. Due to the favourable results with immunotherapy for patients with MSI-H or dMMR mCRC, at present such patients should not be considered for LT.
17. Further molecular profiling of solid lesions and circulating biomarkers is strongly recommended to be performed within research trials.



**B. Evaluation of biological behaviour**

Bridging therapy to transplantation

18. Patients must have had least 1 line of 5-FU-, oxaliplatin-, or irinotecan-based chemotherapy, with response observed for at least 6 months.
19. Matched targeted therapy may be considered in patients with specific molecular subtypes or actionable mutations.
20. Prehabilitation should be considered for potential candidates with NRCLM for LT while undergoing bridging therapy to transplantation to reduce the risk of complications associated with sarcopenia following LT.

Assessment of response and observation time

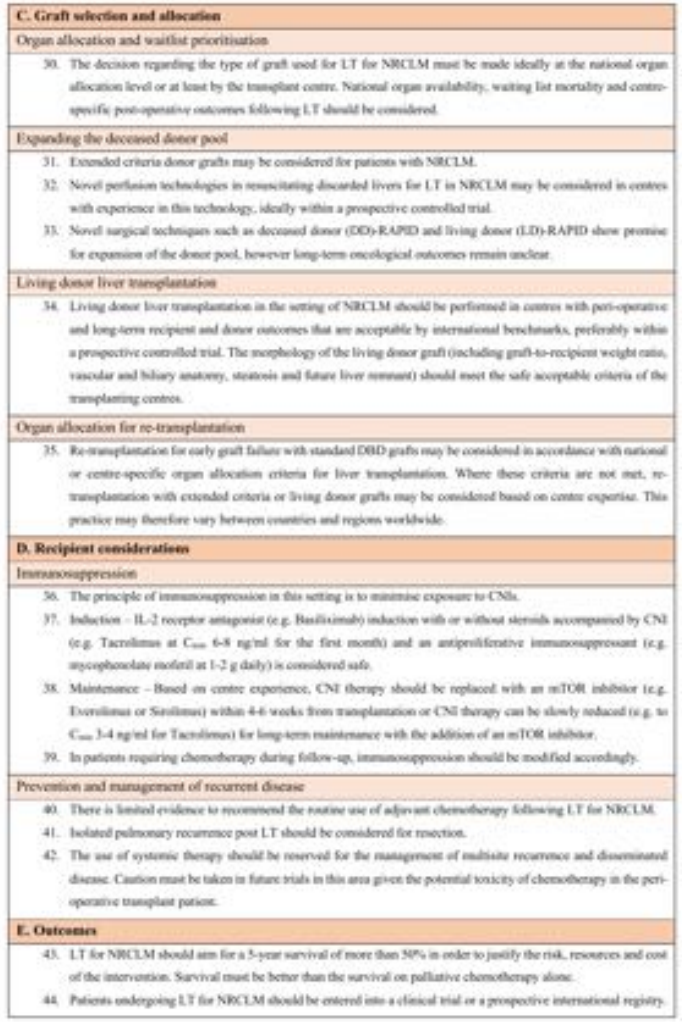
21. Radiological and/or biochemical evidence of progressive disease observed while receiving bridging therapy for transplantation is a contraindication to LT.
22. Radiological imaging with CEA levels should be performed at regular intervals of 2-3 months to evaluate response.
23. Where possible, resection should be considered in patients with liver metastases that are responsive to therapy.
24. Radiological response to chemotherapy should be assessed by CT imaging using the RECIST criteria (+/- Chun criteria) where:
    i. complete response (CR), partial response (PR) of at least 30%, or stable disease (SD) with response using Chun criteria is suggestive of favourable biology.
    ii. progressive disease (PD) is a contraindication to LT.
25. Biochemical response to chemotherapy should be assessed by CEA levels where:
    i. CEA >80ug/L with an increasing trend is a contraindication.
    ii. CEA >80ug/L with a decreasing trend is a relative contraindication in which LT may be considered in the presence of other favourable biological factors
26. Response to bridging therapy to transplantation should be observed for at least 6 months, with an interval from diagnosis of NRCLM of at least 1 year.

Sequencing of treatment in patients with synchronous NRCLM

27. In patients presenting with synchronous NRCLM with an asymptomatic primary
    i. Systemic therapy is administered (as per current practice) with assessment at a maximum interval of every 3 months for treatment response. If favourable response, to proceed with primary surgery if considering LT. For primary rectal tumours, consider pre-operative (chemo)radiotherapy to be given according to current practice.
    Favourable biological response to bridging therapy to transplantation observed for at least 6 months prior to consideration of LT.
    ii. If progressive disease is observed on therapy, then goals of care would become palliative.
28. In patients presenting with synchronous NRCLM with a symptomatic primary requiring surgical resection
    i. Surgical resection of primary tumour.
    ii. Favourable biological response to bridging therapy to transplantation observed for at least 6 months prior to consideration of LT.
    iii. If progressive disease is observed on therapy, then goals of care would become palliative.

Multidisciplinary teams

29. Selection of potential patients with NRCLM for work-up and ultimately consideration for LT should be performed by a multidisciplinary team including colorectal surgeons, hepatobiliary and liver transplantation surgeons, oncologists, transplant hepatologists, radiologists and pathologists.



**C. Graft selection and allocation**

Organ allocation and waitlist prioritisation

30. The decision regarding the type of graft used for LT for NRCLM must be made ideally at the national organ allocation level or at least by the transplant centre. National organ availability, waiting list mortality and centre-specific post-operative outcomes following LT should be considered.

Expanding the deceased donor pool

31. Extended criteria donor grafts may be considered for patients with NRCLM.
32. Novel perfusion technologies in resuscitating discarded livers for LT in NRCLM may be considered in centres with experience in this technology, ideally within a prospective controlled trial.
33. Novel surgical techniques such as deceased donor (DD)-RAPID and living donor (LD)-RAPID show promise for expansion of the donor pool, however long-term oncological outcomes remain unclear.

Living donor liver transplantation

34. Living donor liver transplantation in the setting of NRCLM should be performed in centres with peri-operative and long-term recipient and donor outcomes that are acceptable by international benchmarks, preferably within a prospective controlled trial. The morphology of the living donor graft (including graft-to-recipient weight ratio, vascular and biliary anatomy, steatosis and future liver remnant) should meet the safe acceptable criteria of the transplanting centres.

Organ allocation for re-transplantation

35. Re-transplantation for early graft failure with standard DBD grafts may be considered in accordance with national or centre-specific organ allocation criteria for liver transplantation. Where these criteria are not met, re-transplantation with extended criteria or living donor grafts may be considered based on centre expertise. This practice may therefore vary between countries and regions worldwide.

**D. Recipient considerations**

Immunosuppression

36. The principle of immunosuppression in this setting is to minimise exposure to CNIs.
37. Induction – IL-2 receptor antagonist (e.g. Basiliximab) induction with or without steroids accompanied by CNI (e.g. Tacrolimus at $C_{min}$ 6-8 ng/ml for the first month) and an antiproliferative immunosuppressant (e.g. mycophenolate mofetil at 1-2 g daily) is considered safe.
38. Maintenance – Based on centre experience, CNI therapy should be replaced with an mTOR inhibitor (e.g. Everolimus or Sirolimus) within 4-6 weeks from transplantation or CNI therapy can be slowly reduced (e.g. to $C_{min}$ 3-4 ng/ml for Tacrolimus) for long-term maintenance with the addition of an mTOR inhibitor.
39. In patients requiring chemotherapy during follow-up, immunosuppression should be modified accordingly.

Prevention and management of recurrent disease

40. There is limited evidence to recommend the routine use of adjuvant chemotherapy following LT for NRCLM.
41. Isolated pulmonary recurrence post LT should be considered for resection.
42. The use of systemic therapy should be reserved for the management of multisite recurrence and disseminated disease. Caution must be taken in future trials in this area given the potential toxicity of chemotherapy in the peri-operative transplant patient.

**E. Outcomes**

43. LT for NRCLM should aim for a 5-year survival of more than 50% in order to justify the risk, resources and cost of the intervention. Survival must be better than the survival on palliative chemotherapy alone.
44. Patients undergoing LT for NRCLM should be entered into a clinical trial or a prospective international registry.

44 recommendations withing 4 domains in 12 sub-domains

Bonney et al. Lancet Gastroenterol Hepatol 2021

# Patient Selection (Highlights)

## Clinico-pathological criteria

N2 primary; a relative contra indication. Less in late metachronous

Primary Patho: Signet / Undifferentiated excluded

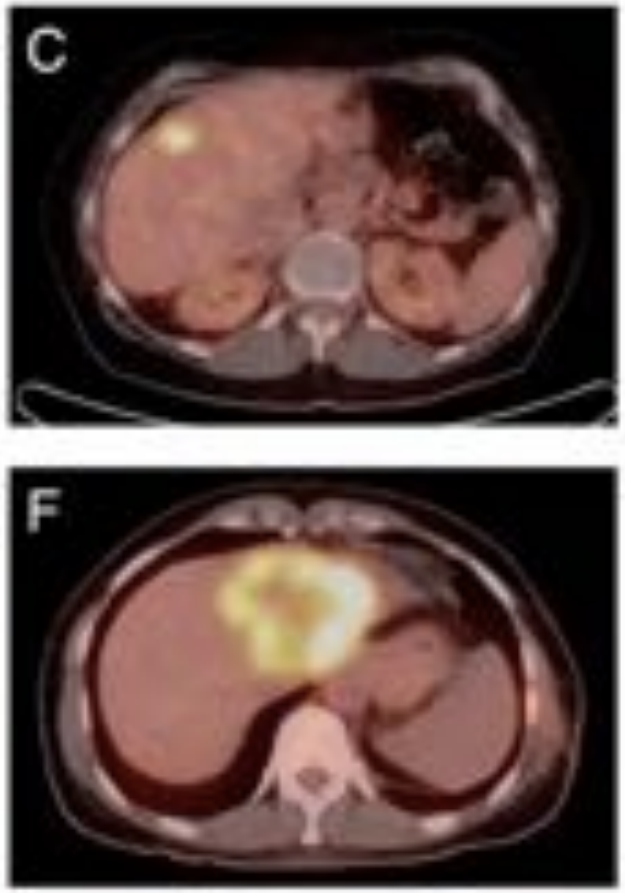
Secondary: May include recurrence post resection

MRI liver and PET

18F-FDG PET: MTV >70cm$^3$ or TLG >260 g *

Intraoperative nodal sampling

# The Prognostic Value of pre-Tx 18F-FDG -PET




- Metabolic tumor volume (MTV):
  - The lesion volume with uptake > 40% of maximal standardized uptake volume ($SUV_{max}$)
  - Calculated for all lesions and summarized
  - MTV > 70cc predicts worse outcome

1. Grut H, Dueland S, Line P-D, Revhaim ME. The prognostic value of (18)F-FDG PET/CT prior to liver transplantation for nonresectable colorectal liver metastases. Eur J Nucl Med Mol Imaging. 2017 Oct 12;4(Suppl 1):283.

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Intraoperative nodal sampling

## Molecular studies

BRAF/ RAS/ MSI/ MMR: BRAF V600E exclusion, RAS (relative), MMR/ MSI (immuno)

Importants of research samples in prospective studies

# *BRAF* V600E potentially determines "Oncological Resectability" for "Technically Resectable" colorectal liver metastases

Shin Kobayashi[1] | Shinichiro Takahashi[1] | Shogo Nomura[3] | Motohiro Kojima[4] | Masashi Kudo[1] | Motokazu Sugimoto[1] | Masaru Konishi[1] | Naoto Gotohda[1] | Hiroya Taniguchi[2] | Takayuki Yoshino[2]

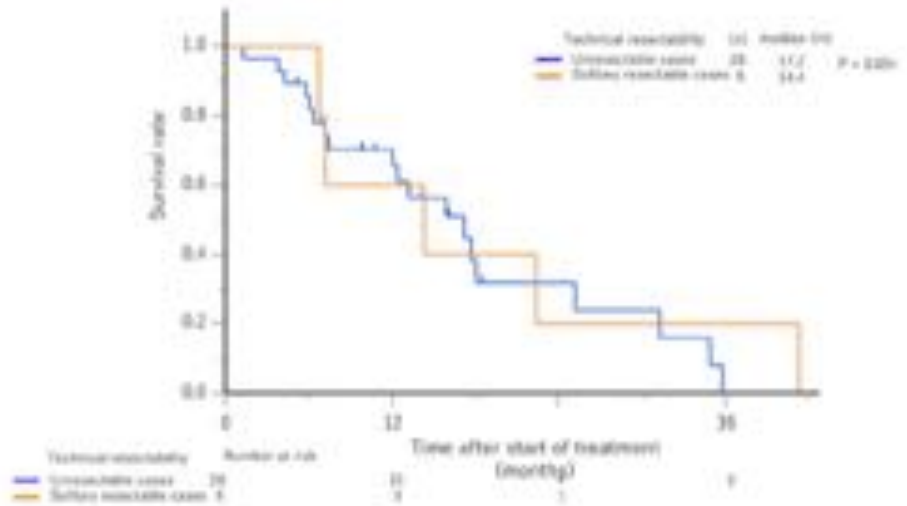
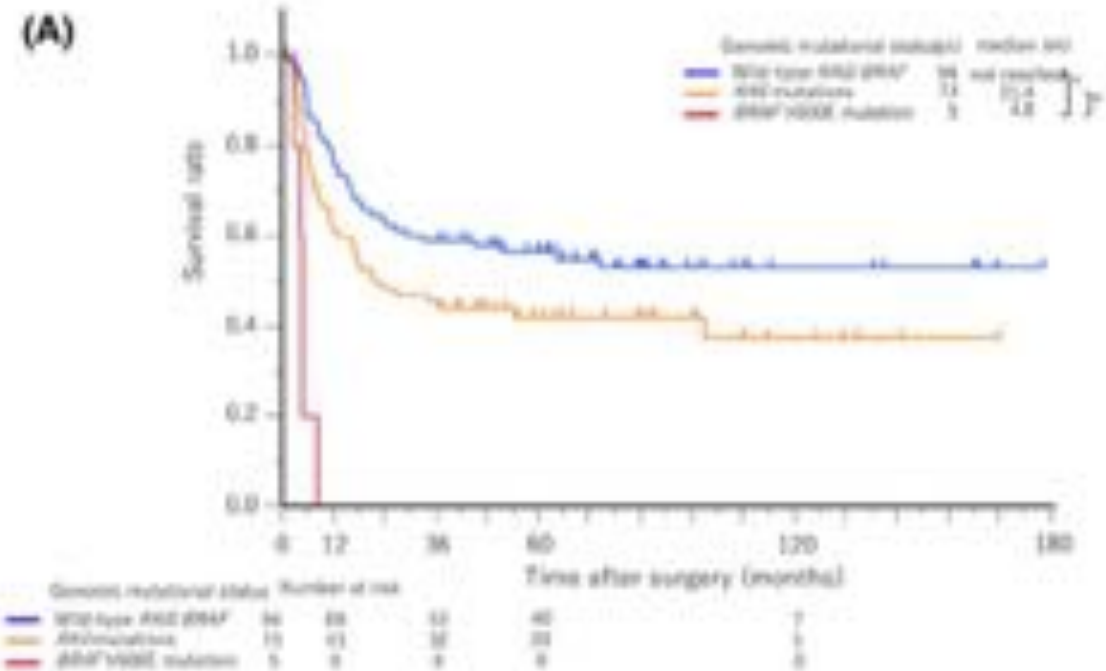
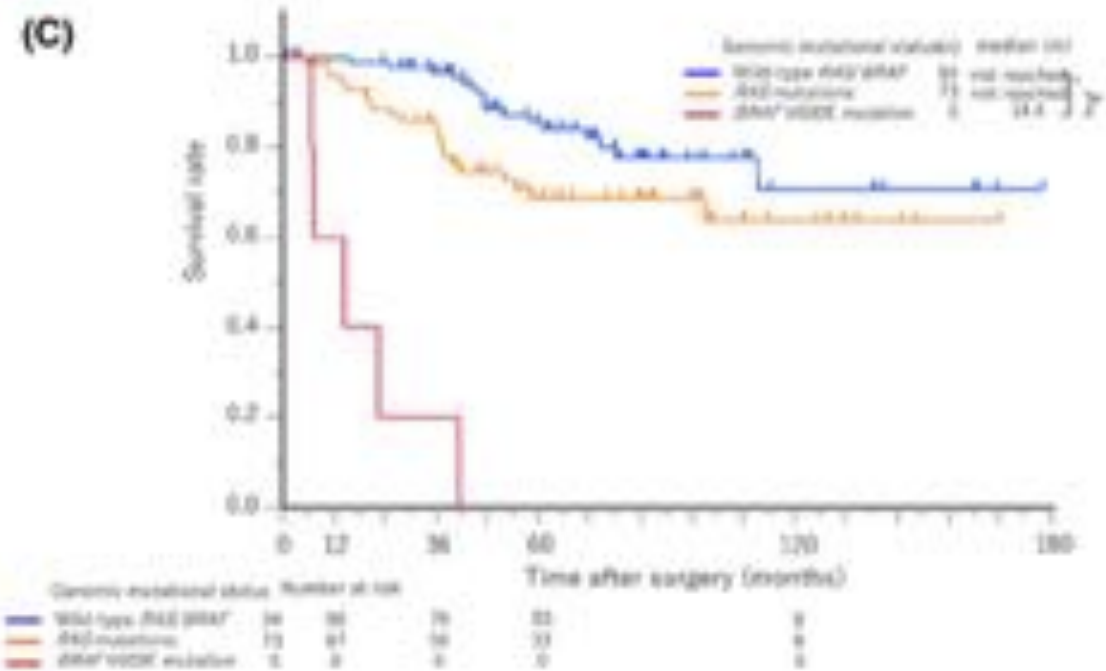



FIGURE 4 Overall survival of patients with *BRAF* V600E-mutant colorectal liver metastases depending on the technical resectability



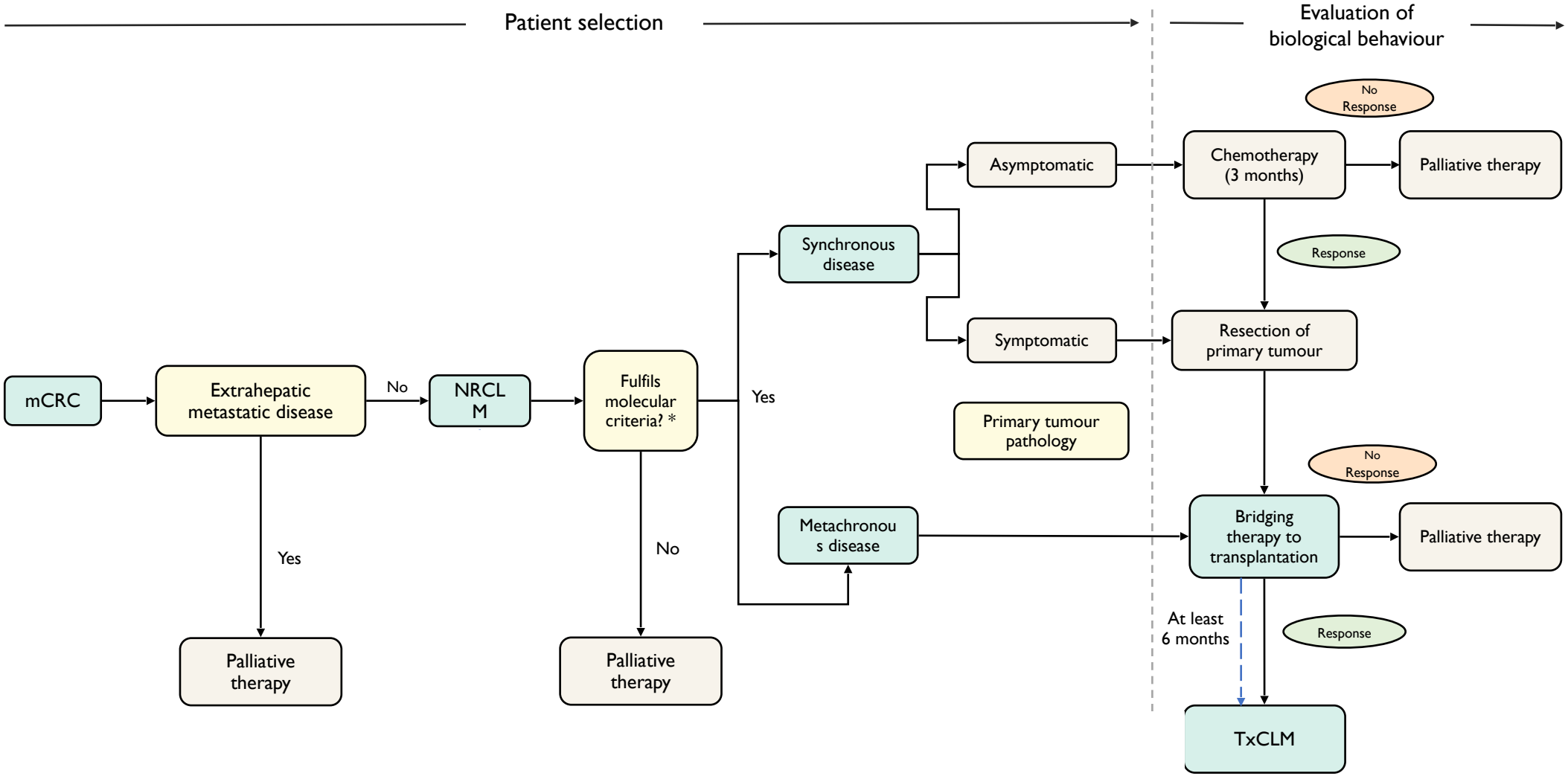

Kobayashi et al Cancer Medicine 2021.

# Evaluation of biological behaviour (Highlights)

- Bridging Chemotherapy to Transplant
  - Must have at least 6 months of standard systemic treatment
  - Observed for 1 year from initial diagnosis of NRCLM
- CEA levels 2-3 months
  - >80 and uptrending contraindicated #
- Radiological evaluation by RECIST and Chun criteria
  - PD excluded. SD reassess with Chun criteria
- Importance of sequencing primary/ chemo and transplant
- Importance and constituents of MDT

#- Hagness M et al Ann Surg 2013

# Evaluation of biological behaviour (Highlights)




Bonney et al. Lancet Gastroenterol Hepatol 2021

# Graft selection and allocation (Highlights)

- Types of graft
  - National agreement. Dependent on waitlist, centre outcomes, organ availability
  - ECD/ NMP / NRP may be considered in centres with experience
- LDLT in centres that achieve international benchmark in donor/ recipient outcome
  - Preferably within prospective trial at least a registry
  - Donor morphology within standard criteria for centre

# Living donor hepatectomy in medium volume liver transplant centre has comparable outcomes to high volume centres: validation of donabedian quality assurance framework

Marcus Wei Xuan Yeow[1], Ning Q. Pang[2,3], Glenn K. Bonney[2,3], Krishnakumar Madhavan[2,3], Wei Chieh Alfred Kow[2,3] & Shridhar Ganpathi Iyer[2,3]

Table 2 Comparing our centre's outcomes with benchmark study and other donor reports

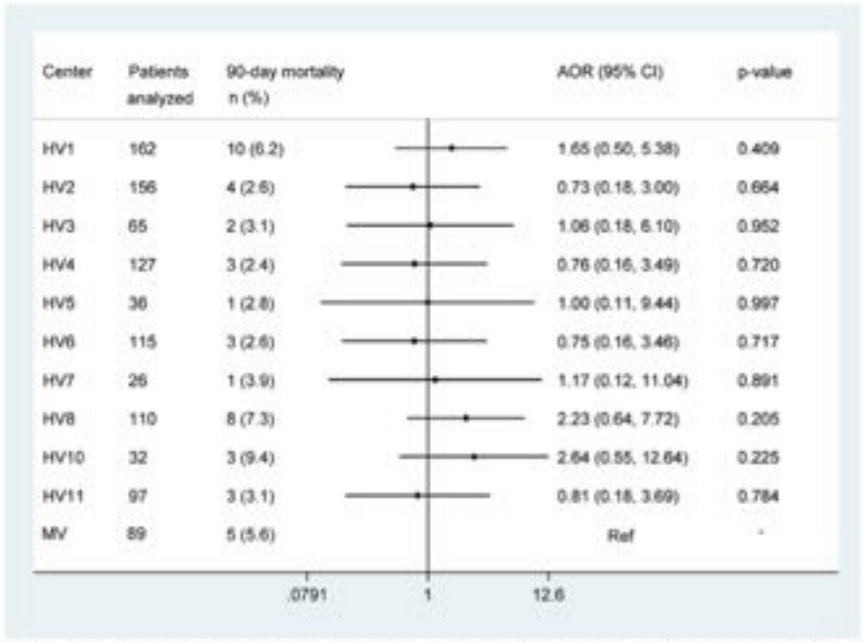
| Parameters | Our Centre | Benchmark study | University of Toronto, Canada[26] | Ege University, Turkey[25] | Medanta, India[24] | First Affiliated Hospital, China[23] |
|---|---|---|---|---|---|---|
| | Outcomes | Benchmark Outcomes determined at 75th percentile of study outcomes[27] | | | | |
| Follow up period | Within hospital stay/ After 3 months/After 6 months | Within hospital stay/After 3 months/After 6 months | Median 39 months (IQR, 12–72) | NA | NA | NA |
| Length of hospital stay (days) | Mean 5.9 ± S.D. 2.1 | Mean 11.7 ± S.D. 5.3 | Median 6 (IQR, 6–7) | Mean 9.4 | Median 6 (range 5–22) | NA |
| Overall Complication Rate (%) | 3.9/9.3/9.8 | 26.9/31.2/31.2 | 23.1 | 41.1 | 29.3 | 40.1 |
| Major Complication Rate (%) | 0.5/1.5/1.5 | 6.0/8.1/9.2 | 9.9 | 3.3 | 3.3 | 7.9 |
| Minor Complication Rate (%) | 3.4/7.8/8.3 | 18.9/22.6/22.6 | 13.2 | 38.6 | 26.0 | 32.2 |
| Median Comprehensive Complication Index | 20.9/20.9/20.9 | 27.9/32.6/32.7 | NA | NA | NA | NA |

NA: Not Available.

Yeow et al HPB 2021.

# Evaluation of Adult Living Donor Liver Transplantation in Largest Southeast Asian Transplantation Center: Benchmarking With Adult-to-Adult Living Donor Liver Transplantation (A2ALL) Experience

Marcus Yeow[a], Ning-Qi Pang[b,c], Zhaojin Chen[d], Priscilla Wee[c], Glenn Kunnath Bonney[b,c], Krishnakumar Madhavan[b,c], Wei Chieh Alfred Kow[b,c], and Shridhar Ganpathi Iyer[b,c*]

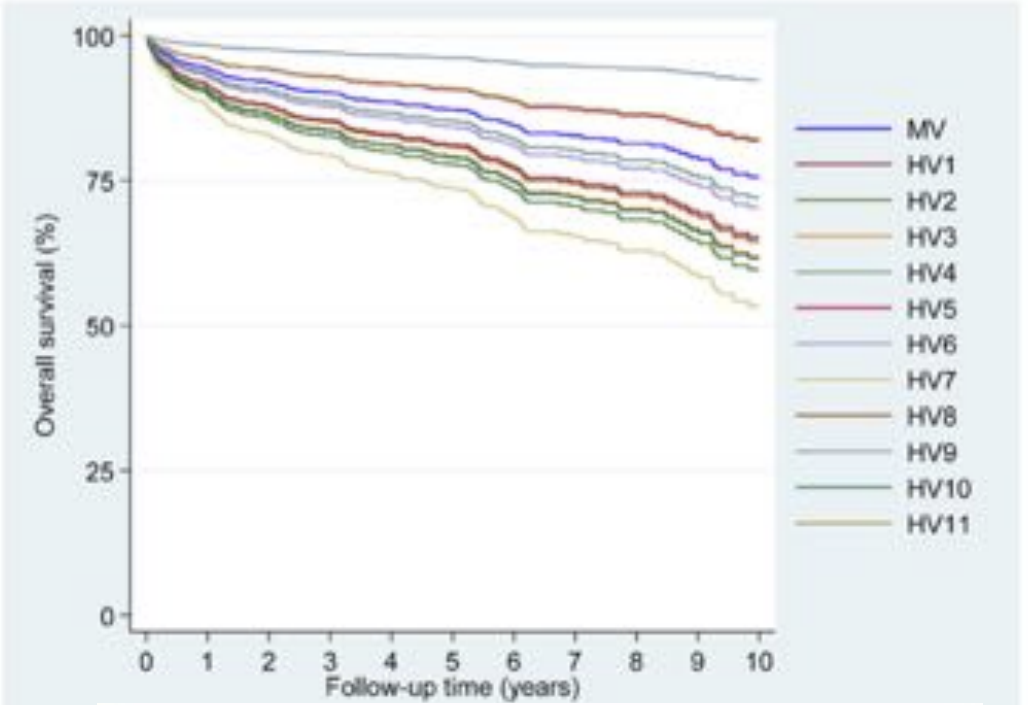


| Center | Patients analyzed | 90-day mortality n (%) | AOR (95% CI) | p-value |
|---|---|---|---|---|
| HV1 | 162 | 10 (6.2) | 1.65 (0.50, 5.38) | 0.409 |
| HV2 | 156 | 4 (2.6) | 0.73 (0.18, 3.00) | 0.664 |
| HV3 | 65 | 2 (3.1) | 1.06 (0.18, 6.10) | 0.952 |
| HV4 | 127 | 3 (2.4) | 0.76 (0.16, 3.49) | 0.720 |
| HV5 | 36 | 1 (2.8) | 1.00 (0.11, 9.44) | 0.997 |
| HV6 | 115 | 3 (2.6) | 0.75 (0.16, 3.46) | 0.717 |
| HV7 | 26 | 1 (3.9) | 1.17 (0.12, 11.04) | 0.891 |
| HV8 | 110 | 8 (7.3) | 2.23 (0.64, 7.72) | 0.205 |
| HV10 | 32 | 3 (9.4) | 2.64 (0.55, 12.64) | 0.225 |
| HV11 | 97 | 3 (3.1) | 0.81 (0.18, 3.69) | 0.784 |
| MV | 89 | 5 (5.6) | Ref | - |



MV – medium volume, HV – high volume, MELD – model for end-stage liver disease, AOR – adjusted odds ratio, CI – confidence interval.

**Fig 4.** Association between liver transplant center and 90-day mortality adjusted for donor age ≥50 years, recipient age ≥55 years and Model for End-stage Liver Disease score ≥30 by multivariable logistic regression (n = 1015).





| Center | Patients analyzed | Survival time mean (SE) | AHR (95% CI) | p-value |
|---|---|---|---|---|
| HV1 | 162 | 9.86 (0.98) | 1.53 (0.80, 2.94) | 0.203 |
| HV2 | 156 | 11.25 (1.50) | 1.85 (0.95, 3.59) | 0.070 |
| HV3 | 63 | 10.60 (1.70) | 1.72 (0.77, 3.81) | 0.184 |
| HV4 | 127 | 12.65 (1.33) | 1.17 (0.58, 2.36) | 0.662 |
| HV5 | 36 | 8.11 (1.53) | 0.71 (0.23, 2.25) | 0.563 |
| HV6 | 115 | 11.16 (1.50) | 1.26 (0.61, 2.57) | 0.531 |
| HV7 | 26 | 6.07 (1.73) | 2.24 (0.94, 5.36) | 0.069 |
| HV8 | 110 | 12.12 (1.39) | 1.57 (0.78, 3.16) | 0.211 |
| HV9 | 36 | 3.11 (0.58) | 0.28 (0.04, 2.20) | 0.227 |
| HV10 | 32 | 4.00 (0.79) | 1.73 (0.55, 5.46) | 0.347 |
| HV11 | 97 | 4.35 (0.83) | 0.70 (0.26, 1.88) | 0.478 |
| MV | 89 | 13.59 (4.39) | Ref | - |



MV – medium volume, HV – high volume, MELD – model for end-stage liver disease, HCC – hepatocellular carcinoma, HCV – hepatitis C virus, SE – standard error, AHR – adjusted hazard ratio, CI – confidence interval.

Yeow et al Transplantation Proceedings 2021.

# Recipient Considerations (Highlights)

Minimise CNI exposure

Induction- IL-2 antagonist + CNI + Antiproliferative

Maintenance- MTOR inhibitor replaces CNI

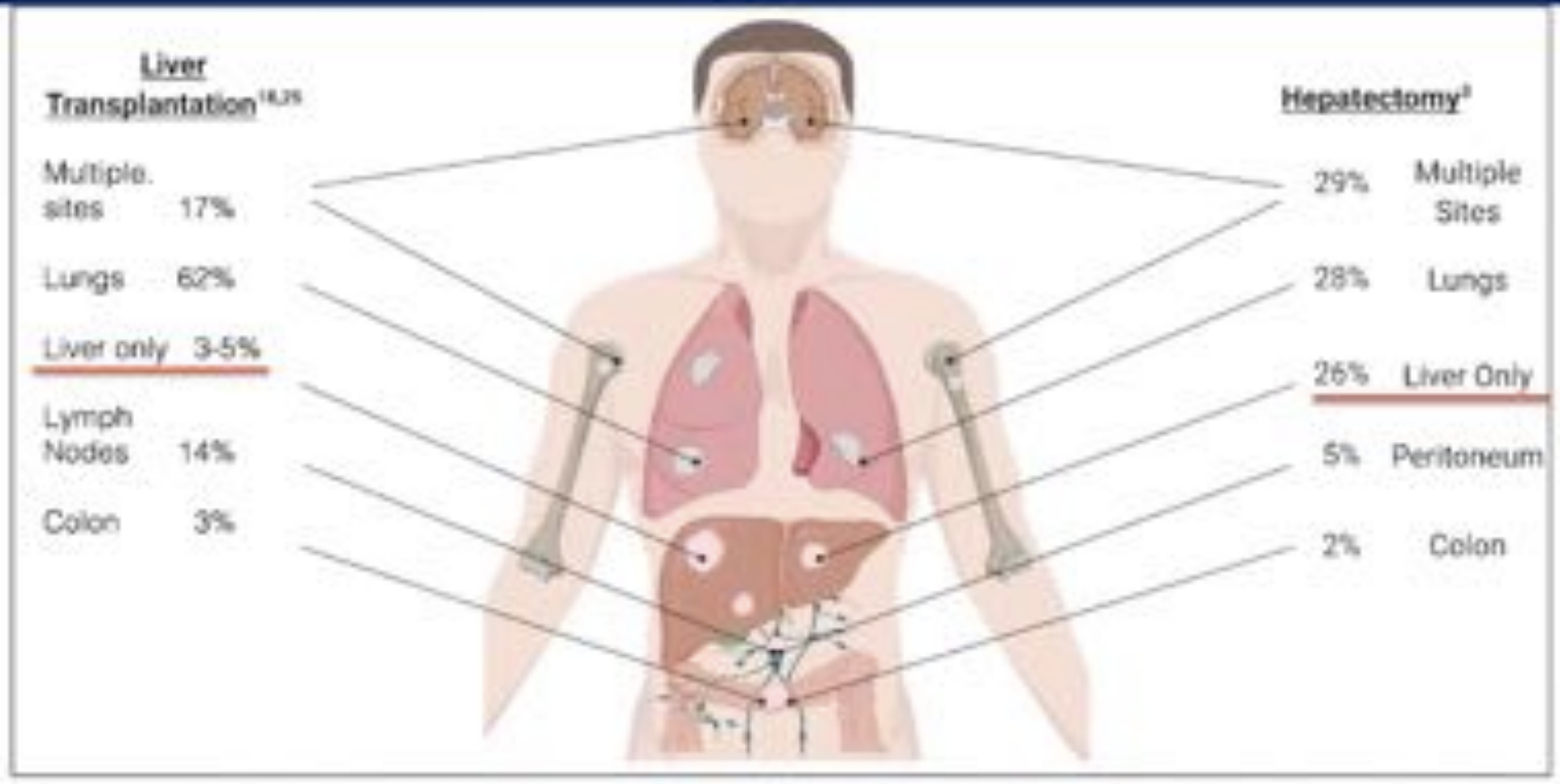
Chemotherapy for recurrence . Immunosuppression must be modified

# Outcome (Highlights)

Transplantation in NRCLM should aim for 5- year survival of more then 50% . Survival must be better then palliative chemotherapy

All patients undergoing transplantation for NRCLM should be entered into a clinical trial or prospective international registry

# First site of recurrence; transplant versus resection





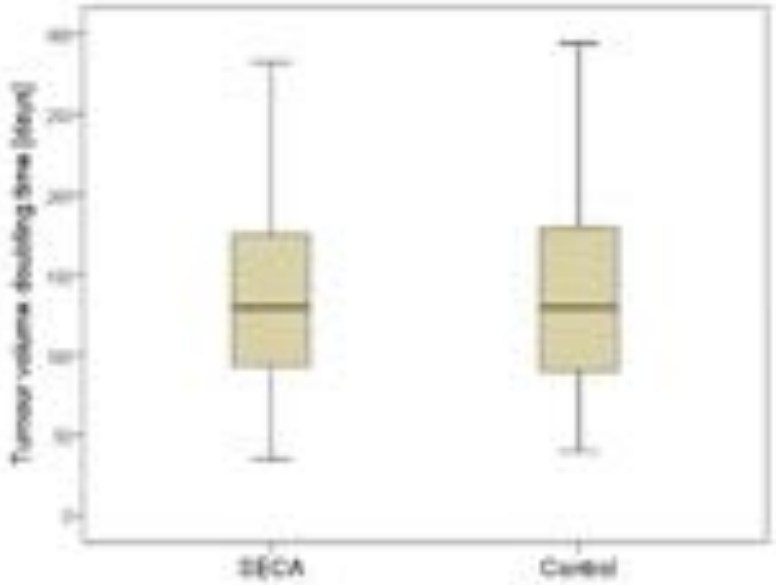
- Butte, J. M. et al. Recurrence After Partial Hepatectomy for Metastatic Colorectal Cancer: Potentially Curative Role of Salvage Repeat Resection. Annals of Surgical Oncology 22, 2761–2771 (2015).
- Hagness, M. *et al.* Liver transplantation for nonresectable liver metastases from colorectal cancer. *Ann. Surg.* **257**, 800–806 (2013).
- Hagness, M., Foss, A., Egge, T. S. & Dueland, S. Patterns of recurrence after liver transplantation for nonresectable liver metastases from colorectal cancer. Ann. Surg. Oncol. 21, 1323–1329 (2014).
- Dueland, S. et al. Survival Following Liver Transplantation for Patients With Nonresectable Liver-only Colorectal Metastases. Ann. Surg. (2019). doi:10.1097/SLA.0000000000003404

**Growth rates of pulmonary metastases after liver transplantation for unresectable colorectal liver metastases**

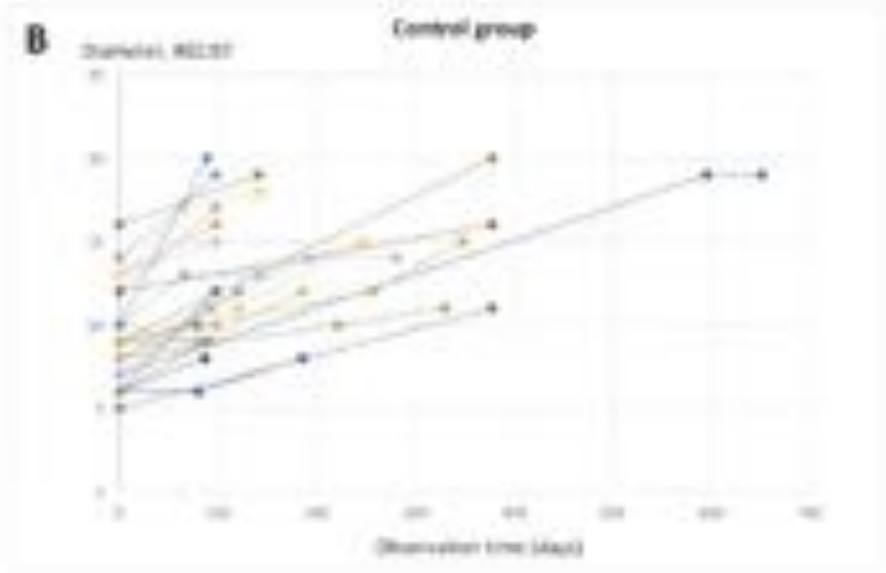
H. Grut[1,4], S. Solberg[2,4], T. Seierstad[3], M. E. Revheim[1,4], T. S. Egge[3], S. G. Larsen[2], P. D. Line[4,5] and S. Dueland[6]

Br J Surg 2017

Lung metastasis growth rate in SECA group compared with patients with rectal cancer and lung metastases only








- Multi-site recurrence is associate with inferior survival
- About 60-70 % of the relapses are pulmonary metastases
- The majority of the pulmonary metastases are resectable
- 40-50% of lung metastases might be staging failures

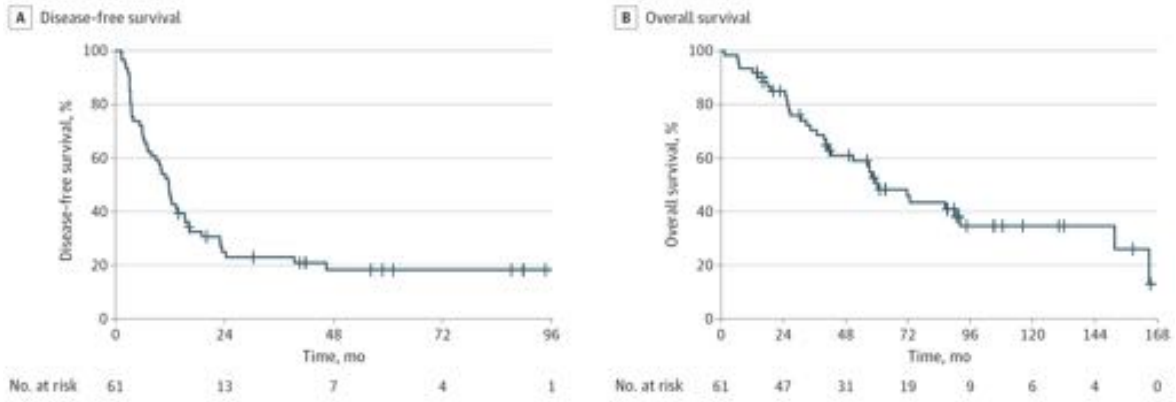
# Outcome

JAMA Surgery | Original Investigation

## Long-Term Survival, Prognostic Factors, and Selection of Patients With Colorectal Cancer for Liver Transplant
### A Nonrandomized Controlled Trial

Svein Dueland, MD, PhD; Tor Magnus Smedman, MD, PhD; Trygve Syversveen, MD, PhD; Harald Grut, MD, PhD; Morten Hagness, MD, PhD; Pål-Dag Line, MD, PhD

Dueland et al JAMA Surg July 2023




2006-2020. 61 patients underwent LT for TxCLM

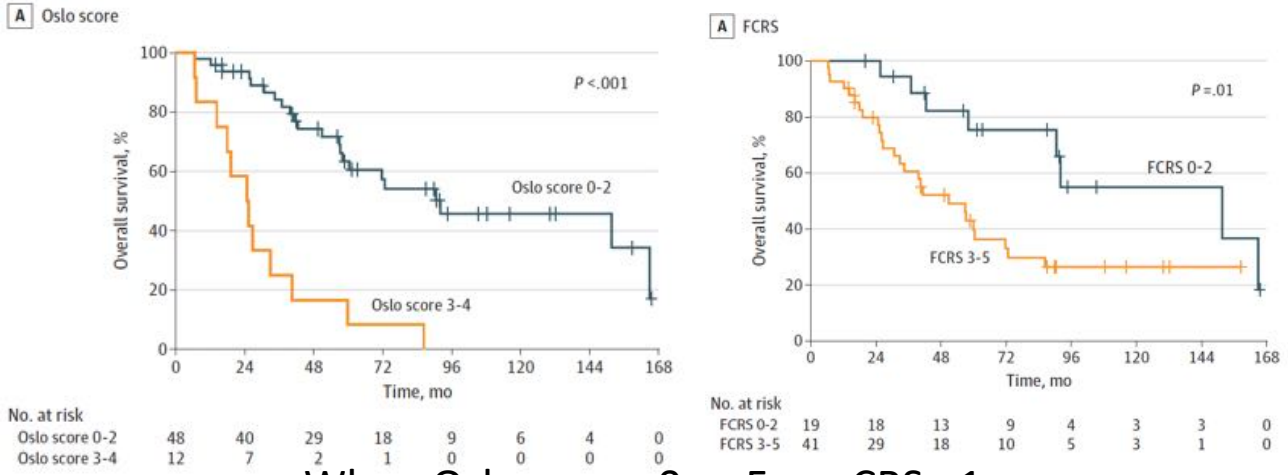
Single centre study

Long term survival that included participants in SECA 1, SECA 2 and RAPID studies

No adjuvant chemo

Follow up = 16-165 months

Median DFS and OS= 12 and 50 months




When Oslo score=0 or Fong CRS= 1, 10y = OS 89% and 80%

| Very good prognosis after LT | No. of patients | Estimated 5-y survival |
|---|---|---|
| Metachronous disease (more than 12 mo from diagnosis of the primary tumor to detection of liver metastases) | 5 | 100% |
| Time from diagnosis to LT >3 y | 9 | 100% |
| Oslo score 0 | 10 | 88.9% |
| Fong Clinical Risk Score 1 | 5 | 100% |
| **Good prognosis after liver transplant** | | |
| PET-MTV value <70 $cm^3$ | 40 | 66.7% |
| Oslo score 1 | 27 | 54.7% |
| Fong Clinical Risk Score 2 | 16 | 63.9% |
| Tumor Burden score, group 2 (score of 3-9) | 25 | 72.3% |

**Fong scoring system**

- Colorectal cancer metastatic to lymph nodes;
- Disease-free interval from the primary to discovery of the liver metastases <12 months;
- Number of tumors in the liver >1;
- Pre-operative CEA level >200 ng/ml;
- Size of the largest liver tumor >5 cm.

Potential cure in patients with stage 4 CLM at the cost of immunosuppression long term

Potentially resectable patients OR may do well with long term systemic treatment

| Oslo Score | |
|---|---|
| Maximal Tumor diameter > 5,5 cm | 1 |
| Pre transplant CEA > 80 µg/l | 1 |
| Progression on chemotherapy | 1 |
| Time interval: diagnosis to tx < 2 yrs | 1 |
| Summary score | 0-4 |

# Early Circulating Tumor DNA Dynamics Predict Neoadjuvant Therapy Response and Recurrence in Colorectal Liver Metastases: A Prospective Study

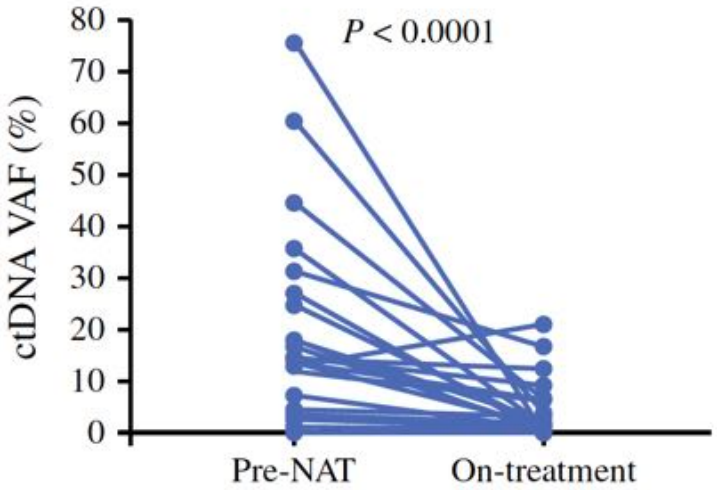
Xiang-Yu Wang, MD, PhD[1], Rui Zhang, MD[1], Jia-Hao Han, MD[1], Shi-Qing Chen, PhD[2], Fei-Long Zhao, PhD[2], Hui Chen, PhD[2], Jing Lin, MD[1], Jie Fan, MD, PhD[3], Wen-Wei Zhu, MD, PhD[1], Lu Lu, MD, PhD[1], and Jin-Hong Chen, MD, PhD[1]

34 patients undergoing NAT

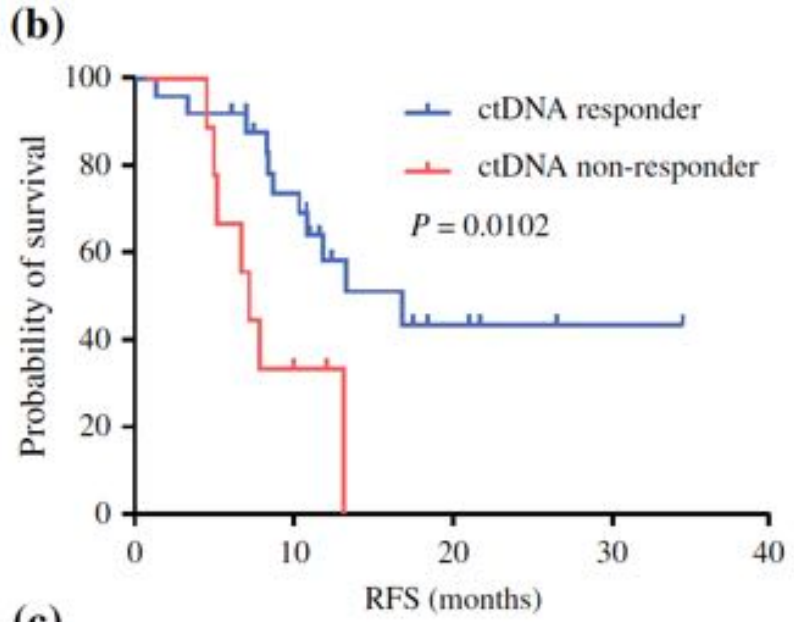
ctDNA collected at time points in treatment

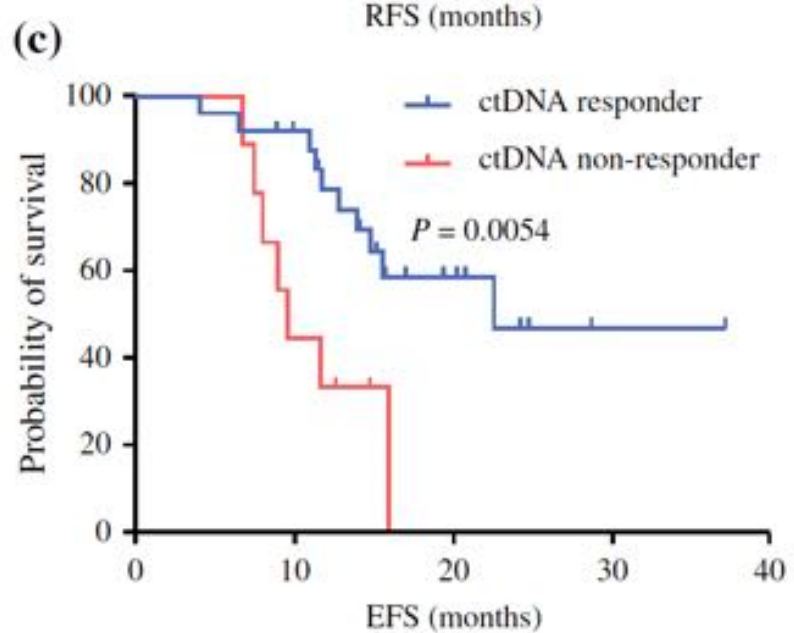
Dynamic mean variant allele mutation changes were calculated

100% of patients had somatic mutations in ctDNA



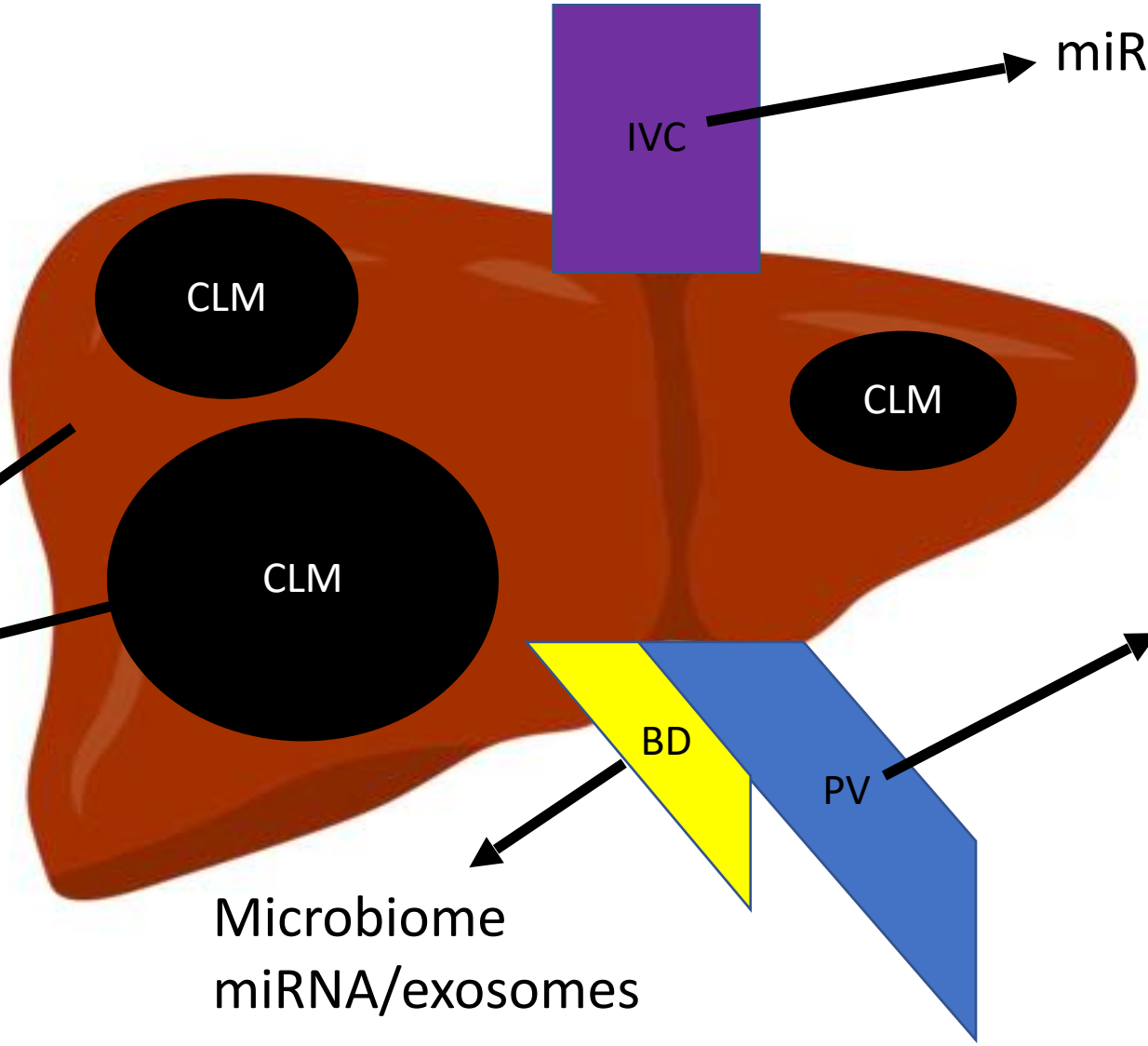

Only independent predictor of tumour response was early dynamic change of ctDNA




Wang et al Ann Surg Onc Aug 2023

# Sample collection and analysis




miRNA/exosomes

scRNAseq
Spatial transcriptomics

miRNA/exosomes
Microbiome

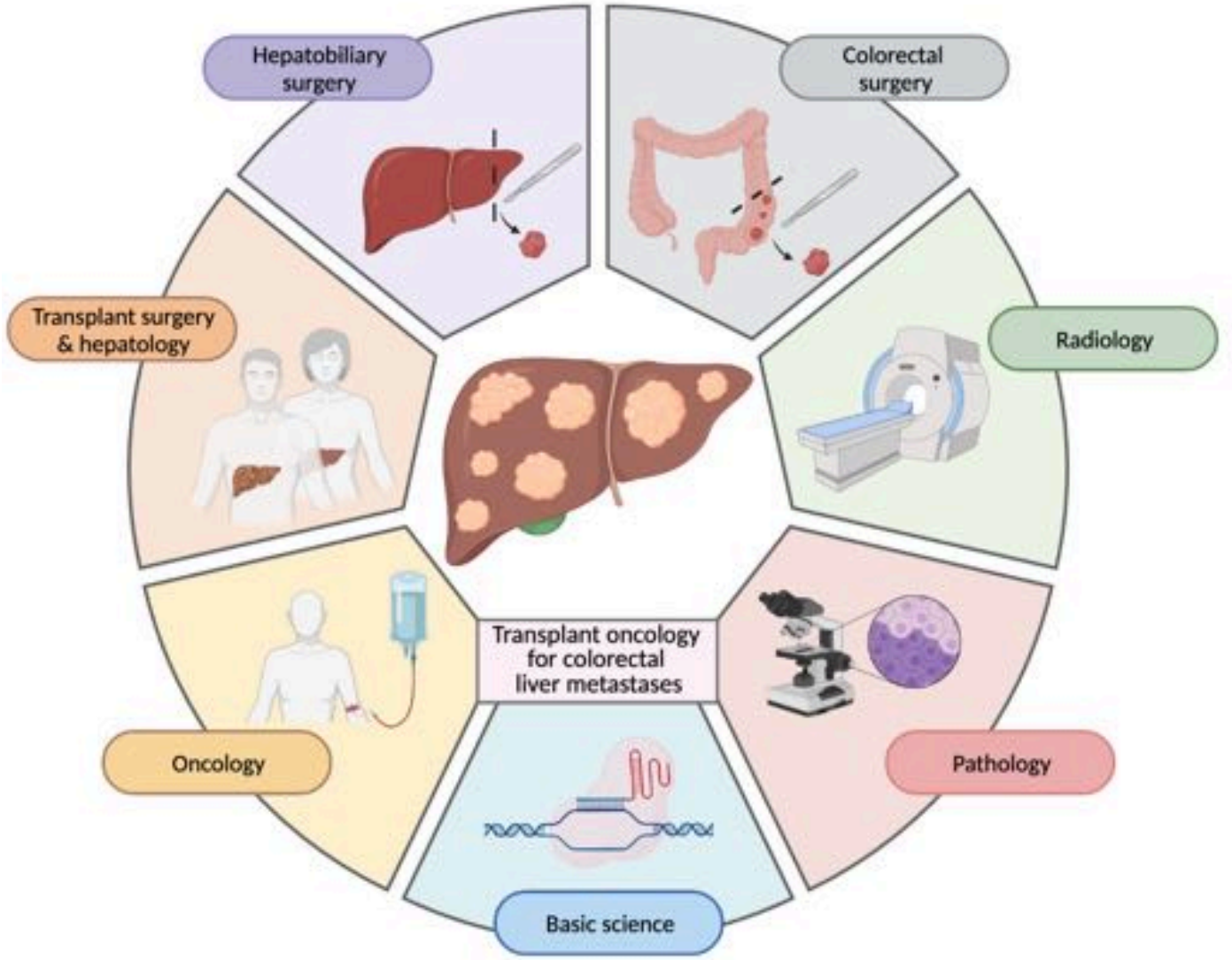
Microbiome
miRNA/exosomes

Courtesy: Dr Nigel Tan

National University Cancer Institute Singapore

NUHS National University Health System

# Transplant Oncology



# Summary

In well selected patients liver transplantation can potentially provide cure in CLM

Early recurrence remains a concern suggesting our selection can be improved

Questions remain:

- Should potentially resectable patients (disappearing mets) be transplanted?
- Are very good biology patients best served with transplant or continue expectant management?

At present criteria in selection is based on morphological (radiological response to chemo) and some phenotype criteria (CEA, mutation etc)

Future studies in molecular markers (genomic, transcriptomic, metabolomic, microbiome) can predict tumour behaviour which will inform transplant and resection decision making.

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"Coming together in the beginning
Staying together is progress
Working together is success"
- Henry Ford

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