NUHS
National University Health System

Liver transplant Symposium 2023

# Challenges and Regulatory Hurdles in Asia for Liver Transplantation of Colorectal Liver metastasis

## 23 September 2023

AP Dan Yock Young
DDGH (HSG), MOH
Dept of Medicine, NUS
Div. of Gastro & Hep, NUH
NUCOT, NUH
Adjunct, Cancer Science Institute NUS
Adjunct, GIS, ASTAR

**Disclaimer**

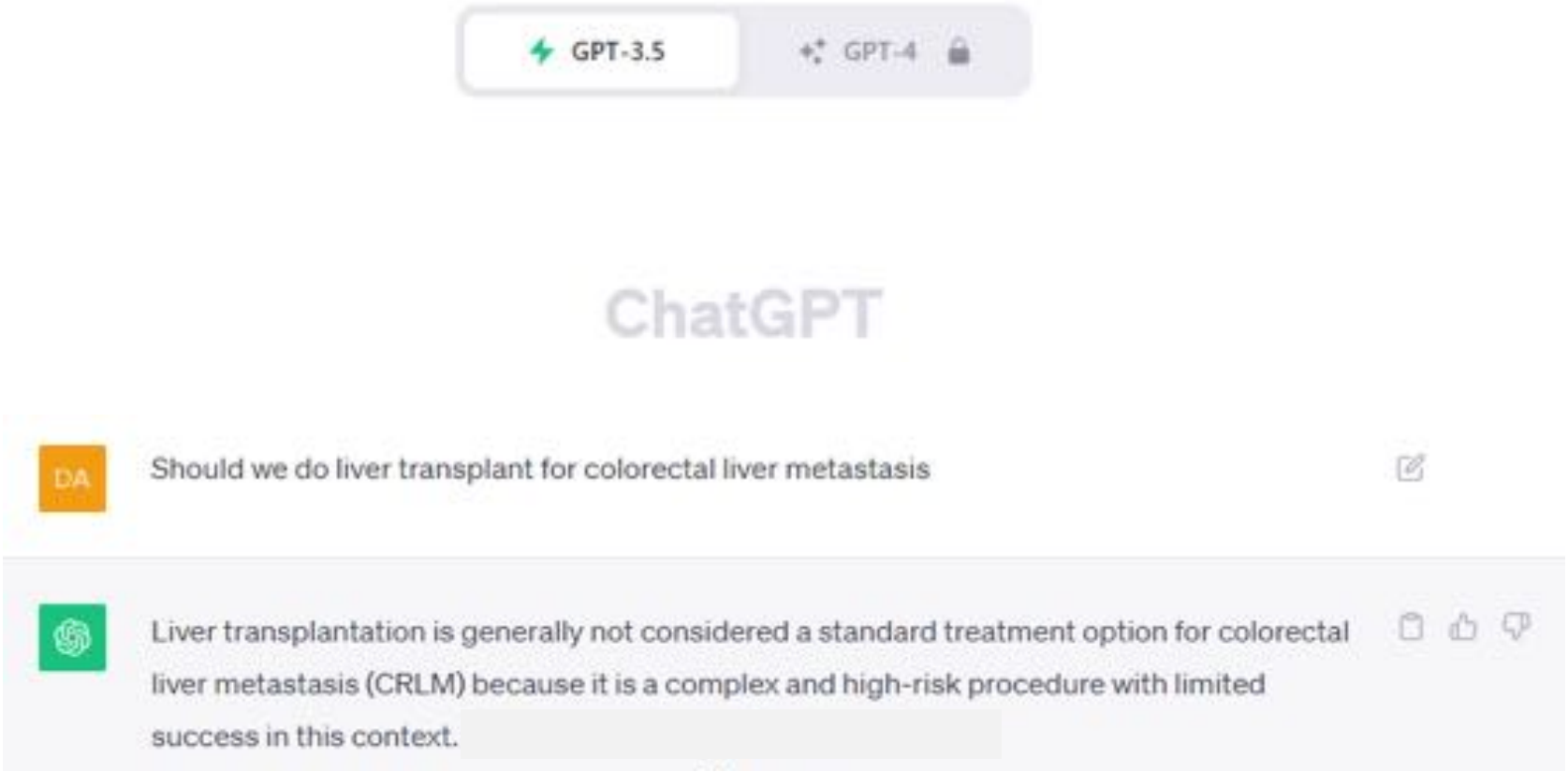
New Title: **Challenges and Considerations of Liver Transplantation for Colorectal Liver metastasis in Asia**

Views are my own and do not represent MOH official policy positions nor intended to specify prerequisite for regulations approval

I have received  funding for research, consultancy, advisory board and/or speaker's agreements with the following

1. Norvo Nordisk, MSD, Boehringer Ingelheim
2. Roche, Gilead
3. Perspectum. Histoindex, AMRA, Siemens

Should we perform liver transplantation for CRLM?



# Scope

1. The basis of justifying  liver transplantation

2. From pushing innovation to salvage to standard of care

3. Implications for Asia

# The Basis of Justifying Liver Transplantation

| Ministry of Health | Director, Transplant | Ethics Comm | Health Finance |
|---|---|---|---|
| Efficacy/ Utility<br><br>1. Curative intent<br>2. Relative benefit<br>3. Compassionate Salvage | Equipoise<br><br>1. Benefit vs Risk<br><br>2. Double equipoise in LDLT | Justice/ Equity<br><br>1. Other demand<br>2. Cost<br>3. Access | Cost Effectiveness<br><br>1. ICER<br>2. Willingness to Pay<br>3. Affordability |

# When is liver transplant justified?

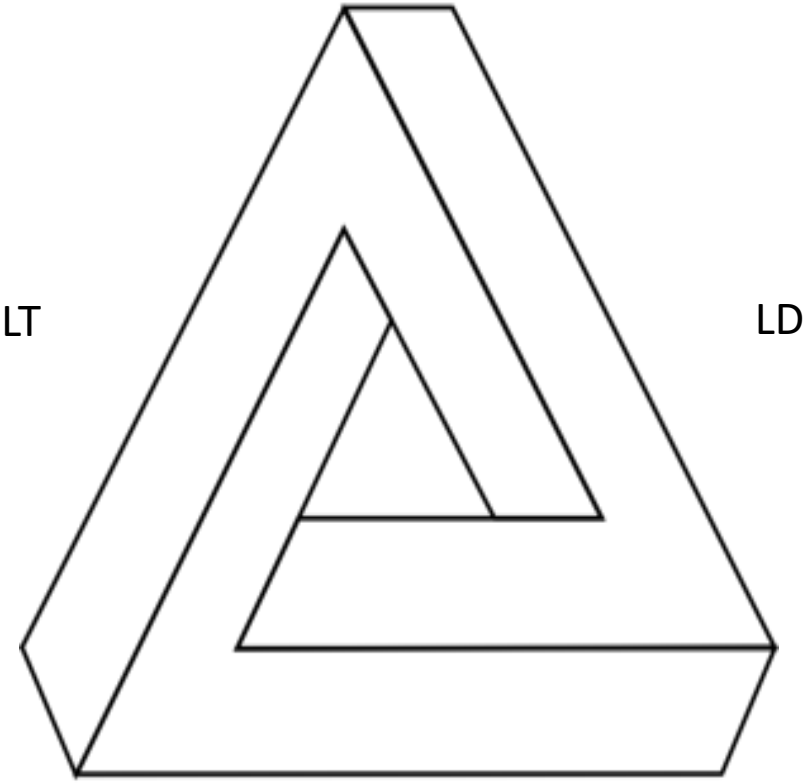
| Efficacy | Utility | CEA | Use case | 5YS |
|---|---|---|---|---|
| Curative | High Utility | V cost-effective | Liver Transplant for CLD or HCC (Milan's) | 75% |
| Superior Survival | Moderate Utility | Moderate CE | Extended criteria, marginal graft | 65% |
| Chance of extending Survival (no option) | Uncertain Utility | Unknown cost-effective ratio | Salvage transplant | Any |

# The Basis of Justifying Liver Transplantation


American Medical Association
Journal of Ethics
Illuminating the art of Medicine

| | No Transplant | Transplant | Milan Criteria |
|---|---|---|---|
| Curative intent | -- | 50% | 95% |
| 1 year Survival | 70-75% | 83- 95-100% | 93% |
| 5 year Survival | 10% (NR)<br>22% (Resected) | 50- 60-83% | 67% |
| Disease Free Survival | 0% | 35%- 48%<br>8 -13 mth median | 0% |
| Morbidity/Quality of Life | 0 | + | ++ |
| Cost-effectiveness | -- | Not proven | Cost-effective |

Transplant Benefit
Is there evidence?



DDLT

LDLT

Not every outcome is the same

0.5% risk to donor
means every 200 donor, 1 will be dead

Morbidity data post transplant
is not well characterised

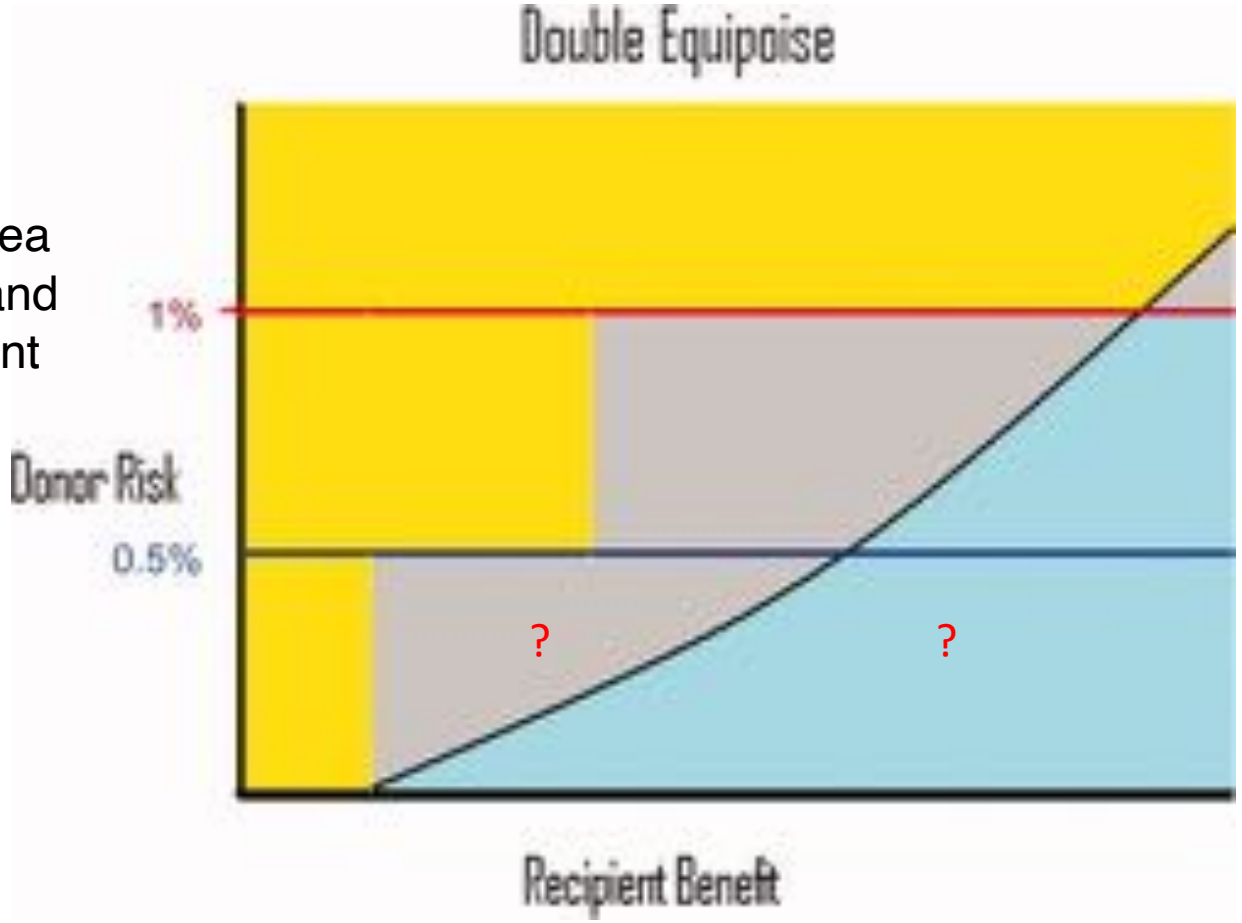
Waiting List candidate
(Equity vs Utility)

Harm to Living Donor
(Double equipoise)

Vitale, WJG 2013

The case for LDLT

The concept of double equipoise suggests that there clearly exists an area of excessive donor risk and unacceptably low recipient benefit.

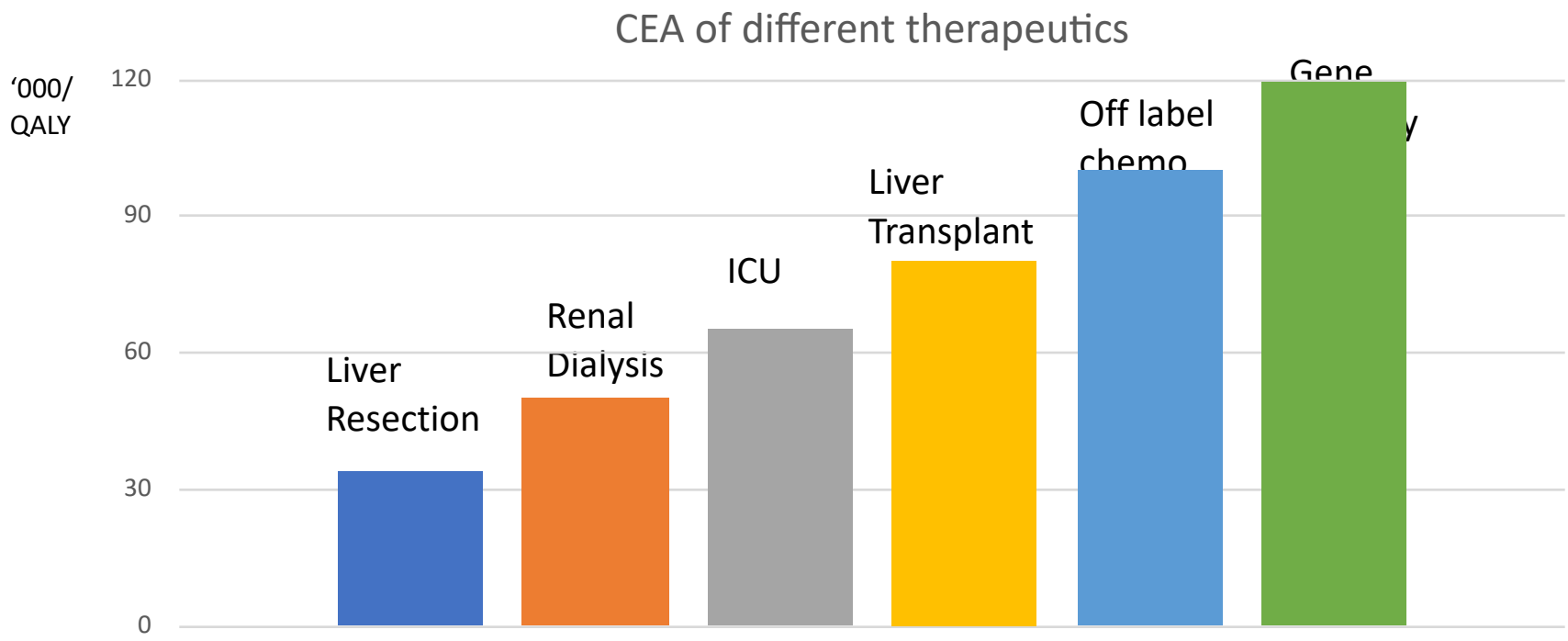



Acceptable risks to donor risk and high benefit to recipient

Pomfret Liver transplantation 2011

Justice

How much does society want to pay to keep a patient alive  for as long as possible?




How many rounds of high-cost treatment is one entitled to and who pays for it?

Challenge of maintaining moral equity in health

# Scope

1. The basis of justifying  liver transplantation

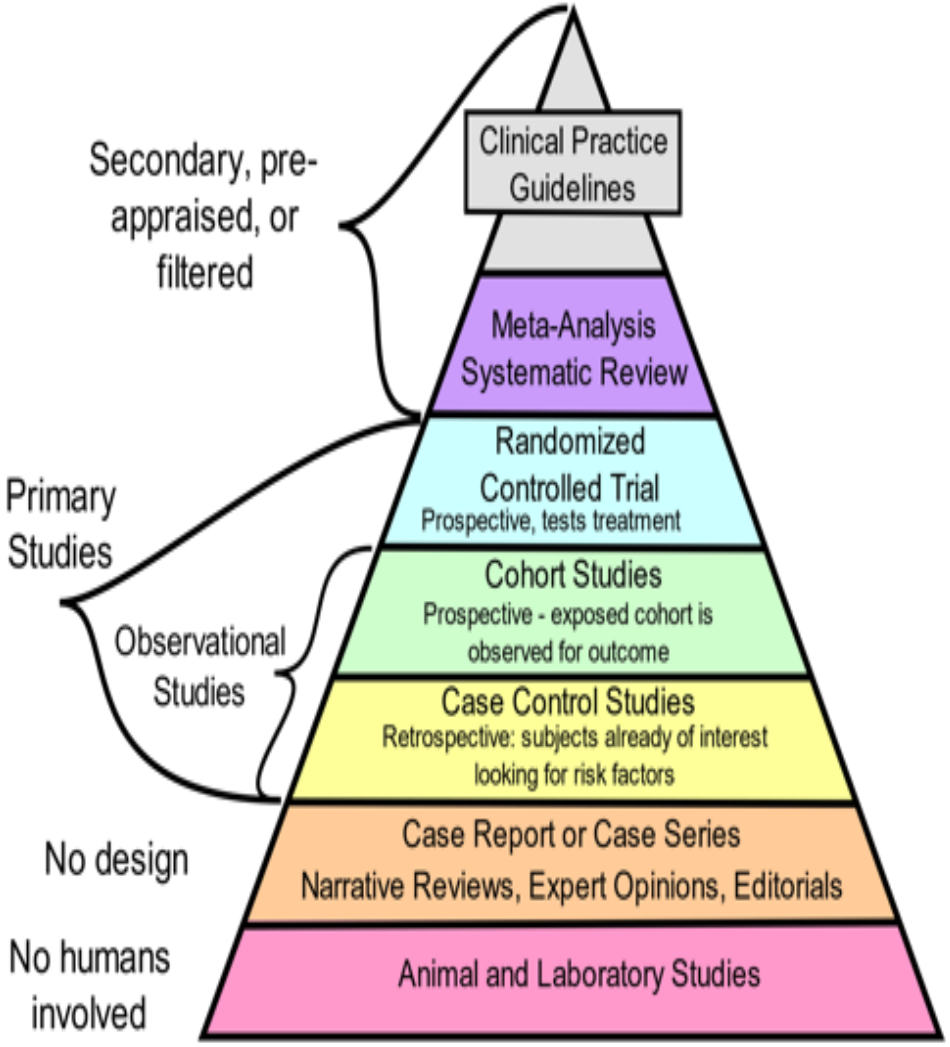
2. From pushing innovation to salvage to standard of care

3. Implications for Asia

Generic Regulatory Framework

| | Approved Clinical Service | Expanded/ Constrained use framework | Research Study | Compassionate Salvage |
|---|---|---|---|---|
| Efficacy and safety |  |  | Hypothesis | None, circumstantial |
| Professional consensus International/ Local |  |  | -- | None |
| Regulation/ Oversight | MOH | MOH | IRB, HSA | Ethics |
| Cost-Effectiveness | Unequivocally Cost-effective | Possibly cost-effective | -- | None |
| Funding | Subsidised/ Insurance cover | Insurance/ Not subsidised | Externally Funded | Recoverable<br>? subsidy |

# How robust is the data for liver transplant CRLM?




1 Guideline

*Bonney, Lancet GH 2022*

1 Systematic Review

*Lee, Cancer 2022*

Published studies included in review (n = 45)
Ongoing studies included in review (n = 13)

**0 RCT**

**2x Single centre prospective**

SECA I: n= 21

*Hagness Ann Surg 2013*

SECA II: n=15

*Dueland Ann Surg 2020*

**1 Retrospective SC**

Compagnons , n=12

*Toso Liver Transpl 2017*

Given the current available data, further evidence from ongoing prospective trials are needed to determine if and to what extent there is a role for LT in liver- limited surgically unresectable metastatic CRC

Using strict selection for pats with good cancer biology, 5Y OS exceeds is near to 80% and exceed traditional 60% threshold for appropriateness of transplant

Disease free recurrence possible up to 7 months in 5/12 patients

| | Historical | SECA I | SECA II | Compagnons Hépato-Biliaires |
|---|---|---|---|---|
| | | P/ SC | P/SC | Retrospective |
| N= | | 21 | 15 | 12 |
| OS 1 Y | | 95% | 100% | 83% |
| OS 5Y | 12-21% | 60% | 83% | 50% |
| DFS | 0 | 35%1Y,<br>5% 18m | 1Y:53%, 5Y:35%<br>Median 13.7m | 42% 6m |

1. When good outcomes are achieved in highly selected group, is the natural history of this highly selected group also much better without specific intervention.
2. Has historical outcomes used to reference comparison also shifted over time?
3. Cost effectiveness is based on total cost and total effectiveness
    a. Additional cost not taken into account: Cost of surgery (CRC) + adjuvant chemotherapy + additional test (PET, gene) + tumour surveillance + chemotherapy (PD1) after recurrence.
    b. Effectiveness (QALY) of patients in transplant with and without chemotherapy
4. Policy and Ethics:
    a. DCD: Implications to organ allocation (without and without additional points to local transplant system is not known
    b. LDLT: Natural history not fully defined

# Ongoing Trials

| Name, NCT Number and Location | Description | Inclusion Criteria | Primary Endpoint |
|---|---|---|---|
| TRANSMET<br>NCT02597348<br>France | A **multicentric randomized trial** comparing 5-year survival of chemotherapy followed by LT vs. chemotherapy alone in patients with confirmed nonresectable liver-only colorectal metastases, well-controlled by chemotherapy | •more than 3 months of tumor control on chemotherapy; BRAF wild-type tumors; 2 or fewer lines of chemotherapy no signs of extrahepatic disease/local recurrence of primary | 5-year OS |
| SECA III<br>NCT03494946<br>Oslo, Norway | A **monocentric randomized trial** comparing the overall survival of patients with nonresectable CRLM receiving LT vs. other treatment that may include further chemotherapy, TACE, SIRT, or other available treatment options. | •no signs of extrahepatic disease, except resectable lung metastases (max 15 mm)progressive disease or intolerance to first-line chemotherapy; Oslo score of less than 3lesion smaller than 10 cm | 2-year OS |
| Rapid trial<br>NCT02215889<br>Oslo, Norway | A clinical trial to evaluate the benefit and efficacy of liver resection and partial liver segment 2/3 transplantation with delayed total hepatectomy as a treatment for selected patients with nonresectable CRLM | •at least 8 weeks of chemotherapy; no signs of extrahepatic metastatic disease, except patients may have 1–3 resectable lung lesions all <15 mm; | % of transplanted patients receiving second stage hepatectomy within 4 weeks of segment 2–3 transplantation |
| LIVERT(W)OHEAL<br>NCT03488953<br>Germany<br>Jena and Tubingen | A bicentric clinical trial to evaluate the benefit and efficacy of liver resection and partial liver segment 2–3 transplantation with delayed total hepatectomy as a treatment for selected patients with nonresectable liver metastases from colorectal carcinoma using living donors | •nonresectable colorectal liver metastases without extrahepatic tumor burden, except resectable pulmonary metastases;stable disease or regression after at least eight weeks of systemic chemotherapy | 3-year OS after the second hepatectomy |
| Toronto study<br>NCT02864485<br>Toronto, Canada | A monocentric study to evaluate the results of live donor liver transplantation to selected patients with nonresectable metastases CRLM | •≤T4a primary tumor;the interval between the resection of primary to transplant is ≥6 months;no major vascular invasion liver metastases; systemic chemotherapy for ≥3 months; stable or decreasing CEA values; BRAF wild-type tumors | 5-year OS<br>5-year DFS |
| SOULMATE study<br>NCT04161092<br>Sweden<br>Gothenburg and Stockholm | A randomized controlled bicentric study evaluating if liver transplantation with liver grafts from extended criteria donors not utilized for approved indications increases overall survival in patients with nonresectable isolated CRLM, in comparison with best alternative care | •at least 2 months of chemotherapy with no progression; at least 1 year from the diagnosis of primary and the inclusion in the study;iver metastases less than 10 cm; BRAF wild-type tumors;MSS tumors | 5-year OS |
| COLT study<br>NCT03803436<br>Italy | A **multicenter, non-randomized**, prospective study assessing the efficacy of liver transplantation in liver only CRLM, compared with a matched cohort of patients bearing the same tumor characteristics, collected during the same period and included in phase III Italian randomized | •primary tumor as pT1-3, pN0, or pN1; RAS and BRAF wild-type and MSS; objective response to first-line treatment, with a sustained response for at least 4 months, OR disease control during second-line treatment for at least 4 months.;a maximum of 2 prior chemotherapy treatment | 5-year OS |

# Scope

1. The basis of justifying  liver transplantation

2. From pushing innovation to salvage to standard of care

3. Implications for Asia

# Capacity for Liver Transplant in Asia

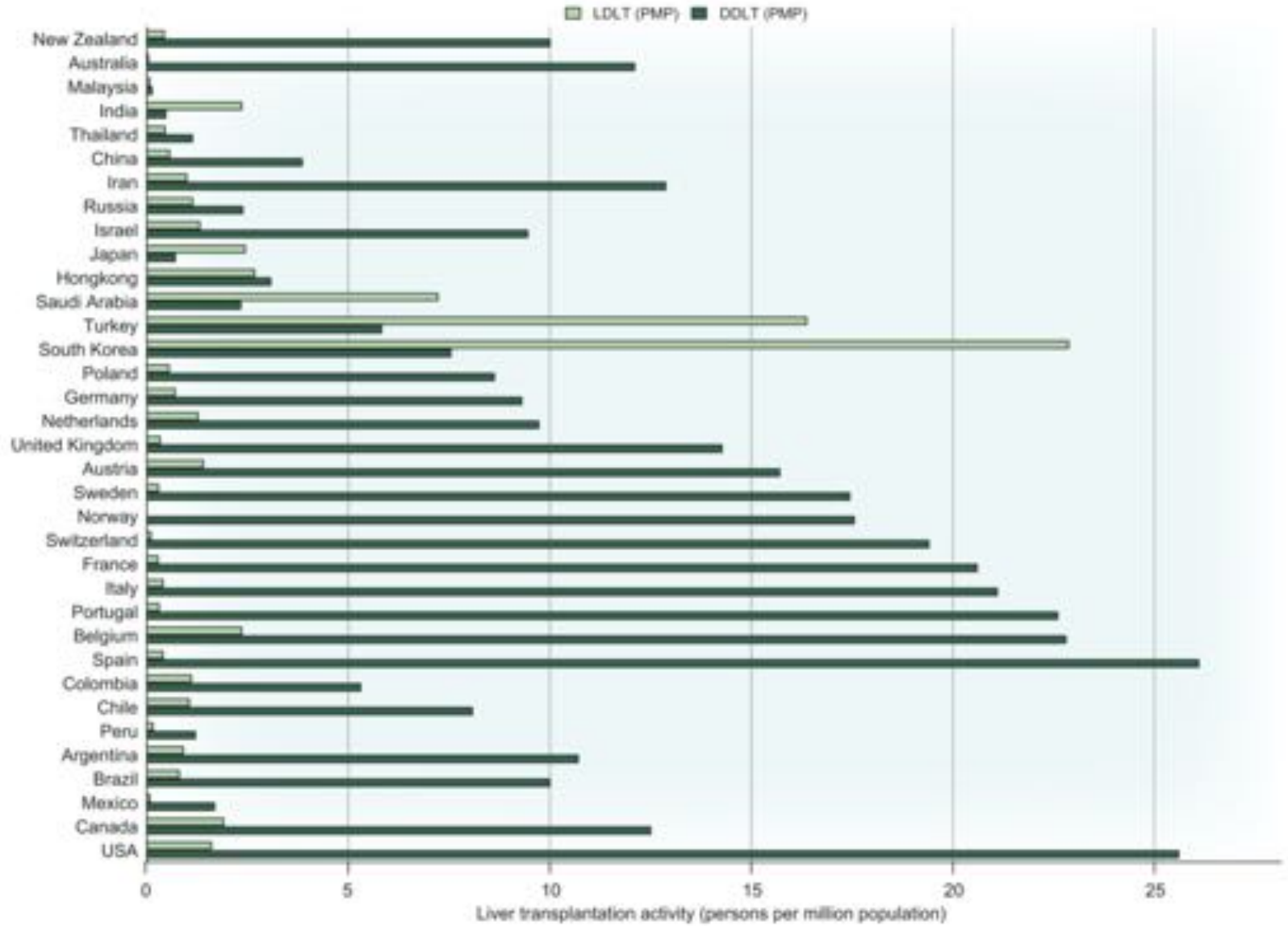
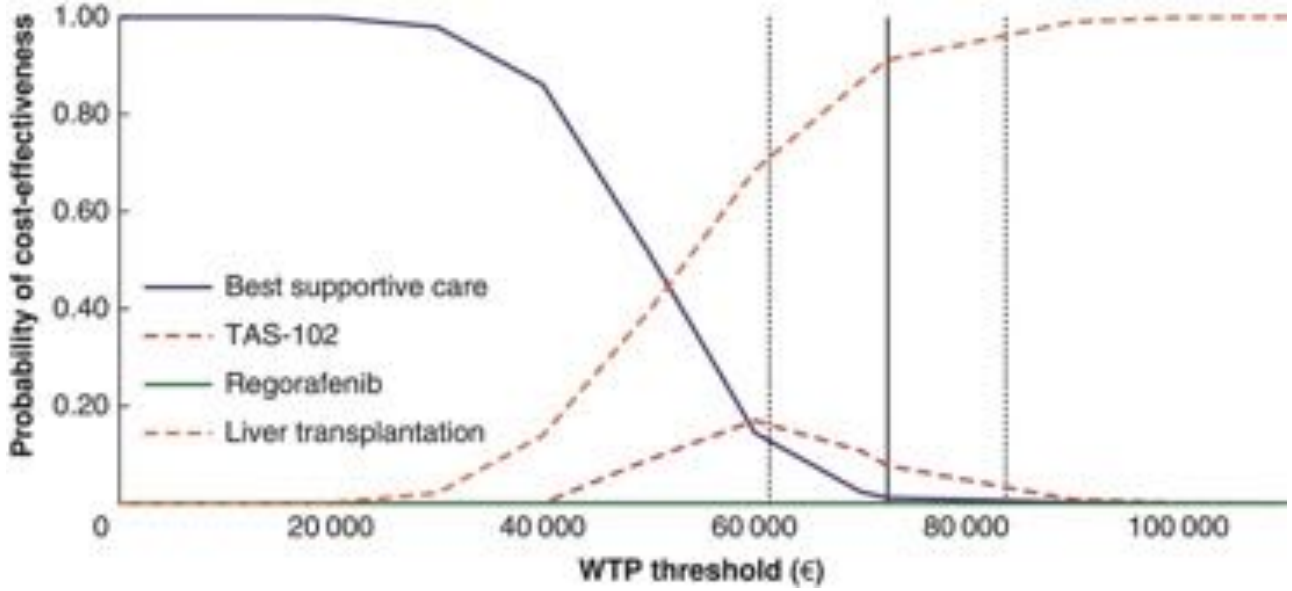


Table 1. Living liver donor deaths – 1989 to 2019.

| Country/continent | Donor death/vegetative state related to the operation | Unpublished donor deaths related to the operation* | Donor death unrelated to the operation | Total |
|---|---|---|---|---|
| Asia | | | | 19 |
| Hong Kong | 1 | | | |
| India | 8 | 3 | | |
| Singapore | | | | |
| Pakistan | 1 | 2 | | |
| Japan | 1 | | | |
| South Korea | 1 | | 52 | |
| Others | 2 | | 6 | |
| North America | | | | 6 |
| USA | 6 | | 13 | |
| South America | | | 2 | 2 |
| Brazil | 2 | | | |
| Africa | | | | 1 |
| Egypt | 1 | | | |
| Europe | 8 | | 1 | 8 |

# Cost-effectiveness of Liver Transplant for CRLM

liver transplantation increased patients' life expectancy by 3·12 life-years (2·47 QALYs), at an additional cost of €209 143, giving an incremental cost-effectiveness ratio (ICER) of €67 140 per life-year (€84 667 per QALY) gained. In selected cohorts (selection based on tumour diameter, time since primary cancer, carcinoembryonic antigen levels and response to chemotherapy), the effect of liver transplantation increased to 4·23 life-years (3·41 QALYs), at a higher additional cost (€230 282), and the ICER decreased to €54 467 per life-year (€67 509 per QALY) gained.




| | |
|---|---|
| Singapore | 157,354 |
| Qatar | 124,834 |
| Macau | 89,558 |
| United Arab Emirates | 88,221 |
| Brunei | 75,583 |
| Taiwan | 73,344 |
| Saudi Arabia | 64,836 |
| Bahrain | 60,596 |
| Hong Kong[n 1] | 59,844 |
| South Korea | 56,706 |
| Israel | 54,997 |
| Cyprus | 54,611 |
| Kuwait | 53,037 |
| Japan | 51,809 |
| Oman | 42,188 |
| Turkey[n 2] | 41,412 |
| Malaysia | 36,847 |
| Maldives | 36,358 |
| Kazakhstan[n 3] | 32,688 |

Bjørnelv, Br J Surg 2019

# Implications for Asia

**Impact on QOL**

The quality of life of the liver transplanted cohort from the SECA trial (using the QLQ-C30 questionnaire) was compared to data obtained from a cohort of patients with metastatic colorectal cancer receiving first-line chemotherapy.

Despite a relapse, in most of the liver transplanted patients, the Global Health Score remained good

*Dueland BJS Open 2022*

**Impact on Organ allocation**

- # of CRCLM requiring liver transplant
- Only LDLT

  Allow DDLT:  sickest first/ exception points / marginal graft

Norway:  1% of liver transplant => very small number

Parity with other cancers

Parity with other diseases:  How much do you want to spend on cancer?

## Current Status

1. We need more data – efficacy – RCT and long term data;  selection criteria; and clinical consensus

2. We need better understanding in local context – waiting time, expertise, cost affordability

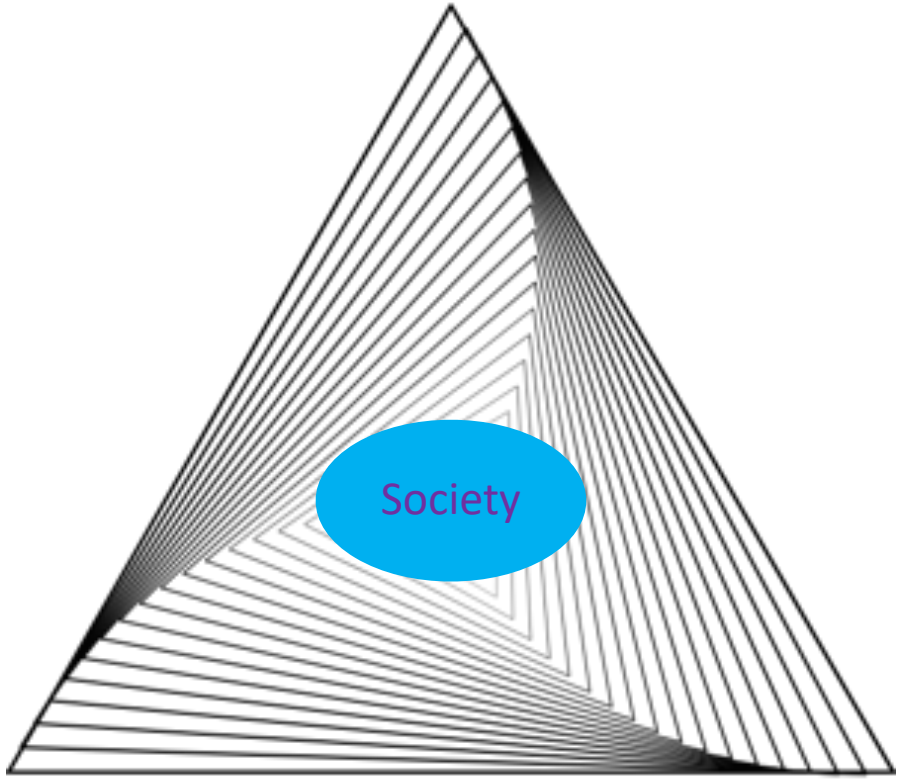
3. Liver Transplant for CRLM – research study or individual salvage case (DDLT)

**Implications**

1. Offering as a standard clinical service  and profiting
2. Ethics of advertising as clinical service
3. Require Research and Ethics Oversight
4. Strict discipline and self-monitoring

# Staying alive

Biomedical Industry




The Doctor

Patient/
Family

Challenges and Regulatory Hurdles?
Who needs to understand the “price” (not just the $) to pay?

Thank You