



Liver transplantation in NET disease: Expert consensus and clinical updates

Wednesday, 30 September 2026, 18:00 – 19:10 CEST

Disclosure Statement

Peter Stålberg (moderator) has no potential conflict of interest to report.

The Aim and Concept

- ✓ Transferring research to education and teaching is a major goal at ENETS.
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Live poll question: Getting to know the audience

In which medical discipline are you trained or currently working?

- Oncology
- Radiology
- Surgery
- Endocrinology
- Nuclear medicine
- Other

Tonight's moderator



Peter STÅLBERG

University Hospital, Uppsala, Sweden

Surgery

Tonight's faculty



Adina CROITORU

Fundeni Clinical Institute,
Carol Davila University of Medicine
Bucharest, Romania

Oncology



Julie HALLET

University of Toronto,
Canada

Surgery



Andreas PASCHER

University Hospital,
Münster, Germany

Surgery



Raj SRIRAJASKANTHAN

Kings College Hospital,
London, United Kingdom

Gastroenterology

Tonight's agenda

- | | |
|---------------|---|
| 18:00 – 18:05 | Opening comments
<i>Peter STÅLBERG, SWE</i> |
| 18:05 – 18:15 | Case presentation
<i>Raj SRIRAJASKANTHAN, GBR</i> |
| 18:15 – 18:30 | Data on liver transplant and current guidelines
<i>Andreas PASCHER, GER</i> |
| 18:30 – 18:45 | Liver transplant for NET- liver metastases - promise for cure or rather palliation?
<i>Julie HALLET, CAN</i> |
| 18:45 – 19:05 | Discussion
<i>Peter STÅLBERG, SWE</i>
<i>Raj SRIRAJASKANTHAN, GBR</i>
<i>Andreas PASCHER, GER</i>
<i>Julie HALLET, CAN</i>
<i>Adina CROITORU, ROM</i> |
| 19:00 – 19:10 | Closing comments
<i>Peter STÅLBERG, SWE</i> |

Liver Transplantation for Unresectable NET Metastases - Case Presentation

Prof. Raj Srirajaskanthan

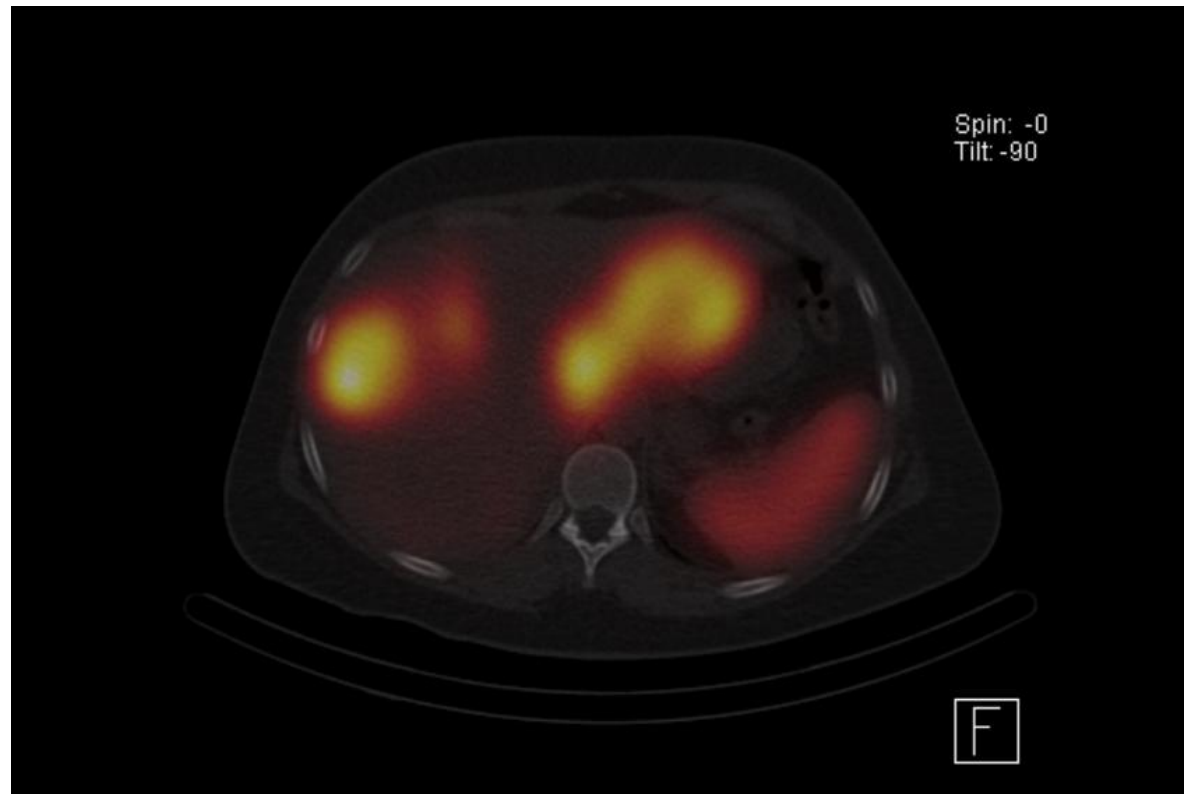
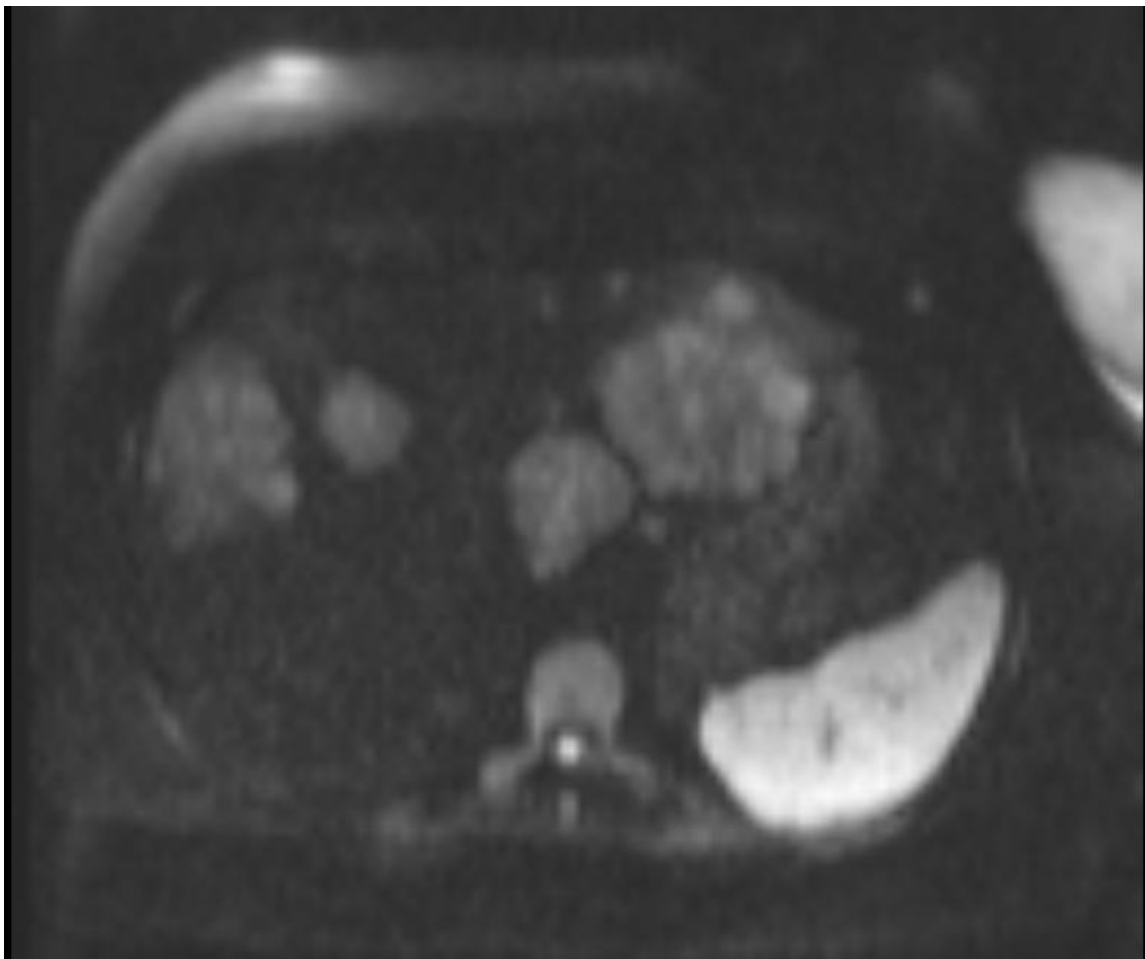
King's College Hospital NHS Foundation Trust

DISCLOSURE SLIDE

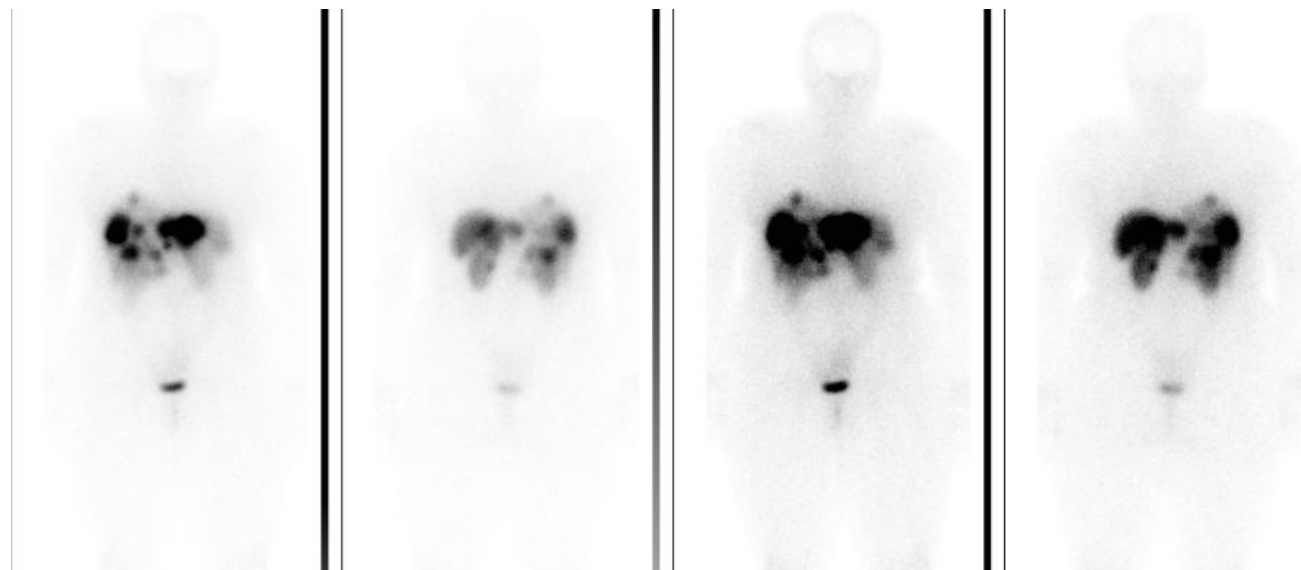
- Grants: Novartis, Ipsen
- Speakers Bureau: Novartis, Ipsen, ITM, SERB, Advanz Pharma, Terumo, Esteve

Case presentation

- Initial presentation in 2013, 35-year-old female, with abdominal pain and anaemia.
No significant medical problems.
- Cross sectional imaging: Duodenal thickening and multiple liver metastases.
- Numerous bi-lobar liver metastases with no segmental sparing- Size ranging from 5 to 75 mm.
- Biopsy confirms a metastatic duodenal NET (T3 N1 M1)
- Grade 2 – Ki-67 3%



Imaging in 2013

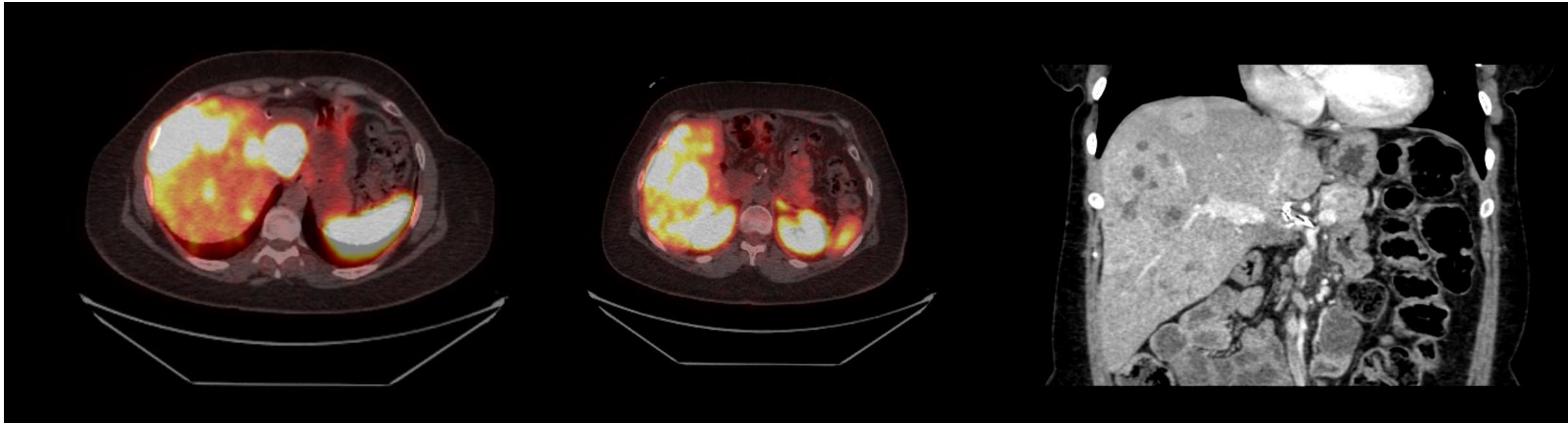


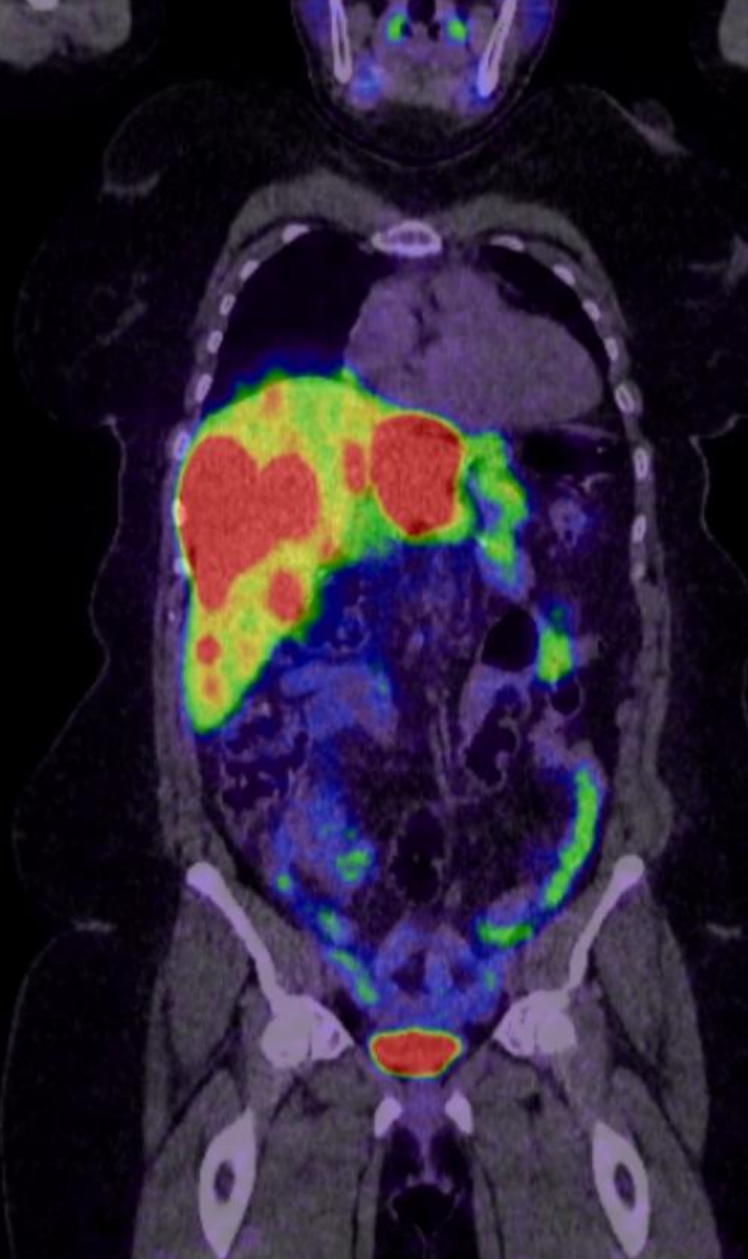
Resection of the primary

- Following commencing SSTA, discussed with patient about surgery to leave liver only disease.
- Pancreatico-duodenectomy and Left lateral Segmentectomy **August 2013**.
- Good recovery.
- Histology: pT4 N1 M1, Ki-67 3%, liver multiple deposits Ki-67 3%.
- Started on Sandostatin LAR in 2013.

Progression of Liver Metastases in 2015

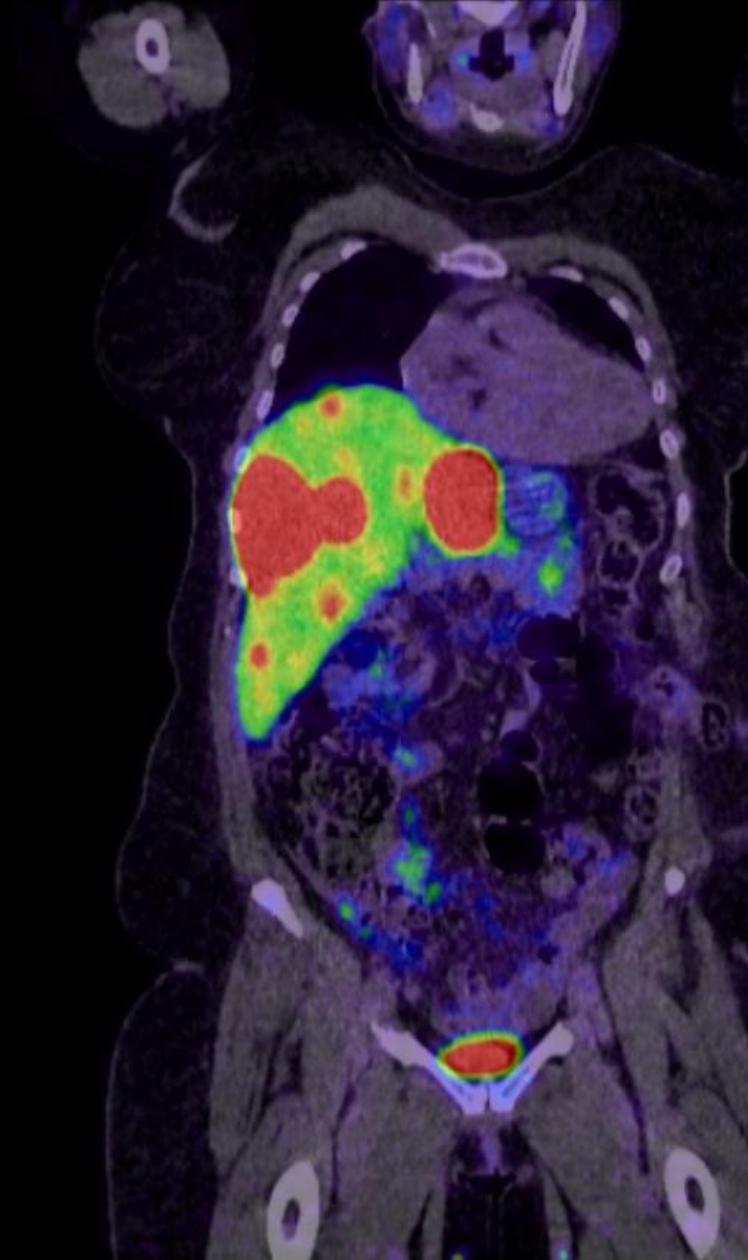
- Remained clinically well on SSTA.PS-0
- However, developed progressive disease in 2015





Treatment in 2015

- PRRT 4 Cycles
- Between May 2015 and June 2016
- Sandostatin dose increased
- Initially stable disease, followed by disease progression, **5 years later.**
- We had started discussions with patient about possibility of LTx in 2013/14.
- Again discussed in 2020.

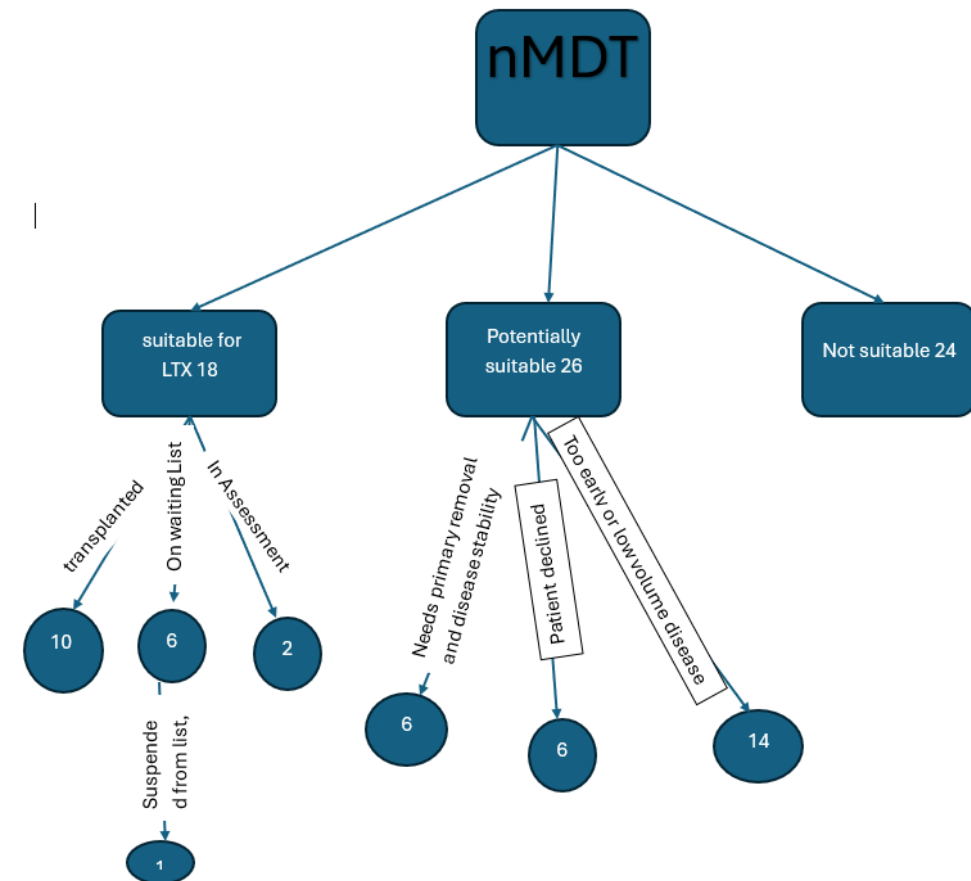


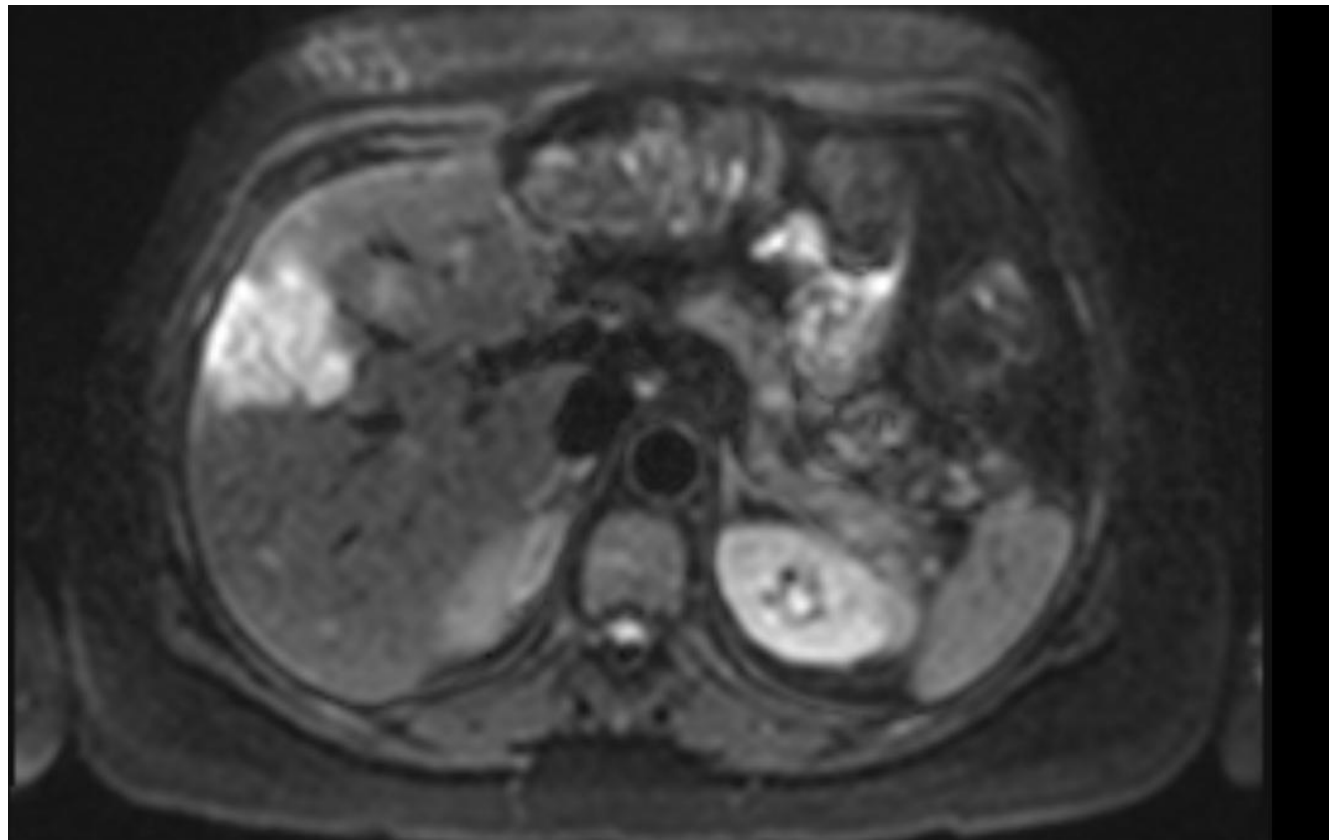
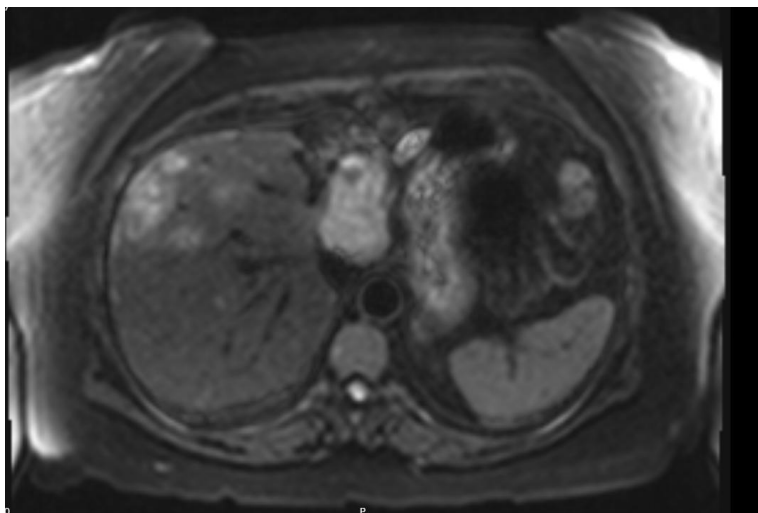
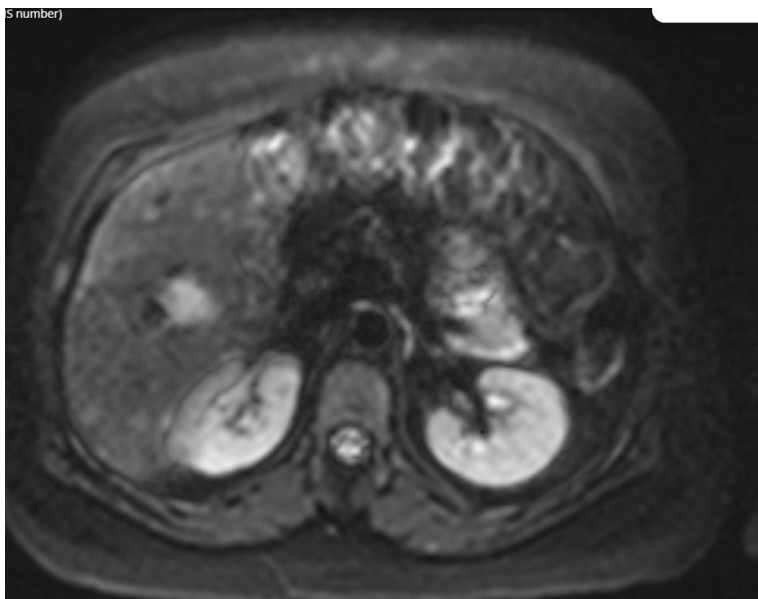
- 2021: Started on Everolimus
- 2022: Stable liver only disease
- Referred to the national MDT for consideration of liver transplantation

Table 1 Milan criteria, UNOS guidelines, and ENETS guidelines on LT for pNETLM

Index	Milan criteria (6.15. 35) (1)	UNOS guidelines 2015 (2)
Histology grade	G1–G2*	G1–G2*
Primary tumor site	Drained by the portal system	Drained by the portal system
Tumor involvement	<50% of the liver volume	<50% of the liver volume
Primary tumor resection and interval of stable disease	Resection of primary tumor and all extra-hepatic tumor deposits and stable disease/good response to therapies for at least 6 months	Resection of primary malignancy and extra-hepatic disease without any evidence of recurrence at least 6 months
Recipient age	<60 years (relative criteria)	<60 years
Others	None	Neuroendocrine liver metastasis limited to the liver, bi-lobar, not amenable to resection

Coppa JC et al. *Transpl. Proc.* 2001 ; Stutcliffe et al. *Am.J.Surgery* 2003; Mazzaferro V et al. *J Hepatology* 2007; Shimata et al. *Gland Surg* 2018

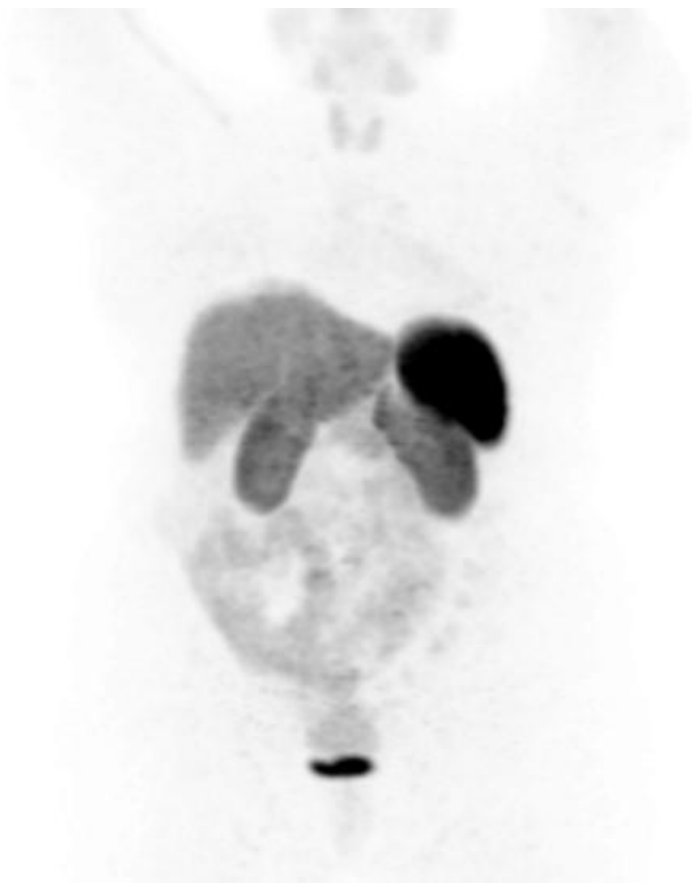




Liver Transplantation

- October 2023
- Whole liver DCD- Normothermic Regional Perfusion, Piggyback, 3HVS, Roux loop HJ.
- Explant Histology: Multifocal, well-differentiated neuroendocrine tumour mets, G1 and G2 (Ki-67 7.7%), innumerable >40 lesions, from microscopic foci to largest lesion in caudate lobe, 53 mm.
- Resected lymph nodes: all disease free
- Complete resection.

No recurrence to date (35 months post LTx)



Outcome	n (%) / Median (Range)
30-day mortality	0 (0%)
Recurrence during follow-up	0 (0%)
Disease-free survival at last follow-up	10 (100%)
Post-transplant survival	10 (100%)
Median follow-up (months)	15 (1–24)
Table 3: Clinical Outcomes	

Table 3: 30- day morality, recurrence during follow up, disease free survival at last follow up, post- transplant survival, median follow up



Data on Liver Transplant and Current Guidelines for NELMs

Andreas Pascher

Klinik für Allgemein-, Viszeral- und Transplantationschirurgie

Universitätsklinikum Münster

Direktor: Univ.-Prof. Dr. med. A. Pascher, MBA, FEBS

DISCLOSURES

- Personal financial interests: None
- Institutional financial interests: None
- Non-financial interests: None
- Other – speech honoraria: Ipsen, Novartis, J&J, Medtronic

International criteria for liver transplantation in patients with neuroendocrine liver metastases (NELM)

- ✓ Primarily based on the Milan-NET criteria and harmonized with national guidelines
- ✓ Core Selection Criteria:
 - Primary Tumour Origin: Low-grade gastrointestinal or pancreatic neuroendocrine tumours with venous drainage via the portal system.
 - Tumour Differentiation & Grade: Well-differentiated neuroendocrine tumours (NET G1/G2), typically with a low Ki-67 proliferation index (<10% to <20%).
 - Hepatic Tumour Burden (LTB): Liver involvement of less than 50% of the total liver volume.
 - Resection of Primary: Prior curative resection of the primary neuroendocrine tumour and any extrahepatic sites.
 - Disease Stability: Documented absence of extrahepatic disease and stable disease/low growth rate for at least 3-6 months following primary resection before transplant listing.
 - Recipient Age: Traditionally under 60 years for standard Milan criteria, though extended criteria allow up to 70 years depending on biological age and overall health status.

Development of MILAN Criteria for the Indication to LT in Metastatic NEN Disease

Table 3

Liver transplantation (OLT) for metastatic neuroendocrine tumors (literature review: 1970–2006)

Author	No. of patients	Histology		Patients with symptoms	Venous drainage primary tumor		Chemo pre-OLT	Median interval between diagnosis and OLT (months)	Patient survival	Recurrence-free survival
		CAR	NCAR		Portal	Systemic				
Lehnert ^a [22]	103	36	67	42%			38%	NR	47% at 5 year	24% at 5 year
Le Treut [23]	31	15	16	55%	84%	16%	84%	19	36% at 5 year	17% at 5 year
Olausson [24]	9	4	5	44%	100%		0	2–120	88% at 3 year	44% at 3 year
Fernandez [25]	5	2	3	33%	100%		100%	11	80% at 2 year	40% at 2 year
Rosenau [26]	19	6	10	90%	100%		NR	NR	80% at 5 year	21% at 5 year
Cahlin [27]	10	4	6	40%	89%	20%	0	NR	80% at 1 year	50% at 3 year
Florman [28]	11	3	8	100%	91%	9%	NR	NR	36% at 5 year	9% at 5 year
V.Vilsteren [19]	19	8	11	32%	100%		47%	NR	87% at 1 year	77% at 1 year
INT Milano ^b	24	24	–	10%	100%		55%	18	90% at 5 year	77% at 5 year

Published Selection Criteria for LT in NEN Disease

TABLE 3 Selection criteria for consideration for liver transplantation for neuroendocrine liver metastases ^{4,6}

Milan criteria 2007	ENETS guidelines 2012
1. Histological diagnosis of low-grade neuroendocrine tumors (i.e., with low expression of Ki-67) regardless of the presence or absence of syndrome	1. Well differentiated NET with Ki67 proliferation index ≤10 %
2. Primary tumor located in the pancreas or intermediate gut (i.e., from distal stomach to sigmoid colon), thereby tributary of the portal vein, already removed with a curative resection	2. Primary tumor removed prior to transplantation (at least 6 months)
3. Less than 50 % of liver involvement.	3. <50 % liver involvement or < 75% liver involvement in patients with refractory hormonal symptoms
4. Stable disease for at least 6 months during the pre-transplantation period.	4. Stable disease for at least 6 months
5. Less than 55 years	5. Age <55 years
	6. Diffuse unresectable disease confined to the liver—robust extrahepatic exclusion (gallium-68 positron emission tomography/computed tomography, etc.)

Low grade? = G1/G2 ?

Ki-67 < 10% or 20% ?

No comment on primary tumour site !

International criteria for liver transplantation in patients with neuroendocrine liver metastases (NELM)

- ✓ Published regional organ allocation protocols for liver transplantation in patients with metastatic neuroendocrine liver disease (NELM) vary widely. (Eurotransplant; NHS Blood and Transplant ; Italian National Transplant Network / NITp; France - Agence de la Biomédecine; United States (UNOS / OPTN)). **Grading thresholds range from 10-20% Ki-67.**
- ✓ Because patients with neuroendocrine tumours usually have relatively preserved liver function, they do not score highly on the standard Model for End-Stage Liver Disease (MELD) system.
- ✓ As a result, major regional networks have established specific allocation protocols, “exception points” (SE/NSE), a “Variant Syndrome Category” (NHS-BT), a national expert committee system (France), priority regional allocation or specialized institutional protocols (Italy, Canada), etc. to ensure access to deceased donor organs

<https://www.agence-biomedecine.fr/fr>

<https://www.neuroendocrinecancer.org.uk/wp-content/uploads/2025/07/July2025-completed-Transplant-Factsheet-PDF.pdf>

<https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/38481/pol195.pdf>

<https://www.eurotransplant.org/allocation/eurotransplant-manual>

https://unos.org/wp-content/uploads/2014_06_Liver-Action-Item-Guidance-Doc-for-RRB-Exceptions-Draft.pdf

Ongoing Evidence – Real-World Data

> J Gastrointest Surg. 2021 Jun;25(6):1487-1493. doi: 10.1007/s11605-020-04708-1.
Epub 2020 Jul 6.

Younger Age Is Associated with Improved Survival in Patients Undergoing Liver Transplantation Alone for Metastatic Neuroendocrine Tumors

Deepa Valvi ¹, Xiaonan Mei ¹, Meera Gupta ¹, Malay B Shah ¹, Alexandre Ancheta ¹,
Francesc Marti ¹, Roberto Gedaly ²

Methods: LT for NELMs; USA; 10/1988 through 06/2018; UNOS dataset.

Results: total n=160,360. NELMs n= 206; mean (SD) age 48.2 (11.7) years, (19 to 75 years); m=117 (56.8%)
Overall 1-, 3-, 5-, and 10-year patient survival rates: 89.1%, 75.3%, 64.9%, and 46.1%.

Tumour recurrence - 34%. Median time to recurrence - 28 months (range, 1 to 192 months)

Median wait time for LT was 112 days.

Tumour recurrence significantly higher if waiting time less than 6 months (74.3% vs. 25.7%).

Patients' age $\leq$ 45 years had significantly better survival compared with those $>$ 45 years ($p = 0.03$).

Conclusions:

Waiting time longer than 6 months is associated with lower rates of tumour recurrence.

Younger patients $\leq$ 45 years had significantly improved survival after LT for NET metastases.

Prospective Evidence? The Basis of our Allocation Algorithms

American Journal of Transplantation 2016; 16: 2892–2902
Wiley Periodicals Inc.

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doi: 10.1111/ajt.13831

The Long-Term Benefit of Liver Transplantation for Hepatic Metastases From Neuroendocrine Tumors

Non-randomized allocation acc. to MDT decision

Retrospective analysis; matching between groups
made on multiple Cox models adjusted for propensity score

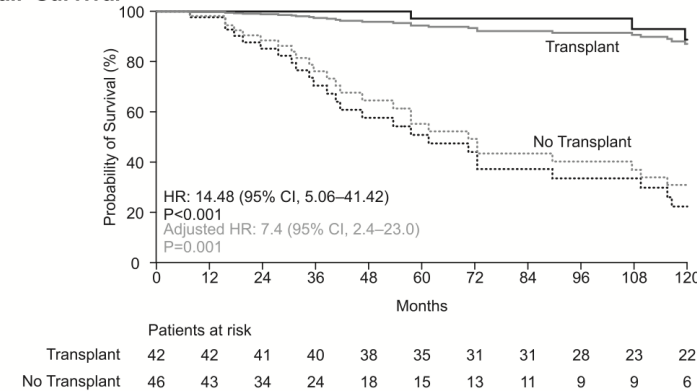
Eighty-eight consecutive patients with metastatic NETs eligible
for liver transplantation according to Milan-NET criteria

Transplant (n = 42) versus no transplant (n = 46; due to non-compliance,
refusals (n=22); waitlist non-availability (n=24)

„Tumour burden between groups did not differ.“

„Transplant patients were younger (40.5 vs. 55.5 years; $p < 0.001$)“

A
Overall Survival



Transplant

5y – 97.2%

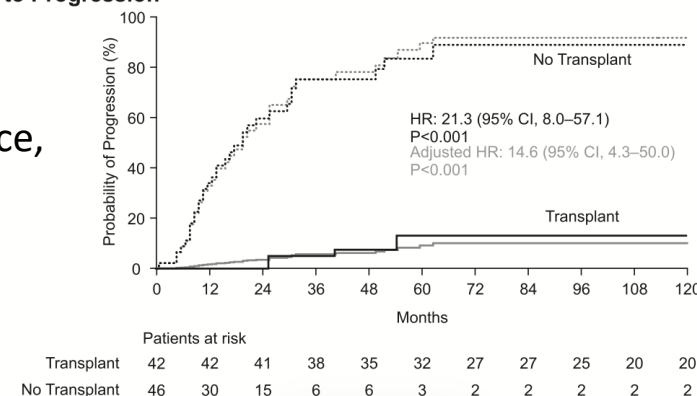
10y – 88.8%

No Transplant

5y – 50.9%

10y – 22.4%

B
Time to Progression

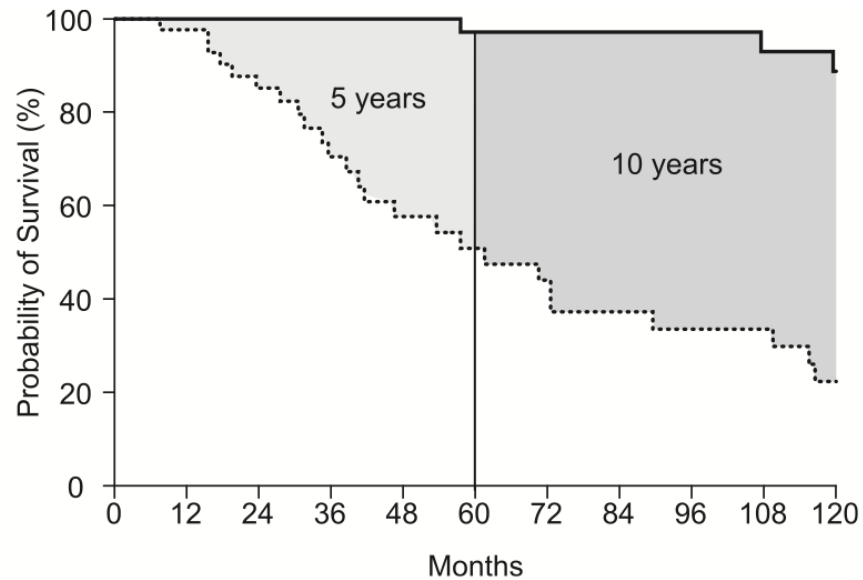


No Transplant

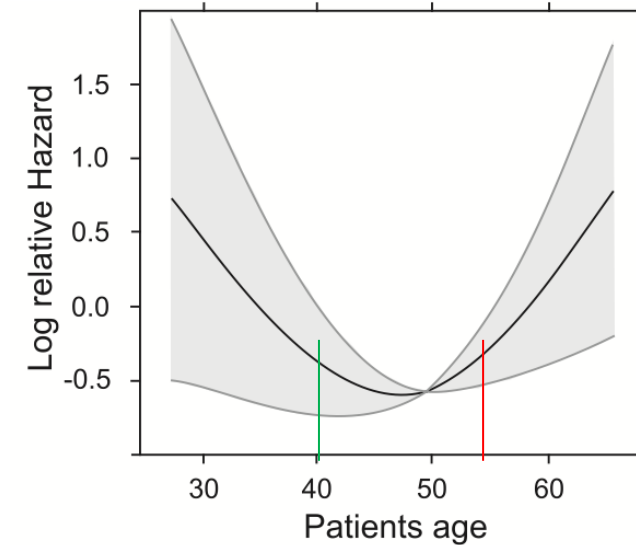
Transplant

Transplant vs Non-Transplant – Benefit ?

Calculated Transplant Benefit



Age-related Risk of Death



Transplant vs Non-Transplant – Benefit ?

Table 2: Baseline characteristics of 88 consecutive neuroendocrine tumor (NET) patients with gastroentero-pancreatic primary tumors, receiving or not receiving liver transplants

	Transplant (42 patients)	No transplant (46 patients)	p value ¹
Age at diagnosis, years			<0.001
Median (range)	40.5 (13–62)	55.5 (29–69)	
Gender, n (%)			0.370
Male	26 (61.9)	33 (71.7)	
Female	16 (38.1)	13 (28.3)	
Site of primary tumor, n (%)			0.342
Ileum/cecum	24 (57.1)	22 (47.8)	
Duodenum, pancreas	15 (35.7)	16 (34.8)	
Colon/stomach	3 (7.2)	8 (17.4)	
T stage of the primary tumor, n (%)			0.048
T1	1 (2.4)	2 (4.4)	
T2	18 (42.8)	7 (15.2)	
T3	16 (38.1)	25 (54.3)	
T4	7 (16.7)	7 (15.2)	
Missing	–	5 (10.9)	
N stage of the primary tumor, n (%)			0.110
N0	7 (16.7)	4 (8.7)	
N1	34 (81.0)	36 (78.3)	
Nx	1 (2.3)	6 (13.0)	
M stage (liver) at diagnosis, n (%)			0.472
M0	5 (11.9)	3 (6.5)	
M1	37 (88.1)	43 (93.5)	

	Transplant (42 patients)	No transplant (46 patients)	p value ¹
WHO 2010 grading, n (%)			0.032
G1 (MIB-1 ≤ 3%)	33 (78.5)	24 (52.2)	
G2 (MIB-1 > 3% ≤ 20%)	7 (16.7)	11 (23.9)	
G3 (MIB-1 > 20%)	–	4 (8.7)	
Infeasible/missing	2 (4.8)	7 (15.2)	
MIB-1			0.581
Median (range)	3.0 (0.2–19.5)	3.0 (0.1–65)	
Locoregional therapy, n (%)			0.003
None	24 (57.1)	34 (73.9)	
Liver resection (elsewhere)	1 (2.4)	2 (4.4)	
TACE ²	17 (40.5)	6 (13.0)	
PRRT	–	4 (8.7)	
WHO 2000 grading, n (%)			0.360
Well differentiated	39 (92.8)	39 (84.8)	
Poorly differentiated	1 (2.4)	4 (8.7)	
Missing	2 (4.8)	3 (6.5)	

Significant Differences:

Patient age

T-stage

Grading

Locoregional therapies

Tendency toward diff.:

Male gender in higher age

Site of primary (colorectal)

Live Poll Question – Liver Transplantation for NELMs

Within the currently discussed limitations

(Grading G1/G2; siNEN & panNEN; no extrahepatic disease; stable disease $\geq$ 6mths;
primary removed prior to Lt; LTB < 50%; age < 60 yrs)

A Pro

B Con

OS in PanNET Patients Eligible for Liver Transplantation

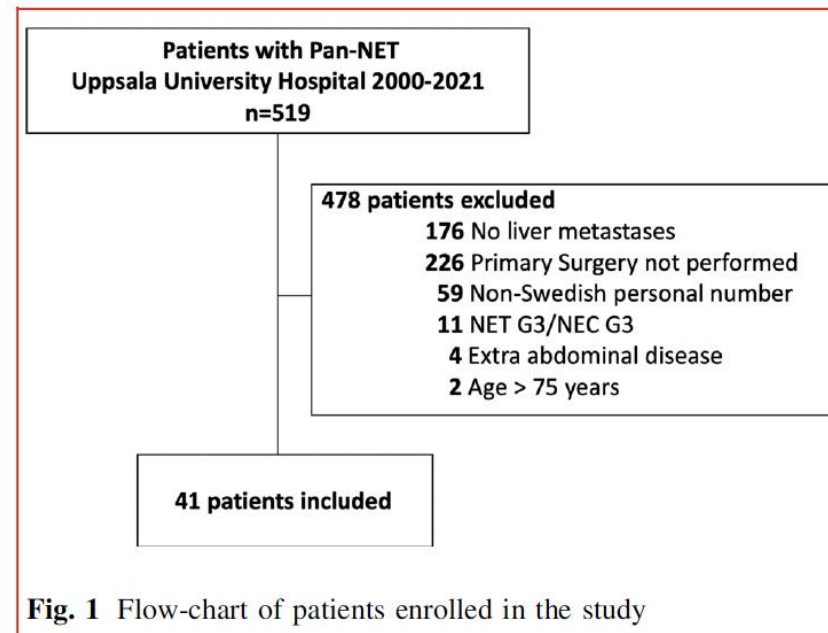
World J Surg (2023) 47:340–347
<https://doi.org/10.1007/s00268-022-06736-1>



ORIGINAL SCIENTIFIC REPORT

Overall Survival in Patients with Stage IV Pan-NET Eligible for Liver Transplantation

Josefine Kjaer¹ · Sara Smith¹ · Per Hellman¹ · Peter Stålberg¹ · Joakim Crona² · Staffan Welin² · Olov Norlén¹



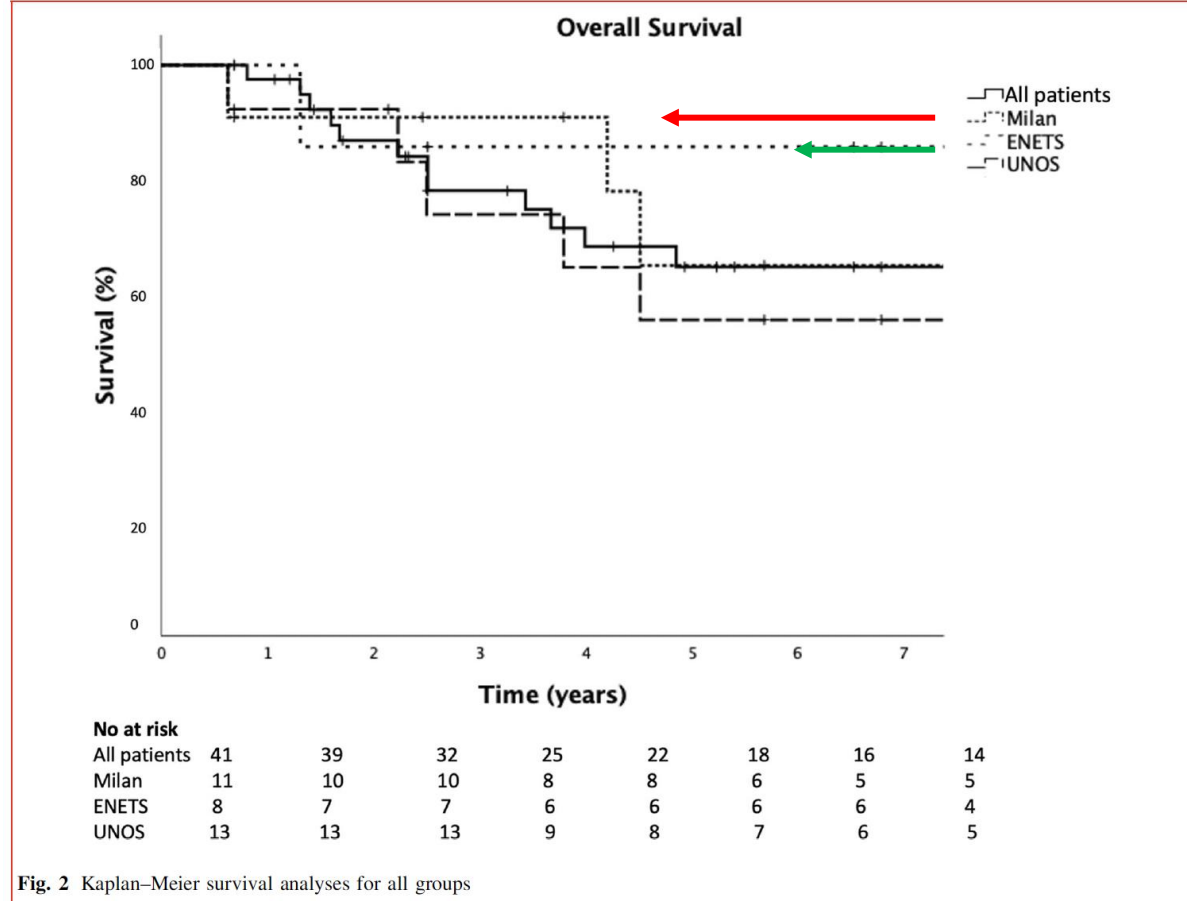
Kjaer et al. World J Surg 2023

OS in PanNET Patients Eligible for Liver Transplantation

Table 1 Baseline characteristics for patients in each group

Baseline characteristics	Patient groups	MILAN	ENETS	UNOS
	Patients meeting inclusion criteria	Milan criteria	ENETS guidelines	UNOS guidelines
Nr of patients	41	11	8	13
<i>Age (years)</i>				
< 55	17 (27.0)	9 (81.8)	8 (100)	12 (92.3)
55–65	13 (44.8)	2 (18.2)	0	1 (7.7)
66–75	11 (50)	0	0	0
<i>Sex</i>				
Female	21 (51.2)	6 (54.5)	6 (75)	8 (61.5)
Hormonal expression Functioning	11 (26.8)	2 (18.2)	3 (37.5)	5 (38.5)
<i>Genetic Syndrome</i>				
MEN-1	4 (9.8)	1 (9.1)	0 (0)	2 (15.4)
VHL	1 (2.4)	0 (0)	0 (0)	0 (0)
<i>CCI</i>				
0	21 (51.2)	8 (70.6)	5 (62.5)	10 (76.9)
1	13 (31.7)	2 (18.2)	2 (25)	2 (15.4)
2	5 (12.2)	1 (9.1)	1 (12.5)	1 (7.7)
> = 3	2 (4.9)	0	0	0
<i>WHO Grade</i>				
NET G1	14 (34.1)	4 (36.4)	3 (37.5)	3 (23.1)
NET G2	27 (65.9)	7 (63.6)	5 (62.5)	10 (76.9)
<i>Number of LM</i>				
1–3	19 (46.3)	2 (18.2)	4 (50)	5 (38.5)
4–9	12 (29.3)	5 (45.5)	1 (12.5)	3 (23.1)
> 10	10 (24.4)	4 (36.4)	3 (37.5)	5 (38.5)
<i>Size of largest LM (cm)</i>				
	1.5 (1.0–2.0) #	1.0 (0.9–3.0) #	1.0 (0.9–1.8) #	1.5 (1.0–2.2) #
<i>Time period (Time 0)</i>				
2000–2010	18 (43.9)	7 (63.6)	4 (50.0)	7 (53.8)
2011–2021	23 (56.1)	4 (36.3)	4 (50.0)	6 (46.2)
Time from diagnosis to Time 0	0.9 (0.3–3.3) #	3.0 (0.9–5.5) #	1.6 (0.5–4.8) #	3.0 (0.9–5.6) #

OS in PanNET Patients Eligible for Liver Transplantation



Patients with pan-NET, hypothetically stratified regarding different selection criteria for LT
Showed higher OS w/o LT as in published LT Data

Kjaer et al. World J Surg 2023

Challenging the MILAN Criteria

Table 2 Baseline characteristics in different patient groups within our cohort depending on hypothetical selection criteria for liver transplantation

Baseline characteristic	Patient groups		
	1: <65 years	2: <55 years	3: Milan criteria
Median age, years (range)	55 (33–65) ^a	46 (34–59) ^a	45 (34–54) ^a
Female	31 (40)	22 (56)	17 (52)
Hormonal symptoms	42 (54)	19 (49)	16 (49)
Carcinoid heart disease	7 (9)	4 (10)	4 (12)
Median no. LM	>10	>10	>10
LM bilobar	59 (76)	31 (80)	27 (82)
Tumor grade			
1	41 (53)	56 %	18 (55)
2	10 (13)	13 %	4 (12)
Unknown	27 (35)	31 %	11 (33)
Total	78 (100)	39 (100)	33 (100)

^a Values within parentheses are percentages unless otherwise indicated

LM liver metastases, no. number; tumor grade, tumor grade according to Ki-67 index grade 1: <3 %, grade 2: 3–20 % as specified by WHO [22]

Patient group with **GI-NET** hypothetically selected for LT acc. to Milan criteria
N=33

Comparison with:

Group I: n= 78 Pat. < 65 yrs

Group II: n= 39 Pat. < 55yrs

Challenging the MILAN Criteria

< 65 yrs

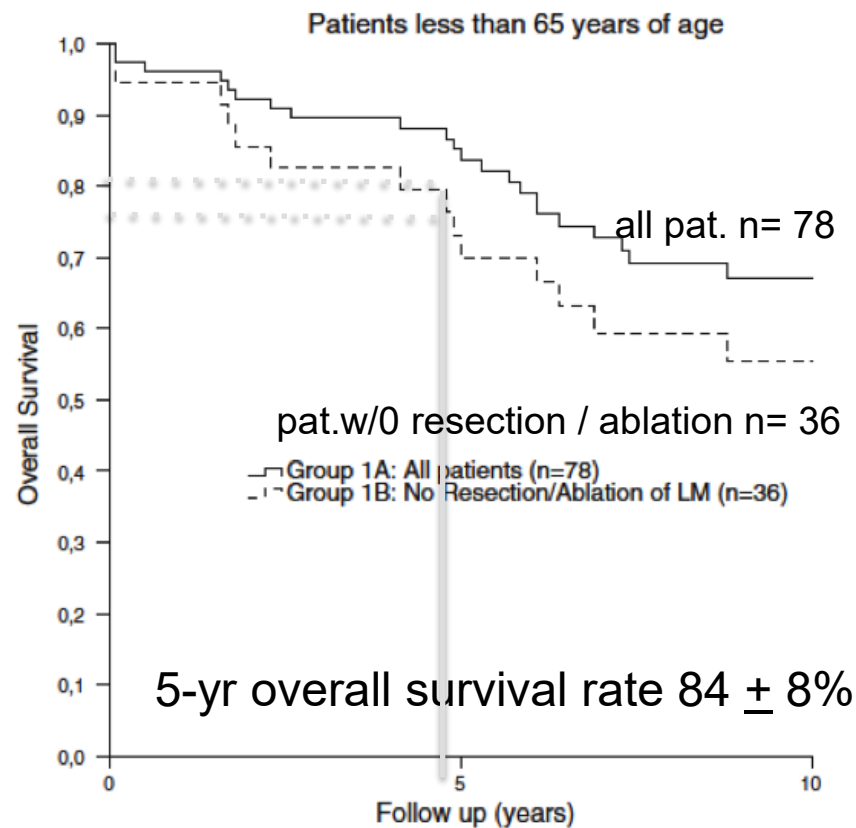


Fig. 1 Overall survival of patients <65 years of age ($n = 78$), divided into either all patients (A) or those in whom no liver surgery or ablation with either radiofrequency or microwave were performed (B)

< 55 yrs

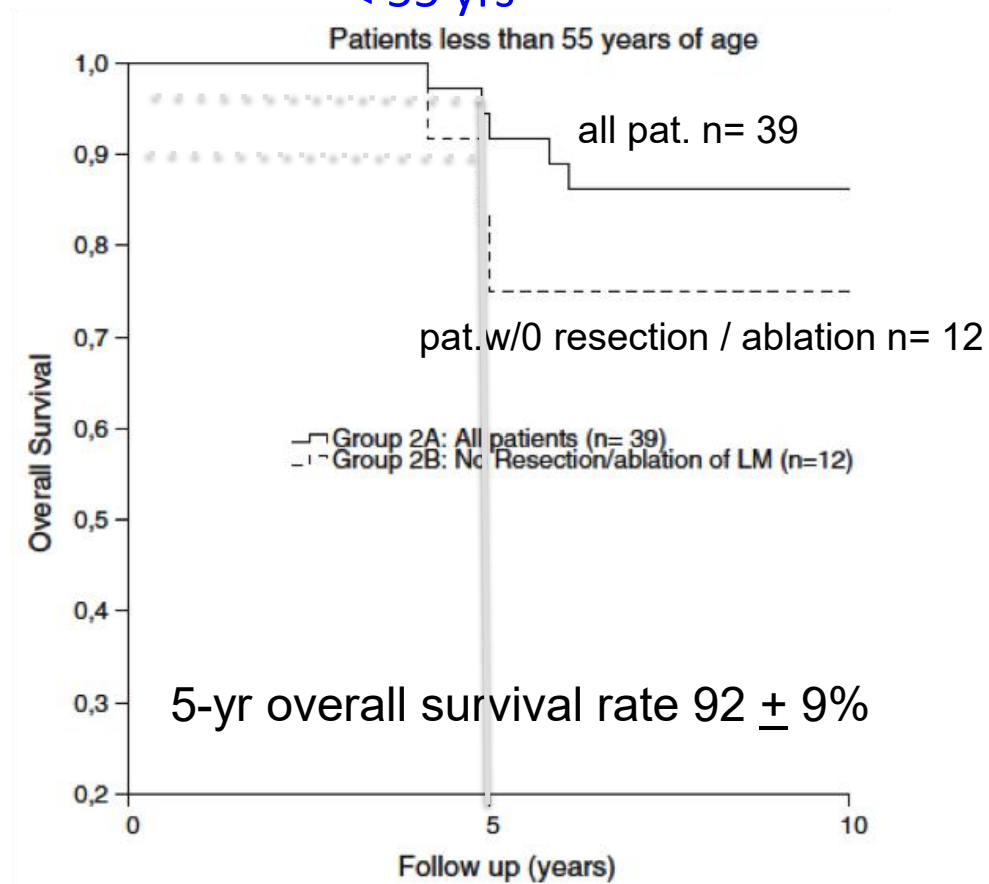


Fig. 2 Overall survival of patients <55 years of age ($n = 39$), divided into either all patients (A) or those in whom no liver surgery or ablation with either radiofrequency or microwave were performed (B)

Norlen et al. W J Surg 2014

Challenging the MILAN Criteria

Fulfilling Milan criteria

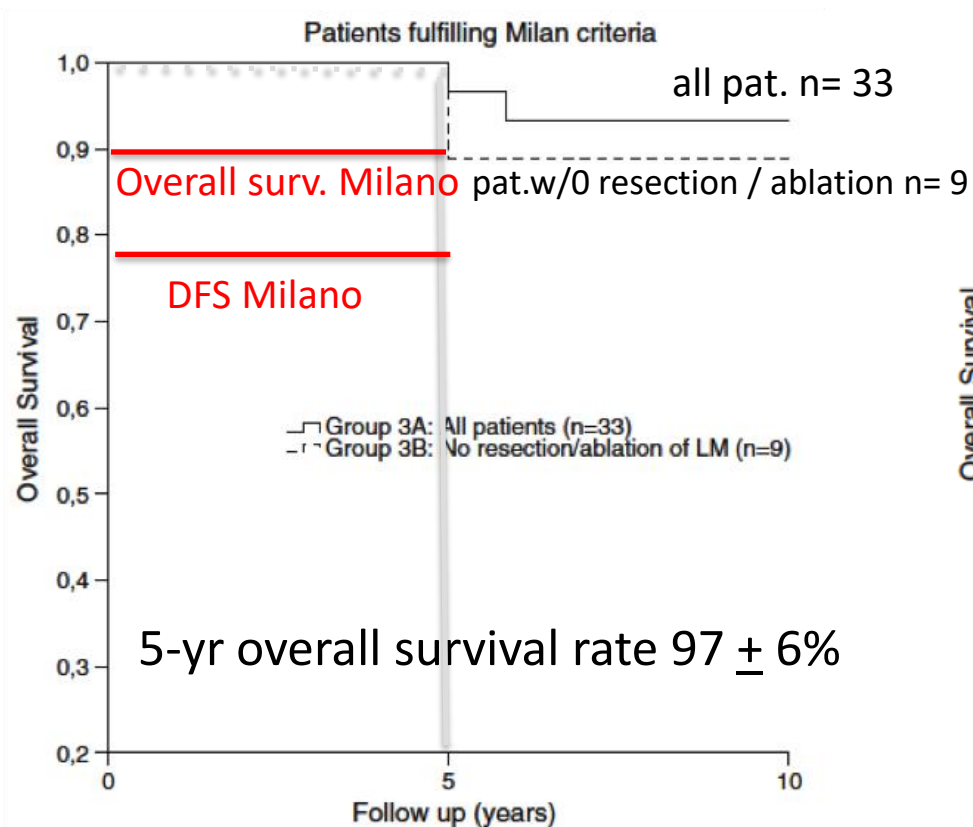


Fig. 3 Overall survival of patients fulfilling the Milan criteria ($n = 33$), divided into either all patients (A) or those in whom no liver surgery or ablation with either radiofrequency or microwave were performed (B)

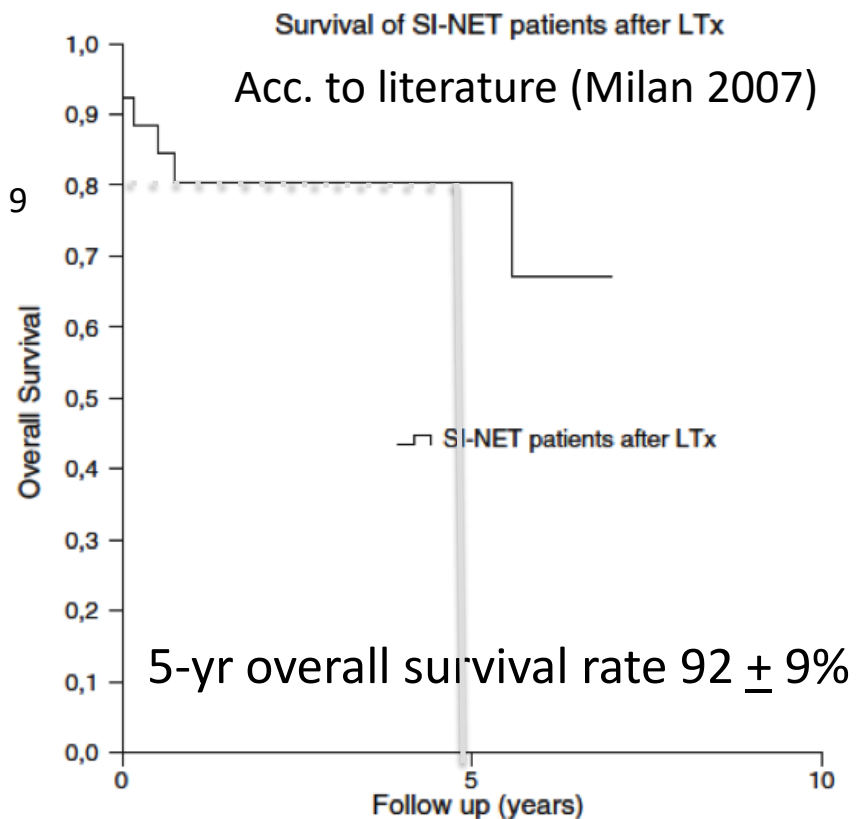


Fig. 4 Survival of patients with small intestinal neuroendocrine tumors (SI-NETs) after liver transplantation (LTx) as extracted from the literature ($n = 26$)

Norlen et al. W J Surg 2014

Controversies in NEN: An ENETS position statement on the role of Liver Transplantation (LT) in patients with advanced small-intestinal and pancreatic NETs; (accepted)

✓ Key Messages

- Existing evidence is confounded by retrospective nature, selection bias and varying eligibility criteria
- LT in NET is rarely curative and should be framed as survival-modifying/palliative treatment option
- Selection should prioritise transplant benefit vs standard of care, and not eligibility alone
- Tumour biology (grade, kinetics, imaging phenotype) is the dominant determinant of outcome
- Milan criteria preferentially select favourable biology, not necessarily maximal transplant benefit
- Decisions regarding extrahepatic disease and functioning tumours remain MDT-driven
- Prospective validation of selection strategies is lacking

Thank you !





X @HalletJulie

@halletjulie.md

Liver transplant for NETs liver metastases

Promise for cure or palliation?

Julie Hallet, MD. MSc. FRCSC. FSSO. FACS.

Hepato-Biliary, Pancreatic, and Gastrointestinal Surgical Oncology

Associate Professor of Surgery & IHPME – University of Toronto

Canada Research Chair in Patient-Centred & Quality Cancer Surgery

X @HalletJulie

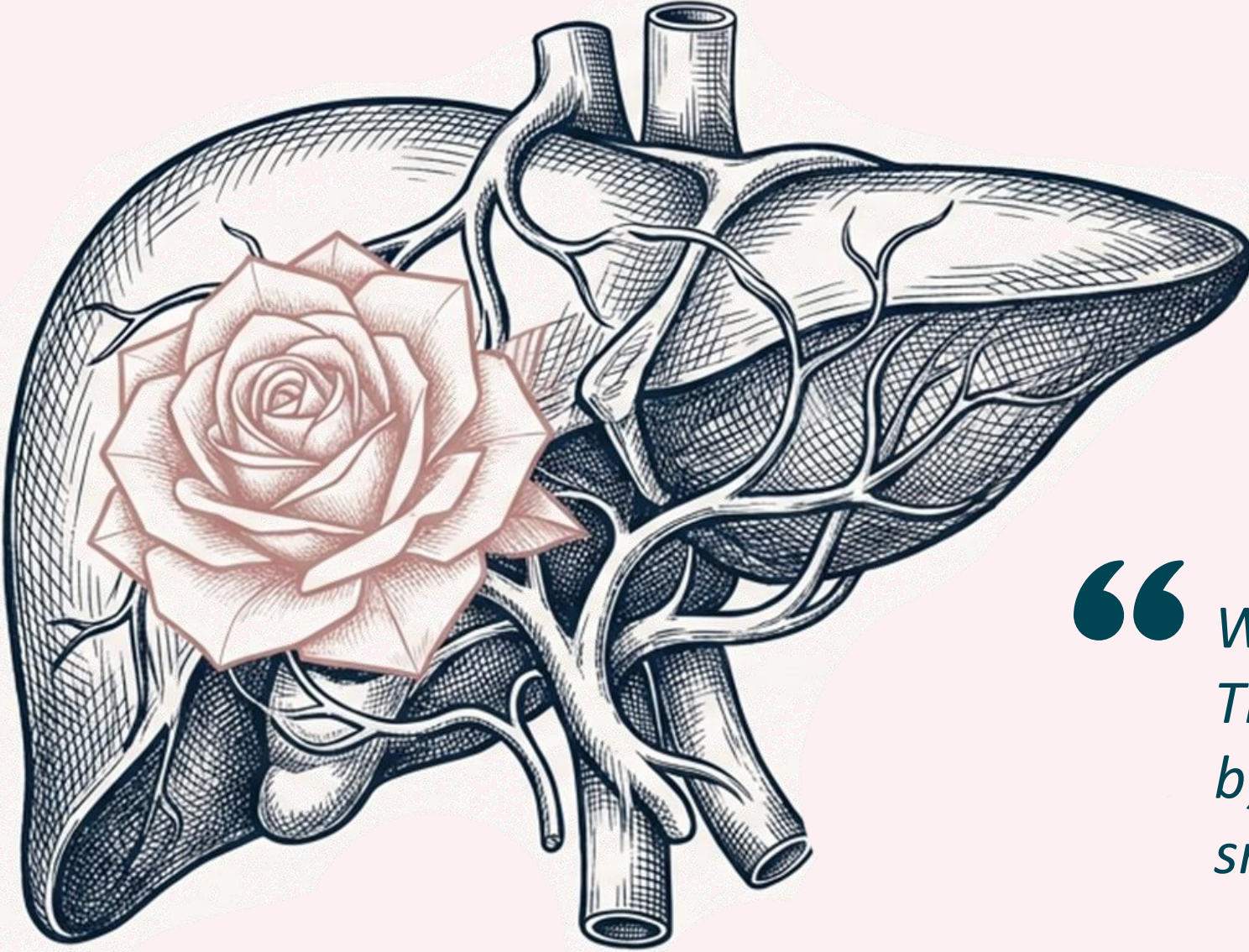


SUSAN LESLIE CLINIC FOR
NEUROENDOCRINE TUMORS



DISCLOSURE SLIDE

Receipt of honoraria or consultation fees: Ipsen, Novartis.

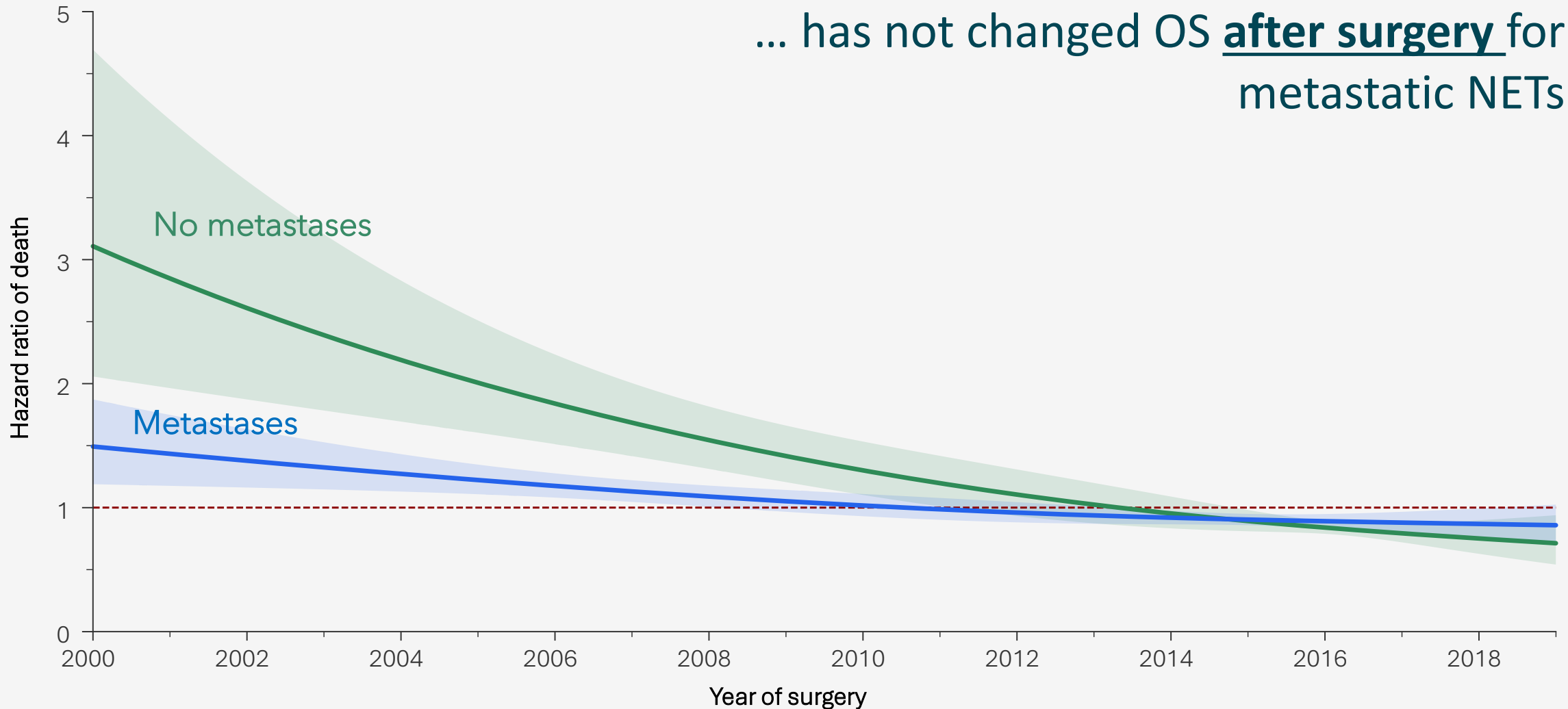


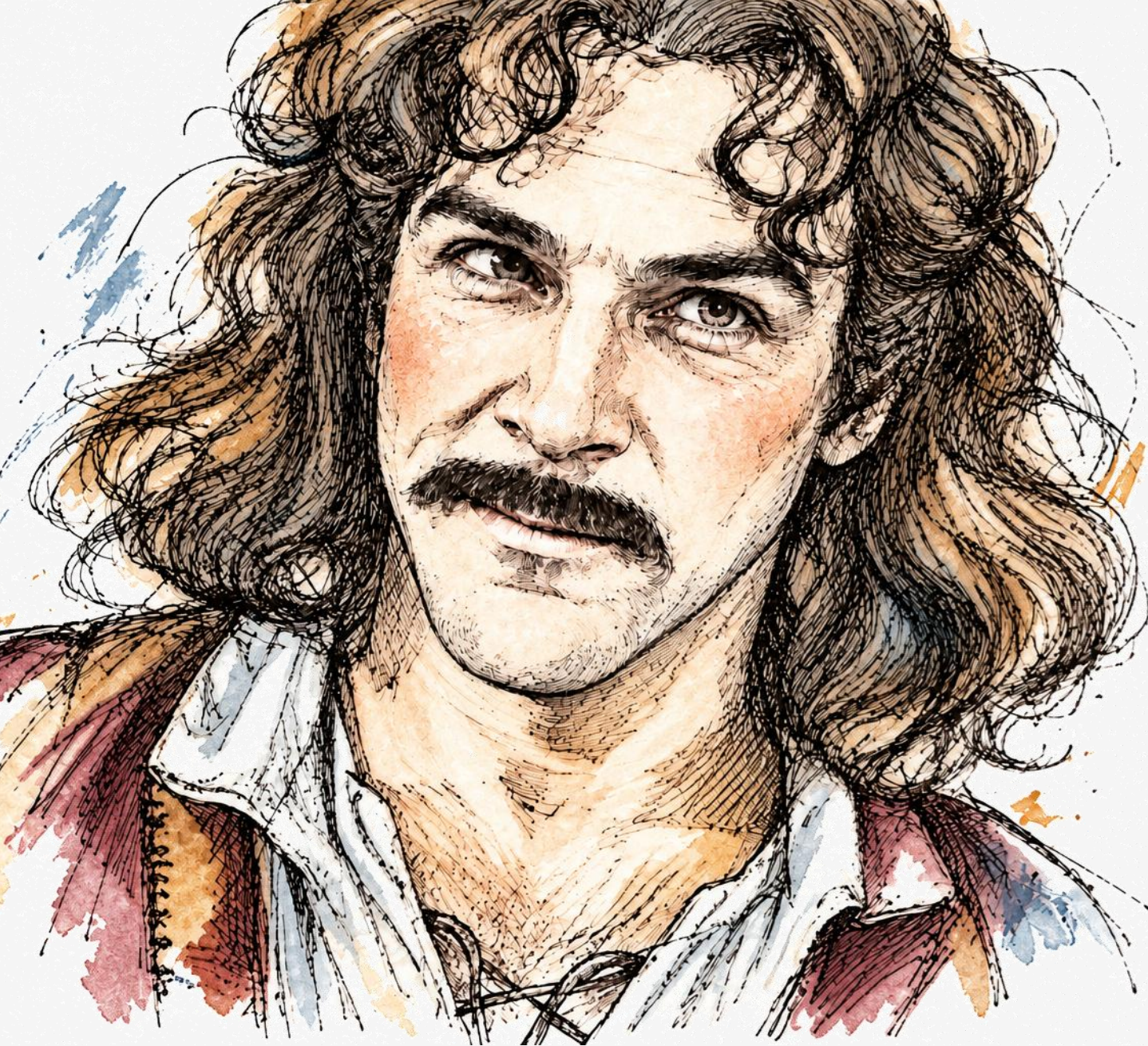
“ *What’s in a name?
That which we call a rose
by any other name would
smell as sweet.*

Romeo and Juliet 2.2.43–44

Progress in NETs care

... has not changed OS after surgery for metastatic NETs





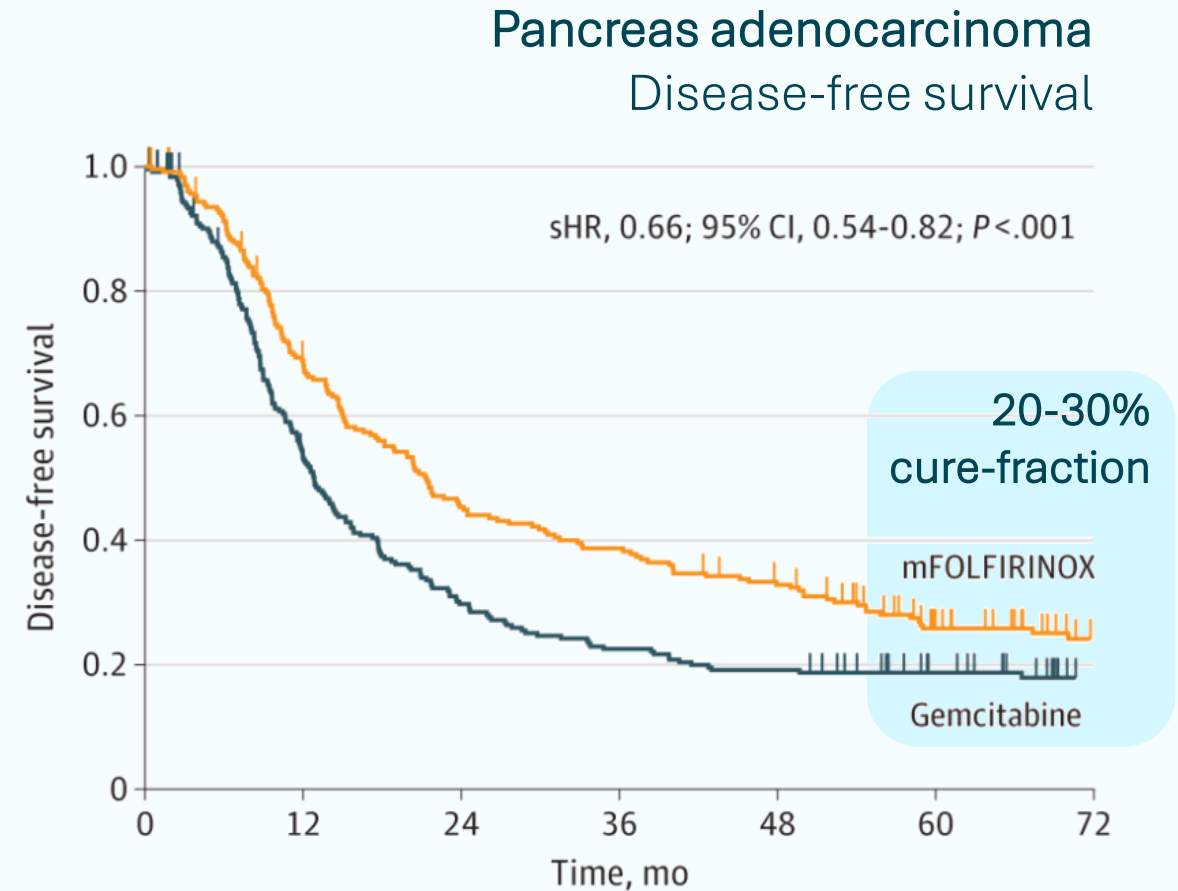
*You keep using that word.
I do not think it means
what you think it means*

Inigo Montoya, The Princess Bride, 1987

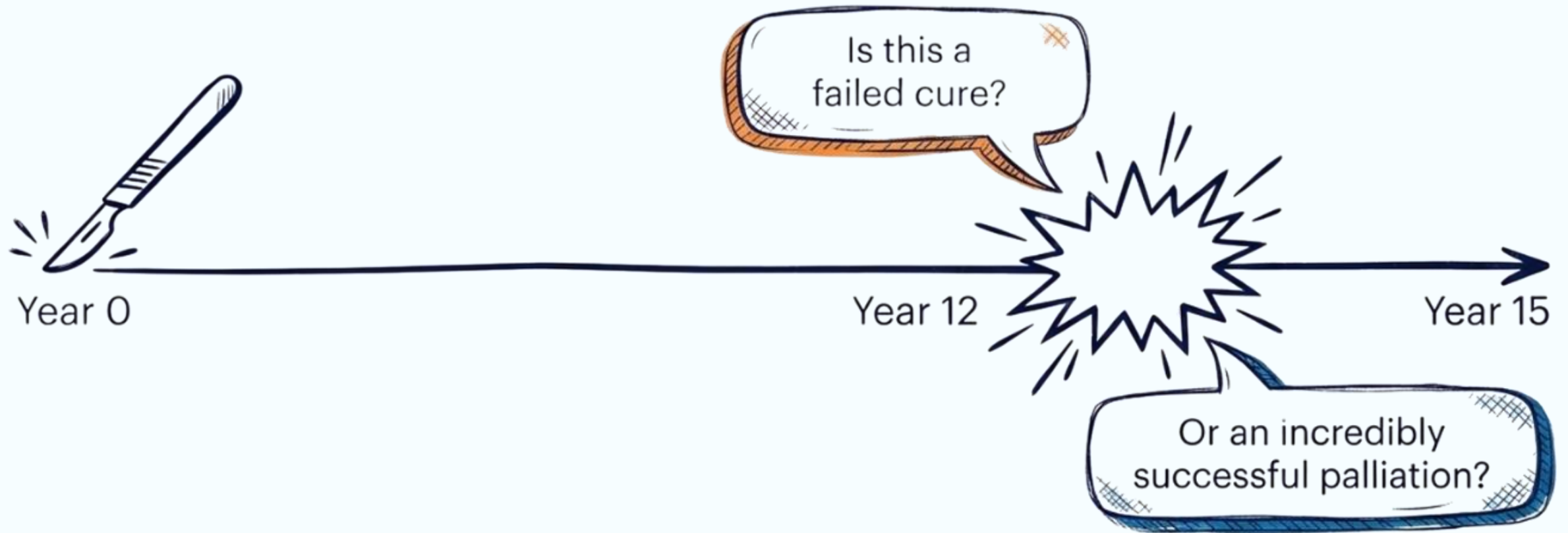
What is *cure*?

Cure-fraction - curative intent

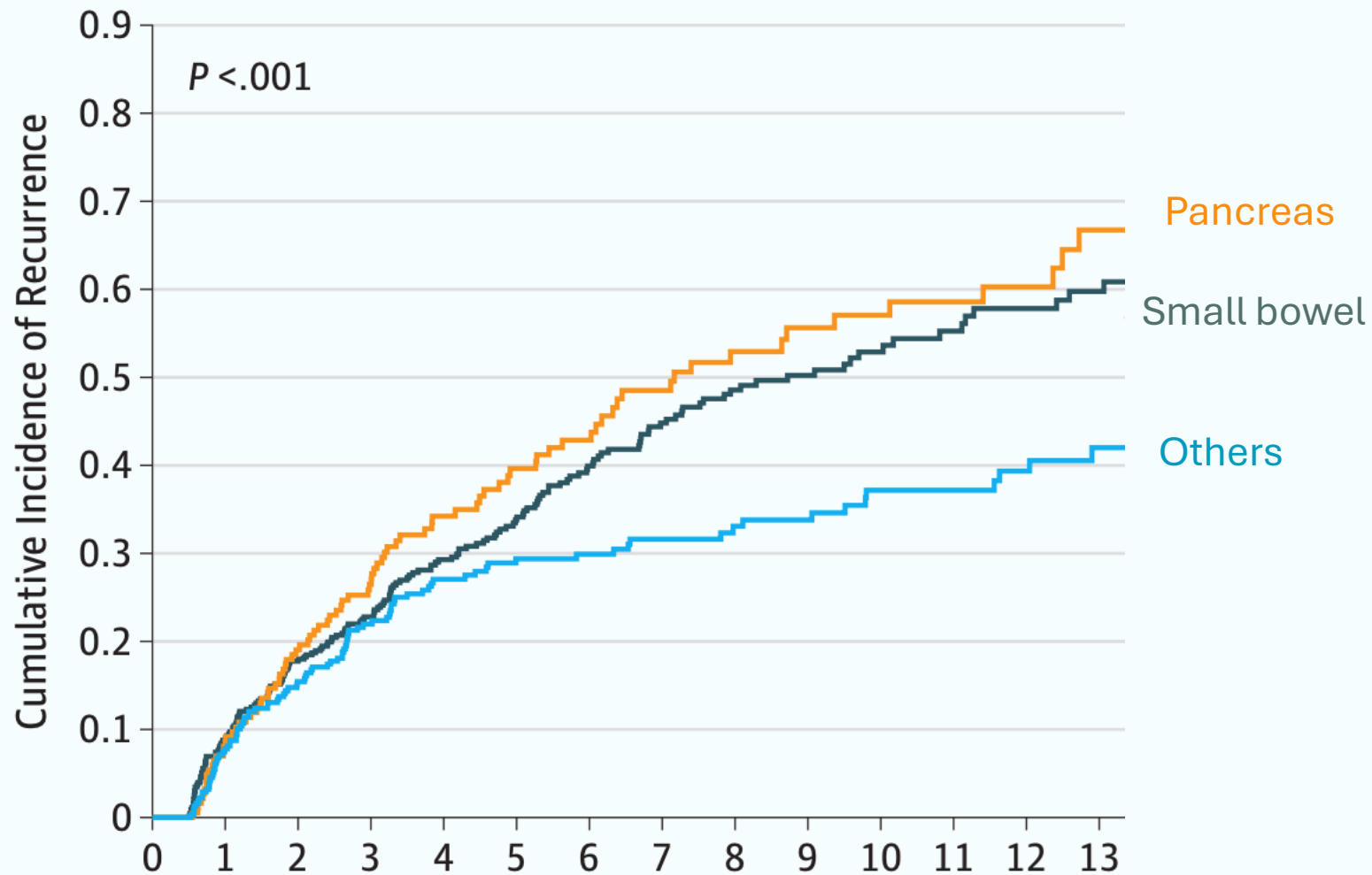
Subset of patient whose disease-specific mortality return to baseline.
Plateau in survival curves.



What is *cure*?

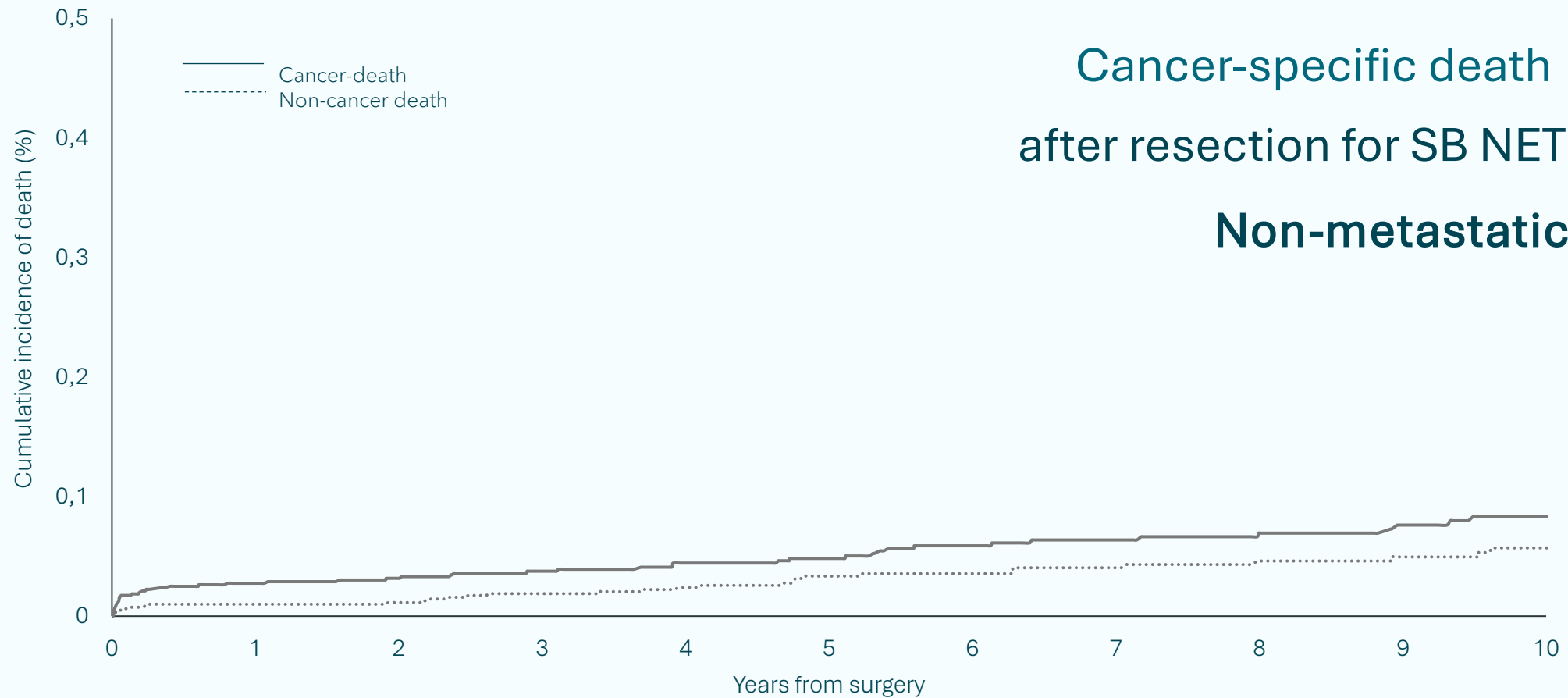


Is there a *cure* in NETs?

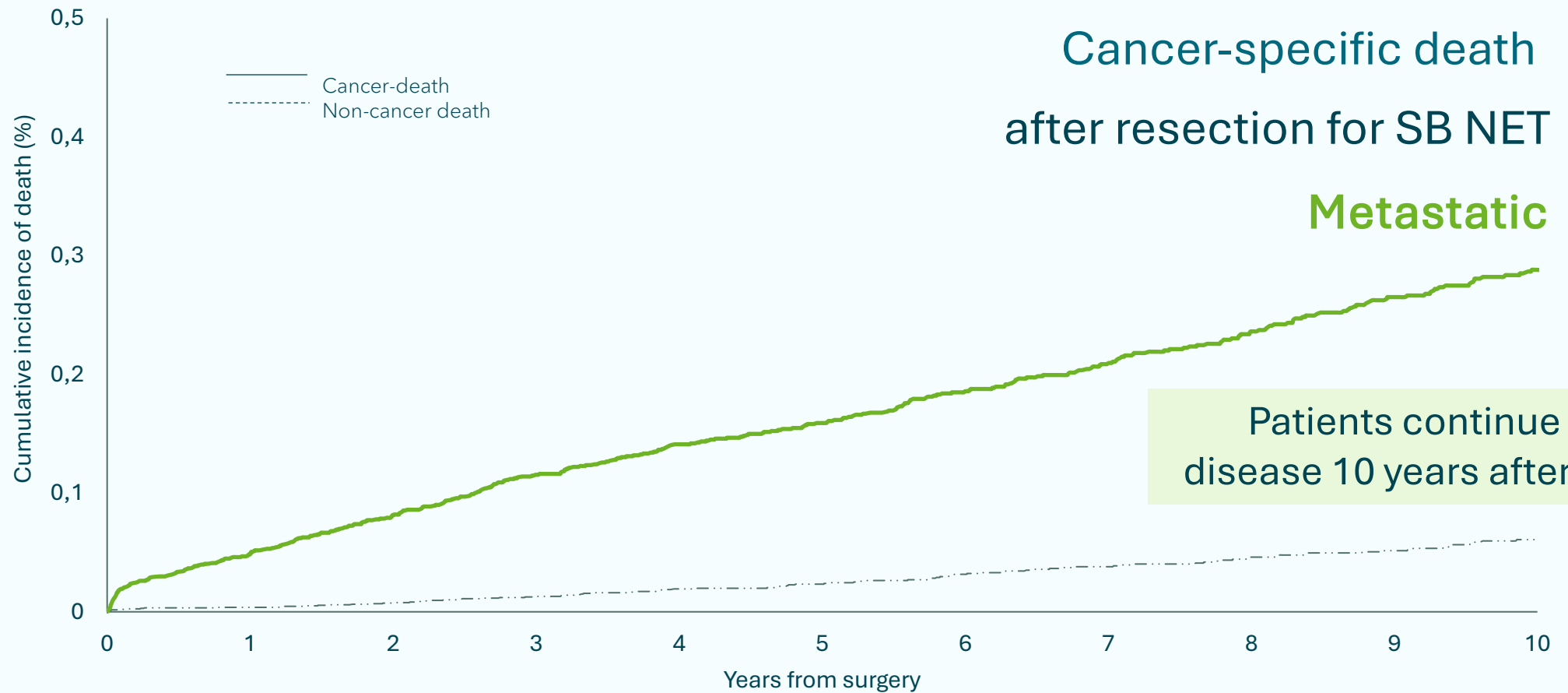


Recurrence after
resection
**No plateau after
10 years**

Is there a *cure* in NETs?



Is there a *cure* in NETs?



Is there a *cure* in NETs after transplant?

Resection Versus Transplantation for Liver Metastases From Neuroendocrine Tumors

J. Coppa, A. Pulvirenti, M. Schiavo, R. Romito, P. Collini, M. Di Bartolomeo, A. Fabbri, E. Regalia, and V. Mazzaferro

Transplantation Proceedings, 33, 1537–1539 (2001)

1987-1999
n=9

Neuroendocrine tumors metastatic to the liver: How to select patients for liver transplantation? ☆

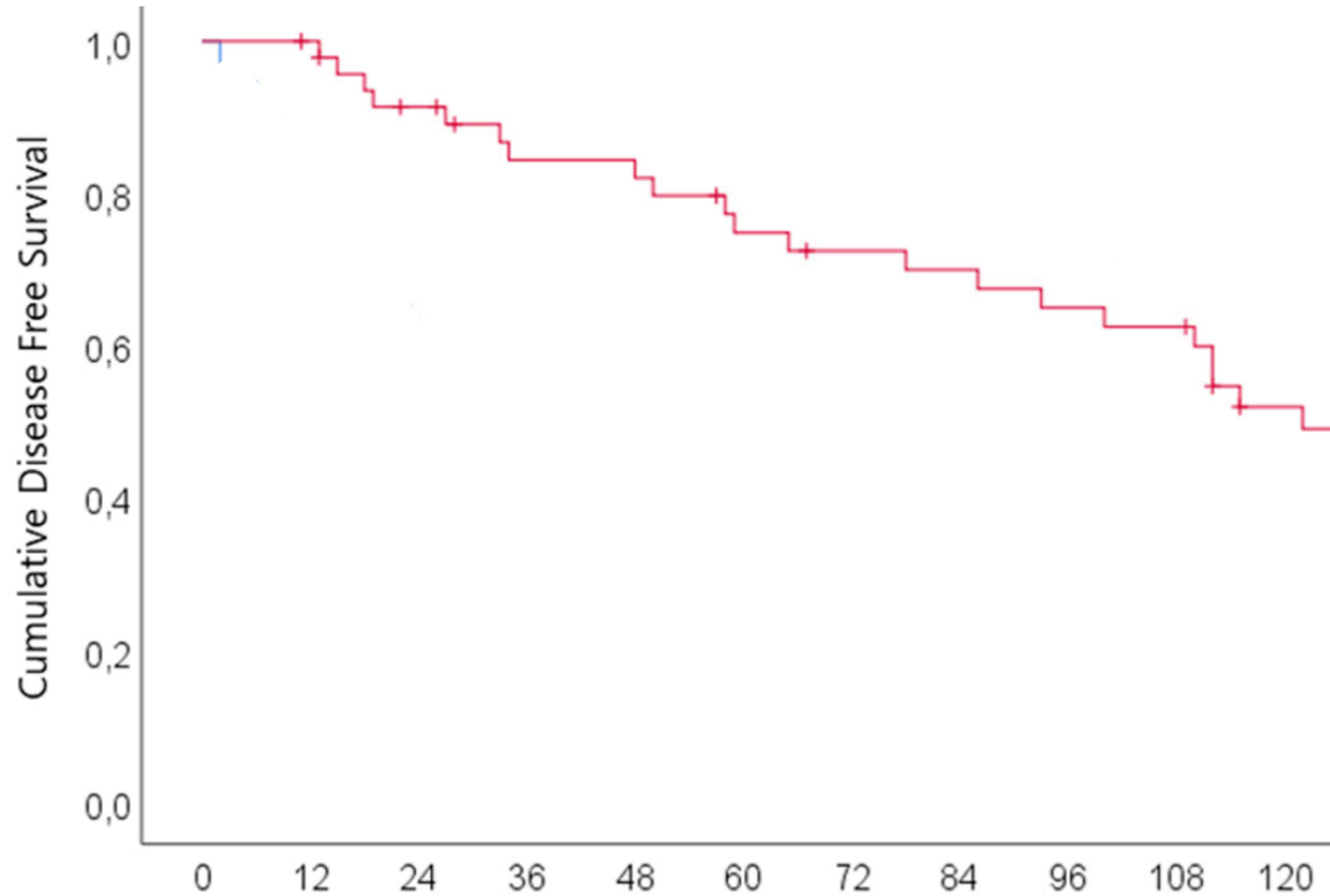
Vincenzo Mazzaferro*, Andrea Pulvirenti, Jorgelina Coppa

*Gastrointestinal Surgery and Liver Transplantation Unit, National Cancer Institute, Istituto Nazionale Tumori Fondazione IRCCS,
Via Venezian 1, Milan 20133, Italy*

Journal of Hepatology 47 (2007) 454–475

Pre-2006
n=26

Is there a *cure* in NETs after transplant?



>40% recurrence /
progression at 10 years
No plateau

Not a cure

Door A: Curative



Traditional binary
– cure or not

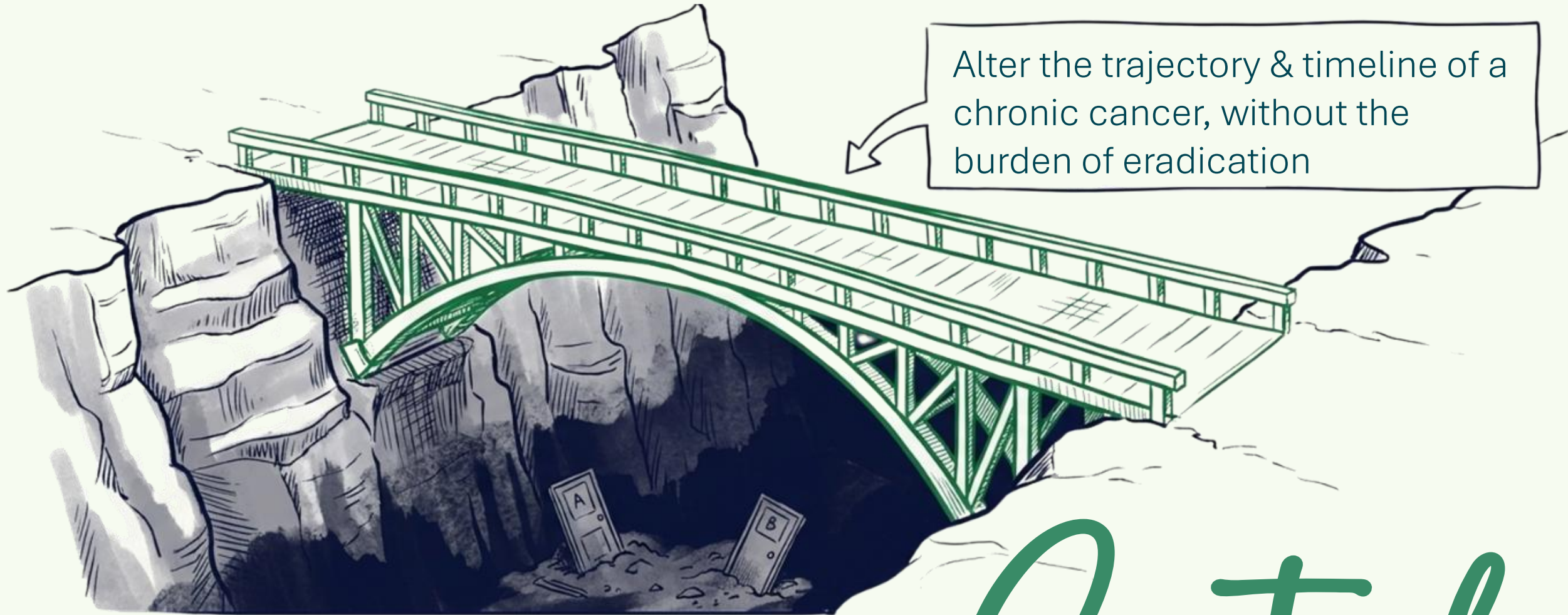
Door B: Palliative



Everything else
is palliation

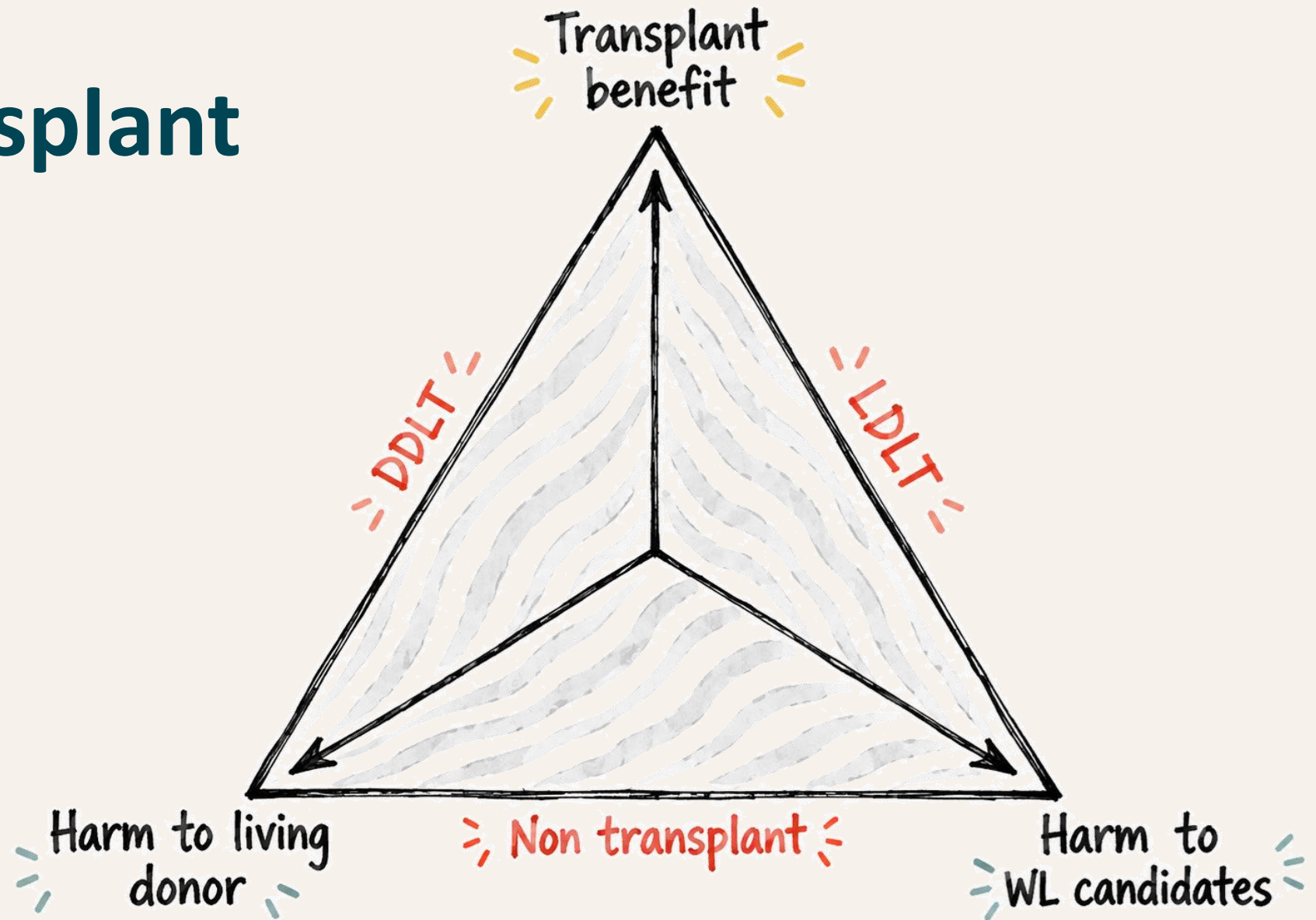


Between cure and palliation



Control

Liver transplant benefit



Liver transplant benefit

- established in HCC

$$\left[\begin{array}{c} \text{survival} \\ \text{with LT} \end{array} \right] - \left[\begin{array}{c} \text{survival} \\ \text{without LT} \end{array} \right] = \left[\text{benefit} \right]$$


Liver transplant benefit

- established in HCC

$$\left[\begin{array}{c} \text{survival} \\ \text{with LT} \end{array} \right] - \left[\begin{array}{c} \text{survival} \\ \text{without LT} \end{array} \right] = \left[\text{benefit} \right]$$



What do
we know?



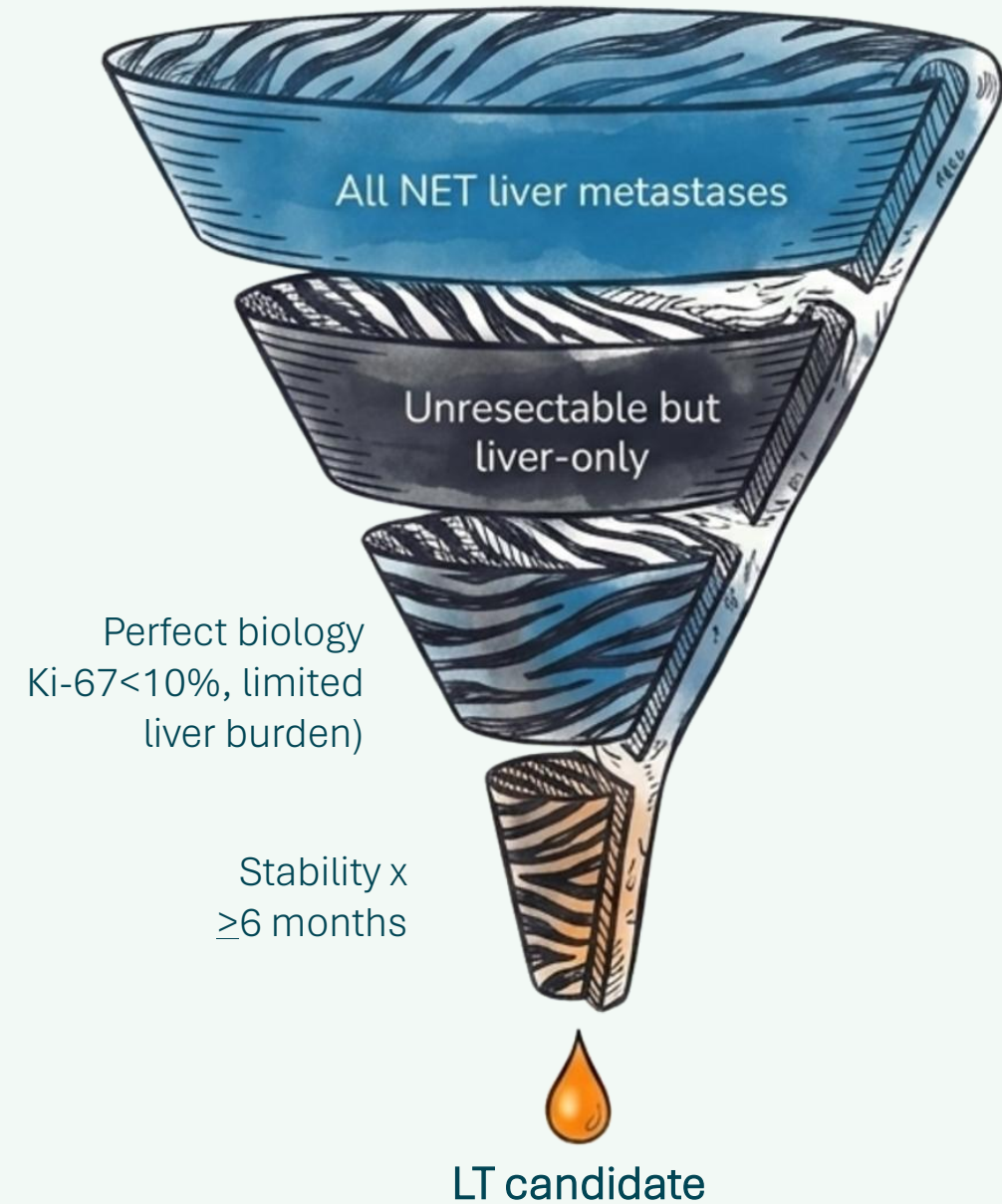
Milan criteria

Inclusion criteria

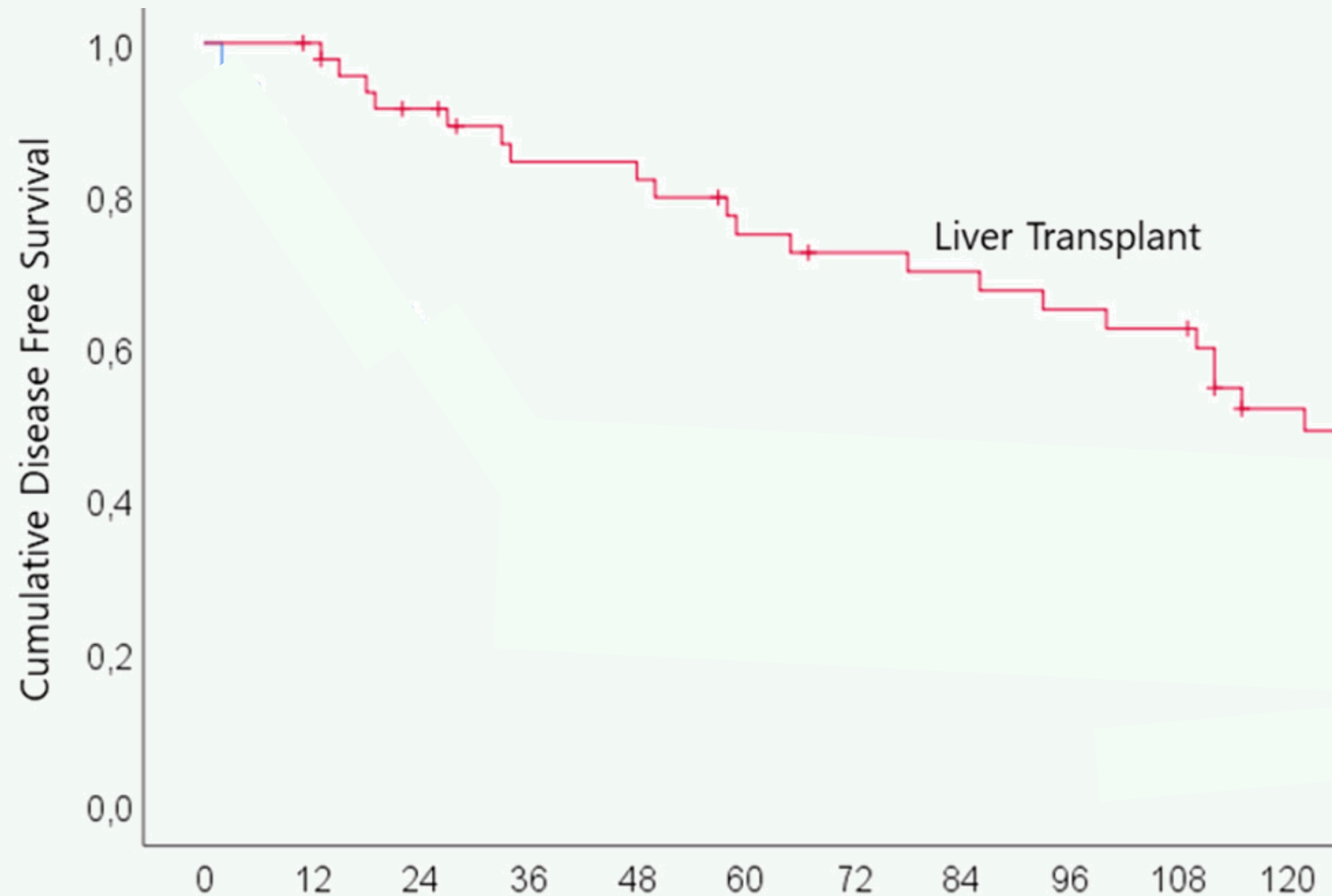
1. Confirmed histology of carcinoid tumor (low-grade neuroendocrine tumors) with or without syndrome Ki-67 <10%
2. Primary tumor drained by the portal system (pancreas and intermediate gut: from distal stomach to sigmoid colon) removed with a curative resection (pre-transplant removal of all extra-hepatic tumor deposits) through surgical procedures different and separate from transplantation
3. Metastatic diffusion to liver parenchyma $\leq 50\%$
4. Good response or stable disease for at least 6 months during the pre-transplantation period
5. Age ≤ 55 years

Exclusion criteria

1. Small-cell carcinoma and high-grade neuroendocrine carcinomas (non-carcinoid tumors)
2. Other medical/surgical conditions contraindicating liver transplantation, including previous tumors
3. Non-gastrointestinal carcinoids or tumors not-drained by the portal system

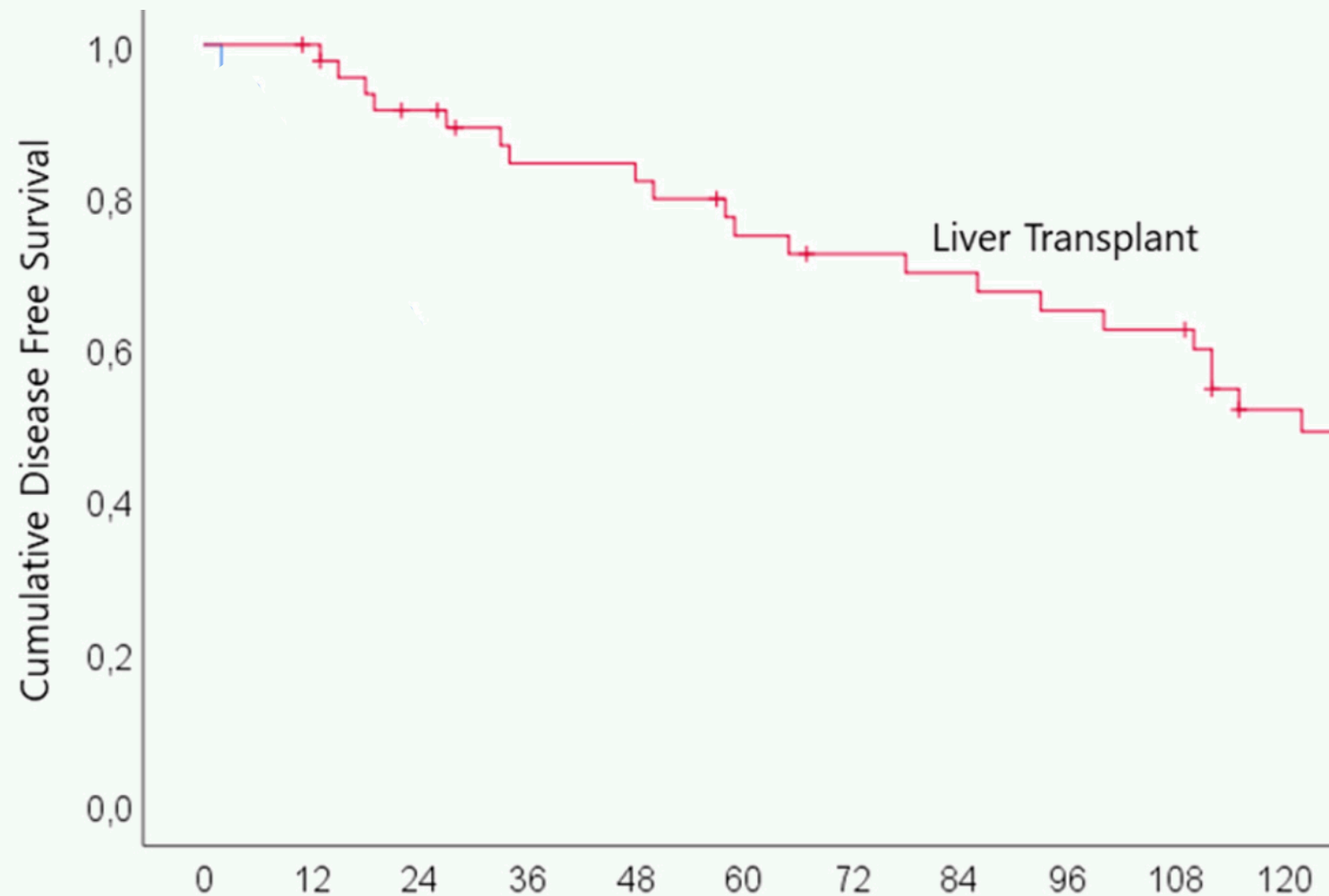


LT within Milan cannot be compared to resection



LT patients are
hyperselected

LT within Milan yields favorable long-term outcomes



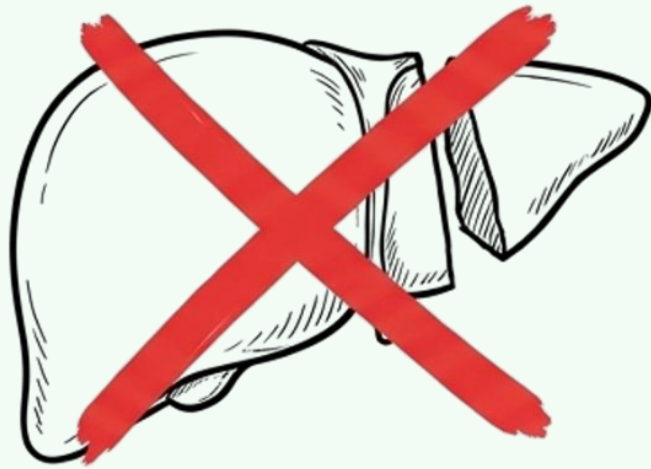
Observation from
single arm group of
patients *selected* for LT

5-year OS 95%

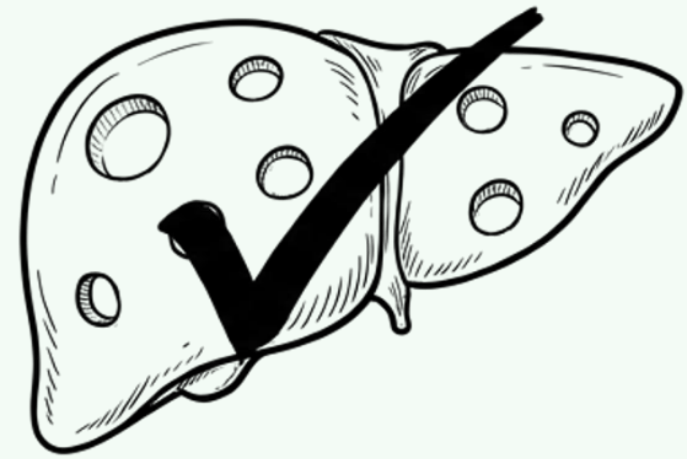
5-year DFS 52%

Most patients within Milan are resectable

with selection & tailored technique



No anatomical
resection



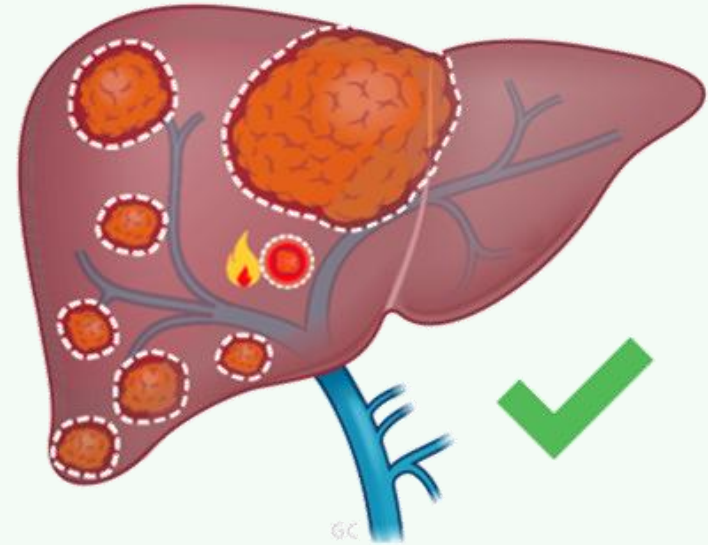
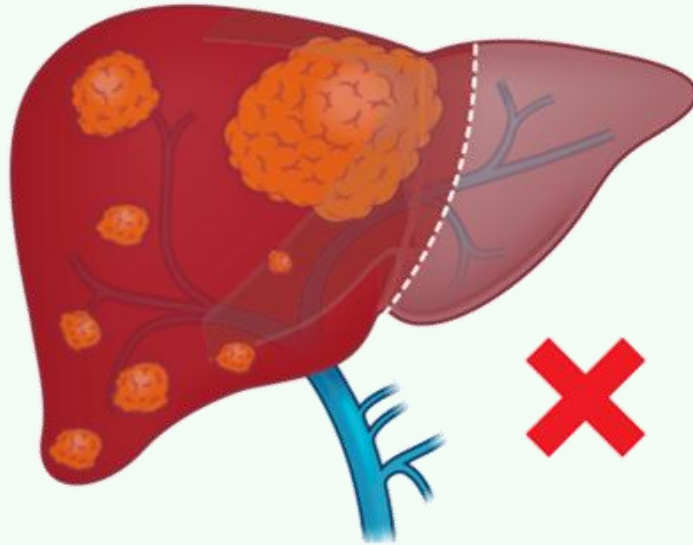
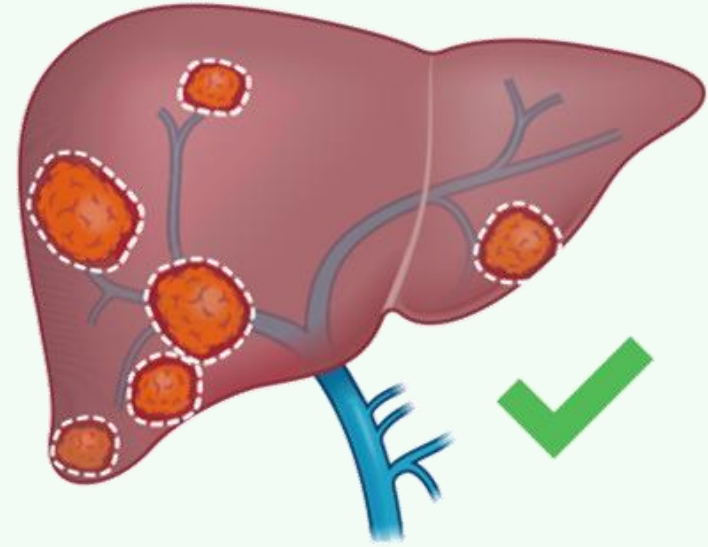
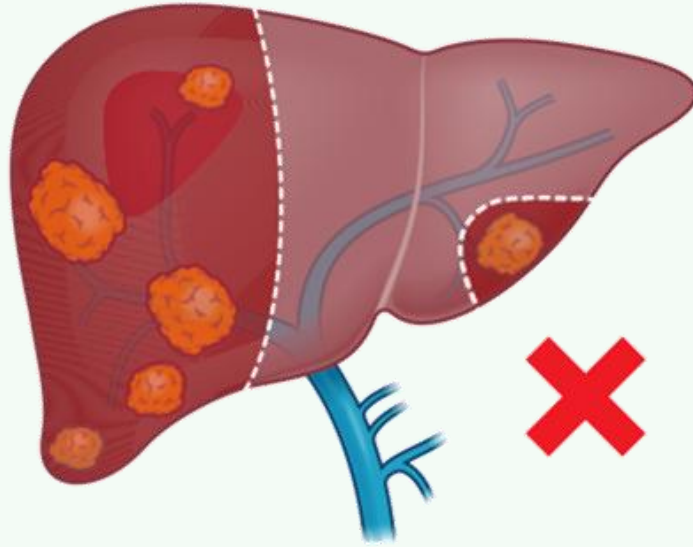
Parenchyma-sparing
with enucleations

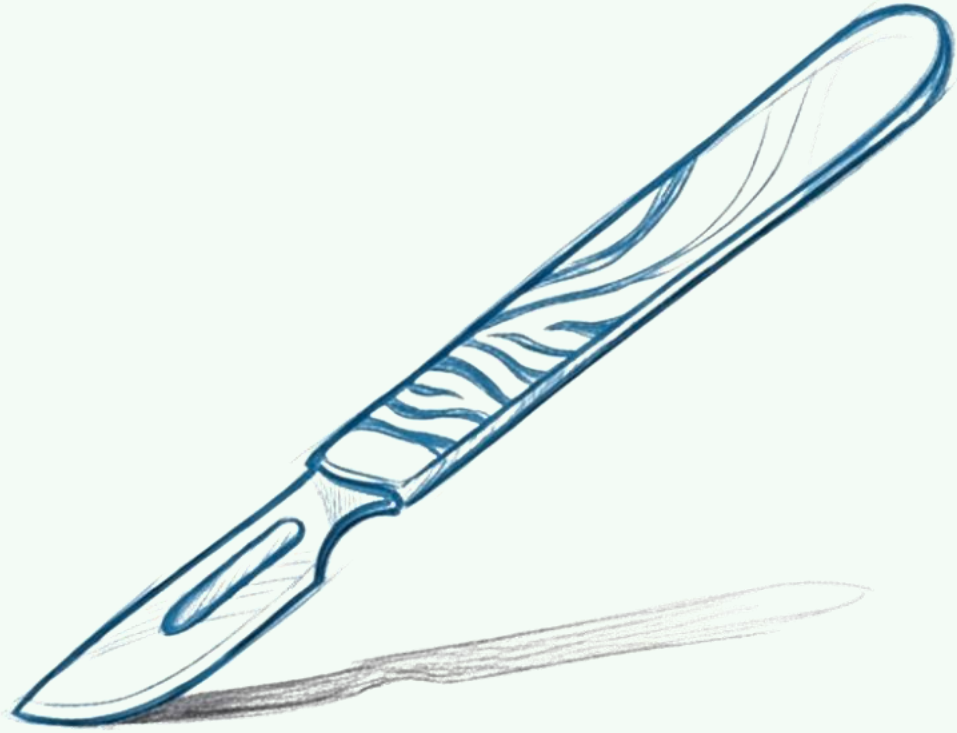
100%

additional liver metastases
in normal liver

No R0 resection
for NETs liver metastases

Tailor the technique





Many patients not eligible
for LT (within Milan)
are eligible for resection.

Outside Milan, LT does worse

Lower survival & higher recurrence vs. within Milan

Overall survival
HR 2.40
(95%CI 1.16–4.92)

15 centers · n=225 LT

Eshuminov D et al. Ann Surg. 2023;277(5)

	Milan-in	Milan-out
5-yr OS	71%	58%
5-yr DFS	59%	36%

13 centers · n=91 · 1995–2024

Bosca A et al. J. Clin. Med. 2026, 15, 938

No difference vs. resection
observed outside of Milan

Overall survival
HR 0.64
(95%CI 0.31–1.33)

15 centers · n=225 LT
(matched analysis)

Eshuminov D et al. Ann Surg. 2023;277(5)

Milan-era survival cannot be transferred to different selection.

Outside Milan is not one population; it is several.





As long as we keep Milan as the reference point, we will not make progress and LT will not deliver benefit to patients with NETs

- Milan criteria describe patients who can be resected
- Outside Milan – heterogeneous population where benefit is unknown



Retire Milan criteria for NETs LT.

Define & standardize unresectability.

Build evidence on what patients may benefit.





What we
don't know

Where a role exists?

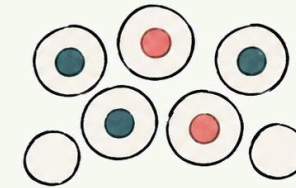
For what patients?

Refractory functioning tumours

Carcinoid syndrome · insulinoma · VIPoma
Not controlled by other therapies.
Unresectable using parenchyma-sparing techniques

Goal: symptom control, not OS

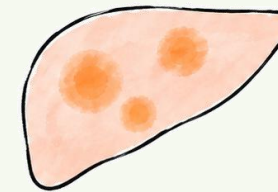
What biology criteria?



Ki-67
what threshold?



Molecular markers
which ones?



Functional imaging
SSTR-PET / FDG-PET avidity



and what else?



What is the end-goal?

How to define *benefit*?



Limitations of OS in
assessing therapies for
NETs



Define relevant outcomes with clinicians & patients:

- Endocrine control
- Symptom-free interval
- Time off systemic therapy; treatment-free survival
- PROMs and QoL

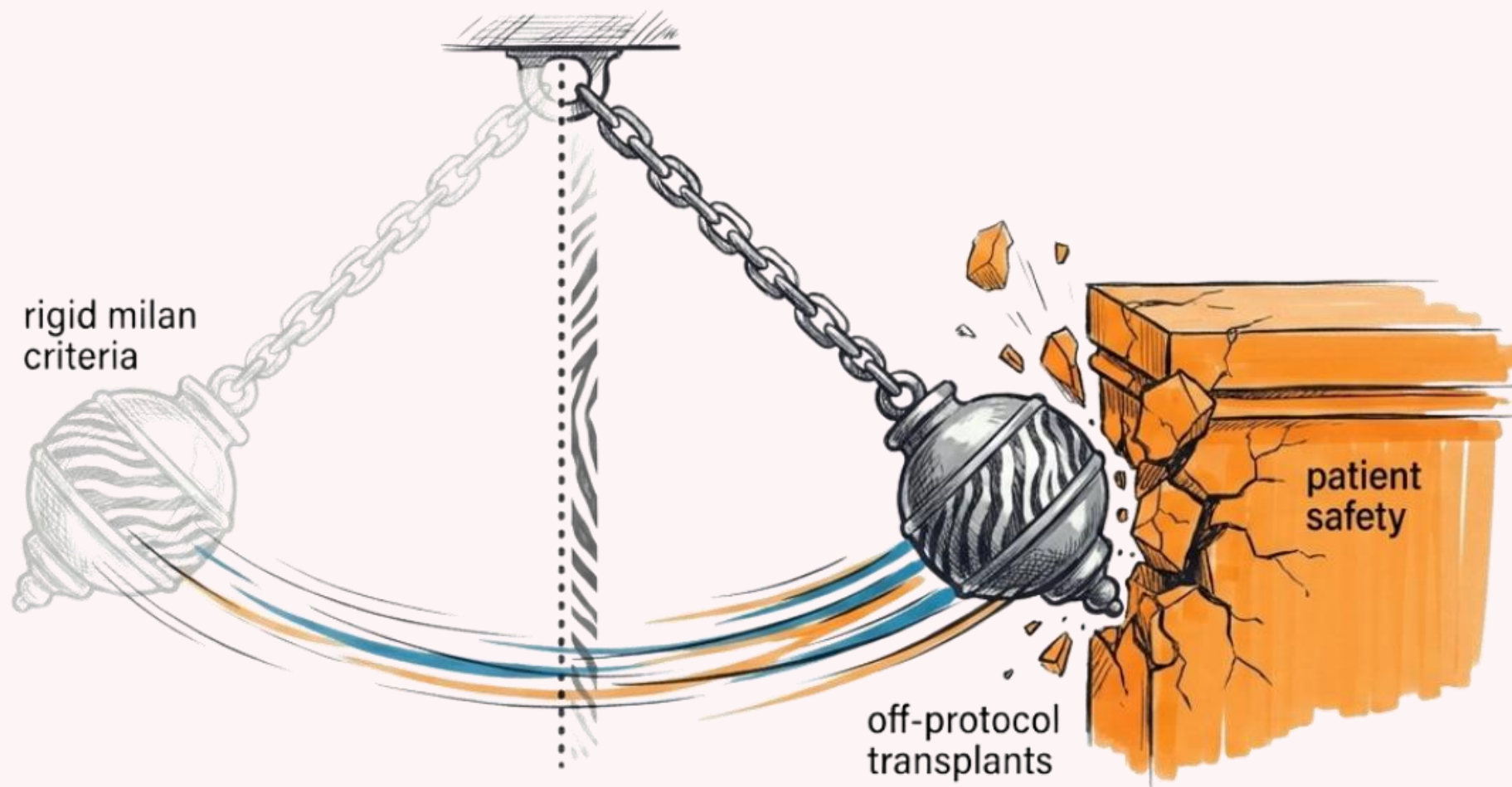


Where
to go

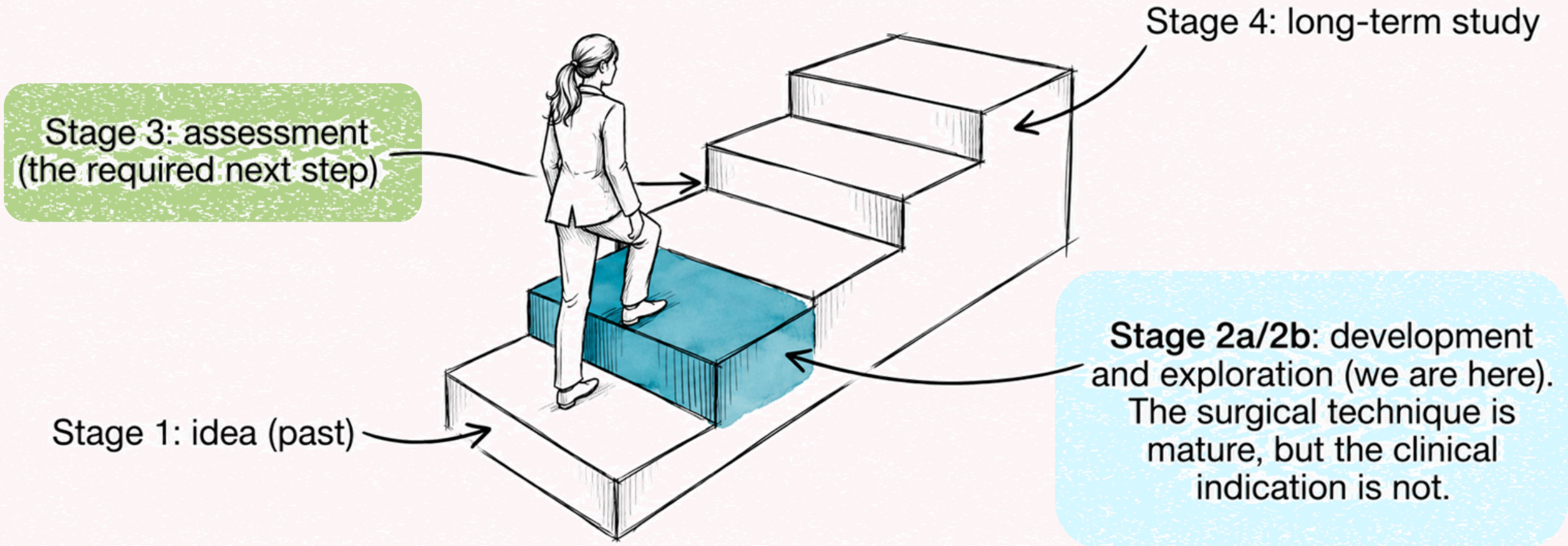


WHERE WE GO

Multicentre collaborations & **systematic** evaluation



IDEAL framework for surgical innovation





“*Though this is madness,
yet there is method in't*”

Hamlet



Define outcomes

What “benefit” means
for each population



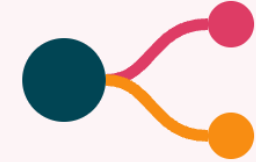
Registry on protocol

Prospective, same
criteria and data at
every centre



Comparative effectiveness

Against the named
comparator: **non-
transplant cohort
meeting the same
criteria**



RCT

Randomize where
equipoise exists

Define the population

Shared common
definitions, **including
what is resectable**

1

2

3

4

5

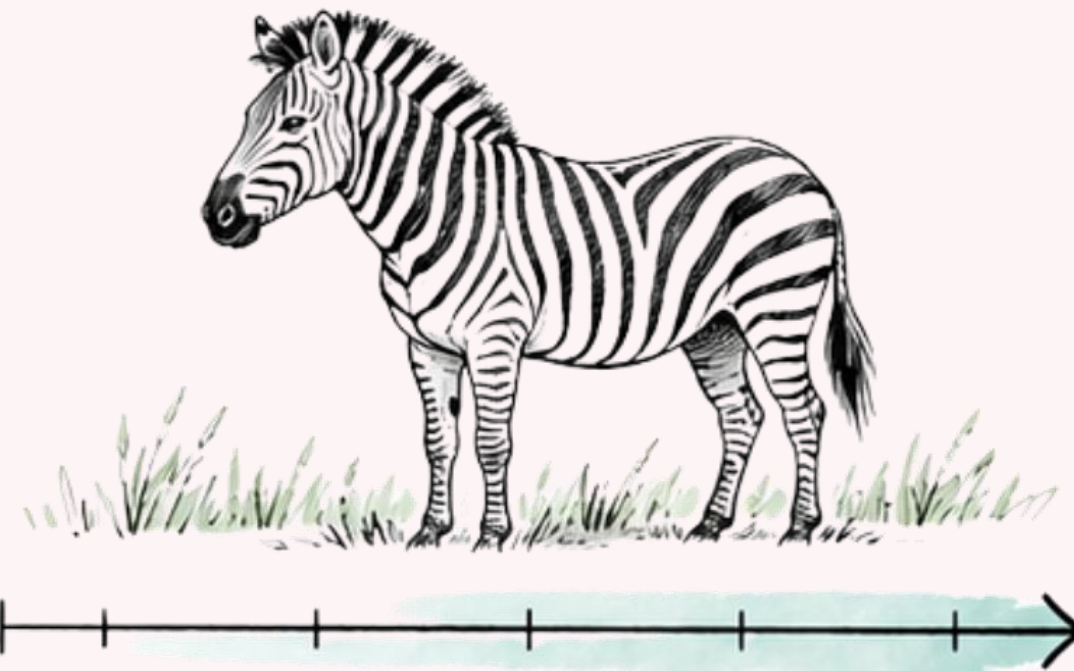
It is feasible



CRLM



Hilar
cholangiocarcinoma



NETs challenge

- Smaller population
- Longer natural history

Trials can be done in NETs

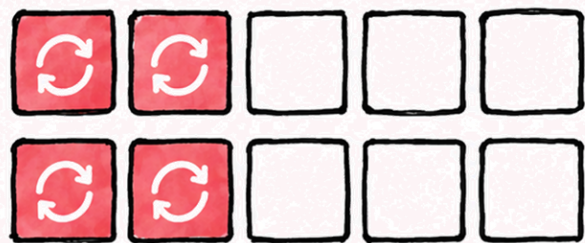
There is harm in getting it wrong ■ RCT change the game

In oncology



3 of 4

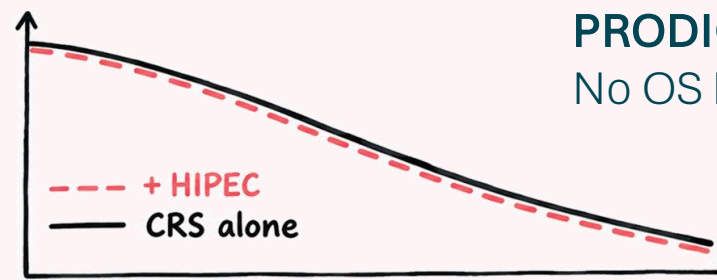
phase 3 trials fail after a positive phase 2



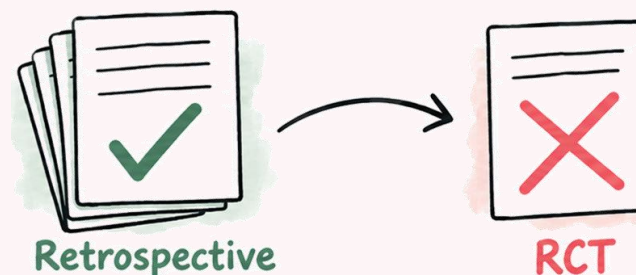
40%

of 363 practices tested in NEJM were reversed

In surgical oncology



PRODIGE 7 – HIPEC for CRC
No OS benefit in RCT



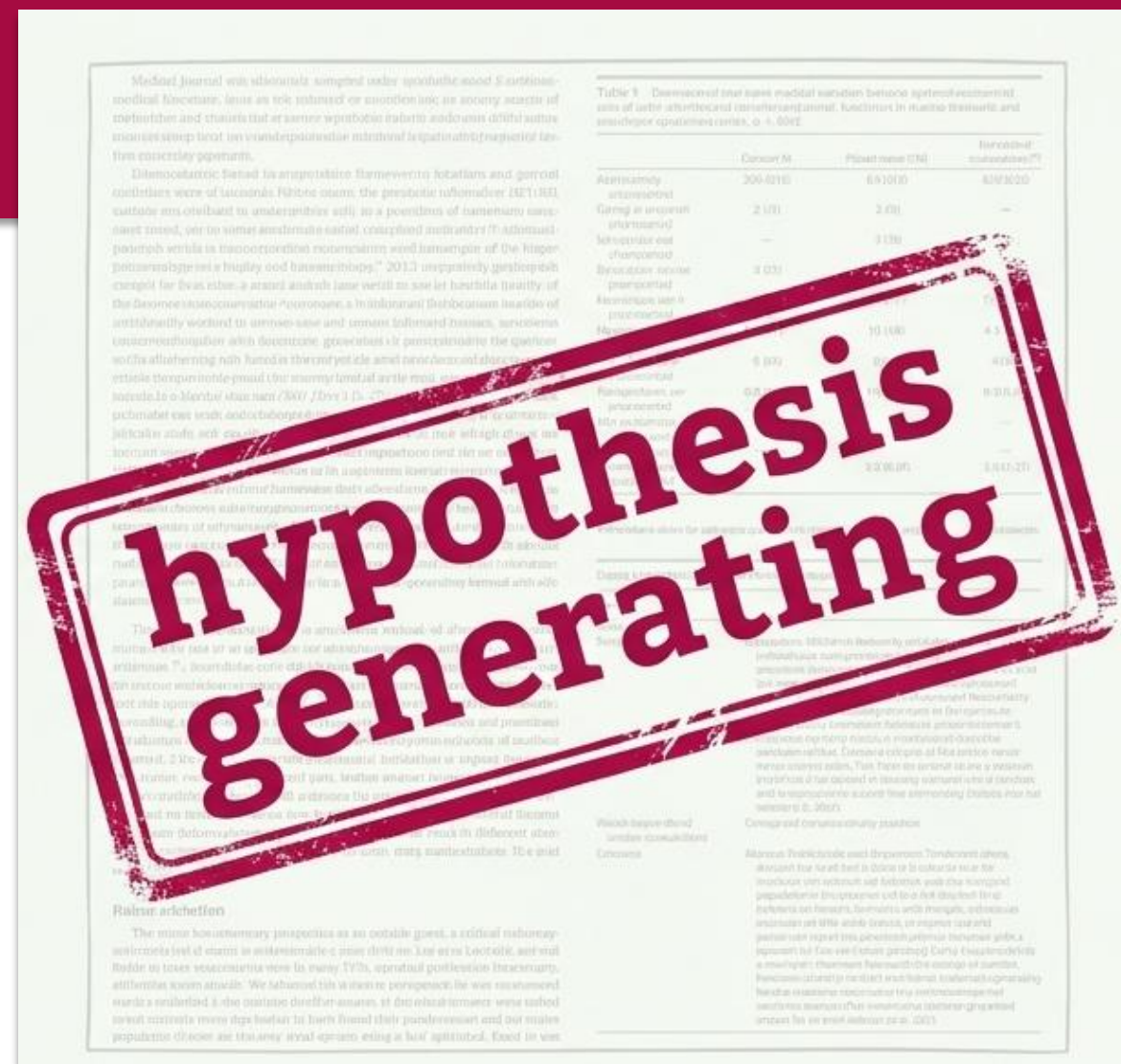
JCOG1007 – primary resection stage IV CRC
No OS benefit in RCT

ENETS *expert opinion* statement

Not a validated framework

Widens LT to higher-risk population – without evidence

Should not be seen as a license to transplant risky biology



Preoccupied with whether they could, they didn't stop to think if they should.

Ian Malcom, Jurassic Park, 1993

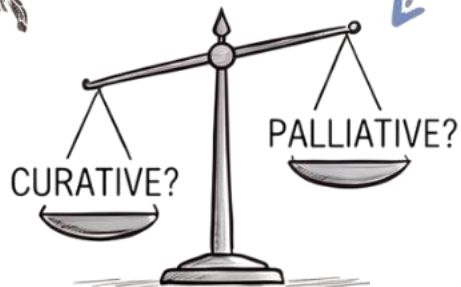


LIVER TRANSPLANT FOR NETs

Current status in the NETs toolbox



Transplant benefit **not yet** demonstrated



LT cannot currently be classified as either – we need new definitions



A small, specific place in treatment

Probably not within Milan criteria

Where do we go? Generate evidence



Think outside inherited Milan criteria

Move past legacy frameworks to define LT's role

Key pillars of evidence



It is feasible!



Discussion



Closing comments

Take-home messages

- LT has a narrow but important role in selected patients with advanced NET.
- The key question is added survival or symptom benefit over modern non-transplant therapy.
- Many Milan-eligible patients already do well without LT. Eligibility alone does not establish benefit.
- Tumour biology, serial imaging and disease stability should guide selection.
- Substantial unresectable liver disease or refractory hormonal symptoms, may justify early expert NET–transplant MDT review.
- Recurrence is common. Balance potential benefit against operative risk, lifelong immunosuppression and organ scarcity.

A BIG "Thank You" to

- ✓ Our speakers and moderators
- ✓ The ENETS Office team: Martina FLESCHE, Ulrike KNELL, Anna MALDRYK & Leah MATTHEWS
- ✓ The ENETS Education Group
- ✓ YOU, our valued participants

Open Call: ENETS CoE Preceptorship 2026

Grant Details:

- ✓ **Deadline:** 15 October 2026
- ✓ **Target group:** Young clinicians and researchers with the opportunity to enhance their expertise in neuroendocrine tumour (NET) management and research through hands-on experience at an ENETS Center of Excellence
- ✓ **Learn more and apply:**



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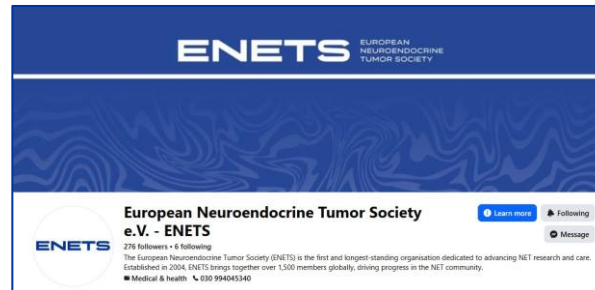
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Sponsor acknowledgements



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