# VIII EDIZIONE
# NEN PRECEPTORSHIP
# LA PRATICA CLINICA NELLE NEOPLASIE NEUROENDOCRINE

16/17 Maggio 2019 | IEO, Istituto Europeo di Oncologia - Milano
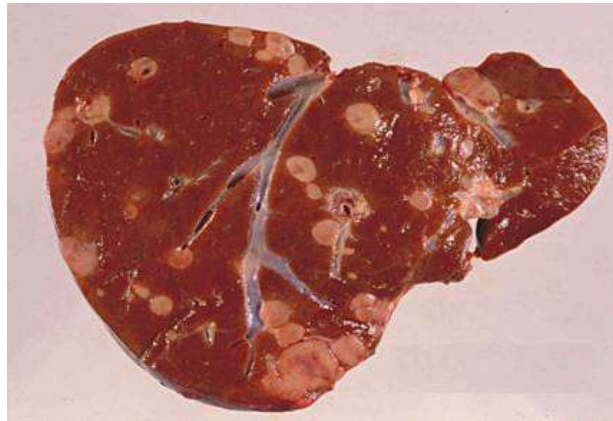
NEN Preceptorship

IEO
Istituto Europeo di Oncologia

# Liver Surgery of NELM



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NET are rare tumors, but incidence is rising and being the second most prevalent in the gastrointestinal tract

Most malignant NETs are slow-growing due to low mitotic activity in the mostly well-differentiated tumors

**50 % of these tumors have metastasized by the time of presentation, and the liver most common site of mets in over 80% of cases**

**Surgery plays a central role in its management, and is the only potentially curative treatment option !!**

**But….**

Only 20 % of pts with NELM are eligibile candidates for surgery

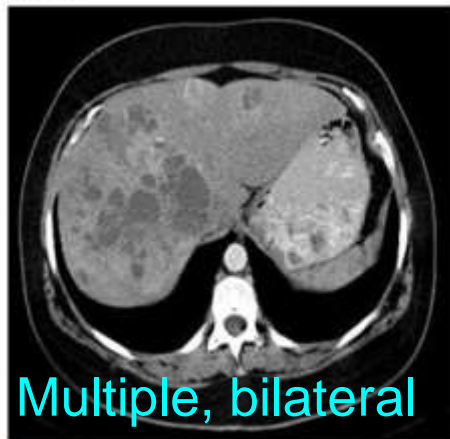Despite curative intention, virtually all pts developed recurrence

We must consider surgical resection a  PALLIATIVE ENDEAVOR ??
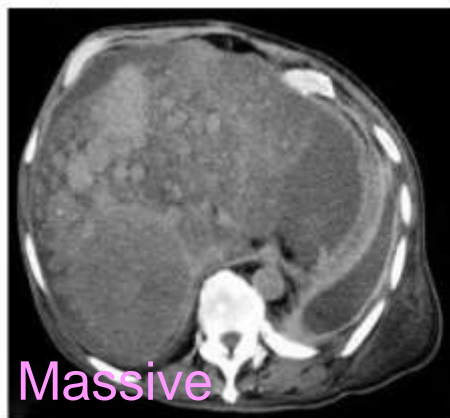
Indications for OLT prove somewhat controversial …

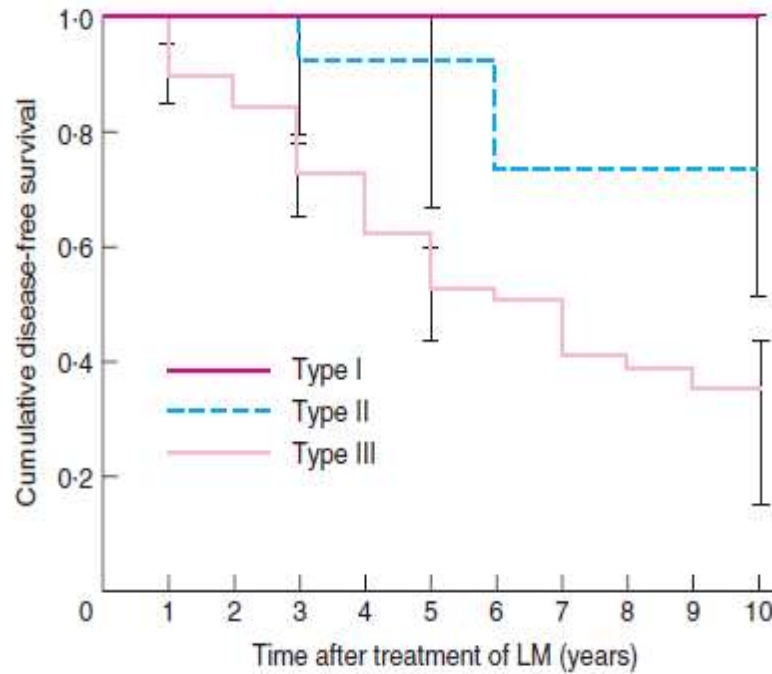There are not universally accepted optimal selection criteria for OLT in NELM

Single, bulky

a Type I

Multiple, bilateral

b Type II

Massive

c Type III

Cumulative disease-free survival vs Time after treatment of LM (years)

— Type I
--- Type II
— Type III

Median follow-up:
Type I-II : 60 mo
Type III : 38 mo

| | Localization type of LM | | |
|---|---|---|---|
| | Type I (n = 23) | Type II (n = 18) | Type III (n = 78) |
| Resection (R0) | 23 | 0 | 0 |
| Palliative cytoreductive resection | 0 | 2 | 0 |
| Palliative cytoreduction + radiofrequency ablation | 0 | 2 | 0 |
| Liver transplantation | 0 | 1 | 16 |
| Transcatheter arterial chemoembolization | 0 | 9 | 32 |
| Selective internal radiotherapy | 0 | 0 | 2 |
| Peptide receptor radionuclide therapy | 0 | 10 | 23 |

Frilling A et al, Br J Surg 2009

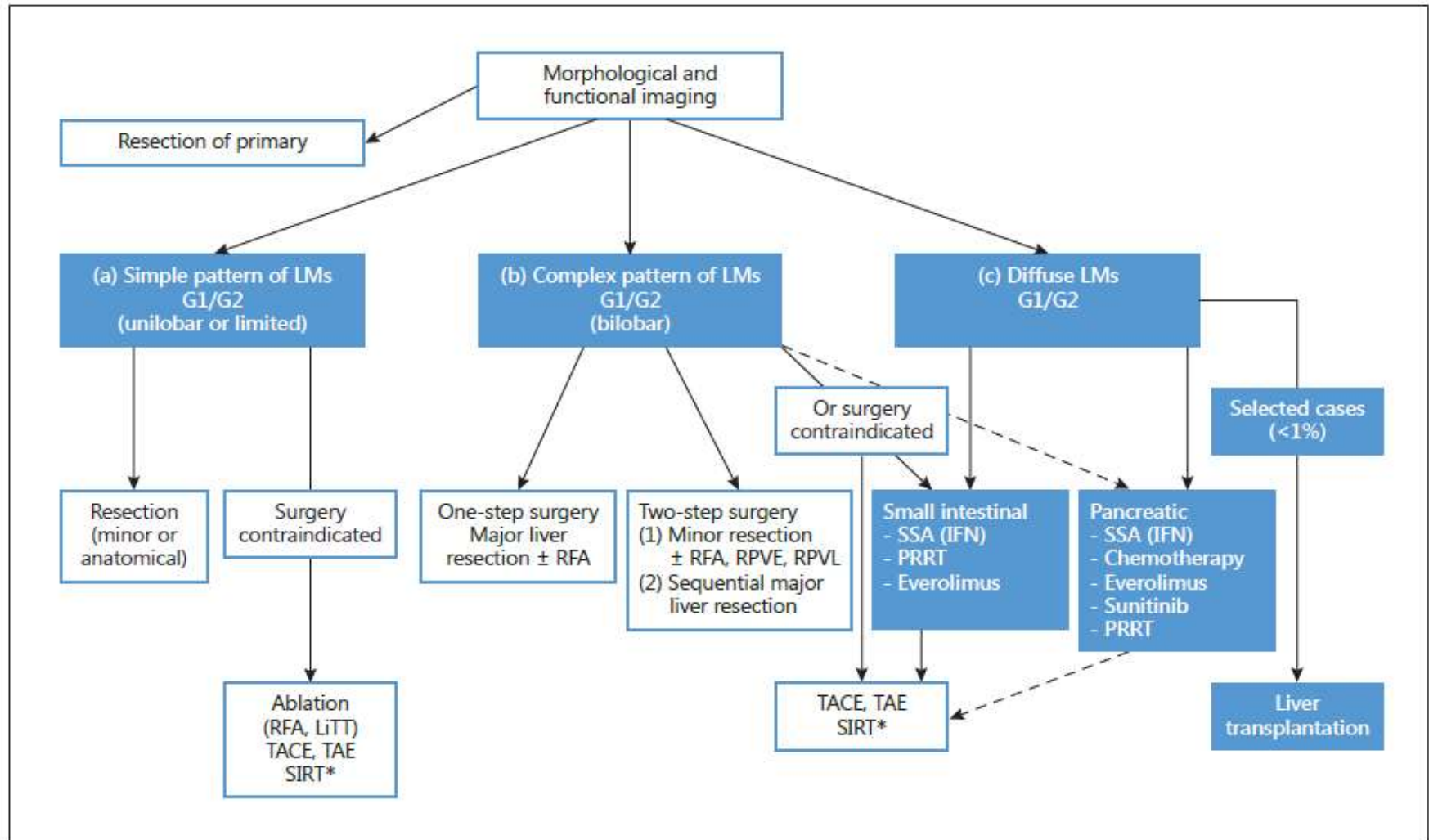# ENETS Guidelines for NET metastatic to the liver



**Fig. 1.** Management of liver metastases without extrahepatic disease in G1/G2 NEN. * SIRT (selective internal radiation therapy) is still an investigational method. LiTT = Laser-induced thermotherapy; LMs = liver metastases; RFA = radiofrequency ablation; RPVE = right portal vein embolization; RPVL = right portal vein ligation; TACE = transarterial chemoembolization; TAE = transarterial embolization.

Pavel et al. Neuroendocrinology 2016

# Guidelines for NET metastatic to the liver

**Liver Resection**

**minimal requirements**

**Liver Transplantation**

- Surgery should be acceptable morbidity and <5% mortality

- Different modalities of resection can be proposed according to complexity

- Absence of right heart insufficiency

- Absence of unresectable lymph node and extra-abdominal metastases, and absence of diffuse or unresectable peritoneal carcinomatosis

- G1-G2 liver disease

- Unresectable liver metastases

- Refractory to all other treatments

- Mortality < 10%

- Absence of extrahepatic disease

- Primary tumor removed prior to LT

- G1, G2  - Low Ki67

- Patients less than 50 years old

# Advanced NET for liver metastases

Discrepancy between the **perception of resectability** among medical oncologist and liver surgeons

Different therapeutic modalities

**Systemic treatment options**

Randomized control trials

**Surgery of primary only
Locoregional approaches
Liver resections
Debulking
OLT**

Retrospective data

# RCTs assessing the efficacy of systemic treatments on NELM

| Trial | Study design | N | ORR | Liver specific response | comments |
|-------|-------------|---|-----|------------------------|----------|
| PROMID | SS +PLACEBO | 85 | 1% | LTB <10% associated with decreased PFS (2,6 fold ) PFS > 10-50% vs >50% LTB ( placebo group) | Midgut NET only 70% of pts <10% LTB |
| CLARINET | Lanreotide v placebo | 204 | N/A | LTB >25% median PFS > in the lanreotide group | 96% had no tumor progression 3 to 6 months prior to inclusion |
| RADIANT 3 | Everolimus v placebo | 410 | 5% | N/AS | pNET only 92% with NELM |
| RADIANT 4 | Everolimus + placebo | 205 | 2% | HR 'positive effect '>25% LTB in everolimus group | Included lung and GEP-NET 80% with NELM |
| SUNITINIB | RCT: sunutinib v placebo | 171 | 9% | N/A | Pancreatic Net only, 95% with NELM |
| NETTER -1 | RCT: 177-dotatate v octreotide LAR | 229 | 18% | N/A | 83%with NELM |

**There are a scarcity of data regarding the efficacy of systemic treatments in reducing or stabilizing NELM**

**Limited data suggest liver tumor burden has an impact on PFS and possibly the effects of therapies of some of these systemic treatments agents**
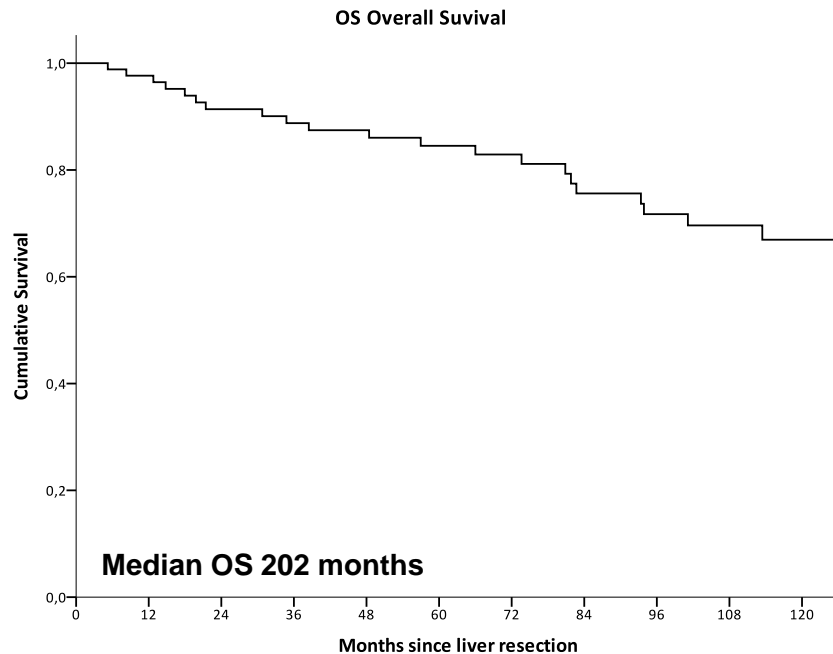
- 29 eligible retrospective series (1469 pts), **level III evidence**

- Majority of pts (95%) attained objective symptomatic relief from surgery

- Median 1-3-5-10-yrs OS: 94%, 83%, 70,5% and 42% respectively

- RO resections 63%; morbility rates 23%

- Median post op mortality : 0%

- RFS rates 1-3-5-10 yrs: 63%, 32%,29% and 1% respectively

- Poor hystologic grade, extrahepatic disease and R1 resection associated with poor prognosis

Liver resection for NELM provides symptomatic benefit and is associated with favorable survival outcomes although the majority of pts invariably develop disease progression
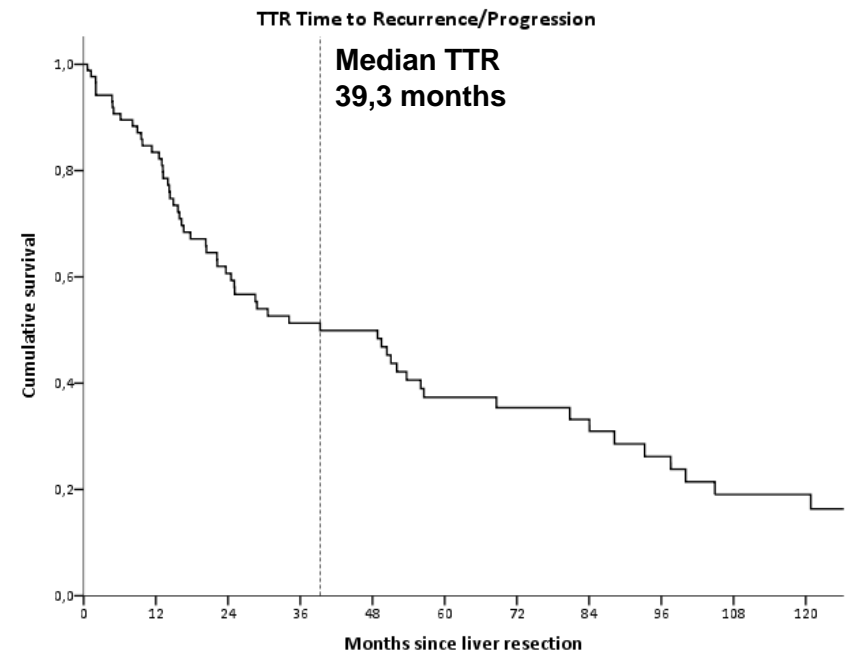
# Analysis of Liver Resection (LR)
# for Gastro-Entero-Pancreatic Neuroendocrine Tumor (GEP-NET)

**87 pts with GEP-NET liver metastases underwent LR with curative intent** according to ENETS proposed criteria (1995-2015)
• Resectable liver mets with curative intent (absence of unresectable lymph node and/or extra-abdominal metastases and/or peritoneal carcinomatosis) and abolished primary tumor
• Acceptable co-morbidity and predicted mortality of <5%

**OS Overall Suvival**

Cumulative Survival

Months since liver resection

**Median OS 202 months**

**TTR Time to Recurrence/Progression**

**Median TTR 39,3 months**

Cumulative survival

Months since liver resection

| | 1Yr | 3Yr | 5Yr | 10 Yr |
|---|---|---|---|---|
| **Overall Survival** | 97% | 88.8% | 84.5% | 66.9% |

| | 1Yr | 3Yr | 5Yr | 10 Yr |
|---|---|---|---|---|
| **Time to recurrence** | 83% | 50% | 35.5% | 20.8% |

# Prognostic Factors after Liver Resection (LR) for Gastro-Entero-Pancreatic Neuroendocrine Tumor (GEP-NET)

| | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|
| **Risk factors associated with *Overall Survival*** | | | | |
| | Hazard ratio (95% CI) | p value | Hazard ratio (95% CI) | p value |
| Syndrome (Yes Vs No) | 2,138 (0,891-5,132) | **0,038** | 1,512 (0,643 – 3,559) | 0,344 |
| Grading (G3 Vs G1-2) | 13,777 (0,896 - 211,740) | **<0,0001** | 11,262 (1,763 – 71,957 | **0,010** |
| Ki-67 (>5% Vs <5%) | 5,127 (1,097 - 23,973) | **0,001** | 5,634 (1,849 – 17,164) | **0,011** |
| Recurrence within 3 years (early Vs late/No recurrence) | 5,597 (2,516 - 12,451) | **0,005** | 7,624 (1,008 – 57,653) | **0,049** |
| **Risk factors associated with *Recurrence*** | | | | |
| | Hazard ratio (95% CI) | p value | Hazard ratio (95% CI) | p value |
| Syndrome (Yes Vs No) | 1,807 0,962 - 3,393) | **0,035** | 1,578 (0,863 – 2,884) | 0,344 |
| Grading (G3 Vs G1-2) | 8,812 (0,906 - 85,727) | **<0,0001** | 5,572 (1,380 – 22,506) | **0,016** |
| Ki-67 (>5% Vs <5%) | 2,206 (0,882 - 5,518) | **0,009** | 3,202 (1,353 – 7,577) | **0,011** |

**Risk factors associated with Early Recurrence (within 3 years) Vs No Recurrence/Late Recurrence**

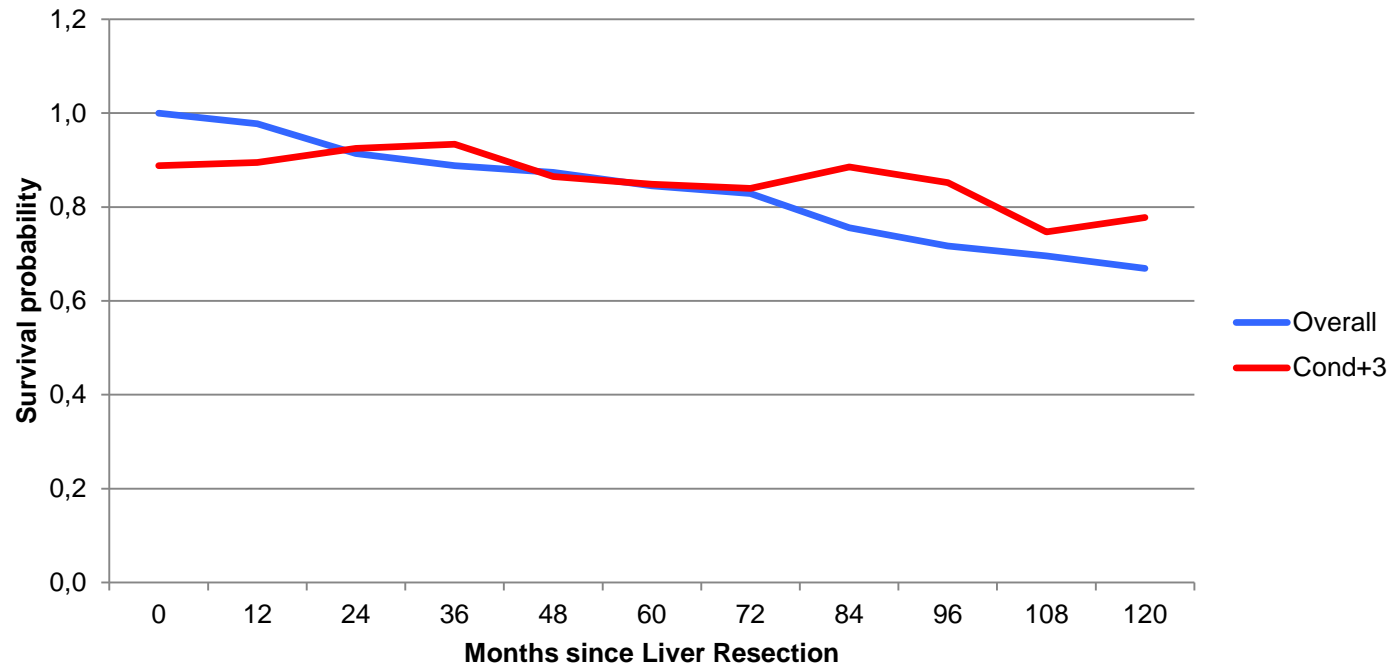| | $X^2$ | p value |
|---|---|---|
| Syndrome (Yes Vs No) | 0,001 | 0,970 |
| **Grading (G3 Vs G1-2)** | **8,414** | **0,004** |
| **Ki-67 (>5% Vs <5%)** | **3,153** | **0,005** |
| Analogues (Yes Vs No) | 0,464 | 0,496 |
| Synchronous (Yes Vs No) | 1,492 | 0,222 |
| Liver involvement (H1 Vs H2) | 0,190 | 0,663 |
| Nodal Status (N+ Vs N0) | 0.785 | 0,376 |

Significant adverse prognosis was observed in presence of:

- carcinoid symptoms (p=0,038),
- G3 (p <0,001),
- MIB-1 >5% (p= 0,001)
- early (<36 months) recurrence (p= 0,005).

# Conditional Survival

Conditional survival (CS) is defined as **the probability of surviving further "t" years, given that a patient has already survived "t" years** since liver resection

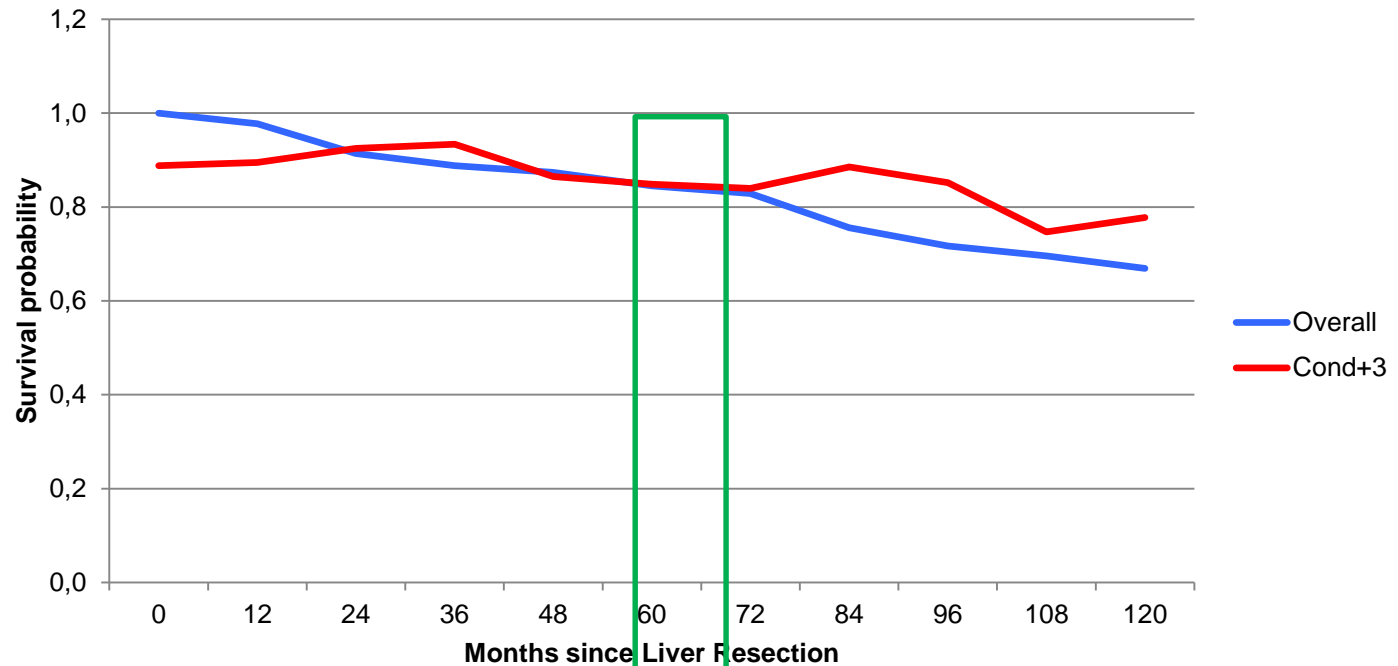[i.e. conditional 3 years survival is: CS (t) = S (t + 3) / S (t)]



| Actual and Conditional Survival rates | | | | | |
|---|---|---|---|---|---|
| | N | 1Yr | 3Yr | 5Yr | 10 Yr |
| **Overall Survival Actuarial** | 87 | 0,977 | 0,888 | 0,845 | 0,669 |
| **Conditional 3 Years Survival** | 87 | 0,887 | 0,873 | 0,843 | 0,776 |

# Conditional Survival

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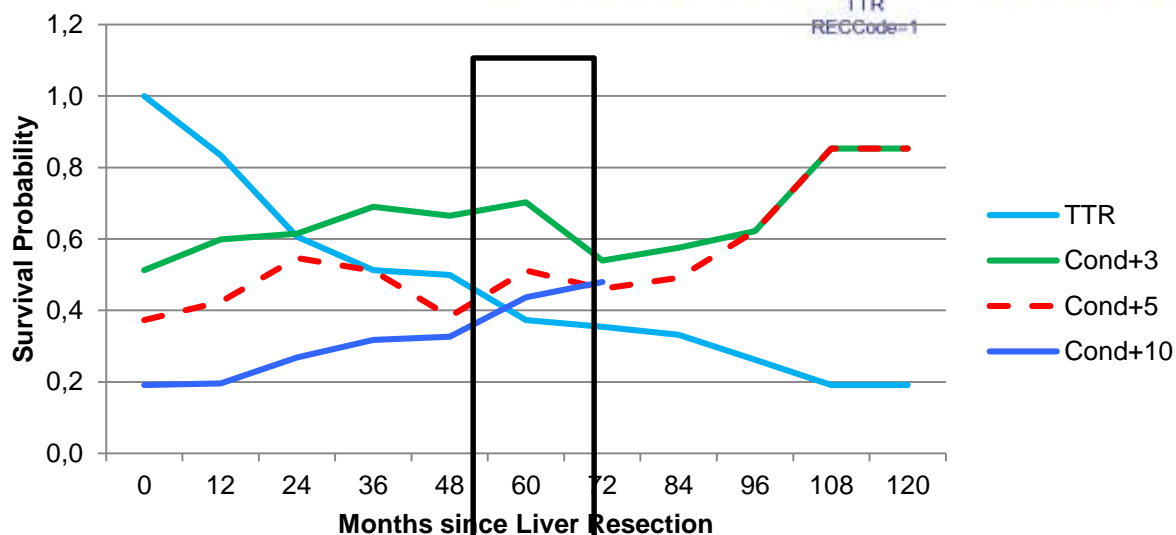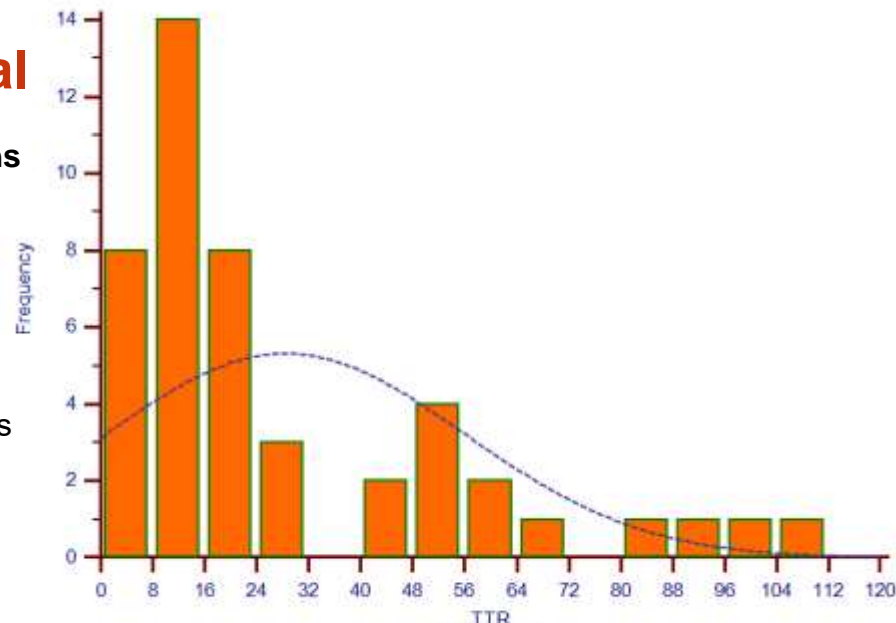# Conditional Recurrence-Free Survival

**46 Recurrence on 87 patients (53%), mostly in the first 24 months**
following liver resection.
Risk factors for recurrences were:
➢ carcinoid symptoms (p=0,038),
➢ G3 (p <0,001),
➢ MIB-1 >5% (p= 0,001)
Conditional recurrence free survival (CS) is the probability of being
alive and without recurrence further "n" years, given that a patient has
already survived free from disease "t" years after the liver resection
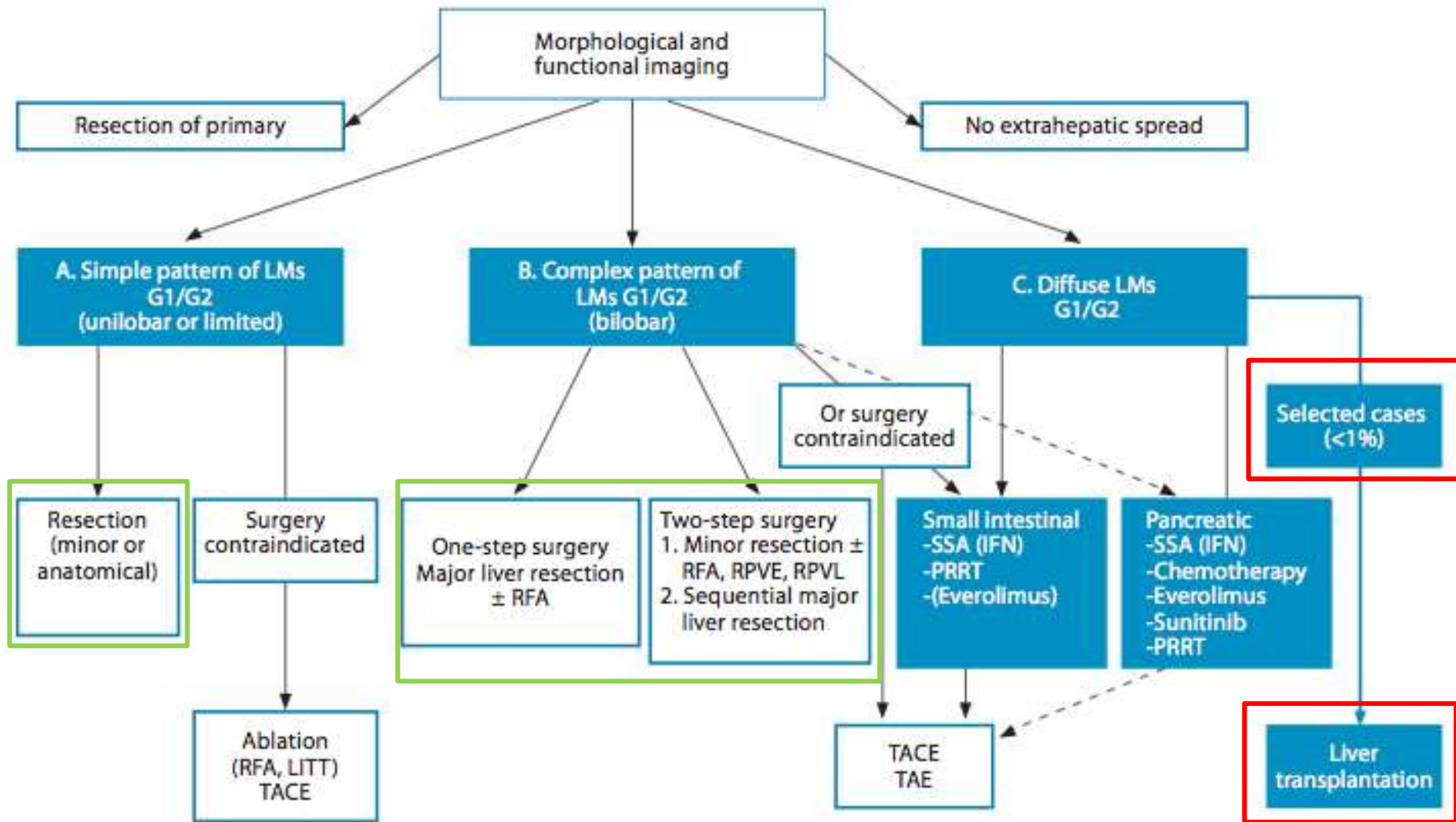CS (t) = S (t + n) / S (t)

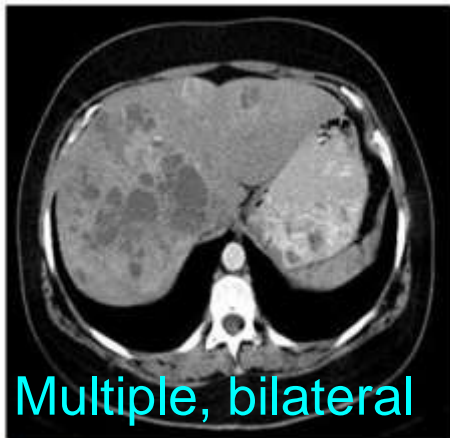| Actual and Conditional recurrence free rates | | | | | |
|---|---|---|---|---|---|
| | N | 1Yr | 3Yr | 5Yr | 10 Yr |
| Time to recurrence Actuarial | 87 | 0,834 | 0,513 | 0,373 | 0,191 |
| Conditional 3 Years recurrence free | 87 | 0,598 | 0,690 | 0,702 | 0,853 |
| Conditional 5 Years recurrence free | 87 | 0,424 | 0,511 | 0,512 | 0,853 |
| Conditional 10 Years recurrence free | 87 | 0,195 | 0,318 | 0,437 | |

# Conclusion : Liver Resection

- Randomized controlled **trials** evaluating patient outcomes after surgical treatments **are very difficult to perform**, due to tumor rarity and heterogeneity. This is a condition likely to persist in the future

- **Disease presentation** (simple/complex) **and tumor biology features deeply affects survival**, being recurrence a very frequent event

- The available evidence tells us that, **within the suggested guidelines for patients selection, surgical resection prolongs survival** of pts with liver metastases from NET with respect to any other treatment

- High recurrence rate after LR is registered (up to 70-80% at 5-yrs) and again, **biologic tumor features seem to impact of the risk of recurrence more than technicalities related to surgery itself**

- As the majority of patients recur within 24-36 months after LR, **conditional survival and recurrence-free survival** show that the probability to survive / be free of recurrence **increases over time**
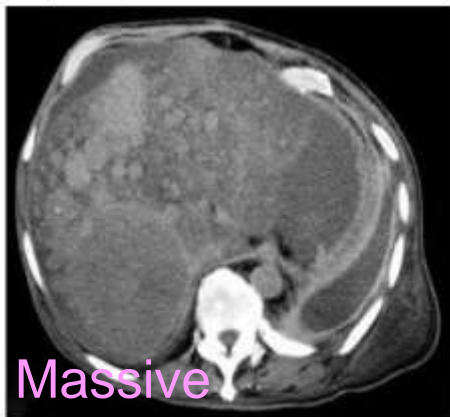
# Advanced NET for Liver Mets



ENETs Guidelines - Neuroendocrinology 2016

Single, bulky

a Type I

Multiple, bilateral

b Type II

Massive

c Type III

Resectable = No transplant

Transplant for cure

Transplant for palliation

# Milan selection criteria [1-3] for patients with liver mets from NETs

1. **Confirmed histology of low-grade (G1-G2) neuroendocrine tumors**

2. **Primary tumor drained by the portal system removed with all extrahepatic deposits in a separated pre-transplant curative resection**

3. **Metastatic diffusion to liver parenchyma < 50%**

4. **Response / stable disease for at least 6 months during the pre-LT period**
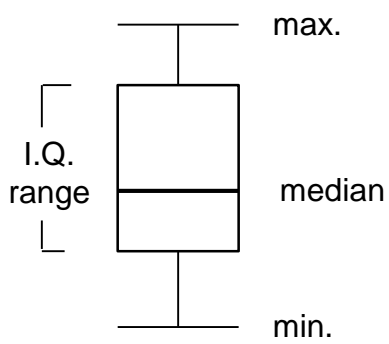
*5. Age < 65 years*

1. [Coppa JC et al, Transpl Proc 2001 ]
2. [Stutcliffe et al. Am.J.Surgery 2003]
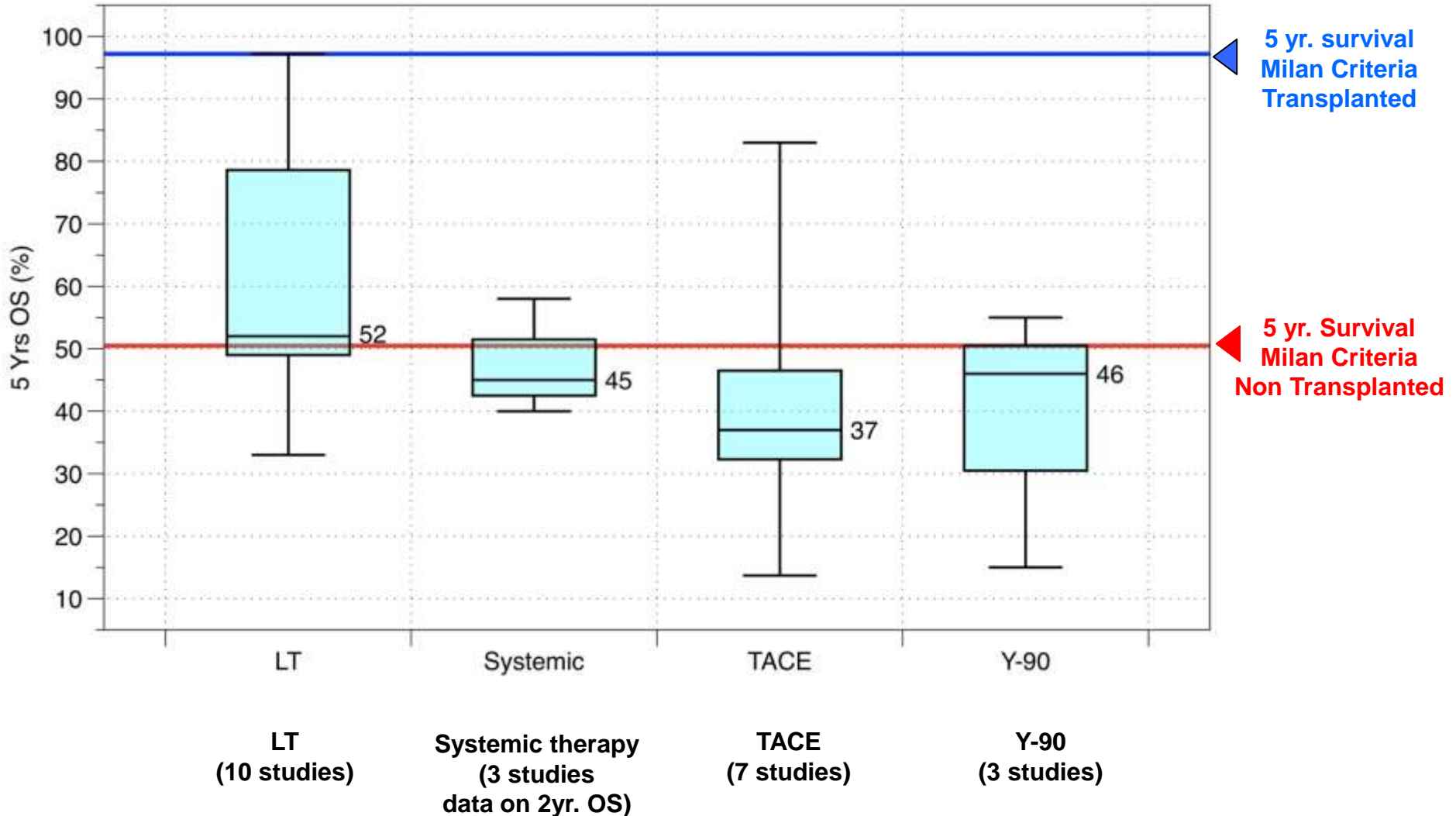3. [Mazzaferro V et al. J Hepatology 2007]

Reduce tumor burden and subtract adverse prognostic factors ⟹ Improve patients outcome

Comparative outcome of non-transplant therapies in metastatic NET (literature review)

# Study design

## From Jun 1995 to Jan 2010
## Prospective monoinstitutional series

**Liver Mets from GEP-NET referred for LT (n=280)**

**1st round exclusion: Resectable patients**
• Primary tumor and Mets resected (n=75)

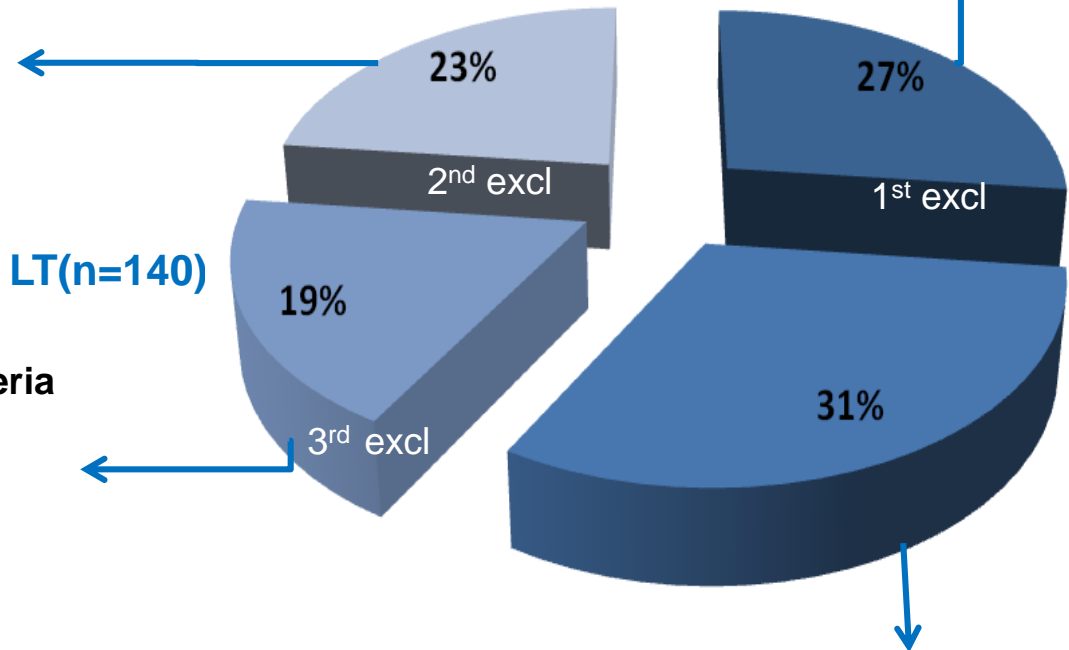**2nd round exclusion: Unsuitable for curative surgery**
• Unresectable primary (n=56)
• Other/unsuitable for LT(n=9)

**Liver Mets from GEP-NET suitable for LT(n=140)**
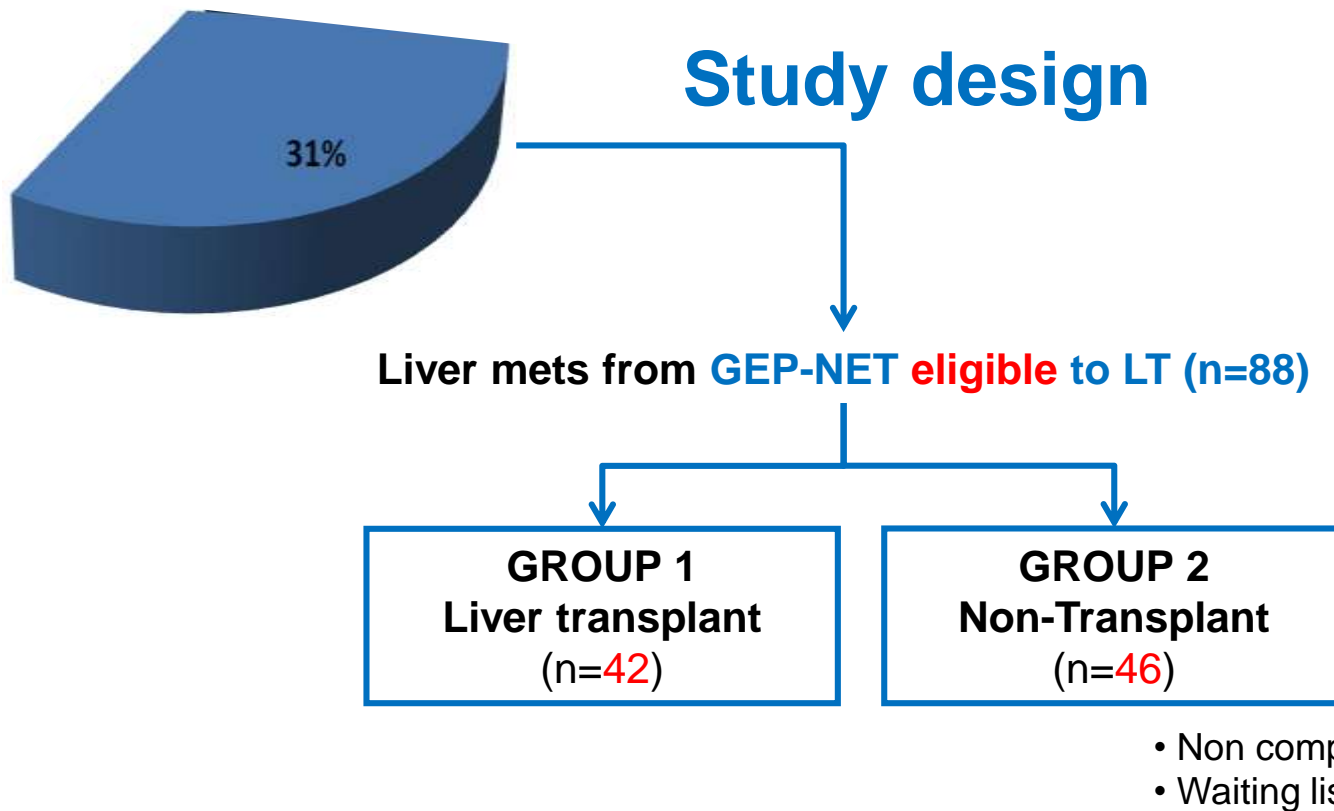
**3rd round exclusion: Exceeding criteria**
• Comorbidities (n=13)
• High grade tumors (n=12)
• Age (n=24)
• Other (n=3)

23%  2nd excl

27%  1st excl

19%  3rd excl

31%

**Patients with liver metastases from GEP-NET eligible to LT (n=88)**

# Study design

**Liver mets from GEP-NET eligible to LT (n=88)**

| GROUP 1<br>Liver transplant<br>(n=42) | GROUP 2<br>Non-Transplant<br>(n=46) |
|---|---|

- Non compliance/refusal (n=22)
- Waiting list unavailability (n=24)

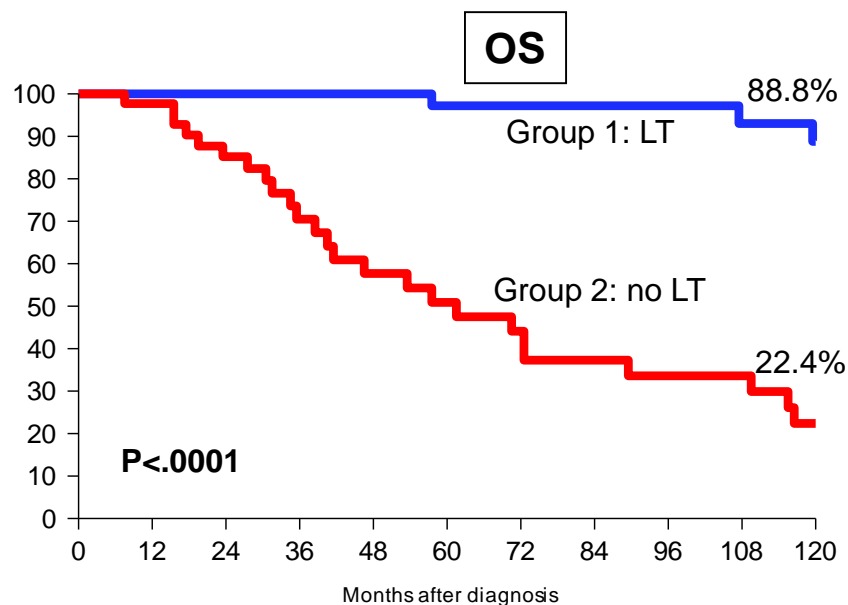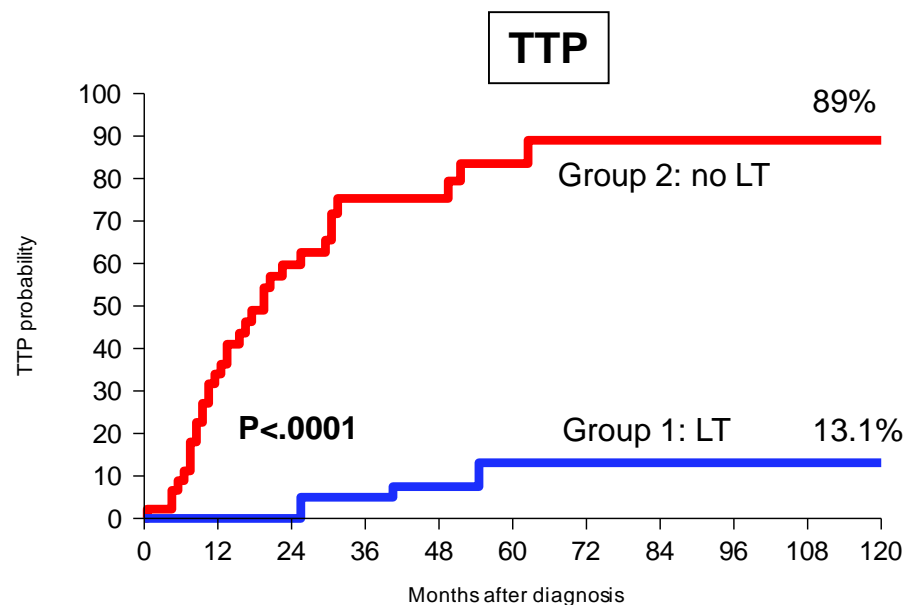**Statistical analysis:**

➢ Evaluation of demographic and general/oncologic **differences between groups**

➢ **Uni/multivariable analysis of prognostic factors of OS** by Cox regression models, with treatment included as stratification factor

➢ **Propensity score estimation** by means of a multivariable binary logistic model, in which the covariates were the variables possibly associated with LT selection

➢ OS analysis according to treatment without and with **adjustment for propensity score**

➢ **Survival benefit estimation** with and without adjustment for propensity score

31%

# Outcomes: Overall Survival and Time to Progression



**OS**

Survival probability vs Months after diagnosis

88.8%
Group 1: LT
Group 2: no LT
22.4%
P<.0001

Patients at risk

| 42 | 42 | 41 | 40 | 38 | 35 | 31 | 31 | 28 | 23 | 22 |
| 46 | 43 | 34 | 24 | 18 | 15 | 13 | 11 | 9 | 9 | 6 |

**TTP**

TTP probability vs Months after diagnosis

89%
Group 2: no LT
Group 1: LT  13.1%
P<.0001

Patients at risk

| 42 | 42 | 41 | 38 | 35 | 32 | 27 | 27 | 25 | 20 | 20 |
| 46 | 30 | 15 | 6 | 6 | 3 | 2 | 2 | 2 | 2 | 2 |

|  | GROUP 1: LT | GROUP 2: no LT |
|---|---|---|
| **5-yr OS** | 97.2% | 50.9% |
| **10-yr OS** | 88.8% | 22.4% |
| **Median OS** | NR | 62 months |
| **Median TTP** | NR | 20 months |

# Survival Benefit estimation according to treatment (with/without adjustment for propensity score)
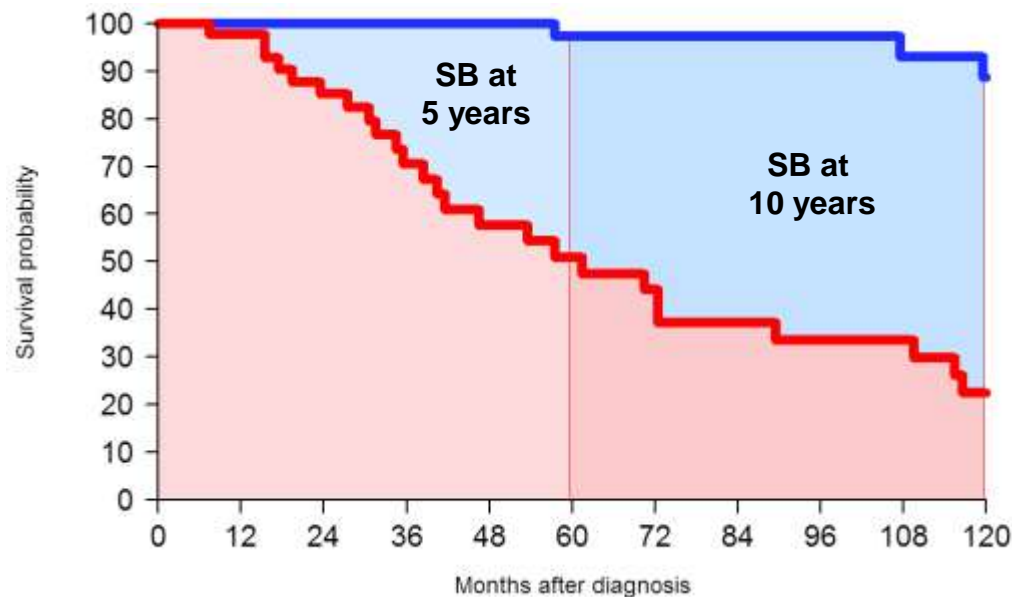


| | SURVIVAL BENEFIT ESTIMATION | | | |
|---|---|---|---|---|
| | *Univariable model* | | *Multivariable model (adjusted for propensity score)* | |
| | D-MST (CI) | p | D-MST (CI) | p |
| **At 5 years** Group1 vs Group 2 | 12.79 (7.95,17.63) | **<0.0001** | 6.82 (1.10,12.54) | **0.019** |
| **At 10 years** Group1 vs Group 2 | 48.62 (35.49,61.75) | **<0.0001** | 38.43 (21.41,55.45) | **<0.0001** |

Mazzaferro V et al Am J Transpl 2016

# Liver Transplantation for NET Hepatic Metastases
## Conclusions

✓  Liver transplantation for metastatic NETs under restrictive criteria provides **unprecedented positive long-term outcome**

✓  Transplant-related survival-benefit increases over time and maximizes after 10 yrs. with a highly **competitive results with respect to any non-transplant option**

✓  Long term survival is associated with an **overt improvement in the quality of life** (QOL) and likely advantages in cost-effectiveness

Guidelines for nonstandard exception[a]

| | |
|---|---|
| Neuroendocrine tumors | Recipient age <60 years, resection of primary malignancy and extrahepatic disease without any evidence of recurrence for 6 months, gastro–entero–pancreatic tumor origin and low/moderate grade, tumor in liver <50% of liver volume |

**UNOS-OPTN. Guidance on MELD PELD exception review**  OPTN [Internet]. OPTN. [cited **2017 March 8**]. Available from: http://optn.transplant.hrsa.gov/resources/by-organ/liver-intestine/guidance-on-meld-peld-exception-review/

# Transplant benefit for metastatic NET

Timing of transplantation should match the natural history of NET and target objective post-transplant benefit in survival with respect to alternative treatments



Fan ST, Le Treut YP, Mazzaferro V HPB 2015

Sistema Socio Sanitario
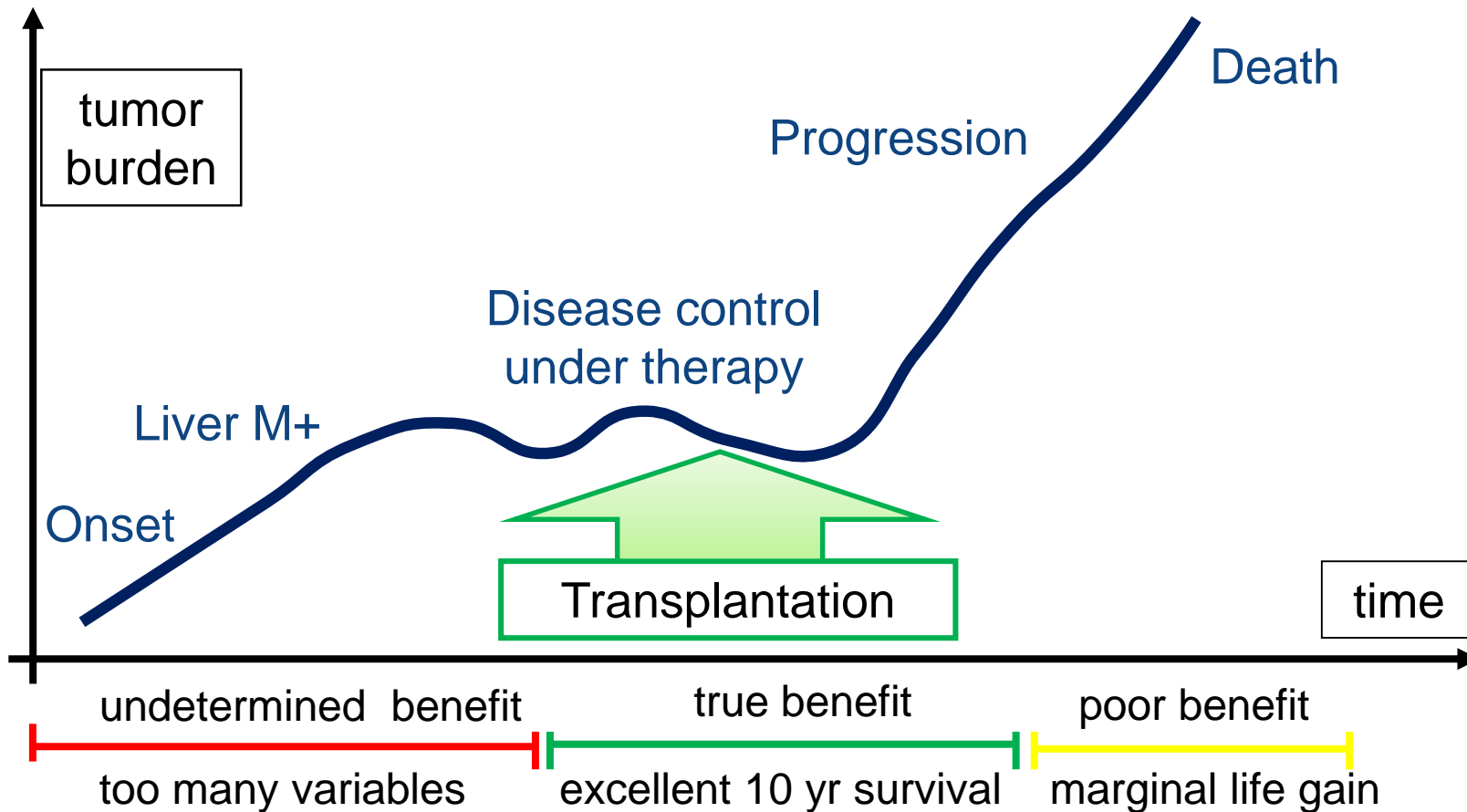
Fondazione IRCCS
Istituto Nazionale dei Tumori

Regione
Lombardia

UNIVE
DEGLI
DI MIL

**Save the D**

# 5ᵗʰ Milan NET Conferenc

A live and web multimodal meet
among active Italian NET Cent

Wednesday June 12ᵗʰ, 20
Mi

# Domanda 4

**Primary tumor resection may improve survival in functional well- differentiated neuroendocrine tumors metastatic to the liver**

Surgery on primary tumor or liver metastases:
1) low perioperative risk was predictable
2) risk of obstruction,bleeding or perforation
3) liver metastases were suitable of curative or subtotal (>90%) tumor removal.

**Table 2**
Prognostic impact of different variables at univariate and multivariate analysis in 139 patients with well-differentiated functioning NET and liver metastases

| Predictor | Category | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|---|
| | | Hazard ratio (95% CI) | p value | Hazard ratio (95% CI) | p value |
| Age | ≥ 55 | 1,37 (0,86-2,19) | 0,206 | | |
| | < 55 | 1 | | | |
| Sex | Male | 1,23 (0,78-1,93) | 0,376 | | |
| | Female | 1 | | | |
| Primary tumor site | pNET[a] | 1,82(1,03-3,22) | 0,018 | 1,17 (0,52-2,61) | 0,703 |
| | Carcinoid | 1 | | 1 | |
| Primary tumor resection | No | 3,64 (2,04-6,51) | <0,001 | 3,17 (1,77-5,69) | <0,001 |
| | Yes | 1 | | 1 | |
| Liver metastases resection | No | 2,51 (1,55-5,09) | 0,002 | 2,08 (0,99-4,39) | 0,054 |
| | Yes | 1 | | 1 | |
| Flushing | No | 1,46 (0,84-2,54) | 0,129 | | |
| | Yes | 1 | | | |
| Diarrhea | Yes | 1,91 (1,20-3,03) | 0,012 | 0,49 (0,27-0,88) | 0,016 |
| | No | 1 | | 1 | |
| Chromogranin-A | ≥200 ng/mL | 2,06 (1,23-3,44) | 0,001 | 0,46 (0,26-0,82) | 0,009 |
| | <200 ng/mL | 1 | | 1 | |
| Hepatic tumor load | >50% (H3) | 2,21 (1,08-4,51) | 0,04 | 2,41 (1,05-5,54) | 0,03 |
| | 25-50% (H2) | 1,76 (0,92-3,37) | | 2,4 (1,13-5,09) | |
| | <25% (H1) | 1 | | 1 | |

[a]pNET indicates pancreatic neuroendocrine tumors

**Primary tumor resection may improve survival in functional well- differentiated neuroendocrine tumors metastatic to the liver**
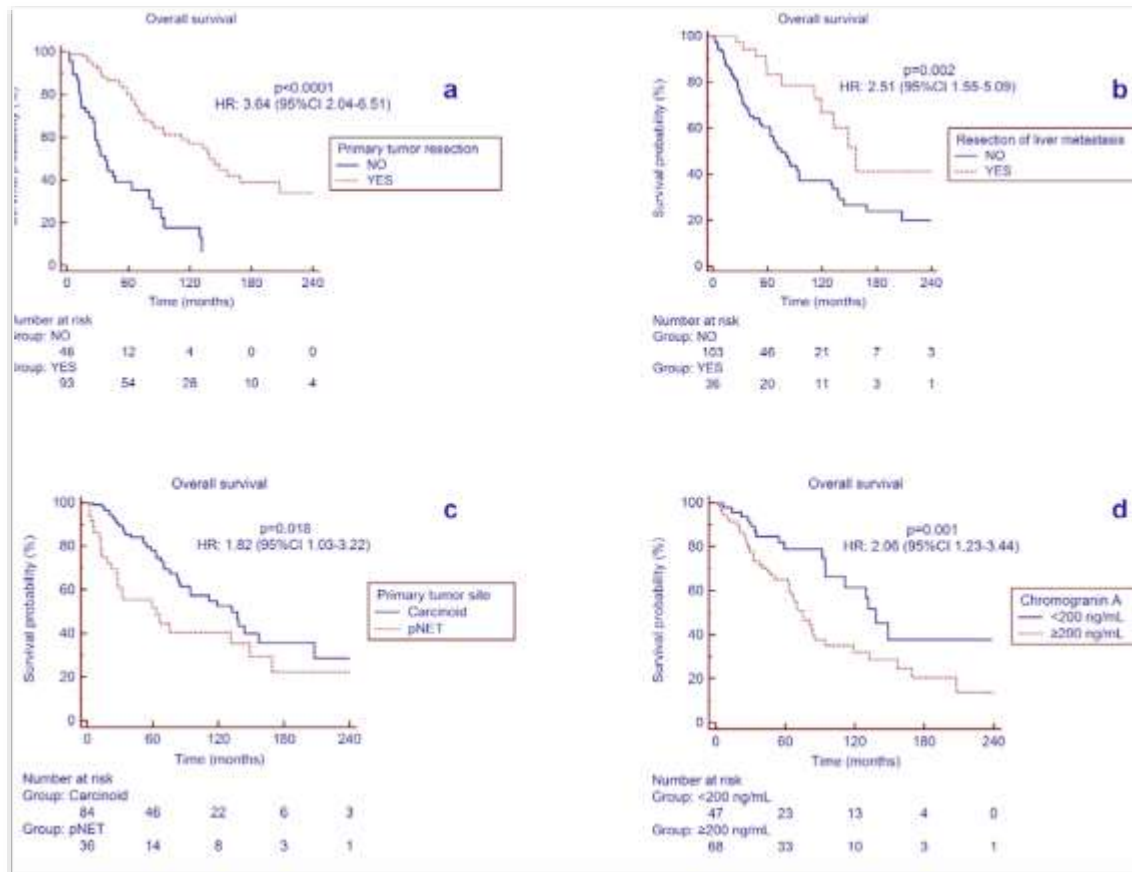


**Conclusions**

Primary tumor resection may improve survival in functional wd NET with liver metastases.
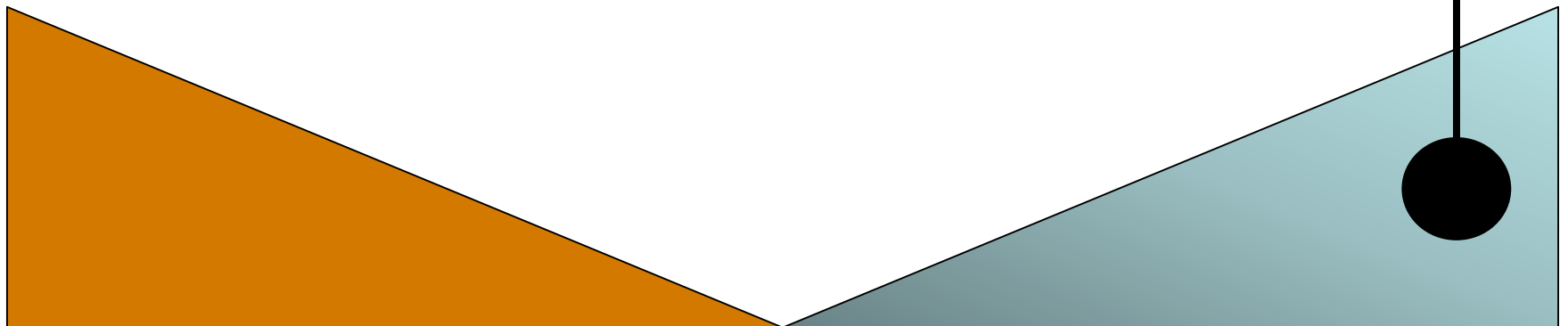
# Domanda 5

Late stage

Early stage

5-yr survival < 50%

5-yr survival > 90%

Reduce tumor burden and subtract adverse prognostic factors

Improve patients outcome

# Domanda 6

# Influence of patients'age

**The following variables were entered:**

-**Year of diagnosis** → **p=0.0351**

-**Patients' age** → **p=0.0025**

-Primary tumor site

-**T stage of the primary** → **p=0.0408**

-N stage of the primary

-Primary surgery

-Syndrome

-Liver involvement

-Tumor grading WHO 2010

-**Serum chromogranin** → **p=0.0068**
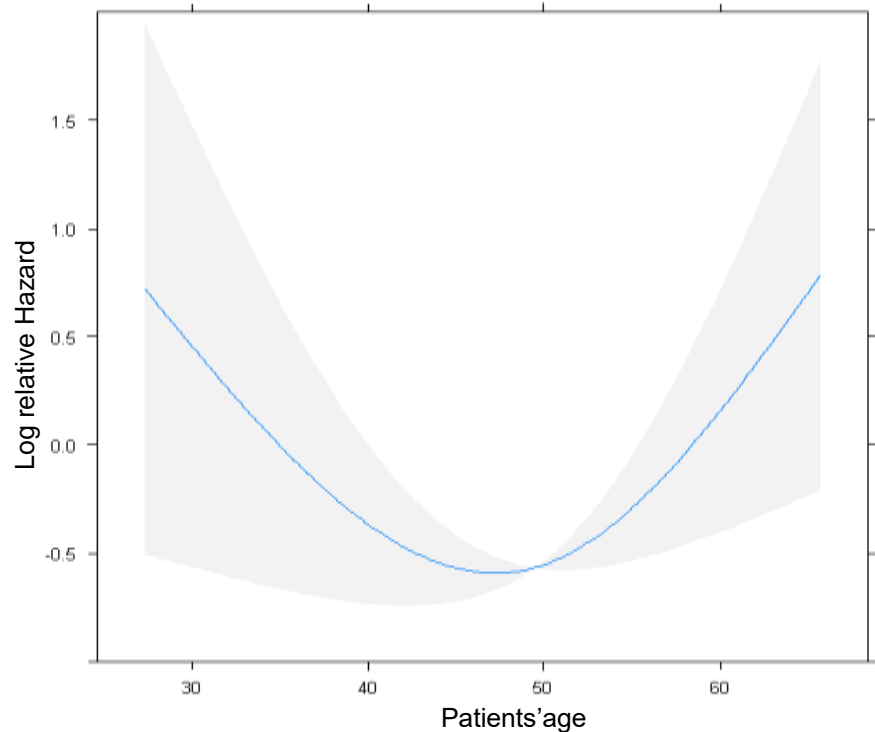


| Patients'age | HR | 95% CI |
|---|---|---|
| 42-54 years | 1 | |
| 13-42 years | 1.51 | 0.56-4.05 |
| 54-71 years | 2.30 | 0.96-5.51 |

# VIII EDIZIONE
# NEN PRECEPTORSHIP
# LA PRATICA CLINICA NELLE NEOPLASIE NEUROENDOCRINE

16/17 Maggio 2019 | IEO, Istituto Europeo di Oncologia - Milano

NEN 🌿 Preceptorship

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