

# MIRAGE: tumori neuroendocrine, uno sguardo al futuro

## Terapia chirurgica epato-bilio- pancreatica

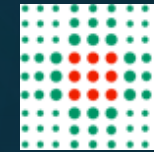
3 Ottobre 2026

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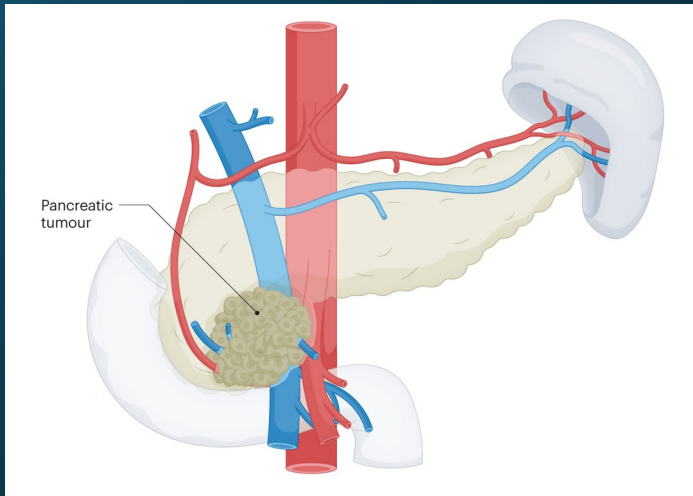
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**Università  
degli Studi  
di Ferrara**



**SERVIZIO SANITARIO REGIONALE  
EMILIA-ROMAGNA**



## La domanda chirurgica: non basta chiedersi "è resecabile?"

La decisione chirurgica integra:

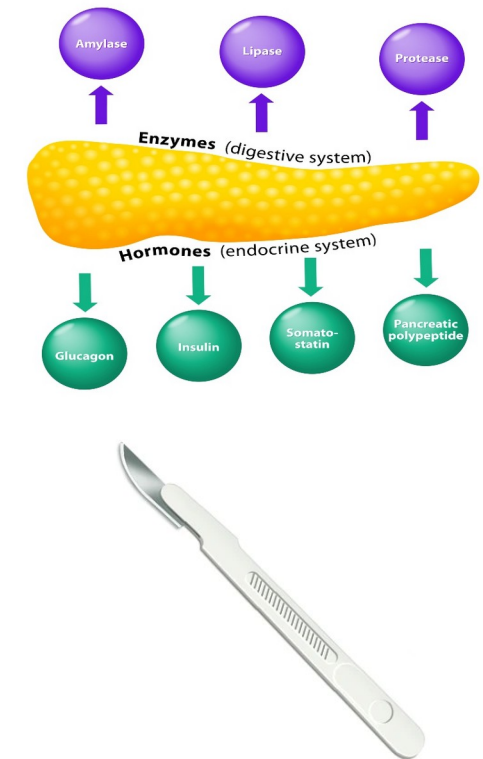
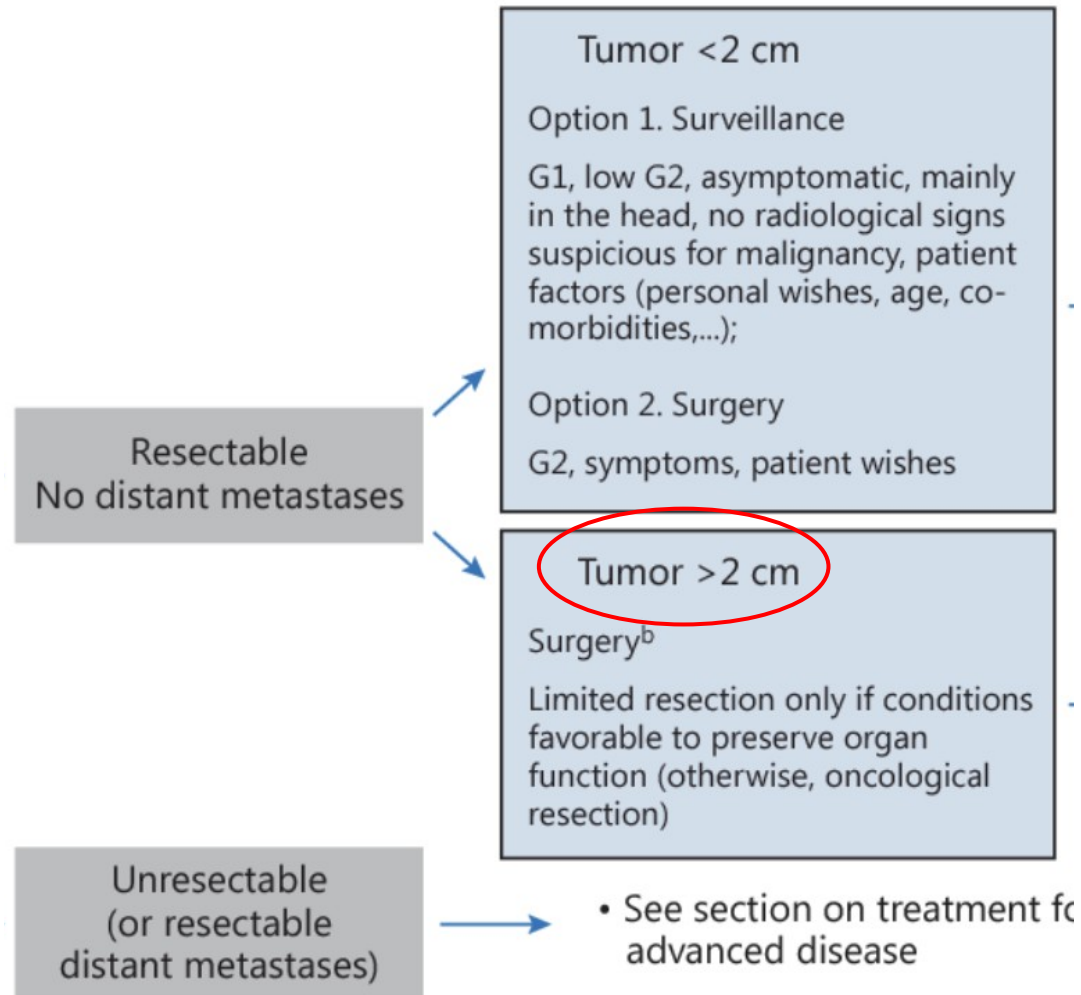
- Biologia: differenziazione, G, Ki-67, velocità di progressione
- Distribuzione anatomica: pancreas, fegato, linfonodi, extraepatico
- Resecabilità tecnica
- Funzione d'organo

**Obiettivo della chirurgia:** R0, debulking, controllo dei sintomi, prevenzione delle complicanze.

***Nei NET la chirurgia è una componente di una strategia oncologica longitudinale, non un singolo atto terapeutico.***



# PARTE I- TUMORI NEUROENDOCRINI PRIMITIVI DEL PANCREAS (PanNET)



# ASPEN TRIAL: sorveglianza attiva vs chirurgia in NET non funzionanti <2 cm

## Management of asymptomatic sporadic non-functioning pancreatic neuroendocrine neoplasms no larger than 2 cm: interim analysis of prospective ASPEN trial

Stefano Partelli<sup>1,2</sup> , Sara Massironi<sup>3,4</sup> , Alessandro Zerbi<sup>5,6</sup>, Patricia Niccoli<sup>7</sup>, Wooil Kwon<sup>8</sup> , Luca Landoni<sup>9</sup>, Francesco Panzuto<sup>10</sup>, Ales Tomazic<sup>11</sup>, Alberto Bongiovanni<sup>12</sup>, Gregory Kaltsas<sup>13</sup>, Alain Sauvanet<sup>14</sup>, Emilio Bertani<sup>15</sup>, Vincenzo Mazzaferro<sup>16</sup> , Martyn Caplin<sup>17</sup>, Thomas Armstrong<sup>18</sup>, Martin O. Weickert<sup>19</sup>, John Ramage<sup>20</sup>, Eva Segelov<sup>21</sup> , Giovanni Butturini<sup>22</sup>, Stefan Staettner<sup>23</sup>, Mauro Cives<sup>24</sup>, Andrea Frilling<sup>25</sup>, Carol Anne Moulton<sup>26,27</sup>, Jin He<sup>28</sup> , Florian Boesch<sup>29</sup>, Andreas Selberheer<sup>30</sup>, Orit Twito<sup>31,32</sup>, Antonio Castaldi<sup>33</sup> , Claudio G. De Angelis<sup>34</sup>, Sebastien Gaujoux<sup>35</sup> , Katharina Holzer<sup>36</sup>, Colin H. Wilson<sup>37</sup>, Hussein Alameam<sup>38</sup>, Emanuel Vigia<sup>39</sup>, Francesca Muffatti<sup>1,2</sup>, Martina Lucà<sup>3,4</sup>, Andrea Lania<sup>5,6</sup>, Jacques Ewald<sup>7</sup>, Hongbeom Kim<sup>8</sup> , Roberto Salvia<sup>9</sup>, Maria Rinzivillo<sup>10</sup>, Alojz Smid<sup>40</sup>, Andrea Gardini<sup>41</sup>, Marina Tsoi<sup>13</sup>, Olivia Hentic<sup>14</sup>, Samuele Colombo<sup>15</sup>, Davide Citterio<sup>16</sup>, Christos Toumpanakis<sup>17</sup>, Emma Ramsey<sup>18</sup>, Harpal S. Randeva<sup>42</sup>, Ray Srirajskanthan<sup>20</sup>, Daniel Croagh<sup>21</sup>, Paolo Regi<sup>22</sup>, Silvia Gasteiger<sup>43</sup>, Pietro Invernizzi<sup>3,4</sup>, Cristina Ridolfi<sup>44</sup>, Marc Giovannini<sup>7</sup>, Jin-Young Jang<sup>8</sup>, Claudio Bassi<sup>9</sup> and Massimo Falconi<sup>1,2,\*</sup>

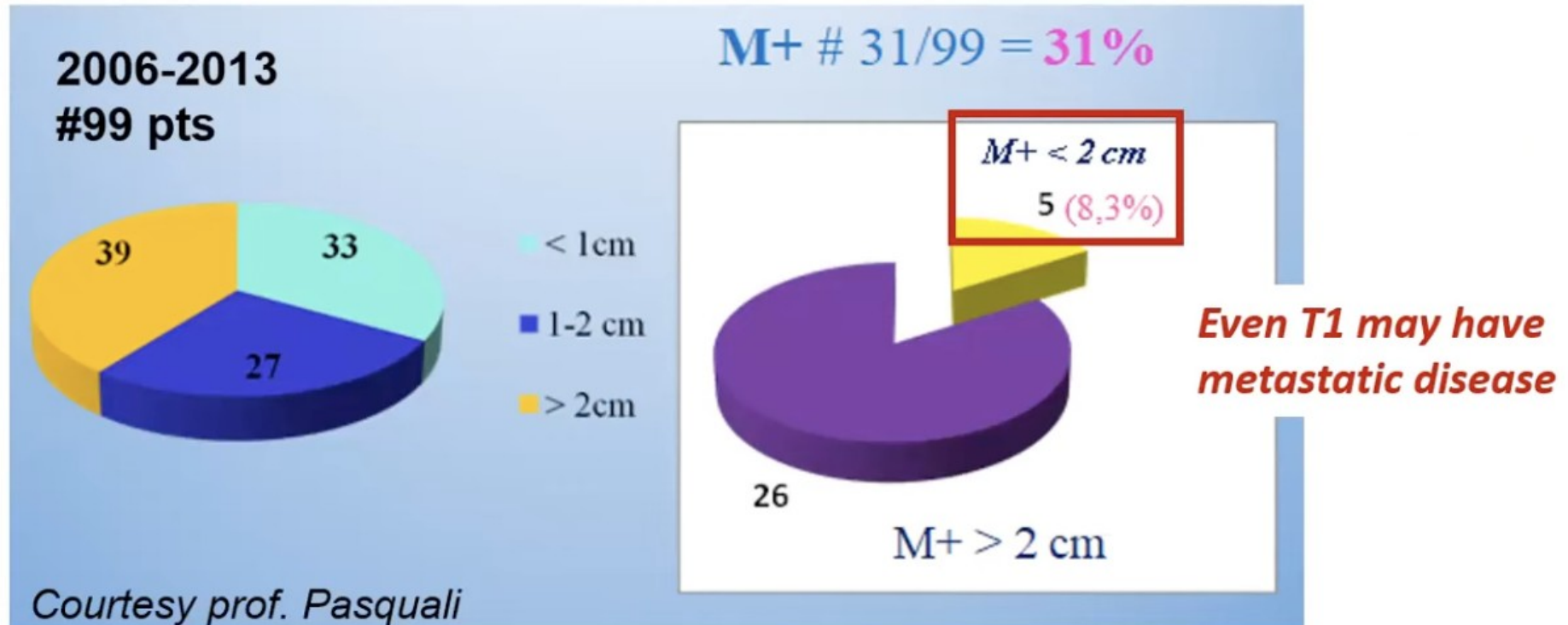
Rischio di M+ o aggressività istologica nel 20% dei tumori operati.

Taylorized management in caso di:

- Lesioni >1 cm
- Pazienti giovani
- Crescita misurabile della lesione

**Risultati preliminari:** crescita tumorale trascurabile in 2 anni di FU (necessità di FU più lungo)

...not without controversy!



- **Stage** (operated pts): 9-31% N+ and **8% M+**
- **Grade**: 37% G2-G3
- **Size**: **>1.5 cm** is associated with an increased risk of N+

PanNETs <1 cm:

Osservazione

PanNETs 1-2 cm:

La decisione se osservare o  
resecare deve essere presa sul  
singolo paziente

## **The North American Neuroendocrine Tumor Society Consensus Paper on the Surgical Management of Pancreatic Neuroendocrine Tumors**

*James R. Howe, MD,<sup>1</sup> Nipun B. Merchant, MD,<sup>2</sup> Claudius Conrad, MD, PhD,<sup>3</sup>  
Xavier M. Keutgen, MD,<sup>4</sup> Julie Hallet, MD, MSc,<sup>5</sup> Jeffrey A. Drebin, MD, PhD,<sup>6</sup>  
Rebecca M. Minter, MD,<sup>7</sup> Terry C. Lairmore, MD,<sup>8</sup> Jennifer F. Tseng, MD,<sup>9</sup>  
Herb J. Zeh, MD,<sup>10</sup> Steven K. Libutti, MD,<sup>11</sup> Gagandeep Singh, MD,<sup>12</sup> Jeffrey E. Lee, MD,<sup>13</sup>  
Thomas A. Hope, MD,<sup>14</sup> Michelle K. Kim, MD,<sup>15</sup> Yusuf Menda, MD,<sup>16</sup>*

Considerare: età e comorbidità, crescita tumorale nel tempo,  
rischio sviluppo di sintomi, caratteristiche radiologiche,  
grado, estensione della resezione richiesta, desiderio del

Functional  
imaging

SSTR-PET avidity

FDG-PET avidity

Ki67 (%)

0 3 20 55 100

WHO

G1 NET

G2 NET

G3 NET (well differentiated)

G3 NEC (poorly differentiated)

NGS

ATRX/DAXX, MEN1, ARID1A

P53; Rb1

Aggressivity



# PanNET: quale resezione?

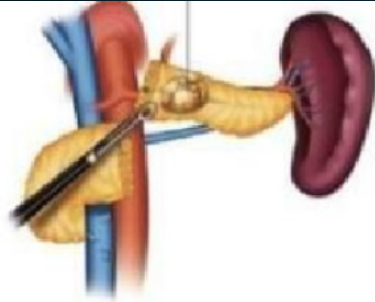


**scelta anatomica + biologica**

Resezione  
formale

Resezione  
parenchyma-  
sparing

# Resezioni formali



## **Distal Pancreatectomy:**

*The tail of the pancreas or a portion of the body of the pancreas is removed, but not the head.*



## **Total Pancreatectomy:**

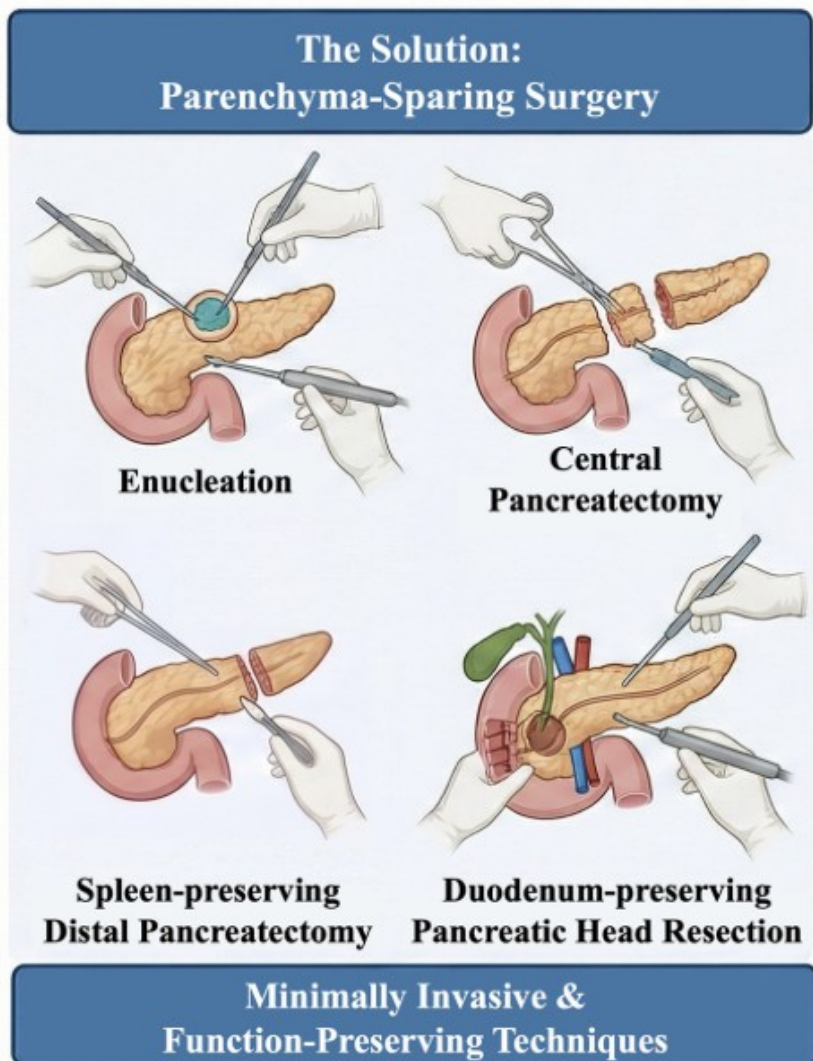
*Removal of the entire pancreas.*



## **Whipple Pancreatectomy:**

*Removal of the head of the pancreas, duodenum, gallbladder, and the bile duct.*

# Resezioni parenchyma-sparing



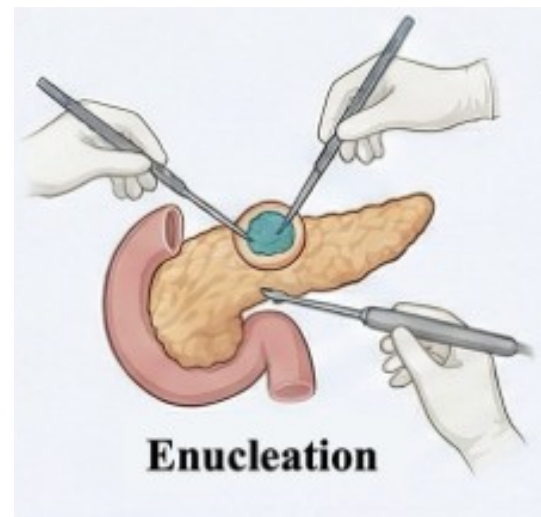
Indicazioni:

- NET funzionanti o NF 1-2 cm
- Stadio 1-2a (T1-T2 N0 M0)
- Grado 1
- Pazienti **giovani** e con lunga aspettativa di vita

Preservazione della funzionalità eso-endocrina  
Eccellente QoL

YES, BUT... **Elevata morbidità**

# Enucleazione



## RESEARCH

### Enucleation for pancreatic neuroendocrine tumors: short- and long-term outcomes in a forty-year single-center experience

Anna Caterina Milanetto<sup>1,2</sup>, Eugenio De Carlo<sup>3</sup>, Daniele Gasparini<sup>4</sup>, Matteo Fassan<sup>5,6</sup> and Claudio Pasquali<sup>1</sup>

#### Short outcome:

- CR POPF 13,5-33%
- Grade C POPF <5,6 %
- Reintervento 3-11% (per PPH dopo POPF)

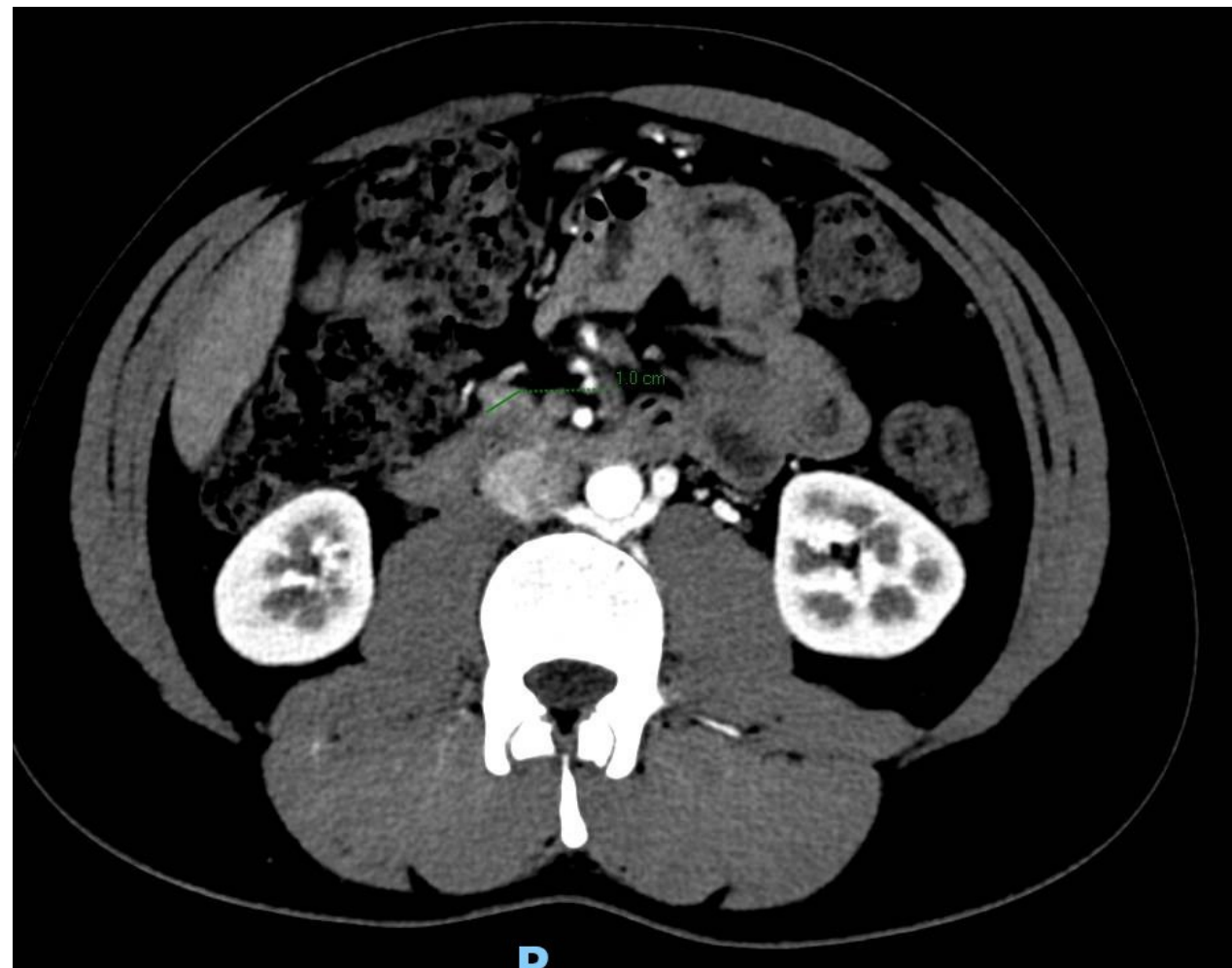
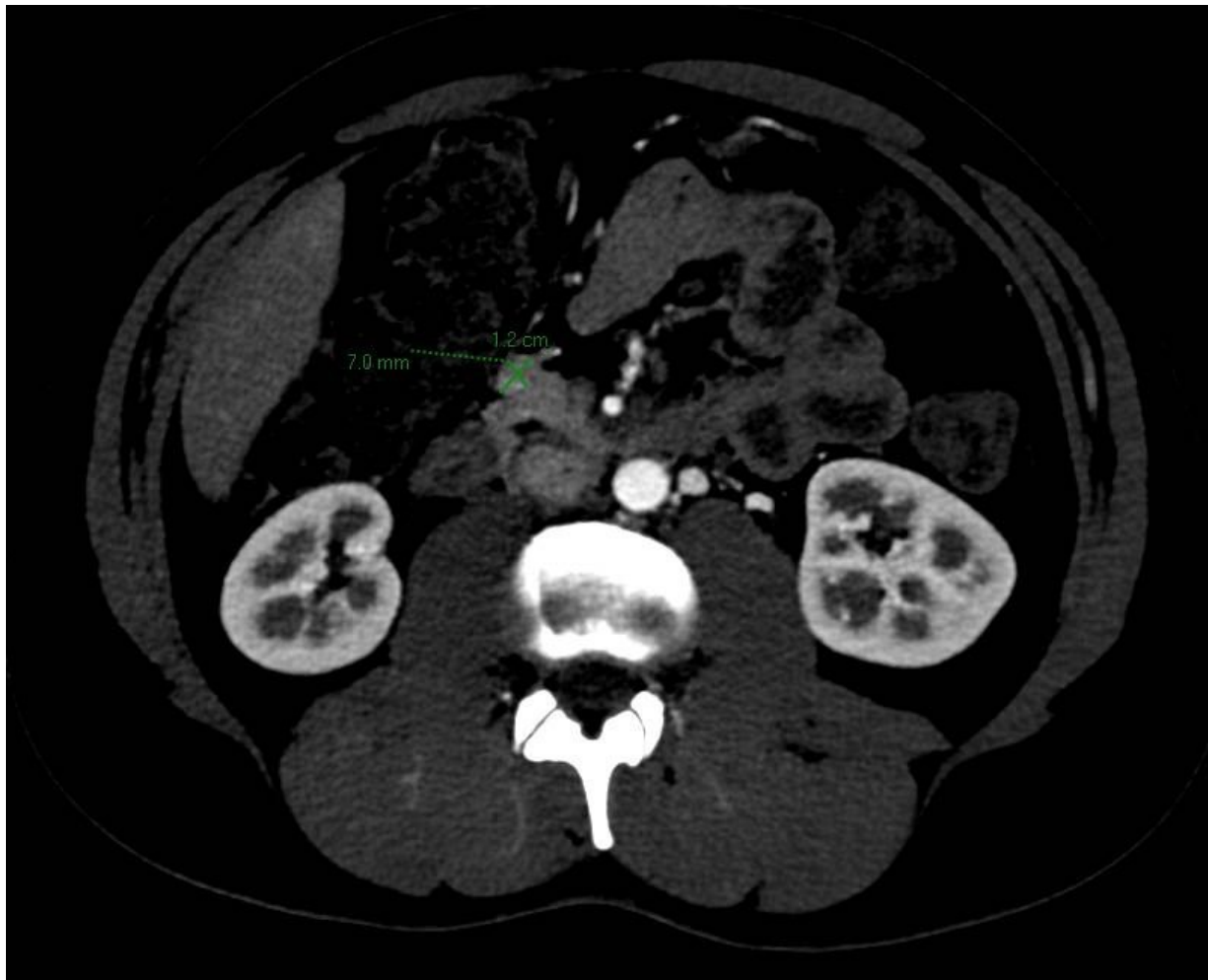
#### Long outcome:

- Recurrence rate 2,6-11% (mediana) dopo 65 mesi
- Diabete legato all'età 3%
- Non insufficienza esocrina

## CASO CLINICO: m, 25 anni, ipoglicemie severe



- TC del 28/01/2025 → tenue iperemia di un'area ovalare di circa 7x12 mm indissociabile dal profilo anteriore del processo uncinato
- EUS per biopsia (sanguinamento post-procedura): esame istologico → neoplasia neuroendocrina ben differenziata, **Ki 67 1%. PanNET G1**
- CPRM del 10/02/2025 → iperintensa in T2, dotata di restrizione del segnale in DWI, **nessun rapporto con il dotto pancreatico**
- PET DOTATOC del 12/02/2025 → aumentata fissazione del radiotracciante
- EUS 12/06/2025 → focalità solida al processo uncinato, distante **> 6 mm dal dotto** pancreatico





Video 1: pancreatic enucleoresection  
From Lancellotti Francesco

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# OUTCOMES

- 23/02/2026 → enucleoresezione pancreatica robotica
- Postoperatorio regolare, paziente dimesso in **IV GPO**
- Esame istologico definitivo: panNET, G1, Ki67 2%, assenza di necrosi
- Follow-up: glicemia a digiuno (95 md/dl), insulina (4.3 U/m), insulina/glicemia: 0.045, diazossido sospeso, asintomatico

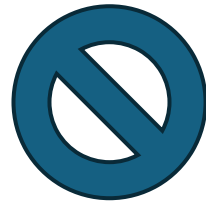


Take home message: GIUSTO CANDIDATO E GIUSTA LESIONE!



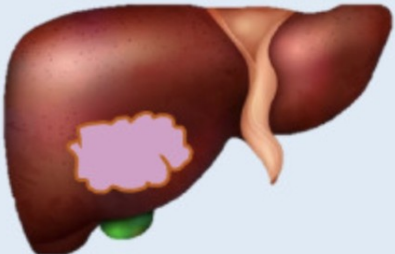
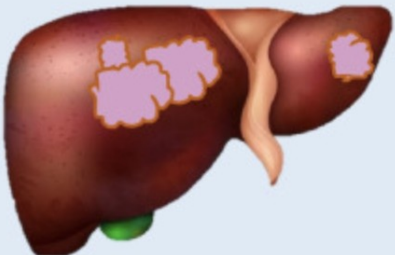
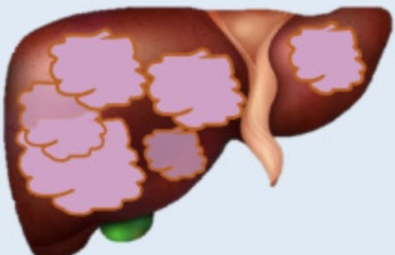
# PARTE II — METASTASI EPATICHE (NELM)

Cosa significa “resecabile”?



Non applicare automaticamente i criteri delle metastasi coloretali!

- numero e dimensioni delle metastasi
- distribuzione mono/bilobare
- rapporti con peduncoli e vene epatiche
- future liver remnant
- funzione epatica
- **malattia extraepatica**
- grado e velocità di progressione

|          |                                                                                       |
|----------|---------------------------------------------------------------------------------------|
| Type I   |    |
| Type II  |   |
| Type III |  |

# Treatment strategies for neuroendocrine liver metastases: a systematic review

## Tre possibili obiettivi:

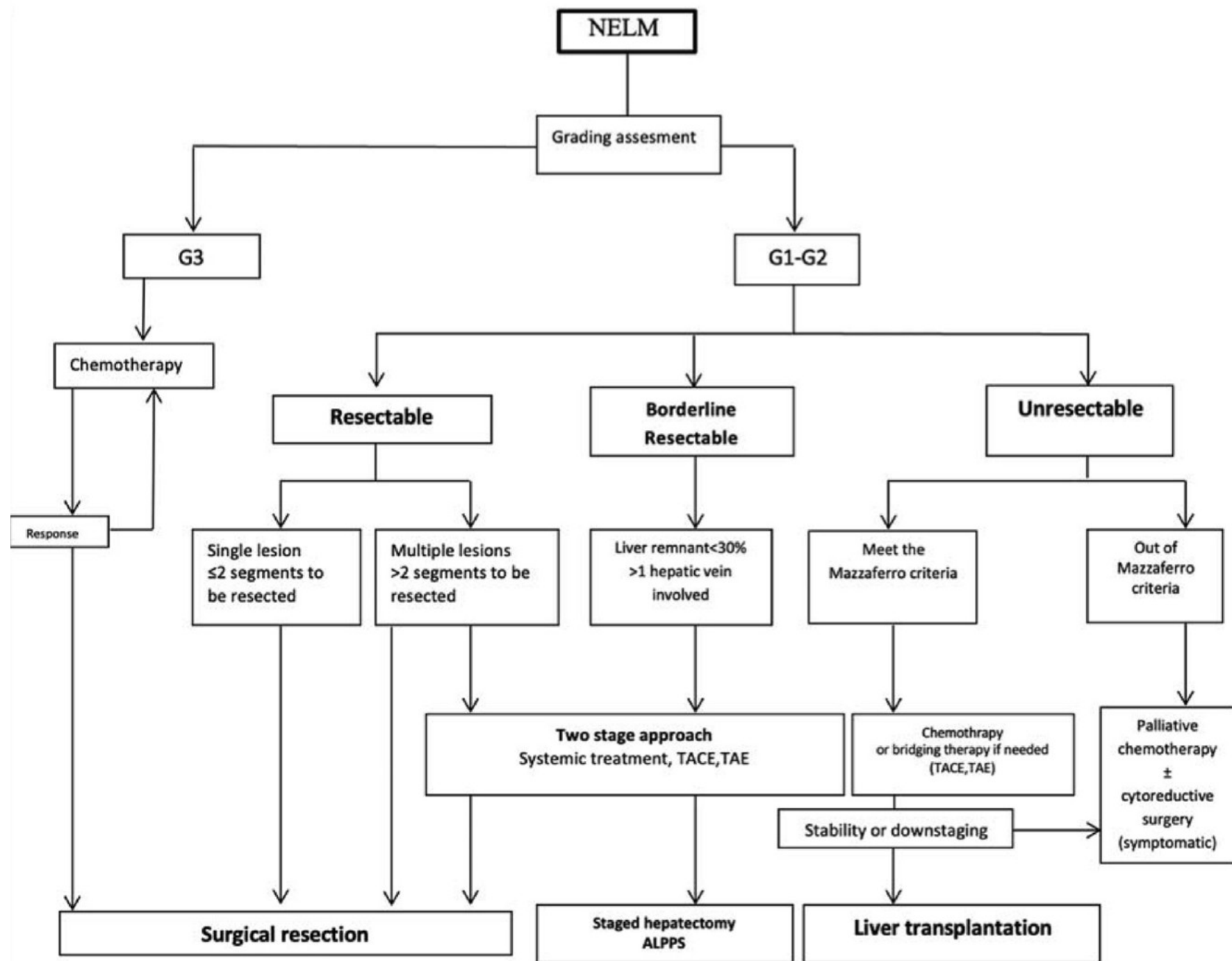
Edoardo M. Muttillio<sup>1,4</sup>, Gennaro Mazzaella<sup>2</sup>, Biagio Picardi<sup>2</sup>, Stefano Rossi<sup>2</sup>, Lorenzo Cinelli<sup>3</sup>, Michele Diana<sup>4</sup>, Andrea Baiocchi<sup>5</sup>, Eric Felli<sup>6</sup>, Patrick Pessaux<sup>4,7</sup>, Emanuele Felli<sup>4,8</sup> & Irnerio A. Muttillio<sup>2</sup>

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**1. RESEZIONE** →  
clearance completa

**2.  
CYTOREDUCTION**  
→ riduzione  
significativa del  
burden tumorale

**3. NON  
CHIRURGICO** →  
terapia sistemica /  
locoregionale /  
PRRT



# Parenchyma-sparing surgery: il paradigma moderno



**From:** massima resezione

**To:** Massima clearance tumorale + minima perdita di parenchima

<https://doi.org/10.1245/s10434-026-20383-z>

Annals of Surgical Oncology



## Tecniche:

- Wedge resection
- Segmentectomie
- Ablazione termica
- Resezione + ablazione

## Perché?

Il paziente può sviluppare nuove metastasi!

## Razionale:

- future resezioni
- future ablazioni

## ORIGINAL ARTICLE

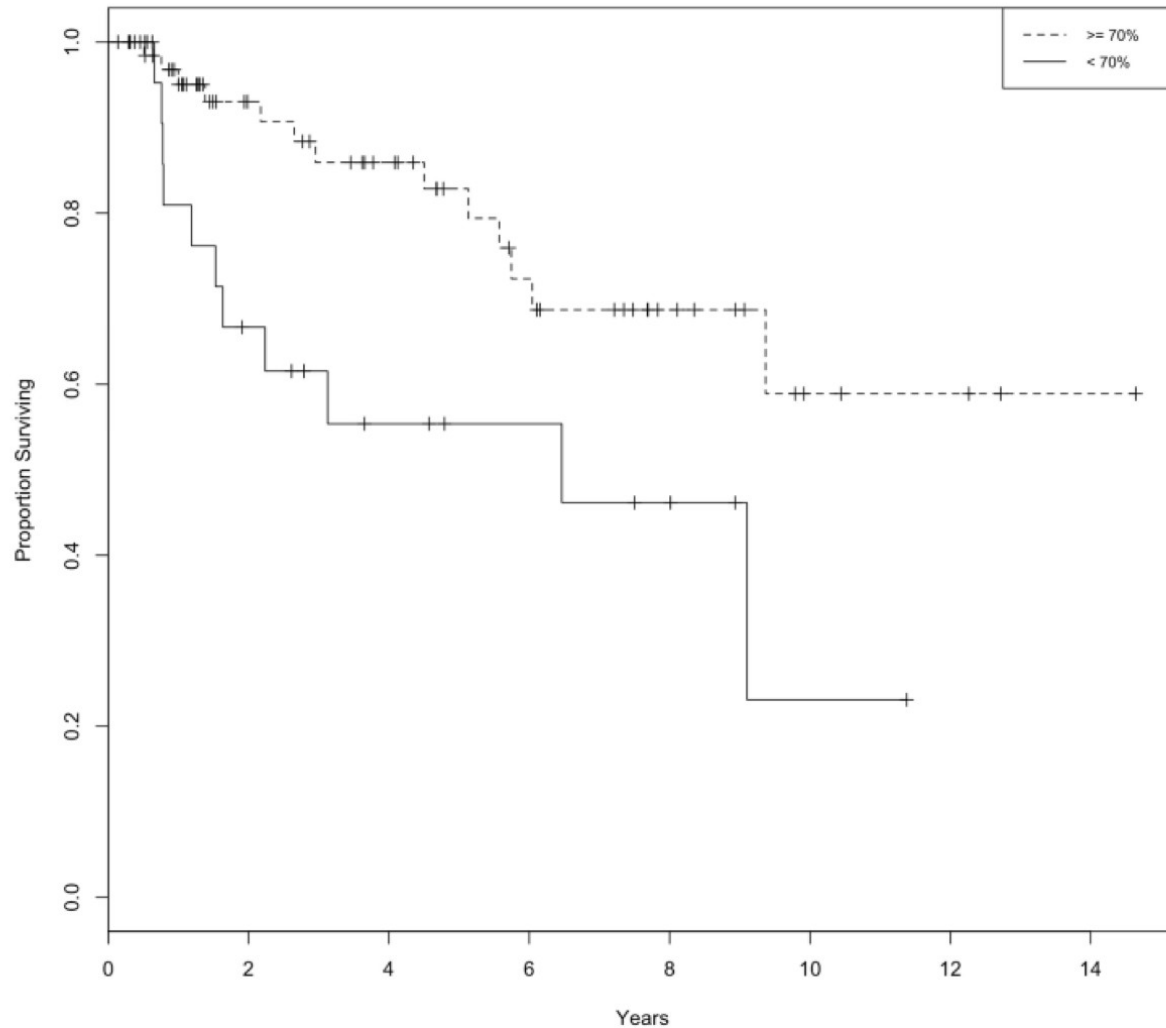
## HEPATOBIILIARY TUMORS

### Changes in Outcomes of Hepatic Cyto reduction for Neuroendocrine Liver Metastases over Two Decades: From Major Hepatectomy to Parenchyma-Sparing Approaches

Kyoji Ito, MD, PhD<sup>1</sup> · Mikel Madi, MD<sup>1</sup> · Jonathan J. Hue, MD<sup>1</sup> · Elsa Melissa Arvide, MS, PA-C<sup>1</sup> · Adriana Gamboa, MD<sup>1</sup> · Timothy E. Newhook, MD<sup>1</sup> · Yun Shin Chun, MD<sup>1</sup> · Hop S. Tran Cao, MD<sup>1</sup> · Ching-Wei D. Tzeng, MD, MS<sup>1</sup> · Arvind Dasari, MD, MS<sup>2</sup> · James C. Yao, MD<sup>2</sup> · Chandrikha Chandrasekharan, MBBS<sup>2</sup> · Matthew H. G. Katz, MD<sup>1</sup> · Jean-Nicolas Vauthey, MD<sup>1</sup> · Jessica E. Maxwell, MD, MBA<sup>1</sup> 

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Overall Survival: SBNET and PNET Patients by % Liver Debulked



**Debulking 70%**

## Principio chirurgico:

**Non chiedersi quanto fegato posso togliere, ma...**

**quanto tumore posso eliminare preservando il futuro del paziente.**

**Figure 1. Kaplan-Meier curve of PFS (a) and OS (b) in all NET patients who were stratified by amount of hepatic disease debulked**

Patients enjoyed longer PFS and OS if 70% reduction of their hepatic tumor burden could be achieved.

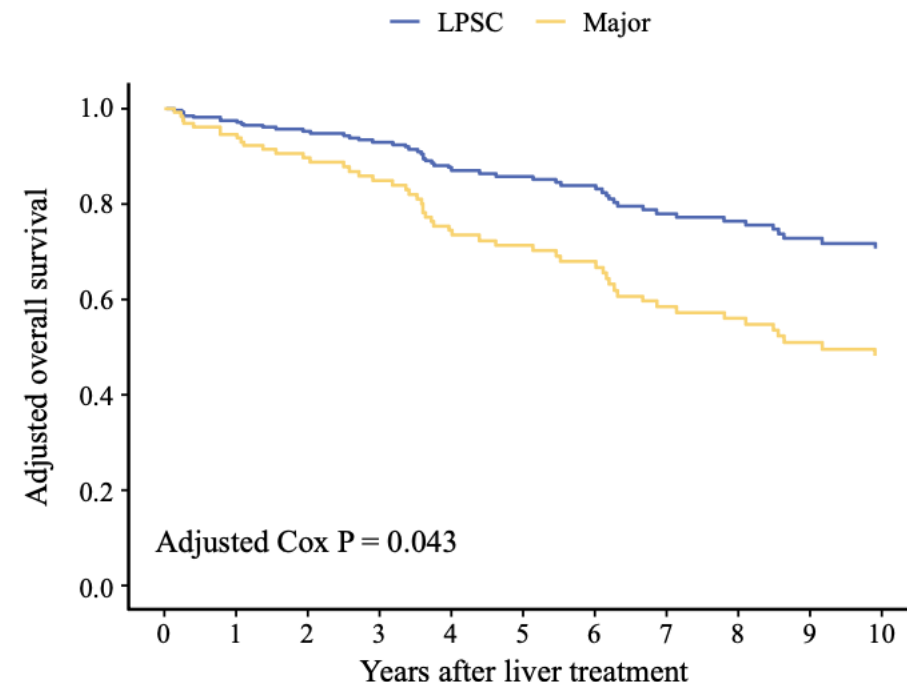
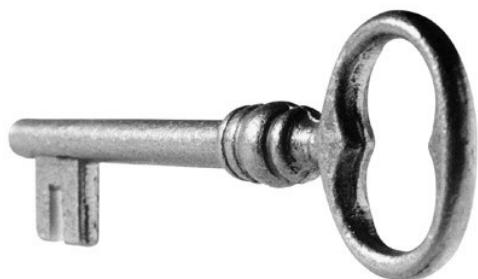
Maxwell JE, Sherman SK, O'Dorisio TM, Bellizzi AM, Howe JR. Liver-directed surgery of neuroendocrine metastases: What is the optimal strategy? *Surgery*. 2016 Jan;159(1):320-33. doi: 10.1016/j.surg.2015.05.040. Epub 2015 Oct 9. PMID: 26454679; PMCID: PMC4688152.

# Quanto debulkare?

≥70% di citoriduzione soglia «storica»  
**Ma...non è un dogma!**

## Considerare:

- burden tumorale
- distribuzione
- biologia
- sintomi
- funzione epatica
- morbidità prevista
- possibilità di **terapia combinata**



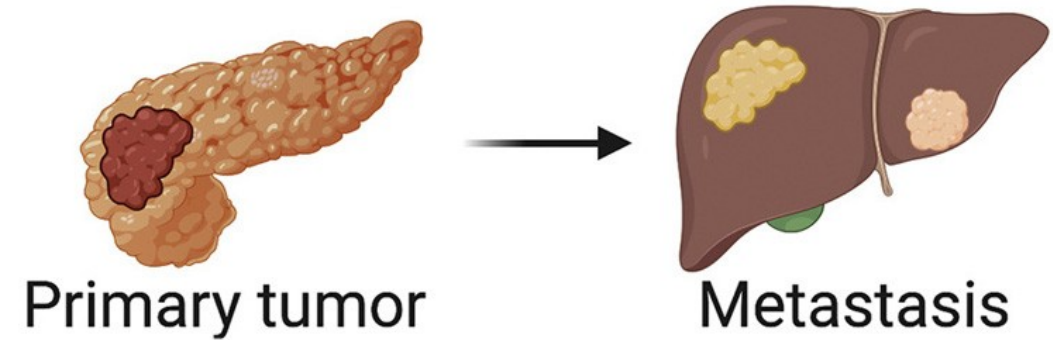
Number at risk

|       |     |     |     |    |    |    |    |    |    |    |    |
|-------|-----|-----|-----|----|----|----|----|----|----|----|----|
| LPSC  | 123 | 113 | 103 | 91 | 77 | 67 | 54 | 46 | 40 | 29 | 23 |
| Major | 73  | 67  | 57  | 50 | 40 | 37 | 31 | 24 | 21 | 15 | 14 |

**Fig. 2** Covariate-adjusted survival curves comparing overall survival between patients who underwent major hepatectomy and those who underwent liver-parenchyma-sparing cytoreduction; curves were generated from the multivariable Cox model presented in Table 2

**Citoriduzione significativa con una morbidità accettabile!**

## PARTE III — PRIMITIVO + METASTASI



**PanNET resecabile + NELM resecabili**

→ possibile chirurgia del primitivo + liver surgery

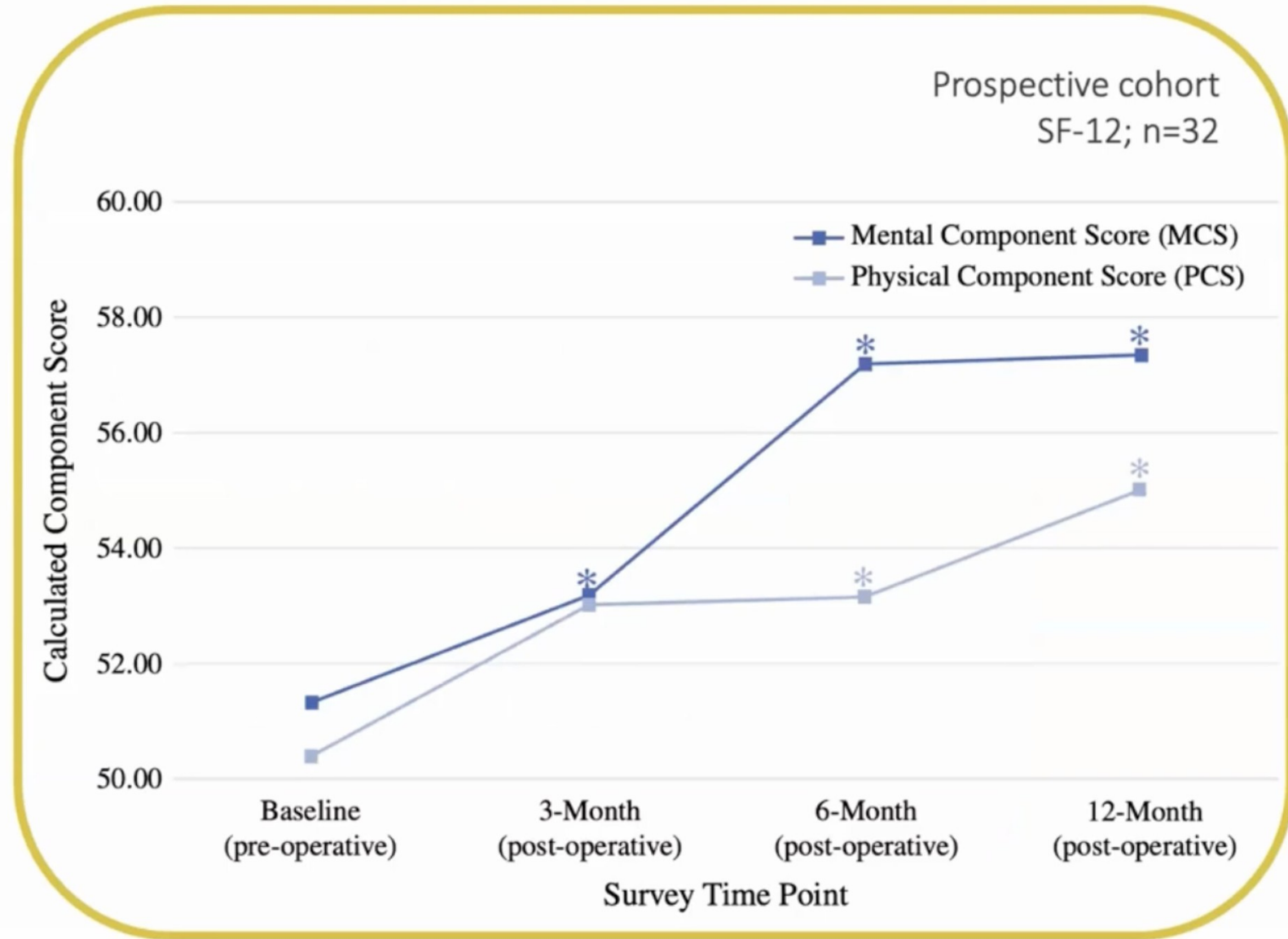
**PanNET resecabile + NELM citoriducibili**

→ chirurgia selezionata con intento di debulking

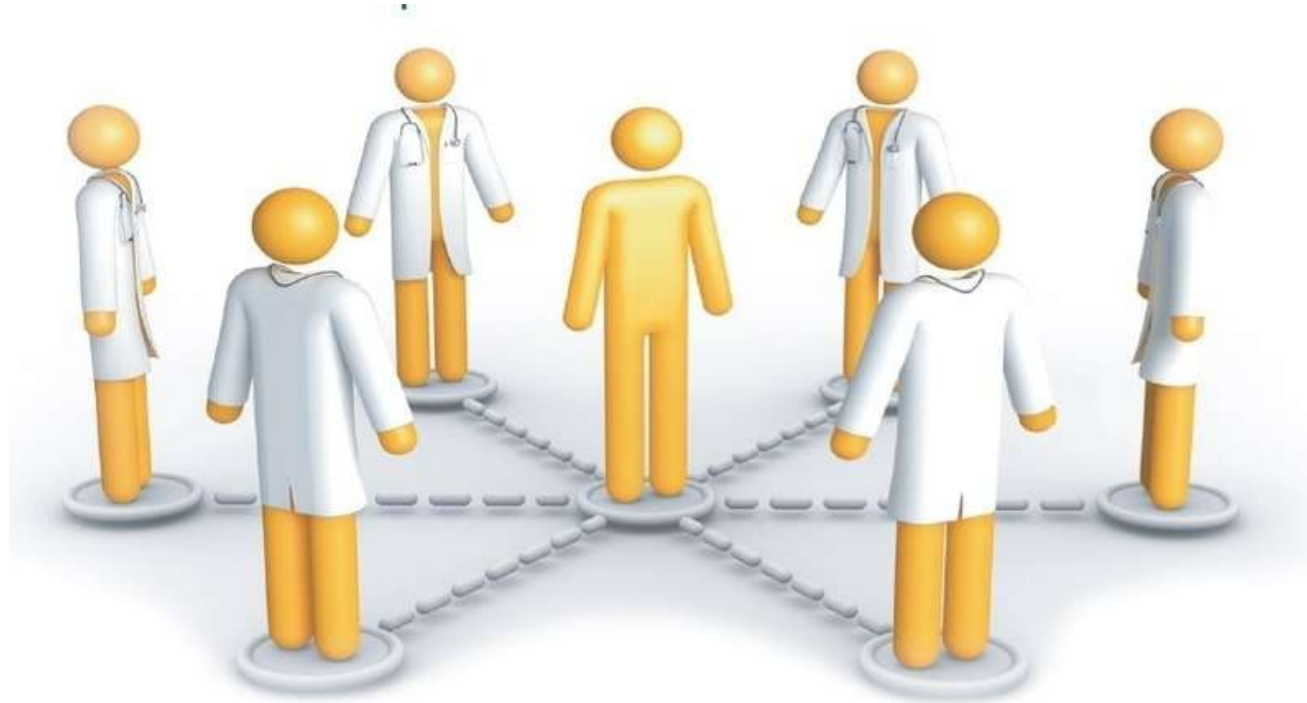
**PanNET + malattia epatica non chirurgicamente controllabile**

→ terapia sistemica/locoregionale ± resezione del primitivo

# Quality of life



# Conclusioni...



Approccio multidisciplinare: unica strategia per personalizzare il trattamento nei pazienti NET

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**GRAZIE PER L'ATTENZIONE!**



