Should we resect the primary tumor in metastatic NENs?

Prof. Reza Kianmanesh, MD, PhD.

(Hôpital Robert Debré, Reims, France, University of Champagne Ardenne, France)
A “reactualized” CONCEPT - Why to resect the PT in stage IV patients?

**3 QUESTIONS**

1. FOR MACROSCOPIC CURE?
2. TREAT OR AVOID COMPLICATIONS?
3. FOCUS ON LIVER TREATMENT?

**Multicompartmental disease**

- Stage IV
  - siNENs
  - pNENs

**Unicompartmental disease**

- Liver Focused Therapies – PRRT...

- MODERN THERAPIES
  - MWA
  - MWA + RIGHT HEPATECTOMY

**Primary Tumor resection**

- FOR MACROSCOPIC CURE
- TREAT OR AVOID COMPLICATIONS
- FOCUS ON LIVER TREATMENT
Primary tumor resection in stage IV NENs?

No prospective RCT

- Retrospective
- Unicenter Studies

Large Historic Data bases → Potential benefit of PTR

Selection Bias
Even in systematic reviews/metanlyses!

Best Indications for PTR +++

Expert – Guidelines recommendations

How to Manage Small Intestine (Jejunal and Ileal) Neuroendocrine Neoplasms Presenting with Liver Metastases?

Bruno Niederle¹ · Andreas Selberherr¹ · Martin B. Niederle²

https://doi.org/10.1016/j.soc.2019.11.008
Role of palliative resection of the primary tumour in advanced pancreatic and small intestinal neuroendocrine tumours: A systematic review and meta-analysis

Almond, L. M.; Hodson, James; Ford, S. J.; Gourevitch, David; Roberts, K. J.; Shah, Tahir; Coles, Jessica; Desai, Anant

N=13 studies, 6 suitable for Meta-Analyse, no RCT!

Pooled multivariate demonstrated significantly longer overall survival in patients undergoing resection of both P-NETs (HR 0.43; 95% CI: 0.34 - 0.57, p<0.001) and SI-NETs (HR 0.47; 95% CI: 0.35 - 0.55, p=0.007).

Why include these 2 studies?
How to conclude or make Meta-analyze?
SiNENs & pNENs are different diseases?
### GEP NENs – Different disease

<table>
<thead>
<tr>
<th></th>
<th><strong>pNEN</strong></th>
<th><strong>siNEN</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Embryo /genetic</strong></td>
<td>For gut / NEM1</td>
<td>Mid gut</td>
</tr>
<tr>
<td><strong>Grade</strong></td>
<td>G1,G2,G3-undiffereniciated</td>
<td>G1,G2 → better prognosis</td>
</tr>
<tr>
<td><strong>Size</strong></td>
<td>1cm to &gt; 10</td>
<td>&lt; 2cm</td>
</tr>
<tr>
<td><strong>Hormonal secretion</strong></td>
<td>F / NF</td>
<td>Serotoninine LN/LM</td>
</tr>
<tr>
<td><strong>LN size</strong></td>
<td>small</td>
<td>large</td>
</tr>
<tr>
<td><strong>Ga-PET / F-DopaPET</strong></td>
<td>Ga</td>
<td>Ga / F-Dopa</td>
</tr>
<tr>
<td><strong>FDG-PET</strong></td>
<td>+ for G2,G3, undifferentiated</td>
<td>-</td>
</tr>
<tr>
<td><strong>Drug (CT, Target) Sensitivity</strong></td>
<td>+++</td>
<td>+/-</td>
</tr>
<tr>
<td><strong>Primary complications</strong></td>
<td>+/-</td>
<td>+ (10-30%)</td>
</tr>
<tr>
<td><strong>Morbidity of primary resection</strong></td>
<td>+++ (PD 30% mb, up to 10% mt*)</td>
<td>+/-</td>
</tr>
<tr>
<td><strong>LM treatment options</strong></td>
<td>-SSA / Chemotherapy / Target therapy</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>-CEIA / Radioembolization</td>
<td>+/-</td>
</tr>
<tr>
<td></td>
<td>-Liver resection-ablation / liver Transplantation</td>
<td></td>
</tr>
</tbody>
</table>

**MULTIMODAL**
siNEN are «Complex Diseases»

**siNET Stage**
- Primary siNET Ileon ++
- MM-Lymph Nodes 80%
  - LN stages (I-IV)
- Liver Metastases 30% to 80%

**Particularities**
- Small < 1 cm
  - (20% to 30% multiple)
- Small/large (± fibr. mesenteritis)
  - Multiple primaries 30%
- Small or large
  - Multiple bilobar (> 70%)
  - Diffuse disease?
  - Recurrence after liver resection: > 80%

**Therapeutic options**
- Surgical Macro. Cure
  - Is a LRT ++++
- Primary + MM
- LN > 8-12 is prognostic
- Liver resection- Ablation
- Analogue sensitive
- Not chemosensitive
- PRRT sensitive
- TACE/TAE sensitive
- Target T ± sensitive
- - RADIANT-4 study
- - NETTER trial
- - CLARINET fort
siNENs Complications are Life-threatening

Symptomatic patients with SiNENs at any stage → Primary resection because life-threatening

**Occlusive syndrome (20% to 30%)**
Endoluminal obstruction of the primary
Exoluminal compression (MM, PC)
Mesenteric mass
  • LN (with localized PC 15%)
  • Fibrosis (desmoplasia)

**Hemorrhage (5%)**

**Mesenteric ischemia (< 3%)**

Primary resection often required even in preclinic signs
What to do with Mesenteric Masses?

Cure → LocoRegional Resection
→ Remove primary + LN + MM

Images courtesy of Kianmanesh R.
pNENS Complications do not require Routine Surgery

Different tumor location from duodenum-head to tail of the pancreas

Primary pNENs Complications (<10%):
- Venous thrombus (splenic, mesenteric, portal)
- Sinital (left) portal hypertension
- Haemorrhage
- Biliary obstruction (Jaundice)
- Duodenum-colon compression
- Wirsung dilatation

pNENs symptomatic patients
→ Surgery is not always required
Place for heparine, stenting, ...

Different morbidity – mortality upon tumor location
Resection of primary tumor may prolong survival in metastatic gastroenteropancreatic neuroendocrine tumors☆

John F. Tierney, MD, Sitaram V. Chivukula, MD, Xuanji Wang, MD, Sam G. Pappas, MD, Erik Schadde, MD, Martin Hertl, MD, PhD, Jennifer Poirier, PhD, Xavier M. Keutgen, MD

Rush University Medical Center, Department of Surgery, Chicago IL.

No propensity score used!

< 10% of stage IV pNENs had PTR versus 59% for siNENs

Resection of Primary Gastrointestinal Neuroendocrine Tumor Among Patients with Non-Resected Metastases Is Associated with Improved Survival: A SEER-Medicare Analysis

Diamantis I. Tsilimigras⁴ J. Madison Hyer⁴ Anghela Z. Paredes³ Aslam Ejaz¹ Jordan M. Cloyd¹ Joal D. Beane¹ Mary Dillhoff¹ Allan Tsung¹ Timothy M. Pawlik¹

The majority of patients with stage IV GI-NETs underwent resection of siNETs or colon NET (539/889=60%)

PTR was associated with a survival benefit among patients with metastatic GI-NETs across all anatomic sites, except for rectal NETs.

Resection of primary GI-NET among patients with stage IV disease and unresected metastases should only be performed in selected cases following multi-disciplinary evaluation.

PTR improved OS in patients with LMs who had liver-directed therapy (median OS: 3.44 years [1.47–3.68] vs 1.44 [1.09–2.04], p = 0.01), and patients with LMs who did not have liver-directed therapies (2.07 years [1.34–2.64] vs 0.73 [0.64–0.88], p < 0.001).

PSM cohort used for N=236 with PTR

For 5-y OS Including all primaries

Complications of primary resection pNENs from siNENs
Postoperative Complications, In-Hospital Mortality and 5-Year Survival After Surgical Resection for Patients with a Pancreatic Neuroendocrine Tumor: A Systematic Review

<table>
<thead>
<tr>
<th>%</th>
<th>PF</th>
<th>DG emptying</th>
<th>Hemorrhage</th>
<th>In-hospital mortality</th>
<th>5-year OS Without LM</th>
<th>5-year DSS Without LM</th>
<th>5-year DSS with LM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enucleation</td>
<td>45</td>
<td>5</td>
<td>6</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal pancreatectomy</td>
<td>14</td>
<td>5</td>
<td>1</td>
<td>4</td>
<td>85</td>
<td>93</td>
<td>80</td>
</tr>
<tr>
<td>Whipple (PD)</td>
<td>14</td>
<td>18</td>
<td>7</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central pancreatectomy</td>
<td>58</td>
<td>16</td>
<td>4</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pancreatic surgery is associated to high rate of morbidity and Mortality Particularly Whipple (PD)

Complications of surgery for gastro-entero-pancreatic neuroendocrine neoplasias

Max B. Albers¹,² • Martin Almquist¹ • Anders Bergenfelz¹ • Erik Nordenström¹

Table 2  Regression analysis of potential risk factors for severe postoperative complications (Dindo-Clavien ≥ 3)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>n</th>
<th>Complication rate</th>
<th>versus</th>
<th>Major complications</th>
<th>n</th>
<th>Complication rate</th>
<th>p</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duodenopancreatic primary tumor</td>
<td>131</td>
<td>22%</td>
<td>Small intestinal primary tumor</td>
<td>133</td>
<td>11%</td>
<td>0.014</td>
<td>2.20 (1.13–4.29)</td>
<td></td>
</tr>
<tr>
<td>Duodenopancreatic primary tumor</td>
<td>131</td>
<td>22%</td>
<td>All non-duodenopancreatic tumors</td>
<td>245</td>
<td>10%</td>
<td>0.003</td>
<td>2.38 (1.34–4.23)</td>
<td></td>
</tr>
<tr>
<td>Curative resection of lymph node metastases</td>
<td>112</td>
<td>21%</td>
<td>No lymph node metastases or palliative aim of resection</td>
<td>264</td>
<td>12%</td>
<td>0.020</td>
<td>1.99 (1.11–3.96)</td>
<td></td>
</tr>
<tr>
<td>Functioning tumor</td>
<td>87</td>
<td>23%</td>
<td>Non-functioning tumors</td>
<td>222</td>
<td>13%</td>
<td>0.042</td>
<td>1.91 (1.02–3.59)</td>
<td></td>
</tr>
<tr>
<td>NET/NEC G3</td>
<td>35</td>
<td>11%</td>
<td>NET G1, NET G2</td>
<td>321</td>
<td>16%</td>
<td>0.505</td>
<td>0.69 (0.17–2.09)</td>
<td></td>
</tr>
<tr>
<td>Age ≥ 60 years</td>
<td>221</td>
<td>14%</td>
<td>Age &lt; 60 years</td>
<td>155</td>
<td>16%</td>
<td>0.573</td>
<td>0.85 (0.46–1.57)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>112</td>
<td>12%</td>
<td>No cardiovascular disease</td>
<td>264</td>
<td>16%</td>
<td>0.249</td>
<td>0.68 (0.32–1.36)</td>
<td></td>
</tr>
<tr>
<td>BMI ≥ 30 kg/m²</td>
<td>59</td>
<td>24%</td>
<td>BMI &lt; 30 kg/m²</td>
<td>193</td>
<td>15%</td>
<td>0.120</td>
<td>1.76 (0.79–3.78)</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>166</td>
<td>17%</td>
<td>Women</td>
<td>210</td>
<td>13%</td>
<td>0.330</td>
<td>0.75 (0.41–1.39)</td>
<td></td>
</tr>
</tbody>
</table>

OR odds ratio; CI confidence interval; NET neuroendocrine tumor; NEC neuroendocrine carcinoma; BMI body mass index

Conclusions  Severe complications are frequent in GEP-NEN surgery. Besides duodenopancreatic tumor location, curative resection of nodal metastases and functioning tumors are risk factors for complications.

PD Surgery  ➔ higher morbidity
Stage IV – Resectable or unresectable LMs?
Stage IV – Different stage IV patients may require PTR

Resectable LM asymptomatic

Unresectable LM symptomatic

Focus on liver treatment ➔ Potential benefit on Overall Survival?

Primary Tumor Resection Better Survival?

Liver directed Treatments ➔ Treat Life-threatening Complications +++ ➔ Potential benefit on Overall Survival?

Systemic Treatments

TNM staging proposal according to Rindi et al.

<table>
<thead>
<tr>
<th>Disease stage</th>
<th>T-primary tumor</th>
<th>N-regional nodes</th>
<th>M-distant metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>T1–2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>T3–4</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>Any T</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

Regional nodes: mesenteric lymph nodes; distant metastases: metastasis at any distant site (including non-regional lymph nodes).

Agressive management of LMs, Associated S-Analogues & PRRT?
Management of Stage IV NENs is Multimodal

**Neuroendocrine Hepatic Metastases**

**Does Aggressive Management Improve Survival?**

John G. Touzios, MD,* James M. Kiely, MD,* Susan C. Pitt, BA,* William S. Rilling, MD,† Edward J. Quebbeman, MD, PhD,* Stuart D. Wilson, MD,* and Henry A. Pitt, MD*

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**Long-Term Survival with Long-Acting Somatostatin Analogues Plus Aggressive Cytoreductive Surgery in Patients with Metastatic Neuroendocrine Carcinoma**

Gary B Deusch, MD, MPH, Ji Hey Lee, PhD, Anton J Bilchik, MD, PhD, FACS

![Aggressive Cytoreductive surgery & S-LAR](image)

N=60 LM from DETs, Milwaukee (1990-2004)

**% Survival**

- *RA (n=19)
- *TRA (n=18)
- NON (n=23)

FIGURE 2. Kaplan-Meier actuarial survival curve comparing Resection/Ablation (RA), TACE ± RA (TRA), and Nonaggressive (NON) treatments. Survival was significantly improved ($p < 0.05$) in the RA and TRA groups.

**Aggressive treatments:**
- resection+Ablation (RA)
- resection+TACE (TRA)

**Non aggressive treatments**

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![Figure 2](image) Overall survival for metastatic gastroenteropancreatic neuroendocrine tumors in the SEER-Medicare population by type of treatment received. S-LAR, long-acting somatostatin analogue.
Management of Stage IV NENs is Multimodal

Management of Neuroendocrine Tumor Liver Metastases: Long-Term Outcomes and Prognostic Factors from a Large Prospective Database

Mark Fairweather, MD¹, Richard Swanson, MD¹, Jiping Wang, MD, PhD¹, Lauren K. Brais, MPH², Trevor Dutton, BA³, Matthew H. Kulke, MD², and Thomas E. Clancy, MD¹

N=939 NENs, N=649 with LM

Better Outcome for:
- SiNENs vs pNENs
- Liver resection vs other
- WD tumors vs other

FIG. 1 Kaplan–Meier overall survival curves for patients with neuroendocrine tumor liver metastases (n = 649) based on primary treatment modality

Aggressive Treatments

LMs from SiNENs
Management of Stage IV NENs is Multimodal

Resection of the Primary Tumor Followed by Peptide Receptor Radionuclide Therapy as Upfront Strategy for the Treatment of G1–G2 Pancreatic Neuroendocrine Tumors with Unresectable Liver Metastases

Emilio Bertani, MD¹, Nicola Fazio, MD², Davide Radice, MSc³, Claudio Zardini, MD⁴, Chiara Grana, MD⁵, Lisa Bodei, MD⁶, Luigi Funicelli, MD⁷, Carlo Ferrari, MD⁸, Francesca Spada, MD⁹, Stefano Partelli, MD, PhD⁹, and Massimo Falconi, MD⁹

Conclusions. Primary tumor resection prior to PRRT can be safely proposed in G1–G2 pNETs with diffuse liver metastases because it seems to enhance response to PRRT and to improve significantly PFS.

Unresectable LMs + Primary pNENs → Primary Resection → PRRT for LMs → Better Survival

FIG. 2 Progression-free survival by resection of the primary (yellow line); p = .002
Prior Resection of the Primary Tumor Prolongs Survival After Peptide Receptor Radionuclide Therapy of Advanced Neuroendocrine Neoplasms

Daniel Kaemmerer, MD,* Matthias Twrznik, MD,* Harshad R. Kulkarni, MD,† Dieter Hörsch, MD,‡ Suzanne Sehner,§ Richard P. Baum, MD, PhD,§ and Merten Hommann, MD*,
Center for Neuroendocrine Tumors, Bad Berka – ENETS Center of Excellence

N=889 Stage IV
pNETS=38%
SiNTS=32%

N=486 Primary removed before PRRT

N=403 no PT before PRRT
Prior Resection of the Primary Tumor Prolongs Survival After Peptide Receptor Radionuclide Therapy of Advanced Neuroendocrine Neoplasms

Daniel Kaemmerer, MD,* Matthias Tworzik, MD,* Harshad R. Kulkarni, MD,† Dieter Hörsch, MD,‡ Susanne Sehner,§ Richard P. Baum, MD, PhD,‡ and Merten Hommann, MD*,
Center for Neuroendocrine Tumors, Bad Berka – ENETS Center of Excellence

### TABLE 3. Median Overall Survival

<table>
<thead>
<tr>
<th>Primary Tumor</th>
<th>n (Resection)</th>
<th>Median OS (months)</th>
<th>HR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Resection</td>
<td>No Resection</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Resection</td>
<td>No Resection</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR</td>
<td>P</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>148</td>
<td>187</td>
<td>140 (108; 200)</td>
<td>58 (46; 64)</td>
</tr>
<tr>
<td>SI (jejenum/ileum)</td>
<td>235</td>
<td>49</td>
<td>142 (118; 184)</td>
<td>80 (59; 125)</td>
</tr>
<tr>
<td>Lung</td>
<td>44</td>
<td>20</td>
<td>124 (93; 137)</td>
<td>76 (43; 106)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>33</td>
<td>11</td>
<td>100 (76; 195)</td>
<td>107 (34; 136)</td>
</tr>
<tr>
<td>Duodenum/stomach</td>
<td>21</td>
<td>11</td>
<td>98 (56;.)</td>
<td>87 (23;.)</td>
</tr>
</tbody>
</table>

Reasons why primaries did not underwent resection ?, more advanced disease, poorer GC, larger primaries, more EHD ?

LMs + Primary siNENs or pNENs

Primary resection

PRRT ⇒ Better Survival pNEN & siNENs
Evolution of the Mesenteric Mass in Small Intestinal Neuroendocrine Tumours

Anela Blažević 1,*, Tessa Brabander 2,4, Wouter T. Zandee 1,3,4, Johannes Hofland 1, Gaston J. H. Franssen 4, Marie-Louise F. van Velthuysen 5, Richard A. Feelders 1 and Wouter W. De Herder 1,6

Table 2. Evolution of mesenteric mass over time.

<table>
<thead>
<tr>
<th></th>
<th>All Patients (N = 530)</th>
<th>Patients with Mesenteric Mass ≥10 mm (N = 340)</th>
<th>Patients without Mesenteric Mass ≥10 mm (N = 190)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No growth</td>
<td>88.3% (N = 468)</td>
<td>83.2% (N = 283)</td>
<td>97.4% (N = 185)</td>
<td></td>
</tr>
<tr>
<td>Growth *</td>
<td>9.2% (N = 51)</td>
<td>13.5% (N = 46)</td>
<td>2.6% (N = 5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Resection</td>
<td>2.1% (N = 11)</td>
<td>3.2% (N = 11)</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

* Growth assessed by RECIST 1.1 criteria and compared to the baseline CT scan. In the case of mesenteric mass at baseline, growth is defined as an increase of ≥20% and ≥5 mm on the short axis of the dominant mesenteric mass. In the case of no mesenteric mass at baseline, growth is defined as the development of a mesenteric node of ≥10 mm on the short axis.

N=530 siNENs
2/3 with MM

MM growth (>20%)
Effect of PRRT on?

MM growth 13.5% patients over 3.4 years, PRRT reduced MM size in only 3.8% of patients!

5. Conclusions

In this study, the data have important clinical implications as they demonstrate the static behavior of the SI-NET-associated mesenteric mass, which should be taken into account when selecting target lesions and assessing disease progression, therapeutic response, and treatment options. PRRT appears not to be effective for size reduction of the mesenteric mass.

Stage IV with extrahepatic disease (EHD)
Small intestinal neuroendocrine tumors with liver metastases and resection of the primary: Prognostic factors for decision making

Emilio Bertani a,*, Massimo Falconi b, Chiara Grana c, Edoardo Botteri d, Antonio Chiappa e, Pasquale Misitano f, Francesca Spada g, Davide Ravizza h, Barbara Bazolli d, Nicola Fazio g

PTR of sINENs with LMs is less effective in patients with extrahepatic disease

--- LMs & Extrahepatic

2 main prognostic factors:
-Tumor burden
-ExtraH disease
The impact of extrahepatic disease among patients undergoing liver-directed therapy for neuroendocrine liver metastasis

Liver-directed therapies are not effective in patients with extrahepatic disease and >50% liver involvement
Actual controversies – Recommendations
Scientific data
SiNEN – Recommendations

NCCN Guidelines Version 3.2021
Neuroendocrine Tumors of the Gastrointestinal Tract
(Well-Differentiated Grade 1/2), Lung, and Thymus

MANAGEMENT OF LOCOREGIONAL ADVANCED DISEASE AND/OR DISTANT METASTASES
GASTROINTESTINAL TRACT EVALUATION\[b,c\]

If complete resection possible\[i,ii\] If complete resection possible\[i,ii\] TREATMENT\[w\] Resect primary\[f\] + metastases

Refer to surveillance for appropriate primary disease sites
(See NET-1 through NET-5)

Abdominal/ pelvic multiphase CT or MRI every 12 wk–12 mo, and chest CT (± contrast) as clinically indicated

Abdominal/ pelvic multiphase CT or MRI every 12 wk–12 mo, and chest CT (± contrast) as clinically indicated

If disease progression, octreotide\[^{w,kk}\] or lanreotide\[^{w,kk}\] (if not already receiving)

If disease progression, everolimus\[^{w}\]
or PRRT with 177Lu-dotatate (if SSRI-positive imaging and progression on octreotide or lanreotide) (category 1 for progressive mid-gut tumors)\[^{w,mm}\]
or Liver-directed therapy for liver-predominant disease\[^{oo}\]
or Palliative RT for symptomatic bone metastases or Cytotoxic chemotherapy\[^{w}\] (category 3) if no other options feasible


Resection of a small asymptomatic (relatively stable) primary in the presence of unresectable metastatic disease is not indicated. However, taking a careful history is recommended as surgery may be an option for asymptomatic patients with previous, intermittent obstructions.
pNEN – Recommendations

NCCN Guidelines Version 3.2021
Neuroendocrine Tumors of the Pancreas (Well-Differentiated Grade 1/2)

**MANAGEMENT OF LOCOREGIONAL ADVANCED DISEASE AND/OR DISTANT METASTASES**

**Evaluation**
- Abdominal ± pelvic multiphasic CT or MRI
- and chest CT (± contrast) as clinically indicated
- SSR-PET/CT or SSR-PET/MRI
- Biochemical evaluation as clinically indicated (See NE-C)
- Consider tumor classification/grade (See NE-A)

**Treatment**
- If complete resection possible
- Resect metastases + primary
- See Surveillance (PanNET-6)
- Observe with markers and abdominal/pelvic multiphasic CT or MRI every 12 wk–12 mo and chest CT (± contrast) as clinically indicated
- Consider octreotide or lanreotide
- Clinically significant progressive disease, see below
- If disease progression:
  - Clinical trial
  - Everolimus (category 1 for progressive disease)
  - Sunitinib (category 1 for progressive disease)
  - Temozolomide + capecitabine
  - PRRT with 177Lu-dotatate, if SSR-positive imaging and progression on octreotide or lanreotide
  - Other cytotoxic chemotherapy
  - Consider liver-directed therapy for liver-predominant disease
  - Palliative RT for symptomatic bone metastases

**Noncurative debulking surgery might be considered in select cases.**

**SSR-based imaging is positive.** If used, they should be used with caution in patients with insulinoma as they may transiently worsen hypoglycemia (See Discussion for details).

**In select cases it may be appropriate to proceed to front-line systemic therapy or liver-directed therapy prior to or concurrently with octreotide or lanreotide.**

**Noncurative debulking surgery might be considered in select cases.**

**PTR FOR UNRESECTABLE G1,G2 LMS → NOT CLEARLY MENTIONED**
Recent Reviews and Larges Series
Resection of the Primary Gastrointestinal Neuroendocrine Tumor Improves Survival with or without Liver Treatment

Aaron Lewis, MD,* Mustafa Raoof, MD,* Philip H. G. Ituarte, PhD,* John Williams, PhD,† Laleh Melstrom, MD,* Daneng Li, MD,‡ Byrne Lee, MD,* and Gagandeep Singh, MD*

Even if the OS is better when LM are treated, Primary Resection seems improve OS of patients with untreated LMs!

N=854 GI stage IV NENs, N=430 LMs, N=392 PTRs

Selection Bias → patients with slow growing LM were observed?

Conclusions:
consider PTR with or without LMs treatment on an individualized basis until prospective findings confirm the presence of a survival benefit for these patients.

PTR for pNEN N=76/372 (20%) PRT for siNENs N=162/200 (81%)

No Propensity score Matching!
A Systematic review and meta-analysis on the role of palliative primary resection for pancreatic neuroendocrine neoplasm with liver metastases

Stefano Partelli¹, Roberto Cirocchi², Paola M.V. Rancoita³, Francesca Muffatti¹, Valentina Andreasi¹, Stefano Crippa¹, Domenico Tamburrino¹,⁴ & Massimo Falconi¹

N=7 Studies, Compared 2 of them published more than 10 years ago! N=251 underwent primary surgery vs N=634 without primary resection

Discussion: pPanNEN-R in patients with unresectable LM seems to be associated with a better OS compared to non-surgical management but the limitations of included studies does not allow firm conclusions.
Palliative resection of the primary tumor in 442 metastasized neuroendocrine tumors of the pancreas: a population-based, propensity score-matched survival analysis

Felix J. Hüttner¹,² · Lutz Schneider¹ · Ignazio Tarantino¹ · Rene Warschkow³,⁴ · Bruno M. Schmied³ · Thilo Hackert¹ · Markus K. Diener¹,² · Markus W. Büchler¹ · Alexis Ulrich¹

Stage IV pNENs - After propensity score-adjusted N=359, PTR N=73 versus noPTR N=286
Role of palliative resection of the primary pancreatic endocrine tumor in patients with unresectable metastatic liver disease: a systematic review and meta-analysis

Bo Zhou, canyang Zhan, Yuan Ding, sheng Yan, shusen Zheng

N=10 Studies, Compared
N=1226 underwent primary surgery vs N=1623 without primary resection

Primary resection increases survival:
- Not for aggressive surgery (morbidity)
- Good general condition
- Less advanced disease
- Body & tail pancreatic NENs

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Log (hazard ratio)</th>
<th>SE</th>
<th>Weight (%)</th>
<th>Hazard ratio IV, fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bertani et al. (2014)</td>
<td>-1.71479843</td>
<td>0.65821858</td>
<td>2.4</td>
<td>0.18 (0.05, 0.65)</td>
</tr>
<tr>
<td>Bertani et al. (2016)</td>
<td>-1.18784342</td>
<td>0.37892481</td>
<td>7.4</td>
<td>0.30 (0.15, 0.64)</td>
</tr>
<tr>
<td>Bertani et al. (2017)</td>
<td>-1.32441896</td>
<td>0.60455034</td>
<td>2.9</td>
<td>0.27 (0.08, 0.87)</td>
</tr>
<tr>
<td>Bettini et al. (2009)</td>
<td>-0.3122356</td>
<td>0.96881611</td>
<td>1.1</td>
<td>4.6 (1.02, 21.08)</td>
</tr>
<tr>
<td>Citterio et al. (2017)</td>
<td>-1.29178388</td>
<td>0.29801777</td>
<td>1.3</td>
<td>0.27 (0.09, 0.81)</td>
</tr>
<tr>
<td>Du et al. (2015)</td>
<td>-1.0712253</td>
<td>0.80099698</td>
<td>1.0</td>
<td>0.31 (0.07, 1.37)</td>
</tr>
<tr>
<td>Franko et al. (2010)</td>
<td>-0.78470718</td>
<td>0.530812</td>
<td>1.0</td>
<td>0.47 (0.19, 1.14)</td>
</tr>
<tr>
<td>Hüttnet et al. (2015)</td>
<td>-0.89108821</td>
<td>0.24306187</td>
<td>1.5</td>
<td>0.40 (0.16, 1.00)</td>
</tr>
<tr>
<td>Nguyen et al. (2007)</td>
<td>-1.25115203</td>
<td>0.6193951</td>
<td>1.0</td>
<td>0.31 (0.10, 0.99)</td>
</tr>
<tr>
<td>Solorzano et al. (2001)</td>
<td>-1.20064501</td>
<td>0.56333531</td>
<td>3.3</td>
<td>0.30 (0.10, 0.91)</td>
</tr>
</tbody>
</table>

Total (95% CI) 100 0.36 (0.30, 0.45)

4 included studies have more than 10 years publications!
3 included studies from the same center...
Association of a Palliative Surgical Approach to Stage IV Pancreatic Neuroendocrine Neoplasms with Survival: A Systematic Review and Meta-Analysis

Marina Tsoli 1, Maria-Eleni Spei 1, Göran Wallin 2, Gregory Kaltsas 1 and Kosmas Daskalakis 1,2.*

Conclusions:
PTR may exert a survival benefit in stage IV pNENs. However, the included studies were subject to selection bias, and special consideration should be given to PPTR anchored to a multimodal treatment strategy.

N=5551 – 6 recent studies - Stage IV pNENs with LMs

<table>
<thead>
<tr>
<th></th>
<th>PTR</th>
<th>PT not resected</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-year OS</td>
<td>56.6%</td>
<td>23.9%</td>
</tr>
<tr>
<td>Complication rate</td>
<td>27%</td>
<td></td>
</tr>
</tbody>
</table>

Figure 4. Cumulative adjusted survival meta-analysis by year of publication.
Resection of the primary tumor improves survival in patients with gastro-entero-pancreatic neuroendocrine neoplasms with liver metastases: A SEER-based analysis


**Effectif N=1547 patients with GEP-NEN with LM**

PRT N=897

<table>
<thead>
<tr>
<th>Differentiation</th>
<th>&lt;.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well differentiated</td>
<td>726</td>
</tr>
<tr>
<td>Moderately differentiated</td>
<td>310</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>352</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>159</td>
</tr>
</tbody>
</table>

**N=726 Well Differentiated NENs !**

**N=511 unD or Poorly D**

**N=310 Moderately Differentiated**

**N=821 !**
Primary Tumor Resection Offers Survival Benefit in Patients with Metastatic Midgut Neuroendocrine Tumors

Monica Polz, MD1, Cameron Schlegel, MD2, Gretchen C. Edwards, MD1, Fei Wang, MD, PhD3,4, Marcus Tan, MBBS1, Colleen Kiernan, MD, MPH1, Carmen C. Solórzano, MD1, Kamran Idrees, MD1, Alexander Parikh, MD, MPH5, and Christina E. Bailey, MD, MSCI1

N=4076 metastatic midgut NENs (Primary resection 62%)

2004-2014 including different centers in USA

TABLE 3 Median survival based on resection of primary tumor

<table>
<thead>
<tr>
<th>Group</th>
<th>Resection of primary tumor&lt;sup&gt;a&lt;/sup&gt;</th>
<th>No resection of primary tumor&lt;sup&gt;a&lt;/sup&gt;</th>
<th>(p) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>71.3 (64.9–78.2)</td>
<td>28.6 (22.5–32.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Small bowel primary</td>
<td>98.6 (87.3–109.5)</td>
<td>53.1 (48.3–67.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Colon primary</td>
<td>14.6 (12.0–18.4)</td>
<td>4.8 (3.7–5.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Well or moderately differentiated</td>
<td>89.6 (78.2–113.7)</td>
<td>48.3 (37.1–65.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Poorly or undifferentiated</td>
<td>6.4 (5.5–7.7)</td>
<td>4.8 (2.9–5.9)</td>
<td>0.0013</td>
</tr>
</tbody>
</table>

<sup>a</sup> excludes 554 patients missing survival data

Interesting large population but retrospective and mainly comparative
Association of a Prophylactic Surgical Approach to Stage IV Small Intestinal Neuroendocrine Tumors With Survival

Kosmas Daskalakis, MD; Andreas Karakatsanis, MD, PhD; Ola Hessman, MD, PhD; Heather C. Stuart, MD, MSc; Staffan Welin, MD, PhD; Eva Tiensuu Janson, MD, PhD; Kjell Öberg, MD, PhD; Per Hellman, MD, PhD; Olov Norlén, MD, PhD; Peter Stålgren, MD, PhD

Uppsala, Sweden, 1985–2015. N=363 Stage IV - SiNETs

- Prophylactic up-front LRS conferred no survival advantage in asymptomatic patients with stage IV SI-NETs.

- Delayed surgery as needed was comparable in all examined outcomes and was associated with fewer reoperations for intestinal obstruction.

- The value of a priori LRS in the presence of distant metastases is challenged and needs to be elucidated in a randomized clinical study.

“Routine resection of the siNETS primary” has never been prospectively demonstrated to increase the overall survival in ASYMPTOMATIC stage IV patients with UNRESECTABLE LMs.

**Need for RCT +++**

In the palliative setting, medical therapy is frequently required pre-, peri- and postoperatively. For further recommendations, please refer to the paper on metastasis [102].
Take Home Messages and Conclusions
Take Home Message  “Primary resection in metastatic disease stage IV”

No Randomized Trial – Multiple selection bias in systematic reviews, meta-analyses without RCT, retrospective data?

- No survival benefit in case of G3 & poorly differentiated lesions (should be excluded from analyzes)
- PTR is recommended in all symptomatic siNET patients
- PTR may improve survival in selected patients with low-grade tumors, low risk resectable primaries and in some patients with LMs in both pNENs and siNENs especially prior to PRRT.
- Patient selection in MDT remains mandatory - Therapeutic strategy upon:
  - Patient’s general condition
  - Tumor grade/differentiation
  - Presence of extrahepatic disease or liver involvement and resectability
  - Risks of PTR upon tumor nature and location, functionality, difficulties of lymphadenectomy (MM)
    - for pNENs, body and tail pNENs rather than head of the pancreas (High morbidity)
    - for SiNENs, remove the primary and LN and the MM (if possible, LN-stages I,II,IIIdown)
  - Possibility of effective treatments including PPRT, LD-therapies, hepatectomy, TA and/or liver transplantation.