**Malignant neuroendocrine tumors**

- Well-differentiated pancreatic endocrine neoplasms:
  - patients: n=163, (166 rendered NED at surgical resection)
  - hepatic recurrence (first site) n=22 (76%).
- Non-functional PNET:
  - 2–6.0 cases/million population
  - all diagnosis: node +: 44%, metastatic disease: 60%
  - median survival M+ disease: 1.4 years.2
- Carcinoid tumors:
  - 38.4 cases/million US population (increasing)
  - presence of metastatic disease varies with tumor size
  - hepatic metastases will occur in 30–50% of patients with tumors >2cm.

**Rationale for regional therapy**

- Regional therapy allows dose escalation to the cancer-bearing region or organ of the body while minimizing systemic exposure and toxicity, via complete separation of the regional and systemic circulation.
- Eliminates or significantly reduces systemic toxicity, and dose escalation of therapeutic agents is limited largely by the tissue tolerance of the perfused organ.
- Based on its unique vascular anatomy the liver is a favorable site for delivery of regional therapy
  - established tumors in the liver derive the majority of blood flow from the arterial tree (tumors 100% versus normal liver 25%).
- Allows treatment of the entire tumor burdened organ (versus local ablative or selective embolization procedures).
- CS-PHP isolates the liver from the systemic circulation using a purpose-designed system of catheters and filters (DaCath Systems Inc., New York, NY).
- Extracorporeal filtration of hepatic venous effluent reduces systemic exposure to chemotherapy by 77% after intrahepatic delivery.

**Management of bilobar liver metastases**

- Carcinoid metastases:1
  - hepatic artery chemoembolization
  - patients: n=122
  - response: radiographic (82%), biochemical (74%), symptomatic (92%)
  - median hepatic progression-free survival: 10.0 months
  - median overall survival: 33.3 months.
- Isolated hepatic perfusion:1
  - melphalan: 1.5 mg/kg
  - patients: n=13
  - response: 50% (all PR)
  - median hepatic progression-free survival: 7.0 months
  - median overall survival: 48 months.

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**Table 1. Treatment response in phase I mixed histology study**

<table>
<thead>
<tr>
<th>Histology</th>
<th>Patients</th>
<th>SD/MR</th>
<th>PR</th>
<th>CR</th>
<th>Overall PR/CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoid</td>
<td>11</td>
<td>1 (100)</td>
<td>–</td>
<td>–</td>
<td>0</td>
</tr>
<tr>
<td>Carcinoid</td>
<td>4</td>
<td>2 (50)</td>
<td>–</td>
<td>–</td>
<td>0</td>
</tr>
<tr>
<td>Neuroendocrine</td>
<td>1</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>0</td>
</tr>
<tr>
<td>Neuroendocrine</td>
<td>1</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
<td>3 (62)</td>
<td>1 (50)</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>TOTAL</td>
<td>29</td>
<td>10</td>
<td>7</td>
<td>2</td>
<td>9 (31%)</td>
</tr>
</tbody>
</table>

**Table 2. PYP response: neuroendocrine tumors (n=24)**

<table>
<thead>
<tr>
<th>NC (baseline template L0)</th>
<th>PD at internal evaluation</th>
<th>SD/MR</th>
<th>PR</th>
<th>CR</th>
<th>Overall response rate 20 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.3</td>
<td>1</td>
<td></td>
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</tr>
<tr>
<td>Overall response rate 20 patients</td>
<td></td>
<td>14 (70%)</td>
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</tr>
</tbody>
</table>

**Table 3. Hepatic progression-free survival (ITT, n=29)**

- Median: 15.5 months

- Figure 3. Hepatic progression-free survival (ITT, n=29)

**Table 4. Overall survival after PYP metastatic neuroendocrine tumor (n=24)**

- Median: 38.4 months
- 34 treated patients

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**Conclusions:**

- Increased drug delivery achieved through novel regional therapeutic approaches may increase efficacy of a given agent (vs. systemic administration) by overcoming a low therapeutic index.
- Neuroendocrine tumors:
  - tumor reduction from regional high-dose melphalan routinely results in durable tumor control, median survival of 38 months, and reduction of hormone-related symptoms
  - retreat upon progression of hepatic disease is possible.

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**References**