



Chemosaturation with percutaneous hepatic perfusion (CS:PHP) using melphalan for unresectable neuroendocrine tumor liver metastases (MNET)

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Malignant neuroendocrine tumors

- Well-differentiated pancreatic endocrine neoplasms:
 - patients: n=183, (166 rendered NED at surgical resection)
 - hepatic recurrence (first site): n=22 (76%).¹
- Non-functional PNET:
 - 2.6–3.0 cases/million population
 - at 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 (Delcath Systems Inc, New York, NY).
- Extracorporeal filtration of hepatic venous effluent reduces systemic exposure to chemotherapy by 77% after intrahepatic delivery.

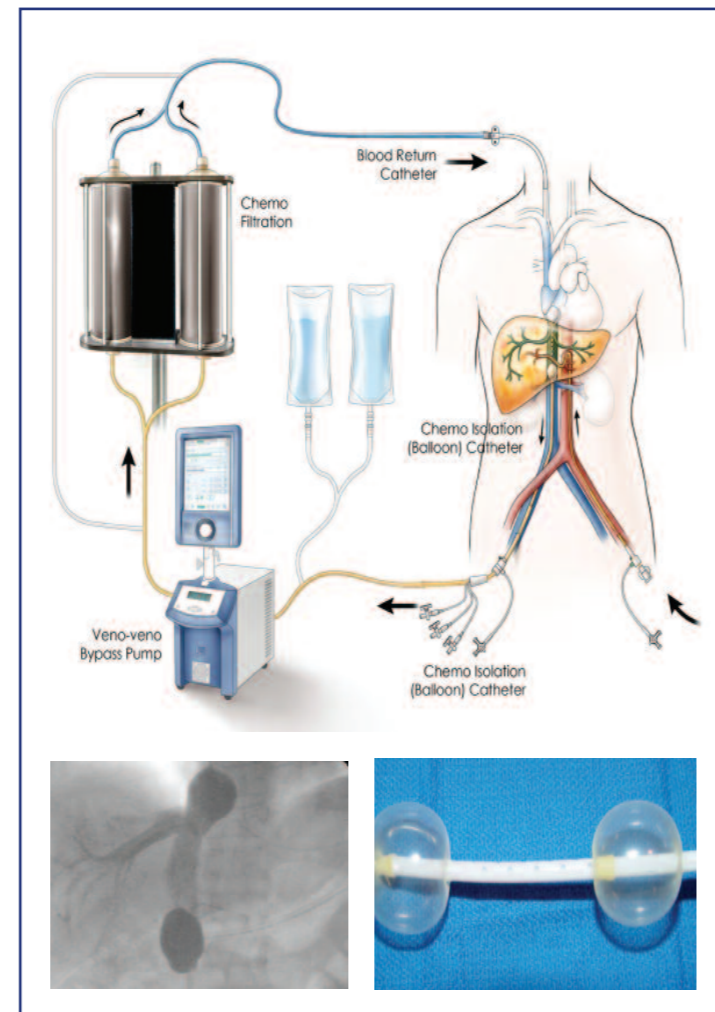
Management of bilobar liver metastases

- Carcinoid metastases:³
 - 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:⁴
 - 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.

Table 1. Treatment response in phase I mixed histology study⁵

Histology	Patients	SD/MR	PR	CR	Overall (PR+CR)
Ocular melanoma	11	3 (14+,9,7)	4 (17,15,7+,7)	2 (11,12)	6 (55%)
Cutaneous melanoma	4	2 (10+,5)	–	–	0
Neuroendocrine	4	1 (25+)	–	2 (22+,17+)	2
Colorectal	2	1 (9)	–	–	0
Adrenal	1	–	1 (10*)	–	1
Other	8	3 (6,4,2)	1 (6+)	–	1
TOTAL	29	10	7	2	9 (31%)

Figure 1. Percutaneous hepatic perfusion



Methods

- All patients treated on an NCI IRB approved phase II protocol utilizing PHP with melphalan (3.0 mg/m²)
- Inclusion criteria:
 - non-resectable hepatic metastases
 - limited, treatable (resection/xrt) extra-hepatic disease
 - adequate hepatic reserve (Bili<3.0, PT within 2 seconds of normal, LFTs <10x ULN).
- Exclusion criteria:
 - portal hypertension
 - inadequate hepatic vascular access.

Figure 2. Protocol schema

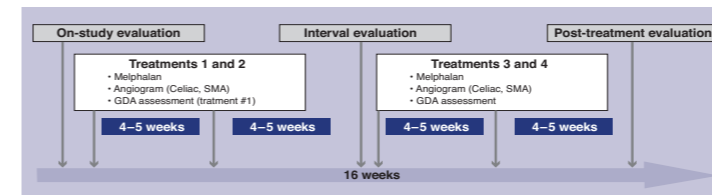
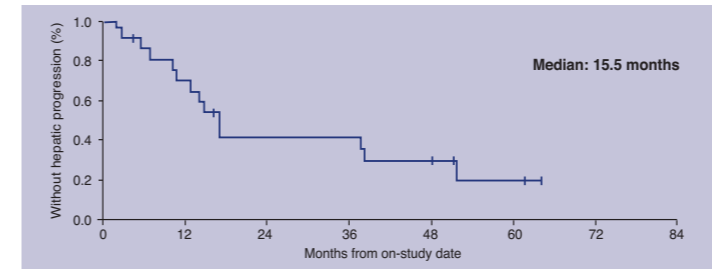


Table 2. PHP response: neuroendocrine tumors (n=24)

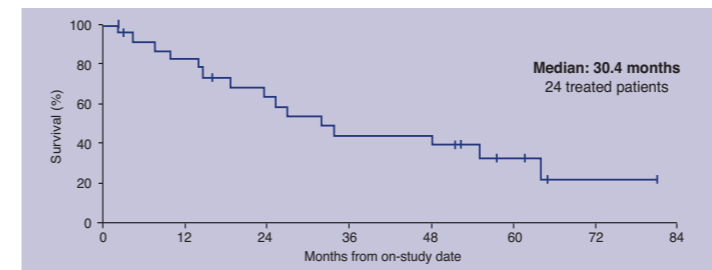
NE (toxicity* incomplete Tx, OLT)	4
PD at interval evaluation	2
SD/MR	4
PR	13
CR	1
Overall response rate (20 patients)	14 (70%)

Figure 3. Hepatic progression-free survival (ITT, n=25)*

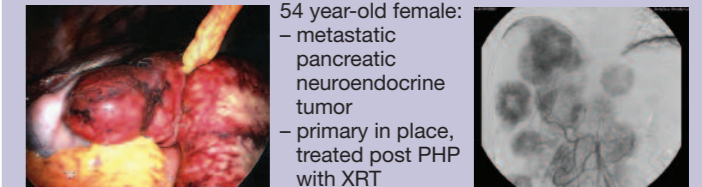


*N=25 because 1 patient was treated twice and progressed twice.

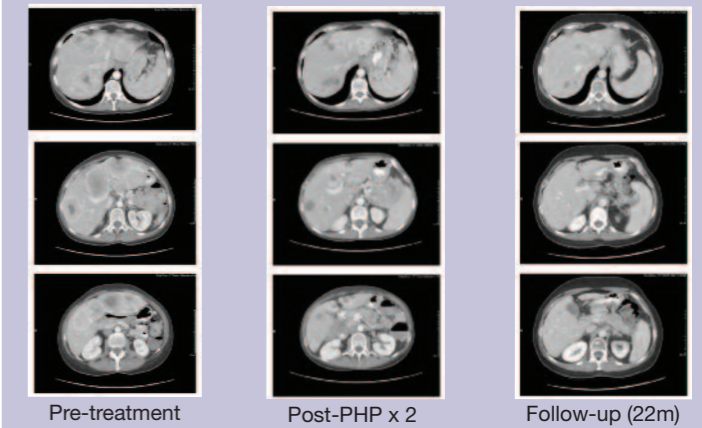
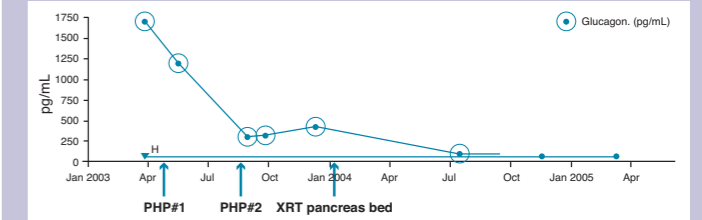
Figure 4. Overall survival after PHP metastatic neuroendocrine tumor (n=24)



Metastatic glucagonoma – case report



54 year-old female:
– metastatic pancreatic neuroendocrine tumor
– primary in place, treated post PHP with XRT



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 30 months, and reduction of hormone-related symptoms
 - retreat upon progression of hepatic disease is possible.

References

- Ferrone CR, et al. J Clin Oncol 2007;25:5609–15.
- Franko J, et al. AHPBA (HPB) 2008;10:30 (abstract 8).
- Bloomston M, et al. J Gastrointestinal Surg 2007;11:264.
- Grover AC, et al. Surgery 2004;136:1176–82.
- Pingpank JF, et al. J Clin Oncol 2005;23:3465–74.