High Dose Intra-Arterial Melphalan Delivered via Percutaneous Hepatic Perfusion (PHP) for Patients with Unresectable Hepatic Metastases from Primary Neuroendocrine Tumors.

James F. Pingpank, Richard E. Royal, Udai S. Kammula, Anthony W. Kam, Bradford J. Wood, H. Richard Alexander, Steven K. Libutti SK, Marybeth S. Hughes, Susan E. Ohl.

Surgical Metabolism Section, Surgery Branch, NCI, Bethesda, MD
Division of Surgical Oncology, University of Maryland, Baltimore, MD

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Delcath double balloon catheter under IDE

Intra-arterial melphalan and Delcath catheter under IND

Malignant Neuroendocrine Tumors

Well-Differentiated Pancreatic Endocrine Neoplasms

Patients: n=183, (166 rendered NED at surgical resection)

Hepatic Recurrence (first site): n=22 (76%) (Ferrone/Allen, MSKCC: JCO 2007 (25):5609)

Non-Functional PNET

2.6-3.0 cases/million population

At diagnosis: Node +: 44%, Metastatic Disease: 60%

Median Survival M+ Disease: 1.4 years (Franko/Moser, UPMC: AHPBA 2008)

Carcinoid Tumors

38.4 cases/million US population (increasing)

Presence of metastatic disease varies with tumor size.

Hepatic metastases will occur in 30 to 50% of patients with tumors >2cm

Survival Following Hepatic Metastasectomy for Non-Colorectal Histologies

Author	Histology	N	Actuarial 5-yr Survival	Median Survival (Months)
Chen et al	Neuroendocrine	15	73%	NR
Que et al	Neuroendocrine	74	73%	NR
Harrison et al	Genitourinary	34	60%	NR
Jaques et al	Sarcoma	14	0%	30
Harrison et al	Breast/Melanoma/ Sarcoma	41	26%	32
Elias et al	Breast	21	9%	26
Raab et al	Breast	34	18%	27
Ochiai et al	Gastric	21	19%	18
Bines et al	Gastric	7	14%	15
Harrison et al	Gastrointestinal	7	0%	25

NR - not reached

Management of bilobar liver metastases

Carcinoid Metastases:

Hepatic Artery Chemoembolization (Bloomston, OHSU: JGISurg 2007 (11): 264)

- Patients: n=122
- Response: Radiographic (82%), Biochemical (74%), Symptomatic (92%)
- Median Hepatic Progression-Free Survival: 10.0 months
- Median Overall Survival: 33.3 months

Staged Surgical Resection (Kianmanesh/Belghiti, Ann Surg 2008; 247: 659.)

- Patients: n=23 (of 41 patients with bilobar mets)
- 3 patients not resectable at laparotomy
- Single patient with interval hepatic progression between liver resections
- R0 Resection: 14 of 19 patients (74%)
- 2-year Disease Free and Overall Survival: 94%, 85% respectively
- Exclusion: High mitotic index/poorly differentiated, Rapid disease progression

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/limb

- Improved efficacy/tumor response

Based on its unique **vascular anatomy** the liver is a favorable site for delivery of regional therapy

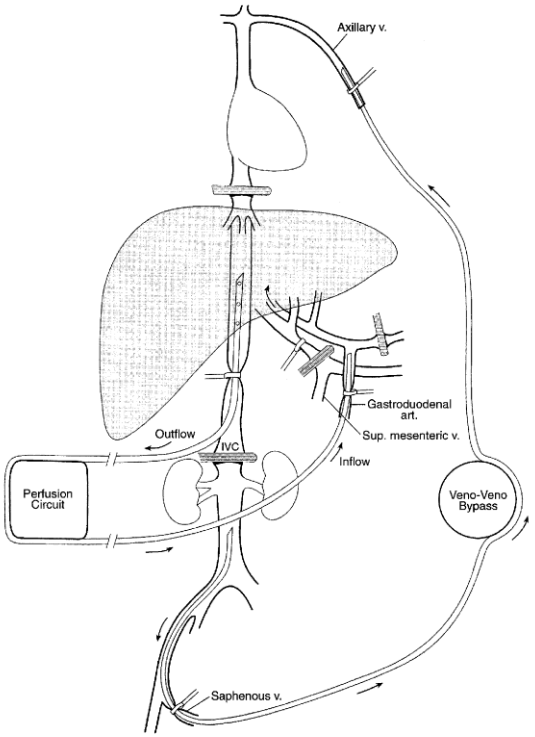
- Established tumors in liver derive the majority of blood flow from the arterial tree (tumors: 100% versus normal liver: 25%)

Potential for delivery of clinically relevant levels of **hyperthermia** or **biologic agents**

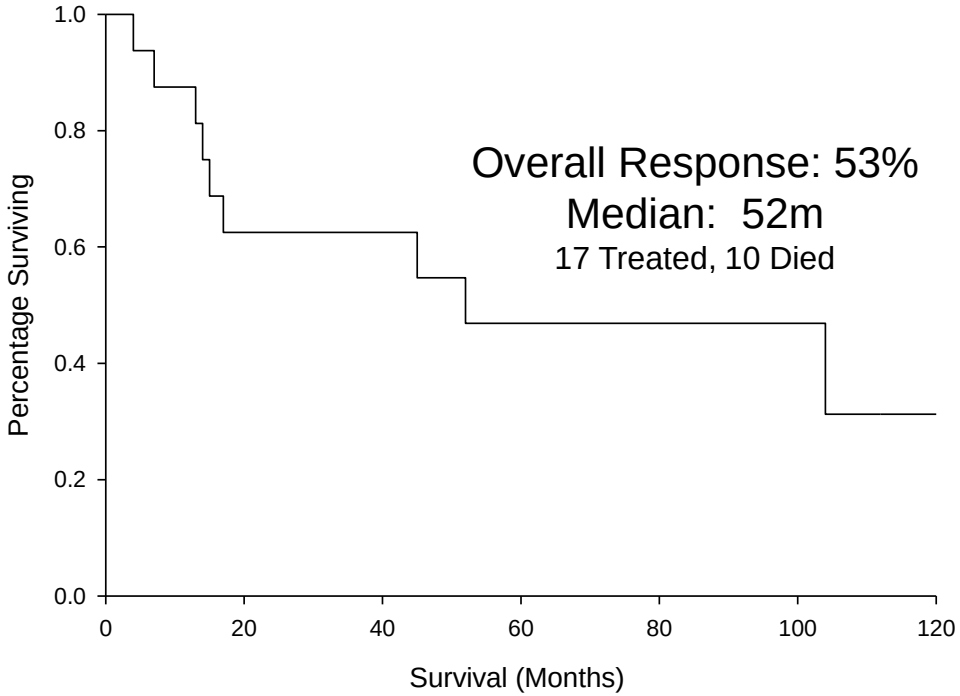
Allows treatment of the **entire tumor burdened organ**

- Versus local ablative or selective embolization procedures

Isolated Hepatic Perfusion
Overall Survival
(n=17)

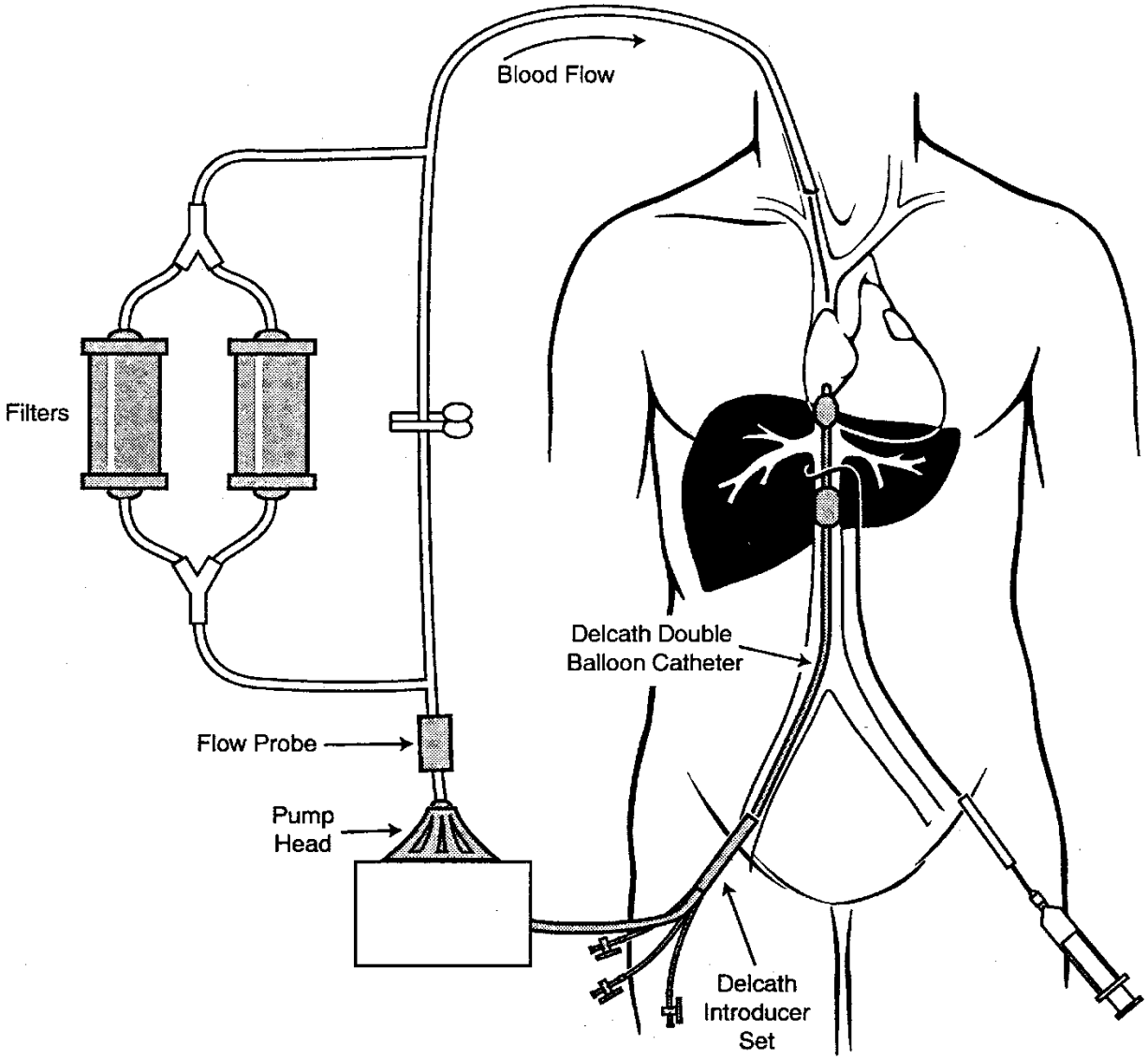


Isolated Hepatic Perfusion Circuit



Surgery 2004;136:1176-82.
(Updated March, 2008)

Percutaneous Hepatic Perfusion



Methods

All patients treated on an NCI IRB approved phase I or phase II protocol utilizing PHP with Melphalan

Inclusion Criteria:

- Non resectable hepatic metastases
- Limited, treatable (resection/xrt) extra-hepatic disease
- Adequate hepatic reserve
  - (Bili<3.0, PT w/in 2 seconds of normal, LFTs <10x ULN)

Exclusion Criteria

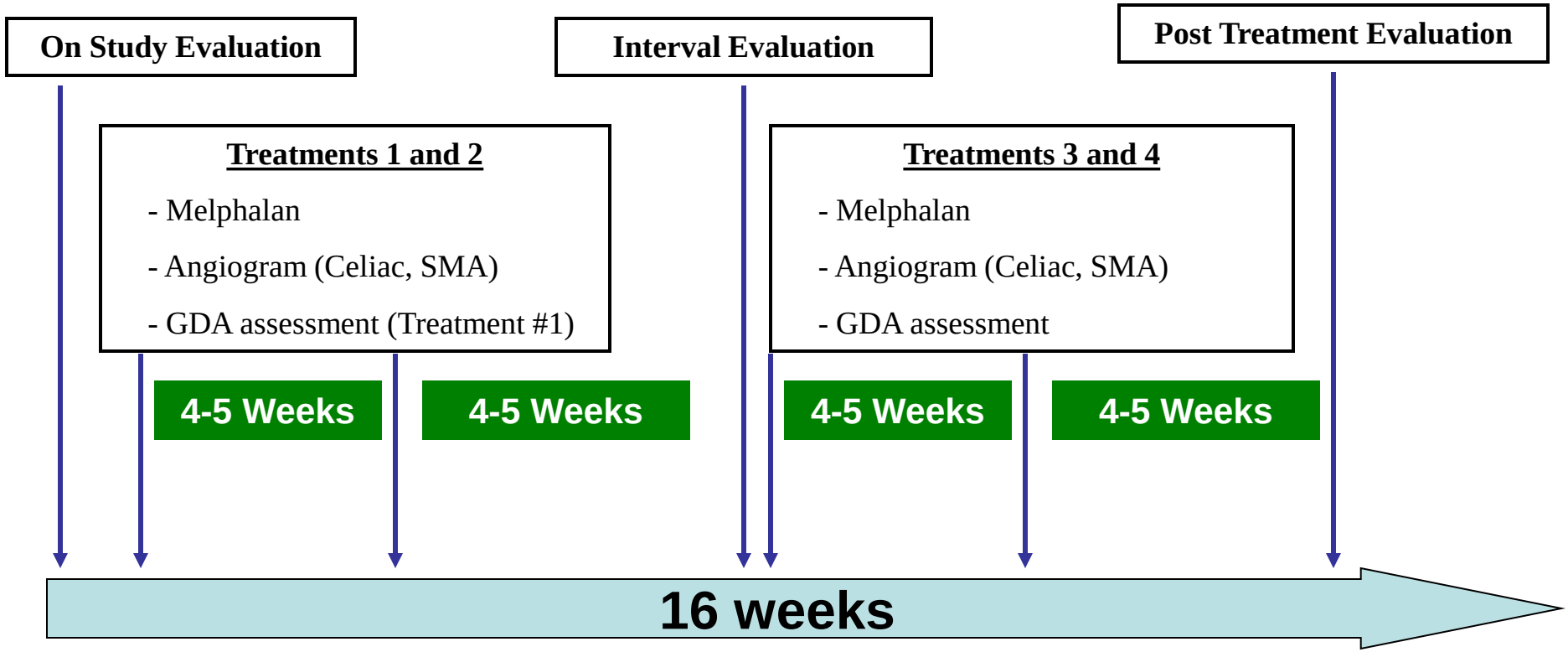
- Portal hypertension
- Inadequate hepatic vascular access

PHP Patient Demographics

Neuroendocrine Tumors (n=23)

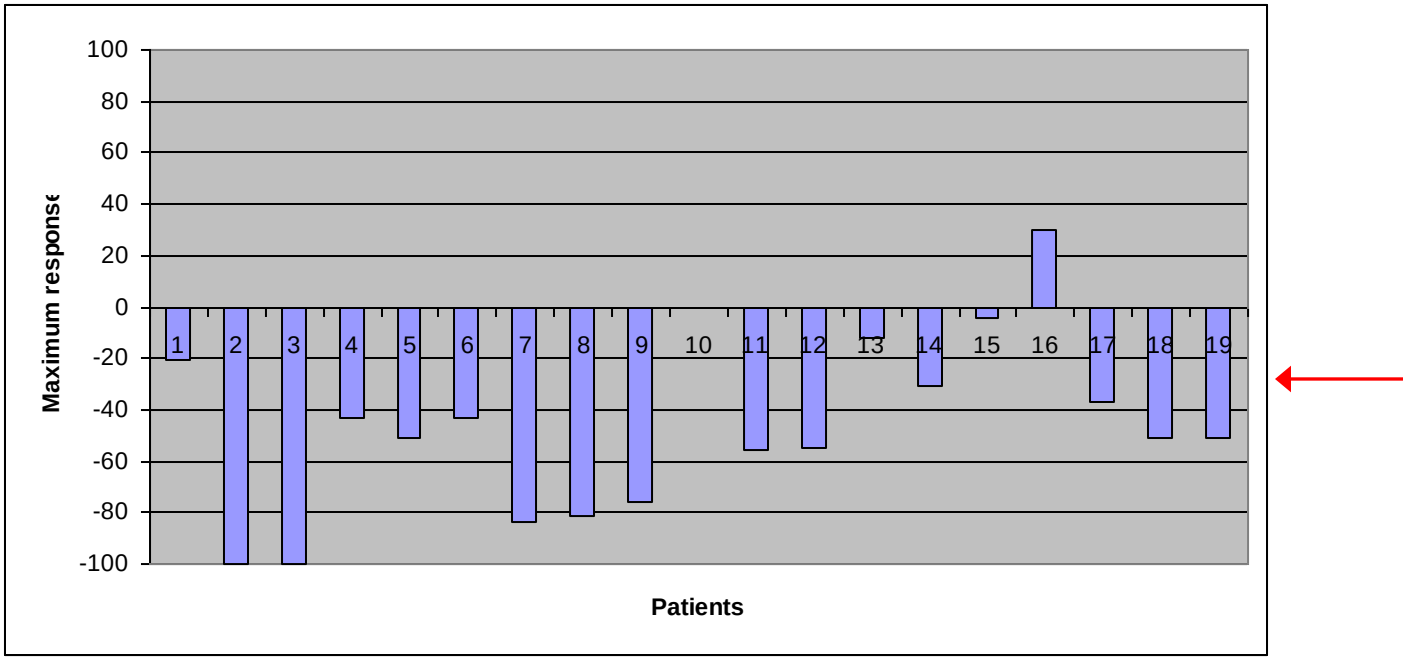
Median no. of hepatic lesions	15
Mean diameter of largest lesion	4.8 cm
Extrahepatic Disease	9 (39%)
Subsequent Resection: n=7	
Percentage hepatic replacement	
<25%	12 (52%)
25-50%	5 (22%)
>50%	6 (26%)
Primary Tumor Histology	
Carcinoid	6
PNET	17

Protocol Schema



PHP Response: Neuroendocrine Tumors
(n=23)

NE (Toxicity*, Incomplete Tx, OLT)	4
PD at interval evaluation	1
SD/MR	3
PR	13
CR	2
Overall Response Rate (19 patients)	15 (79%)



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PHP Results: Neuroendocrine Tumors
(68 Treatments)

Mean Melphalan Dose at 3.0 mg/kg: 180 mg (126-220)

Unsuccessful Therapy

- Sclerotic hepatic artery (n=1)
- MEN-1 associated Hypercalcemia (n=1)

Median Length of Stay: 3 days

Procedure and Treatment Related Toxicities

(68 Procedures; March 2008)

Procedure Related Complications	N
Carcinoid Crisis	1
CNS Tumor Hemorrhage (Grade 3)	1
Tumor Lysis Syndrome (Grade 3)	1

Treatment Related Toxicity, Grade 3-4 (n,%)

Hematologic	Early (n=68)	Late (n=68)
Neutropenia	0	32 (47%)
Thrombocytopenia	14 (21%)	20 (29%)
Anemia	11 (16%)	10 (15%)
Hepatic		
Transaminitis	15 (22%)	0
Hyperbilirubinemia	6 (9%)	0
Other GI **Includes single Grade 5		
Cholangitis	1**	0
Gastric Ulcer/perforation	1/1	1/1

Mortality Rate (Phase I, II, III Protocols):

103 patients (2.9%), 234 procedures (1.3%)

Treatment Related Deaths:

Hepatic Insufficiency (n=1), Gastric Perforation (n=1), HA pseudoan. rupture (n=1)

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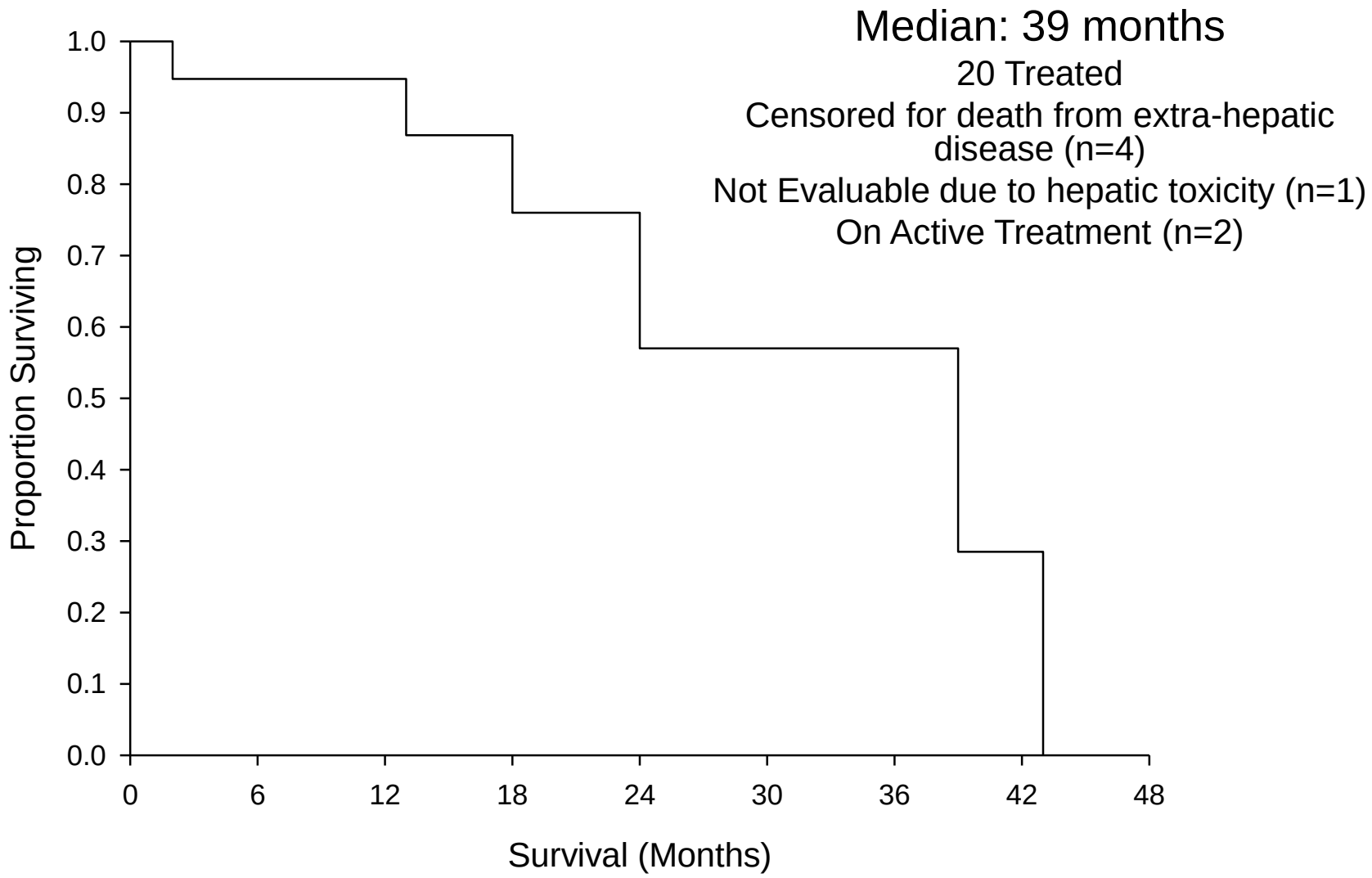
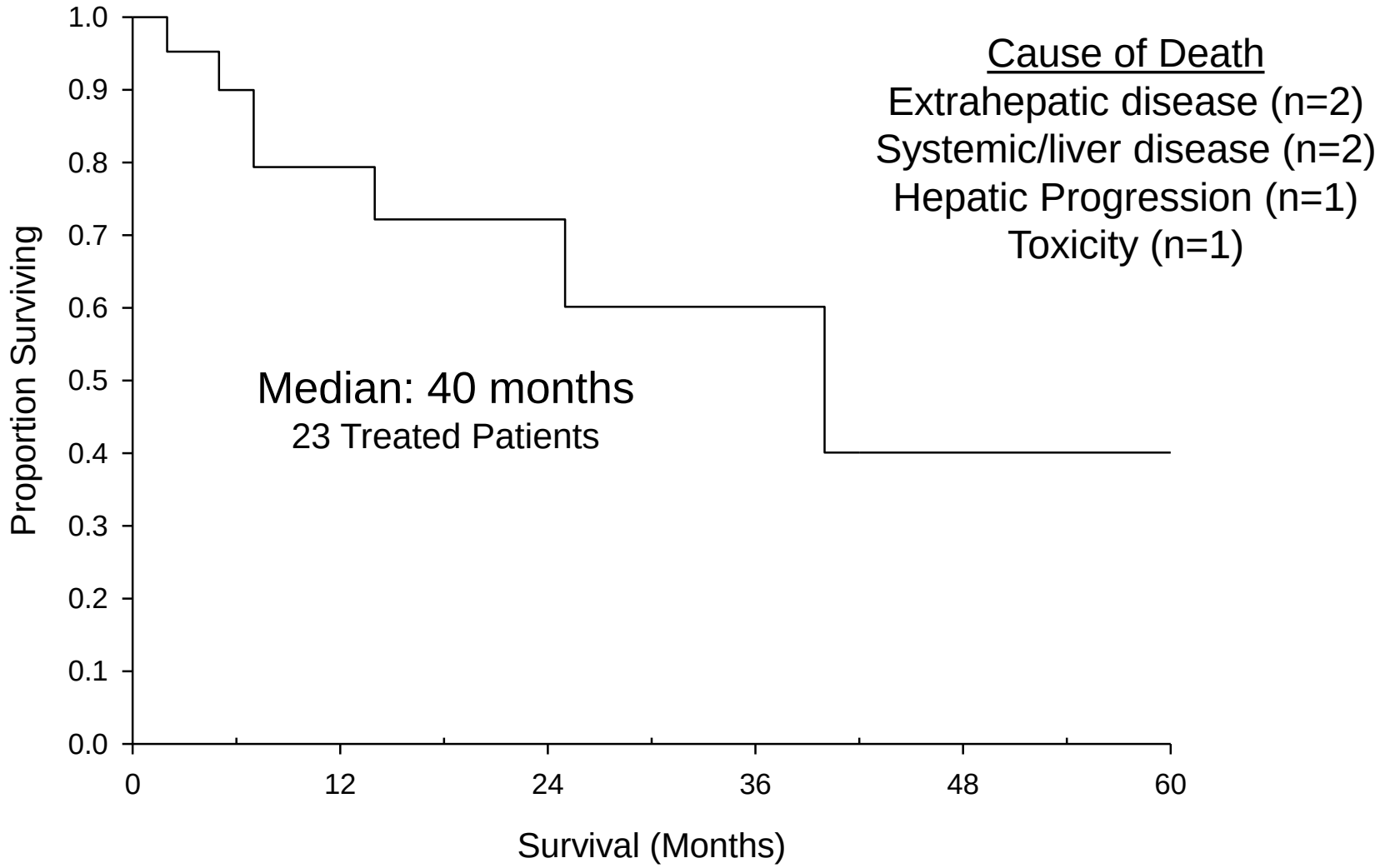
Hepatic Progression-Free Survival After PHP

Metastatic Neuroendocrine Tumor (n=20)



Overall Survival After PHP Metastatic Neuroendocrine Tumor (n=23)



Conclusions

High-dose Melphalan, delivered via intra-arterial administration is effective against hepatic metastases from neuroendocrine tumors

Tumor reduction from PHP routinely results in durable control of hormone-related symptoms

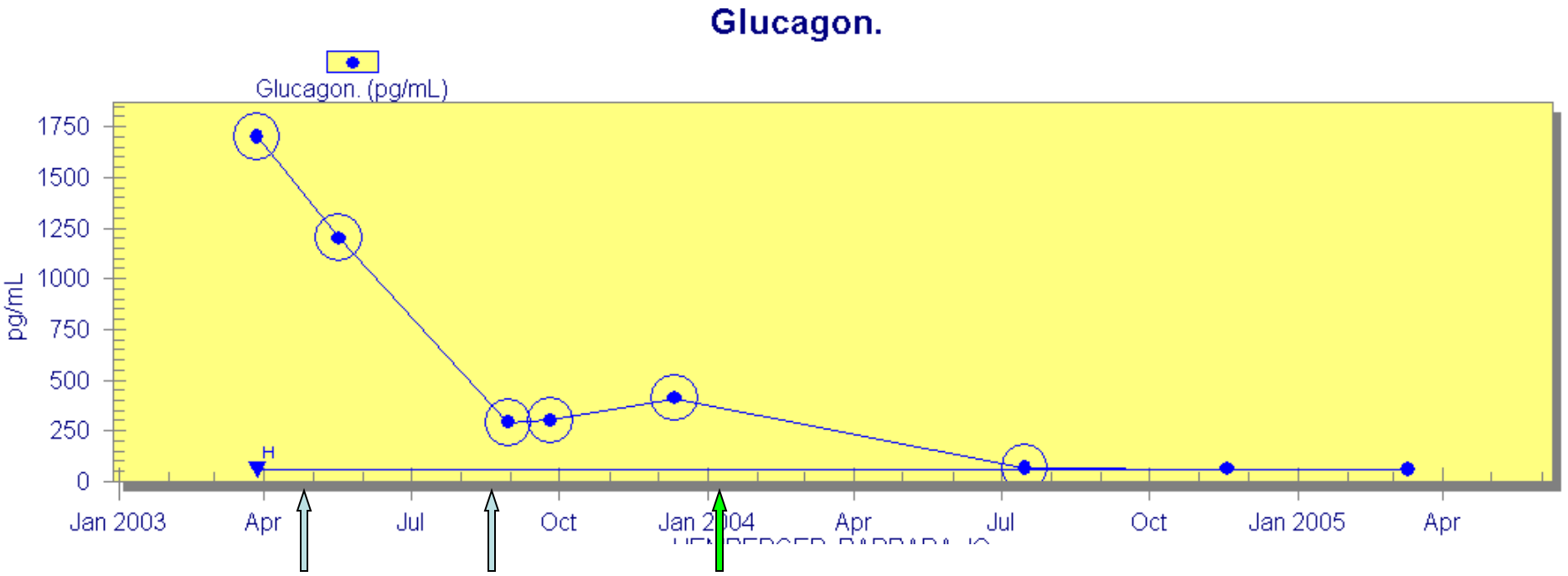
An expanded, phase II multi-center confirmatory trial is planned, with stratification for metastatic pancreatic neuroendocrine and carcinoid tumors

Metastatic Glucagonoma

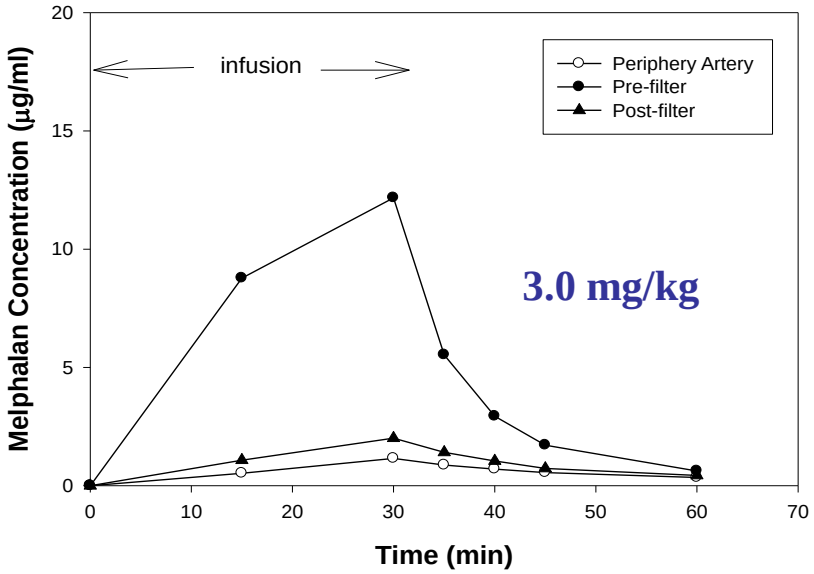
54 year-old female

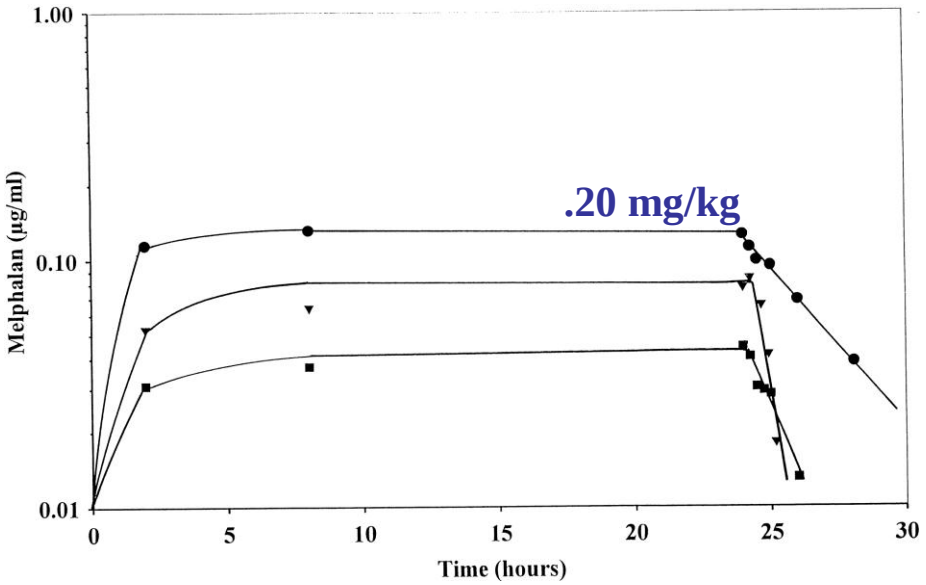
Metastatic pancreatic neuroendocrine tumor

Primary in place, treated post PHP with XRT



Chemotherapy Levels During Therapy PHP vs Systemic





Percutaneous Hepatic Perfusion

Systemic Continuous Infusion (MTD)

Alternate Melphalan Dosing Regimens

Chemoembolization: 0.62 mg/kg

Myeloabation: 2.5 – 3.5 mg/kg

Management of Liver Metastases from Neuroendocrine Tumors

48 patients

- Carcinoid (n=36), Islet Cell (n=12)

Therapy (non-randomized)

- Resection/Ablation: 13 pts
- Chemo-embolization: 18 pts
- Conservative therapy: 17 pts

No difference in volume of hepatic disease

No difference in symptom palliation

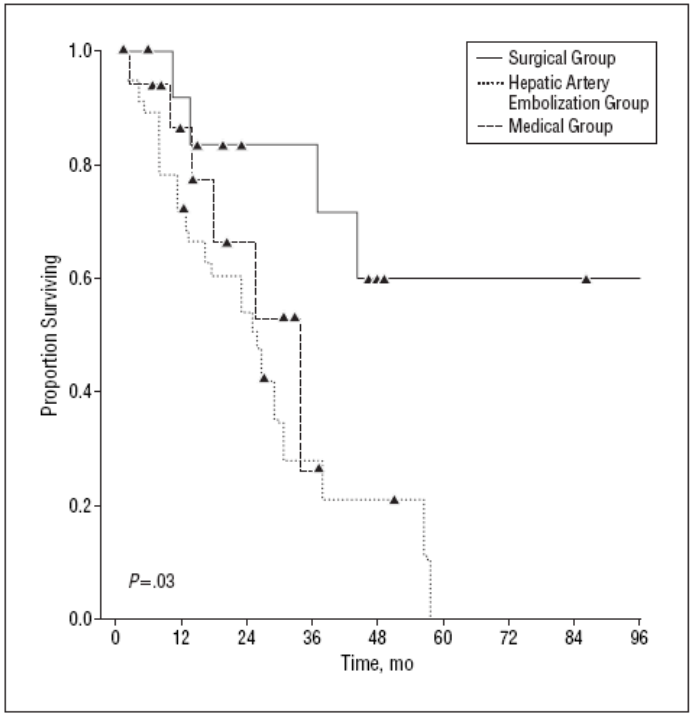


Figure 1. Overall survival for patients with metastatic liver-only neuroendocrine tumors who received surgical treatment, hepatic artery embolization, or medical treatment.

Arch Surg 2006; 141: 1000-1004.