



Analysis of Clinical Toxicity in Patients Undergoing Percutaneous Intra-Arterial Hepatic Perfusion (PHP) with Melphalan for Unresectable Hepatic Malignancies

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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

Treatment of Hepatic Metastases

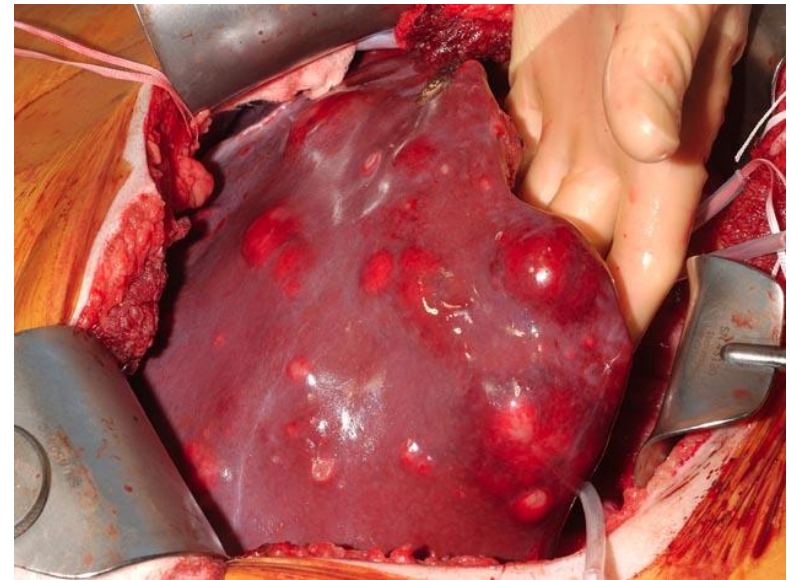
Rationale for Regional Therapy

Unresectable cancers (primary or metastases) confined to liver are a significant clinical problem:

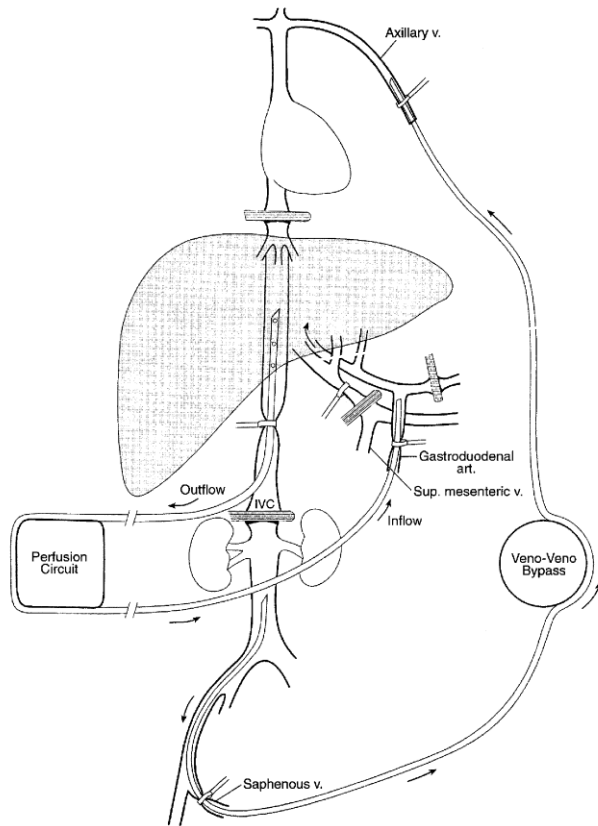
Colorectal cancer:	30,000/yr
Hepatocellular carcinoma:	16,000/yr
Ocular melanoma:	2,000/yr
Neuroendocrine tumors:	2,000/yr
Other histologies:	?

Therapeutic options are limited and survival after diagnosis of liver metastases is short.

Morbidity and mortality in this setting is invariably secondary to disease progression in the liver.



Background: Isolated Hepatic Perfusion



Colorectal Metastases

n=120 pts

RR: 60%, Median OS: 17.4m

Ocular Melanoma Metastases

n=29 pts

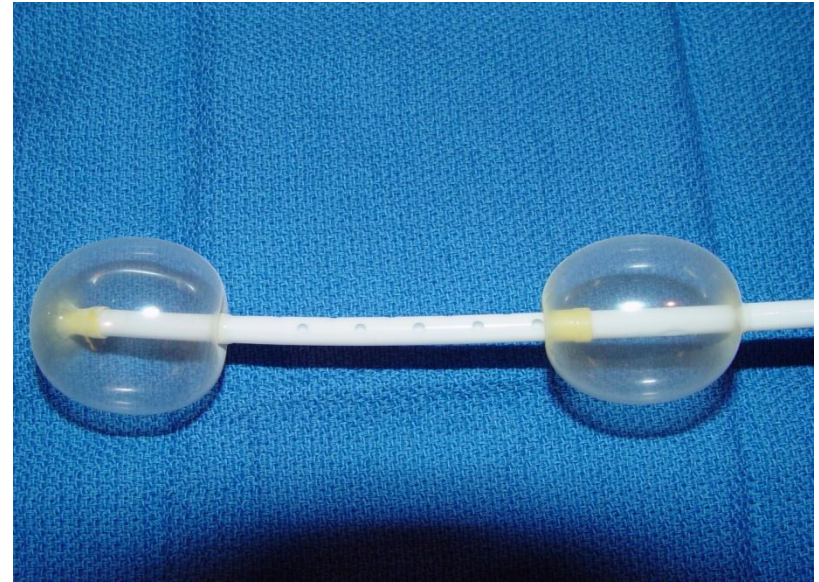
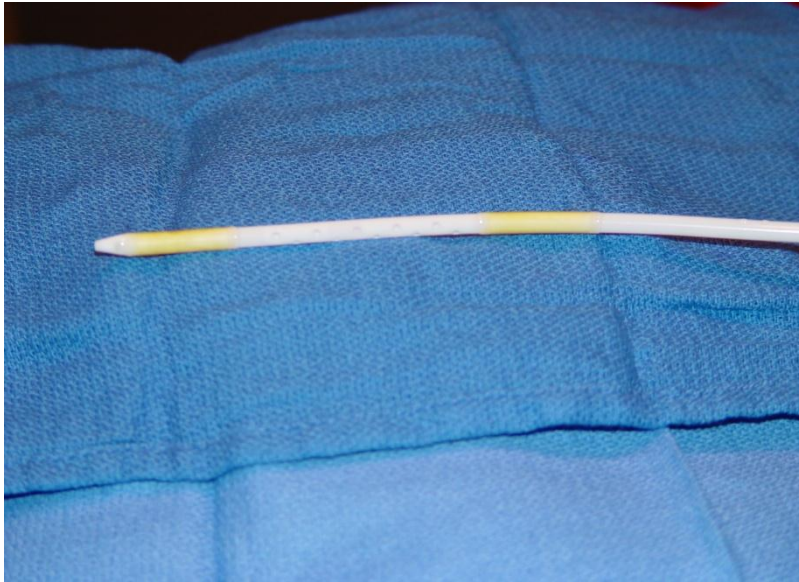
RR: 62%, Median OS: 12.1 m

Neuroendocrine Metastases

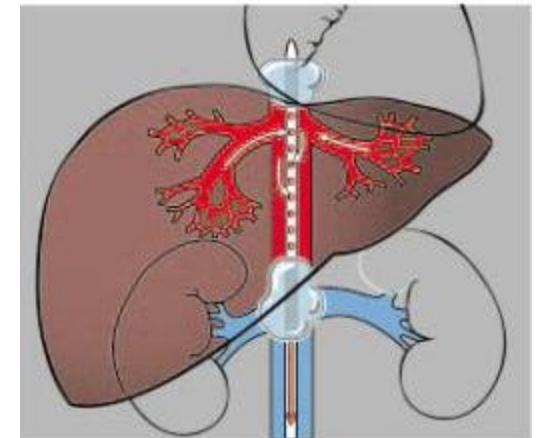
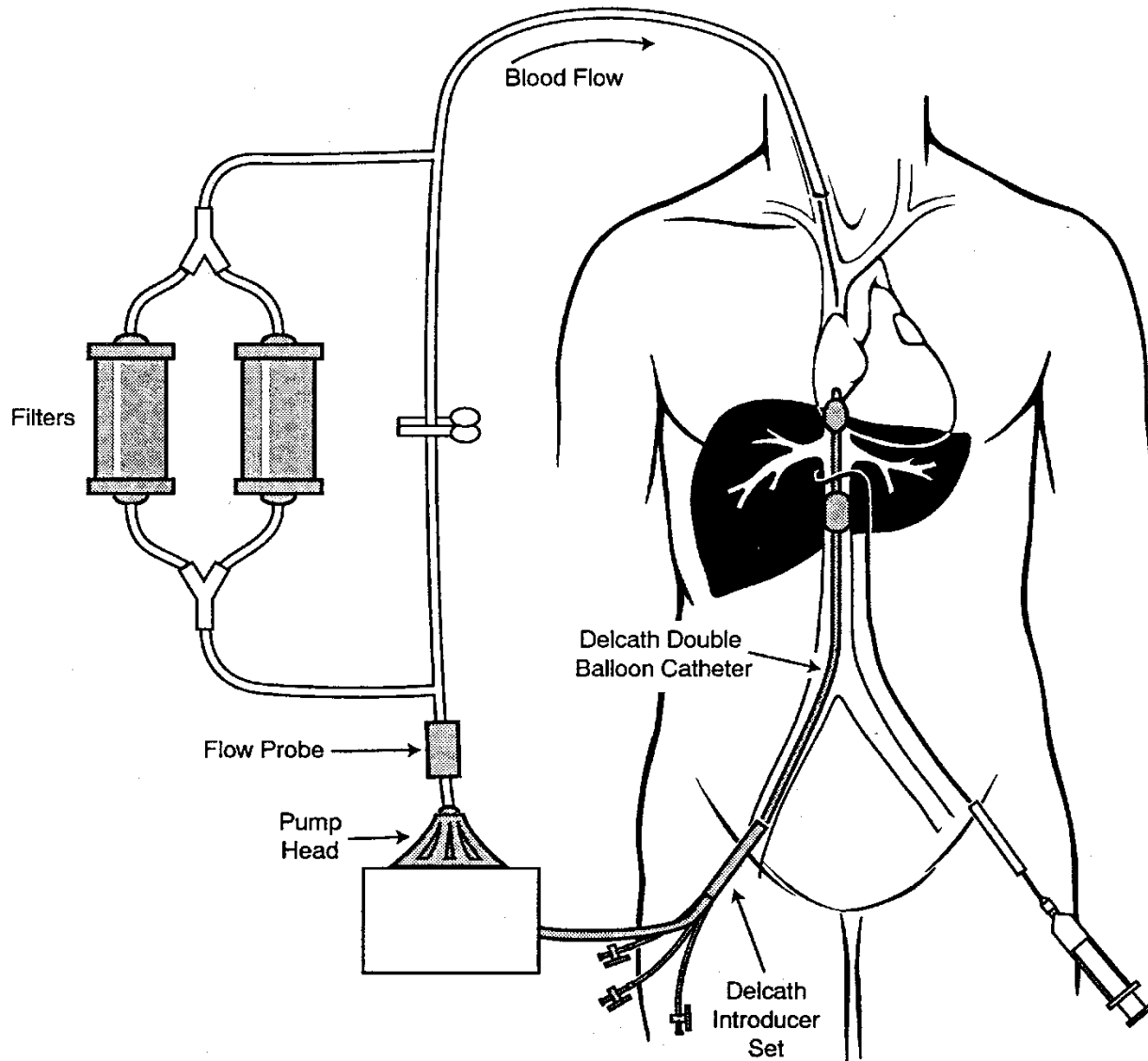
n=13 pts

RR: 50%, Median OS: 48 m

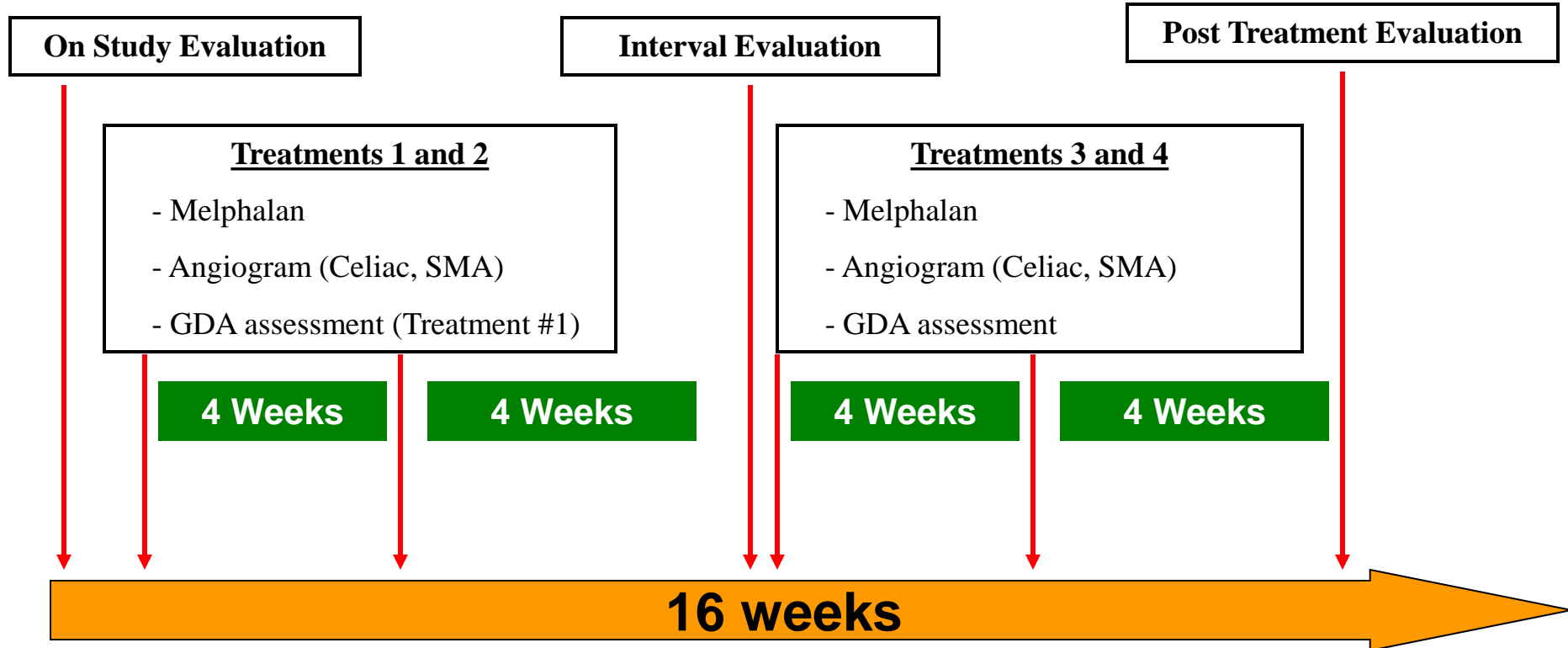
Delcath Systems double balloon IVC catheter



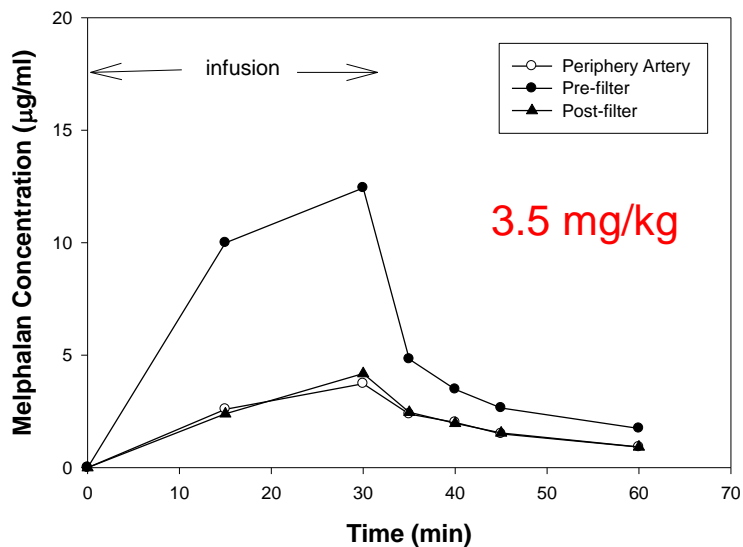
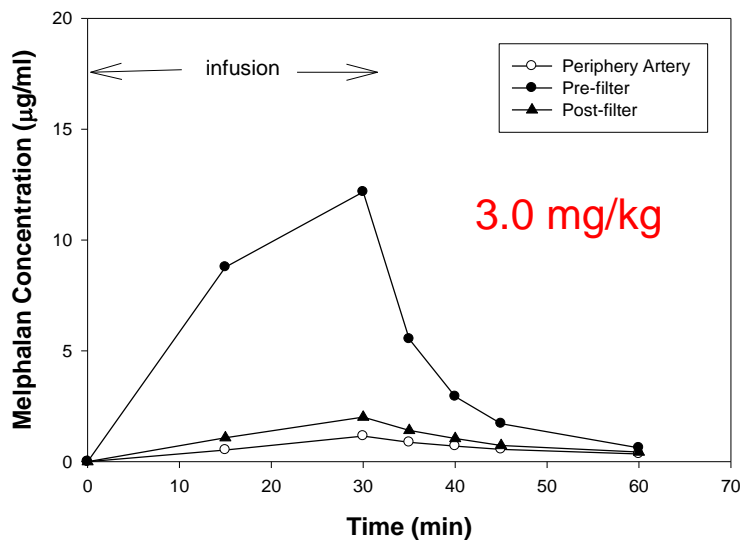
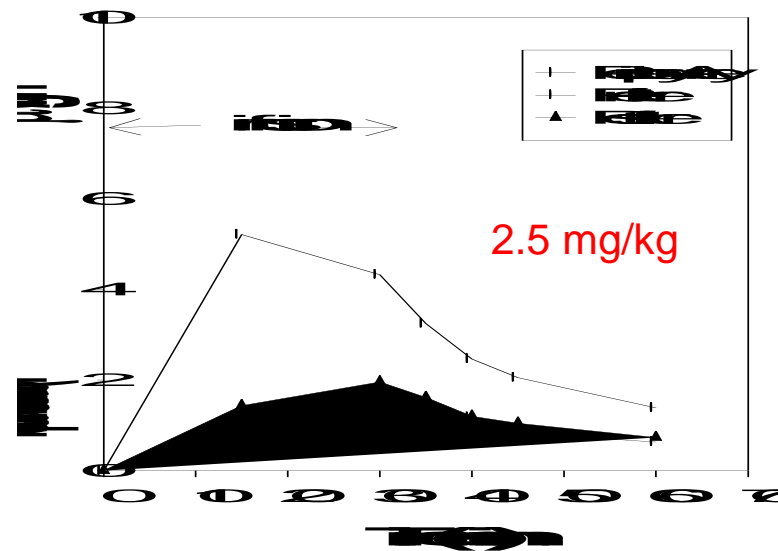
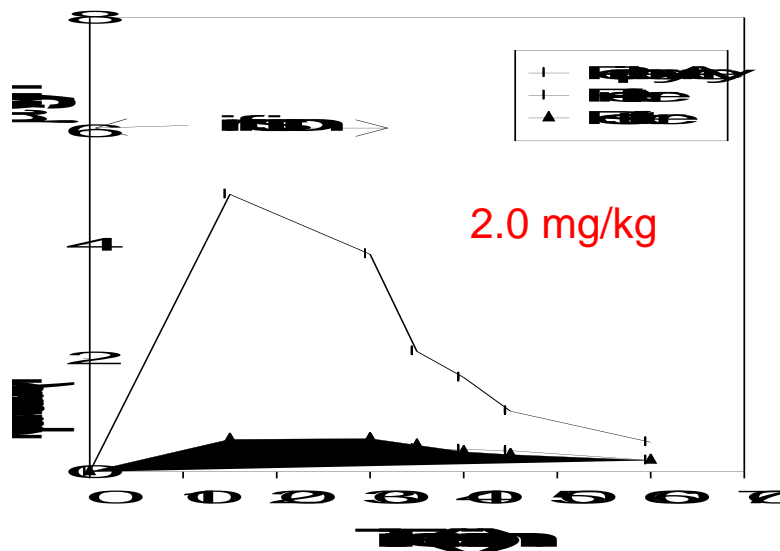
Percutaneous Hepatic Perfusion



Protocol Schema



Chemotherapy Levels During Therapy



Results: Toxicity

(198 Treatments)

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

Unsuccessful Therapy

Hepatic artery dissection (n=2)

Sclerotic hepatic artery (n=3)

Hepatic venous anomaly (n=3)

Toxicity (Grade III/IV)

Neutropenia: 120 (60.6%)

Thrombocytopenia: 96 (48.5%)

Anemia: 36 (18%)

Hepatic (LFTs, Bili): 31 (15.7 %)

Median Length of Stay: 3 days

Results: Patient Demographics

Patients: 76

Number of Treatments: 198

Unsuccessful Treatments: 8

Histology:

Melanoma: 26

Neuroendocrine: 19

Results: Complications

(198 Treatments)

Arterial or Venous Catheters

Hepatic Artery Dissection (n=2)

Cervical Hematoma (n=1)

Pneumothorax (n=1)

Bleeding

Intrahepatic (Tumor) Hemorrhage (n=1)

Excessive Menstrual Bleeding (n=2)

Gross Hematuria (n=1)

Other

Heparin Induced Thrombocytopenia (n=1)

Transient Ascites (n=1)

Protamine Reaction (n=1)

Melphalan Anaphylaxis (n=1)

Hepatorenal Syndrome (n=1)

PHP for Patients with Metastatic Melanoma

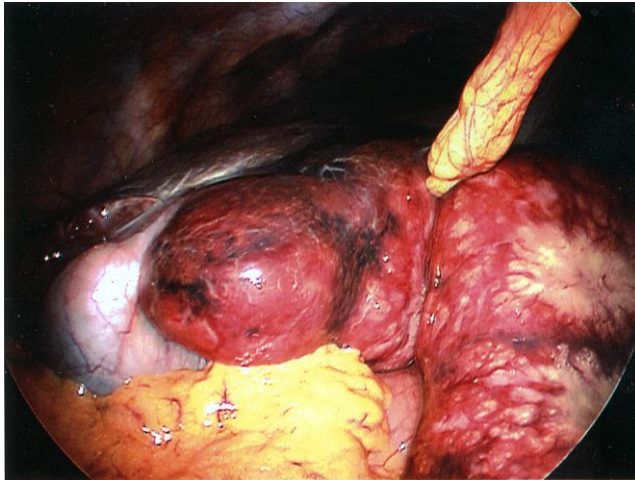
Radiographic Treatment Response

	(n=16)		
<u>Response</u>	<u>n</u>	<u>%</u>	<u>Duration</u>
Overall	8	50	
Complete	2	13	10, 15
Partial	6	37.5	2+, 8, 8, 12, 15, 16
Stable Disease	4	25	7, 7, 8, 8+
Progressive Disease	4	25	
Follow-up Status			
AWD ^b	1	6	
DOD	15	94	
Site of Disease Recurrence/Progression (n=11 responders)			
Hepatic	6	50	
Systemic	4	33	
Both	2	17	

^a + censored with stable or responding hepatic disease with systemic progression

^b AWD, alive with disease; DOD, dead of disease

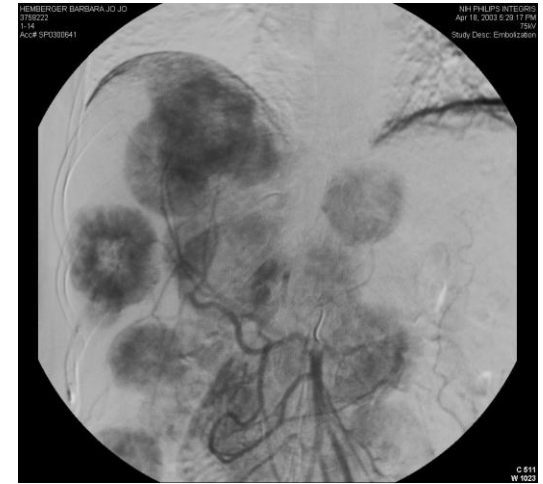
Metastatic Glucagonoma



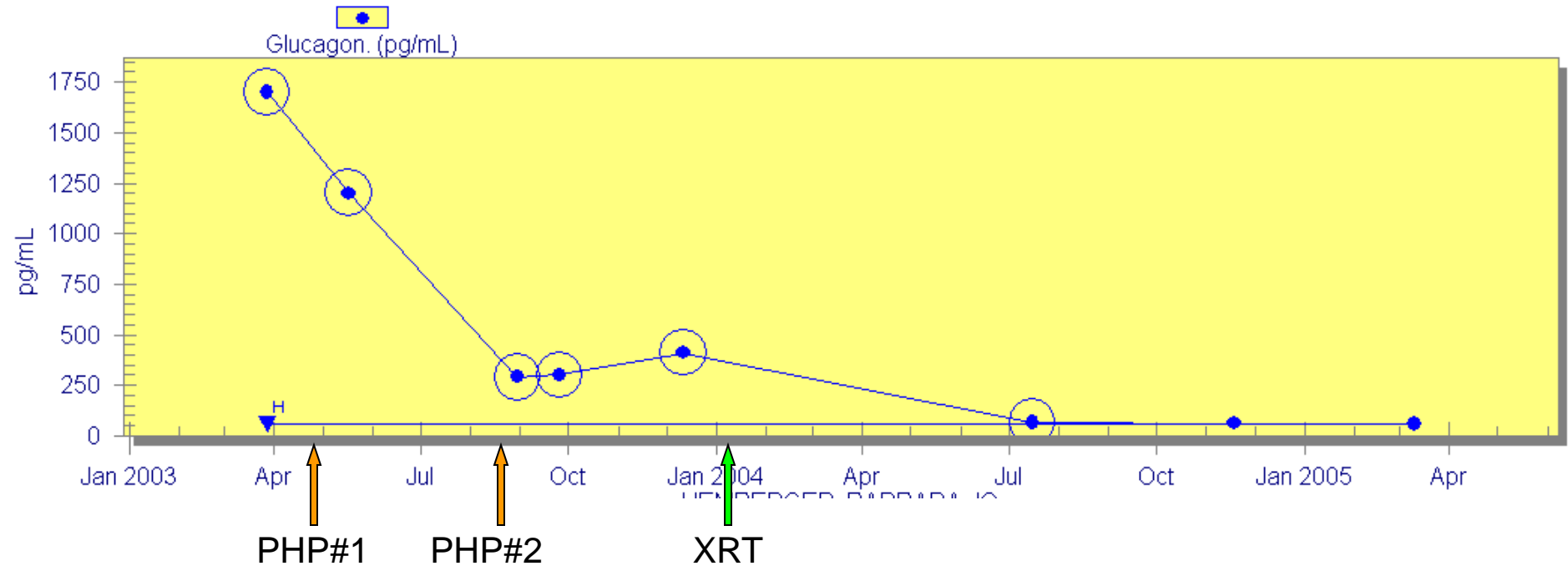
54 year-old female

Metastatic pancreatic neuroendocrine tumor

Primary in place, treated post PHP with XRT



Glucagon.

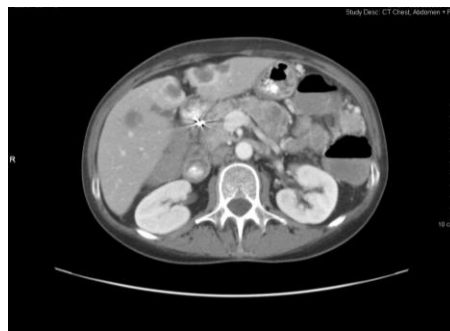


Metastatic Glucagonoma



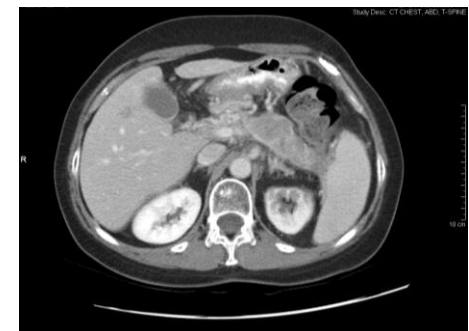
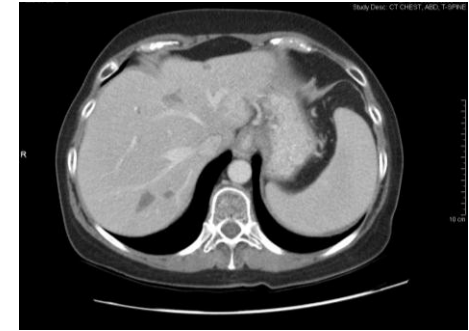
Pre-Treatment

April 2003



Post-PHP x 2

November 2003



Follow-up (22m)

March 2005

Conclusions

This strategy allows for the delivery of high-dose, intra-arterial cytotoxic chemotherapy with manageable regional and systemic toxicity

Regional delivery of chemotherapy paired with hemofiltration allows for an increased therapeutic index for cytotoxic agents such as melphalan

PHP with Melphalan is effective in patients with hepatic metastases from melanoma and gastrointestinal neuroendocrine metastases

Future Directions

Metastatic Ocular Melanoma

Phase III random-assignment trial vs. Best alternative care

Primary endpoint: Hepatic DFS (cross-over permitted)

Conversion to multi-center trial

Metastatic Neuroendocrine Tumors

Phase II trial, completion of second stage, expand to multicenter phase II

Hepatocellular Carcinoma

Completion of Phase II study

Metastatic Colorectal Cancer

Phase I trial with Oxaliplatin post completion of pre-clinical animal studies

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